

Clinical Pharmacokinetics

6th Edition

**JOHN E. MURPHY, PharmD,
FASHP, FCCP**

*Professor of Pharmacy Practice and Science and
Associate Dean, College of Pharmacy
Professor of Clinical, Family and Community Medicine
College of Medicine
The University of Arizona
Tucson, Arizona*

*Honorary Professor
The University of Otago School of Pharmacy
Dunedin, New Zealand*

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DEDICATION

This sixth edition is again dedicated to:

Our patients, to whom we devote our professional lives; to my past and present students and residents who continue to inspire me;

My mother and father, for their nurturing; to my family (and my four grandchildren) for making life interesting and fun;

Mercer University and the University of Arizona for providing me the best jobs I could have ever hoped for; and

The pharmacy profession for giving me opportunities I never dreamed existed for a guy like me way back when it all started.

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Pharmacokinetic studies have continued to be published since the first edition of the *Clinical Pharmacokinetics*. The second, third, fourth, fifth and now sixth edition authors have taken advantage of advances in understanding to update the chapters. In many cases more judicious monitoring of drug concentrations is suggested compared to the early editions. For some drugs, the dosing approaches are radically different now. For others, new prediction approaches are available that have been tested in larger numbers of patients or with more sophisticated data analysis. Because the impact of drug interactions and the determination of the appropriate dosing weight on pharmacokinetics and pharmacodynamics on obese patients can be important to dosing decisions, the authors include this information when available. Pharmacogenomic issues are increasingly essential in decisions about drug dosing or who should receive certain drugs; therefore, most of the relevant chapters are updated regarding the impact of pharmacogenetic studies on dosing. In addition, a specific chapter has been added to help interpret issues related to applying pharmacogenomics to drug dosing. All of these updates and additions should be helpful to users of pharmacogenomics to inform drug dosing.

This book was originally designed to help predict drug doses to achieve target drug concentrations from doses administered to patients. However, important chapters on rational use of drug concentration measurements; dosing in overweight and obese patients; pharmacogenomics; dosing considerations for a wider variety of drugs used in neonatal, pediatric and geriatric patients; drug dosing in renal disease (and dialysis); and creatinine clearance estimation (the precursor to dose and concentration estimates for a number of drugs) have been added over the years and round out the sixth edition. Tables on international and traditional units for drugs and laboratory tests are included as well as specific content on the use of both types of units, which should facilitate worldwide use of the textbook.

As with every edition, I gratefully acknowledge the chapter authors who volunteered a portion of their lives to this book's creation and to the authors' support staff for their assistance. Finally, without a doubt, many thanks are due to the best collaborators in the world—the ASHP staff. I would particularly like to thank the staff editors—Michael Soares (1st edition), Con Ann Ling (2nd edition), Dana Battaglia (3rd to 5th editions), and Ruth Bloom (6th edition) for their outstanding dedication to making these editions happen. They all did much work and receive little of the credit, but I know their value and it is tremendous. Thanks.

John E. Murphy

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Douglas M. Anderson, PharmD, BCPS

Executive Director, Medical Affairs
Regeneron Pharmaceuticals, Inc.
Tarrytown, NY

Jacquelyn L. Bainbridge, PharmD, FCCP, MSCS

Professor
Department of Clinical Pharmacy and Department of Neurology
University of Colorado
Anschutz Medical Campus
Aurora, CO

Stanley W. Carson, PharmD, FCCP

Senior Director, Neurology Clinical Development
UCB Biosciences
Research Triangle Park, NC

Cheryl D. Cropp, PharmD, PhD

Assistant Professor
University of Arizona College of Pharmacy, Phoenix Biomedical Campus
Translational Genomics Research Institute
Phoenix, AZ

William E. Dager, PharmD, BCPS (AQ Cardiology), MCCM, FCSHP, FCCP, FCCM, FASHP

Pharmacist Specialist, University of California Davis Medical Center
Clinical Professor of Medicine, University of California Davis School of Medicine
Sacramento, CA
Clinical Professor of Pharmacy, University of California San Francisco School of Pharmacy
San Francisco, CA
Clinical Professor of Pharmacy, Touro School of Pharmacy
Vallejo, CA

Robert DiDomenico, PharmD

Clinical Professor
University of Illinois at Chicago
College of Pharmacy
Chicago, IL

Monica A. Donnelley, PharmD, BCPS (AQ-ID)

Senior Infectious Diseases Pharmacist
University of California Davis Medical Center
Department of Pharmacy Services
Sacramento, CA

Thomas C. Dowling, PharmD, PhD, FCCP

Assistant Dean and Professor
Director, Office of Research
Ferris State University College of Pharmacy
Grand Rapids, MI

Jeremiah J. Duby, PharmD, BCPS, BCCCP

Clinical Pharmacy Specialist, Critical Care
Critical Care Residency Program Director
Assistant Clinical Professor
University of California Davis Medical Center
Sacramento, CA
Associate Clinical Professor
Touro University, College of Pharmacy
Vallejo, CA

CONTRIBUTORS

Mary H. H. Ensom, PharmD, FASHP, FCCP, FCSHP, FCAHS

Professor, Faculty of Pharmaceutical Sciences

Distinguished University Scholar

Clinical Pharmacy Specialist, Children's and Women's Health Centre of British Columbia

University of British Columbia

Vancouver, British Columbia, Canada

Brian L. Erstad, PharmD, FASHP, FCCP, MCCM

Professor and Head, Department of Pharmacy Practice and Science

University of Arizona College of Pharmacy

Tucson, AZ

Patrick R. Finley, PharmD, BCPP

Professor of Clinical Pharmacy

University of California at San Francisco School of Pharmacy

San Francisco, CA

Barry E. Gidal, PharmD, FAES

Professor

School of Pharmacy & Department of Neurology

University of Wisconsin-Madison

Madison, WI

Lisa W. Goldstone, MS, PharmD, BCPS, BCPP

Associate Professor of Clinical Pharmacy

University of Southern California School of Pharmacy

Los Angeles, CA

Felecia M. Hart, PharmD, MSCS

Clinical Neurology Research Fellow

Skaggs School of Pharmacy and Pharmaceutical Sciences

Department of Clinical Pharmacy and Department of Neurology

University of Colorado

Anschutz Medical Campus

Aurora, CO

Brett H. Heintz, PharmD, BCPS (AQ-ID), AAHIVE

Pharmacy Specialist, Medicine/Infectious Disease

Iowa City Veterans Affairs Medical Center

Clinical Associate Professor

University of Iowa College of Pharmacy

Iowa City, IA

Tony K. L. Kiang, BSc Pharm, ACPR, PhD

Assistant Professor, Translational Pharmacotherapy

Faculty of Pharmacy and Pharmaceutical Sciences

University of Alberta

Edmonton, Alberta, Canada

Kathryn R. Matthias, PharmD, BCPS (AQ-ID)

Assistant Professor

Department of Pharmacy Practice & Science

University of Arizona

Tucson, AZ

James P. McCormack, BSc Pharm, PharmD

Professor

Faculty of Pharmaceutical Sciences

University of British Columbia

Vancouver, British Columbia, Canada

Susan W. Miller, BS Pharm, PharmD

Professor
Mercer University College of Pharmacy
Atlanta, GA

John E. Murphy, PharmD, FASHP, FCCP

Professor of Pharmacy Practice and Science, Associate Dean
College of Pharmacy
Professor of Clinical, Family and Community Medicine
College of Medicine
The University of Arizona
Tucson, AZ
Honorary Professor
The University of Otago School of Pharmacy
Dunedin, New Zealand

Milap C. Nahata, MS, PharmD, FASHP, FAPhA, FCCP

Director, Institute of Therapeutic Innovations and Outcomes
Professor Emeritus of Pharmacy, Pediatrics and Internal Medicine
Colleges of Pharmacy and Medicine
The Ohio State University
Columbus, OH

Robert E. Pachorek, PharmD

Clinical Pharmacist
Sharp Grossmont Hospital
La Mesa, CA
Adjunct Assistant Professor of Pharmacy Practice
University of Southern California
Los Angeles, CA
Assistant Clinical Professor of Pharmacy
University of California
San Diego and San Francisco, CA

Robert L. Page II, PharmD, MSPH, FCCP, FHFSa, FAHA, FASHP, FASCP, BCPS, BCGP

Professor of Clinical Pharmacy & Physical Medicine
Clinical Specialist, Division of Cardiology
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences
Aurora, CO

Vinita B. Pai, MS, PharmD

Associate Professor of Clinical Pharmacy
College of Pharmacy, The Ohio State University
Advanced Patient Care Pharmacist
Pediatric Blood and Marrow Transplantation Program
Nationwide Children's Hospital
Columbus, OH

Hanna Phan, PharmD, FCCP

Associate Professor, Department of Pharmacy Practice and Science
University of Arizona College of Pharmacy
Associate Professor, Department of Pediatrics
University of Arizona College of Medicine
Tucson, AZ

A. Joshua Roberts, PharmD, BCPS (AQ Cardiology)

Senior Clinical Pharmacist, University of California Davis Medical Center
Associate Clinical Professor of Pharmacy, University of California San Francisco School of Pharmacy
San Francisco, CA
Associate Clinical Professor of Medicine, University of California Davis School of Medicine
Sacramento, CA

CONTRIBUTORS

Kimberly B. Tallian, PharmD, APH, BCPP, FASHP, FCCP, FCSHP

Advanced Practice Pharmacist—Psychiatry

Scripps Mercy Hospital, San Diego

Adjunct Clinical Professor at the University of California, San Diego Skaggs School of Pharmacy & Pharmaceutical Sciences

San Diego, CA

Chelsea L. Tasaka, PharmD, BCPS, BCCCP

Critical Care Pharmacist

Seattle Children's Hospital

Department of Pharmacy

Seattle, WA

Toby C. Trujillo, PharmD, FCCP, FAHA, BCPS (AQ Cardiology)

Associate Professor

University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

Clinical Specialist, Anticoagulation/Cardiology

University of Colorado Hospital

Aurora, CO

Dean A. Van Loo, PharmD

Professor of Pharmacy Practice

Ferris State University College of Pharmacy

Clinical Specialist, Bronson Methodist Hospital

Kalamazoo, MI

Michael E. Winter, PharmD

Professor Emeritus

Department of Clinical Pharmacy

University of California San Francisco School of Pharmacy

San Francisco, CA

Ann K. Wittkowsky PharmD, CACP, FASHP, FCCP

Director, Anticoagulation Services

University of Washington Medical Center

Clinical Professor

University of Washington School of Pharmacy

Seattle, WA

Pei Shieen Wong, PharmD, BCPS

Principal Clinical Pharmacist

Pharmacy Department

Singapore General Hospital

Singapore



GENERAL PHARMACOKINETIC PRINCIPLES

John E. Murphy

INITIATING THERAPY

When therapy is initiated in a patient, a standard dose and interval may be used, or the dose and interval may be individualized by use of population means of clearance or volume of distribution and half-life. These population pharmacokinetic parameters are useful for estimating drug concentrations based on an administered or planned dose and dosing schedule. To adjust therapy, these values then may be compared to actual drug concentration measurements (DCMs) and integrated with the patient's therapeutic outcome.

Using population mean values

Unfortunately, not all patients fit closely to the population means, and some of these means were developed on small samples that may not represent the general population or the patient being monitored. However, for a number of drugs, population means with standard deviations can provide useful information on reasonable ranges of the concentration values to expect.

In any case, a patient's actual pharmacokinetic values (i.e., clearance, volume of distribution, and half-life) may need to be determined to adjust therapy for a desired outcome.

Considering other factors in pharmacokinetic monitoring¹

In addition to the problems with population pharmacokinetic means, unexpected drug concentration measurements can occur for various reasons. Some patients may not be adherent with drug therapy, taking either more or less than was prescribed for them. In the institutional setting, administration errors can account for unexpected results; a patient may be given the wrong dose of a drug, may be given the drug at the wrong time, or may not receive the scheduled drug at all.

Errors on medication administration records also can occur. For example, it might be indicated that a drug was given at a time other than the actual time it was received by the patient. Furthermore, incomplete drug delivery due to patient problems (e.g., infiltration of an IV fluid or clogging of a nasal cannula) can influence drug concentration measurements.

Problems in sample collection can lead to unexpected drug concentration measurements. A blood sample may be drawn at the wrong time, or the time the sample was collected may be reported incorrectly. Samples can be taken from the wrong patient or obtained incorrectly (e.g., through a drug administration line that was inadequately flushed prior to sample withdrawal). In addition, samples may be improperly stored. The drug concentration sampling strategy may also impact the ability to best design a new dosing schedule to target desired concentrations.²

Other things to consider include drug or disease state interactions that may influence the prediction of drug concentration measurements and the use of inaccurate assays.

Some reasons drug concentration measurements may fall outside of the range predicted by population estimates:

- Patient truly does not well fit the population average values (i.e., falls outside of one standard deviation of the mean).



- Population values used for the predictions were determined in patients unlike the patient being monitored.
- Patient has not been adherent with therapy (may have taken either more or less than prescribed).
- Nurse did not give the dose at the time prescribed (whether it has been signed off as given on time or not).
- Dose not given at all (whether it is signed off as given or not). Also doses are occasionally administered but not signed off as being given.
- Wrong dose is given (either once or more often).
- Error made in dosing schedule on medication administration record (e.g., every 18-hr schedule is put on record such that patient is given doses 18 and 30 hr apart).
- Complete dose was not administered prior to sample withdrawal because of patient problems (e.g., infiltration of an intravenous (IV) line, clogging of nasal cannula).
- Phlebotomist drew blood at a time other than requested and:
(1) reported that it was collected on time, or (2) or inaccurately reported, and it is incorrectly assumed to have been drawn at the scheduled time.
- Sample was taken from the wrong patient.
- Sample was obtained incorrectly (e.g., through a drug administration line which has been improperly flushed prior to sample withdrawal).
- Sample was not stored properly, leading to artifactual results.
- Assay or assay instrument quality is not satisfactory, or the reported result is not accurate.
- Pharmacokinetic drug interaction has occurred, which was not accounted for correctly in estimation of DCMs.
- In vitro drug interaction occurred, resulting in artifactual results.
- Disease interaction occurred that was not considered, such as reduced absorption rate due to poor blood flow.
- Patient has reduced plasma binding proteins or a drug–drug interaction has displaced the drug from protein (see Protein binding issues, below).

Protein binding issues

When patients have reduced plasma proteins or highly bound drugs are displaced from plasma proteins by drug or endogenous compound interactions, there may be increased free fraction (unbound concentration/total concentration) and movement of drug out of the bloodstream into tissue. Movement of drug out of the bloodstream can lead to decreases in total (bound and unbound) plasma or serum drug concentrations even when the unbound concentration remains unchanged. Since total concentration is what is usually reported when drug concentration measurements are ordered, this can lead to incorrect assumptions that a dose may need to be increased. Increased unbound fraction can also lead to increased elimination, which will also decrease total concentration. If there is no increase in elimination, the unbound concentration may remain the same as when plasma proteins are normal or no interaction exists, even though the total concentration is decreased. In some cases of highly bound drugs (e.g., phenytoin), an unbound concentration measurement may be warranted if the total concentration is low, to ensure that adequate unbound concentrations exist.

Verifying drug concentration measurements

If measured values fall outside the range estimated using $\pm$ one standard deviation of the predicted clearance, volume of distribution, and/or half-life, concentrations should generally be re-checked before the initially measured concentration(s) are accepted as valid. This step does not preclude changing

the dose or interval if such a change would have been made empirically at the start of therapy. If the measured concentrations are far from those predicted, a determination must be made as to whether the measured drug concentrations are reasonable (i.e., within reasonable expectation based on the range of population values) or whether one or more of the problems noted above occurred.

The occurrence of certain problems can be determined with detective work. For example, a patient can be questioned about compliance, past outpatient pharmacy records can be checked, and the nurse administering the drug or the phlebotomist drawing the blood sample can be interviewed. Unfortunately, the validity of the information gathered after the fact may be questionable.

Because of these potential problems, measured drug concentrations may not be a true reflection of the patient's actual drug distribution and clearance. Therefore, an erroneous decision about the dosing needs of the patient can be made. Accurate information is essential to quality therapeutic drug monitoring.

A well-coordinated system of communication is needed between those administering or taking a medication and those collecting blood (or other body fluid or tissue) for analysis. Such a system can prevent many of the problems associated with assessing the validity of reported drug concentrations and dose/sample collection timing. It also can reduce erroneous decision-making based on faulty data as well as the expense of repeating questionable drug concentration measurements. The lack of such a system is a waste of resources and provides the potential for harming patients secondary to a high incidence of debatable data.

After as many causes of discrepancy as possible are eliminated, a decision must be made as to whether the difference between predicted and actual values is due to patient variability from population averages or to erroneous values. If the values are judged to be erroneous, drug concentrations probably should be re-measured, although the need for further evaluation should be as carefully considered as the original decision to monitor (see Chapter 1, Rational Use of Drug Concentration Measurements).

Determining need for dosage adjustments

Once the drug concentration measurement and dosing information is determined to be as accurate as possible, the need for dosage adjustments are determined based on pharmacodynamic response and patient outcome. The need for dosage adjustment or the continuation of therapy should be based on patient response relative to measured drug concentration rather than on drug concentration alone.

This approach may not be proper, however, when the disease or symptoms are not continuous or easy to quantify. For example, keeping an anticonvulsant drug within the therapeutic range can be important when seizure activity is infrequent. Without an adequate seizure history, the maintenance of a dosing schedule that produces drug concentration measurements above or below the normal accepted therapeutic range may not be prudent.

Deciding on monitoring frequency and sample timing

How frequently a patient should be monitored for efficacy or side effects related to drug therapy varies with the drug, the intensity of the disease, the stability of body functions, and other factors. In general, the more severely compromised the patient, the more frequently the patient should be monitored. This is essentially the same as would be recommended for most laboratory tests and monitoring schemes.

Clinicians should be aware of the many factors that can alter a drug's pharmacokinetic and pharmacodynamic activities. Addition or deletion of other drug therapy (or diet) that may interact with the drug being monitored should signal the need for closer inspection. Changes in the function of the primary organs of drug elimination (e.g., liver and kidneys) or in cardiac function also should signal the need for closer monitoring.

Patient (or caregiver) adherence to the treatment regimen must be assessed whenever a decision is based on a drug concentration measurement. Simply assuming appropriate adherence to the prescribed regimen can lead to grave errors in the worst case and a waste of resources in others.

Single samples provide useful feedback from the patient as to clearance of the drug, but at least one sample is necessary to calculate each pharmacokinetic parameter. For example, if knowledge of a patient's V and CL or V and k are desired for dosing adjustment, two samples are necessary. The time of sampling can also be optimized to determine the pharmacokinetic behavior of a drug and provide the best future predictions.² Trough samples are not optimum DCM collection times, but they are often used by clinicians when desired concentrations have been based on the trough (e.g., current approaches to vancomycin dosing). Trough concentrations are also least impacted when errors occur in the time a dose is given or sample collected.² Thus, even though more robust pharmacokinetic information may be obtained by other sampling times, approaches such as drawing an aminoglycoside “peak” 30 min after the end of a dosing infusion rather than the true peak and measuring troughs instead of earlier concentrations are often used for therapeutic drug monitoring.

A BASIC PHARMACOKINETIC GLOSSARY

As the science of pharmacokinetic evaluation of drug therapy has progressed, the terminology used has grown as well. Although terms such as *half-life* and *volume of distribution* are standardized in most pharmacokinetic texts, a wide variety of terminology is used to describe other basic concepts.

For this reason, an attempt was made to standardize the terminology used throughout this book. The wide collection of studies used to reference the chapters somewhat hindered this effort.

With that understanding, the following terminology is offered as a guideline to interpreting the values and terms in this book.

Selected pharmacokinetic terminology

Actual body weight (ABW)—Patient's measured body weight; equivalent to total body weight.

Average steady state concentration (Css_{av})—Concentration measured approximately halfway between the peak and trough (except for some sustained-release preparations) for a drug administered long enough to be at steady state. Hence, for an IV bolus regimen on an every 6-hr interval, the Css_{av} would be at 3 hr after a dose. For a dose requiring absorption that peaks 2 hr after administration, the average would occur at approximately 4 hr on a 6-hr interval.

Ideal body weight (IBW)—Ideal weight for a patient based on his or her height and sex according to insurance actuarial tables for longevity.

Lean body weight (LBW)—Patient's body weight plus some but not all fat weight. It is often used interchangeably with IBW, but LBW increases as patients increase in weight, while IBW is constant.

Peak concentration (C_{peak})—Peak concentration is the highest or maximum concentration after any type of dosing method. It is the concentration of drug that occurs immediately after an IV bolus dose, at the end of a dose infusion, or at a particular time (t_{peak} or t_{max}) after dose administration for a drug requiring absorption. It may also be called C_{max} or Css_{max} . Occasionally, the “peak” is considered the concentration measured within 30–60 minutes after the true peak time (e.g., 30 min after the end of a dose infusion for aminoglycosides); this peak might be considered a “therapeutic peak” for assessment of patient response rather than the actual peak. This time lag before collection in part acknowledges the reality that doses are not always given precisely on time and that blood samples are not always drawn precisely when scheduled for a true peak.

Steady state—Point in time reached after a drug has been given for approximately five elimination half-lives (97% of steady state has been achieved after five half-lives). At steady state, the rate of drug administration equals the rate of elimination, and drug concentration-time curves found after each dose on an even schedule (e.g., every 8 hr) should be approximately superimposable (i.e., if one graph of a drug concentration-time curve were laid on the next dose graph, they would be the same).

Administration of a loading dose can affect the time to steady state if the loading and maintenance doses are matched correctly. If the loading dose provides exactly the amount needed to achieve the steady state concentration that will be achieved by the maintenance dose, then steady state is achieved immediately. If the loading dose is too small or too large relative to attainment of the concentrations that will occur with maintenance doses, five half-lives will be required to achieve 97% of the *difference* between the loading dose concentrations and the final steady state concentrations.

Therapeutic range—Range of concentrations where optimum outcome is expected, based on results of groups of individuals taking the drug. In reality, each person has his or her own therapeutic range for each drug. As concentrations rise to the upper limit of the therapeutic range and beyond, the probability of drug toxicity increases. As concentrations fall to or below the lower limit of the range, the probability of inadequate response increases. This range should be viewed only as an initial target, because patients may respond when below it and may not be toxic when above it. Furthermore, minor toxicity above a therapeutic range might be acceptable to a patient if efficacy increases. Serious toxicity is a definite upper limit to any individual's therapeutic range.

Trough concentration (C_{trough})—Lowest or minimum concentration after a dose given intermittently (also called C_{min} or $C_{\text{ss min}}$). It is the concentration that occurs immediately before the next dose for drugs given intermittently in a multiple-dose fashion. However, quite often the “trough” is the concentration measured within 30–60 minutes of the next dose. This trough might be considered a “therapeutic trough” related to this time in pharmacokinetic and pharmacodynamic studies of the drug. This time period in advance of the true trough also acknowledges variance in compliance with precise dose administration time and phlebotomist arrival time.

Selected pharmacokinetic symbols used in this text

These symbols generally follow the nomenclature suggested by the Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology.³ An exception is volume of distribution (V versus V_z).

- C** = concentration of drug (plasma, serum, blood, urine, saliva, etc.).
- C_i** = initial concentration. The larger of two measured concentrations in an elimination portion of a concentration-time curve. For example, in Equation 1 (see “General Pharmacokinetic Equations,” below), C_i is the largest of two concentrations, C_i and C . Some authors designate the two concentrations as C_1 and C_2 .
- C_{max}** = maximum drug concentration after a dose (also C_{peak}).
- C_{min}** = minimum drug concentration after a dose (also C_{trough}).
- Css** = concentration at steady state.
- $C_{\text{ss max}}$** = maximum drug concentration after a dose at steady state (also $C_{\text{ss peak}}$).
- $C_{\text{ss min}}$** = minimum drug concentration after a dose at steady state (also $C_{\text{ss trough}}$).
- $C_{\text{ss avg}}$** = average steady state concentration. The concentration approximately halfway between $C_{\text{ss max}}$ and $C_{\text{ss min}}$ at steady state.
- CL** = apparent total body clearance (either in units of volume per time, such as liters per hour, or in units of volume per time per body weight, such as liters per hour per kilogram). $CL = k \times V$.
- CrCl** = creatinine clearance; the clearance of creatinine (in units of milliliters per minute or liters per hour).
- D** = dose (in amount, such as milligrams, or amount per patient body weight, such as milligrams per kilogram).
- F** = bioavailability fraction of a dose (no units). It is the fraction or percent of an administered dose that reaches the systemic circulation.

- k = first-order elimination rate constant (in units of 1/time or time⁻¹). $k = 0.693/t_{1/2}$.
- k_a = first-order absorption rate constant (in units of 1/time or time⁻¹). $k_a = 0.693/t_{1/2a}$.
- K_m = Michaelis-Menten constant (in units of concentration such as milligrams per liter). It is the concentration at which the metabolic system is one-half saturated.
- R_o = zero-order infusion rate (in amount per time such as milligrams per hour).
- S = fraction of a dose that is parent drug (i.e., the drug that is measured in plasma or serum). For example, phenytoin sodium is 92% phenytoin. Thus, $S = 0.92$ for phenytoin sodium products. No units.
- S_{Cr} = serum creatinine (in mg/dL or $\mu\text{mol/L}$).
- t = elapsed time. For example, it is the time between two concentrations, known or estimated, in the elimination phase of a drug following first-order elimination.
- t' = time of an infusion (i.e., duration of infusion, usually in hours).
- t_{peak} = time to peak (maximum concentration) of a drug that requires absorption (e.g., oral, intramuscular, inhaled, rectal, or buccal). Also called t_{max} .
- $t_{1/2}$ = half-life of a drug (in units of time). It is the time needed to reduce the drug concentration or amount of drug in the body by one-half. $t_{1/2} = 0.693/k$.
- $t_{1/2a}$ = absorption half-life of a drug product administered in a dosage form requiring absorption (in units of time). $t_{1/2a} = 0.693/k_a$.
- T = time elapsed after the *end* of an infusion.
- Δt = change in time (usually the time between two measured concentrations).
- τ = dosage interval (in units of time, usually hours or days).
- V = apparent volume of distribution (either in units of volume, such as liters, or in units of volume per body weight, such as liters per kilogram).
- V_{max} = (V_m) maximum velocity of drug elimination for a drug following Michaelis-Menten (enzyme saturable) elimination. It is the amount of drug that can be biotransformed per unit of time (in units of amount per time, such as milligrams per day or in mg/kg/day).

GENERAL ESTIMATING EQUATIONS

Like the above terms and symbols, several equations are frequently used in pharmacokinetic calculations and are considered to be standards. Frequently used equations for calculating ideal or lean body weight and body surface area are as follows. Additional information is provided in Chapter 4, Medication Dosing in Overweight and Obese Patients. Creatinine clearance estimations are provided in Chapter 2, Estimating Creatinine Clearance.

Calculating ideal body weight (IBW) in adults⁴

males = $50 \text{ kg} + [(2.3)(\text{Ht} - 60)] \text{ kg}$

females = $45.5 \text{ kg} + [(2.3)(\text{Ht} - 60)] \text{ kg}$

where Ht is a patient's height in inches.

Or,

males = $50 \text{ kg} + [(0.9)(\text{Ht} - 152)] \text{ kg}$

females = $45.5 \text{ kg} + [(0.9)(\text{Ht} - 152)] \text{ kg}$

where Ht is a patient's height in centimeters.

Note: For patients who are less than 60 inches tall (152 cm), the weight should be decreased more conservatively than 2.3 kg/inch (2.3 kg/2.54 cm).

Calculating ideal body weight in children aged 1–18 years⁵

For children **less than 5 feet (152 cm)** tall

$$IBW = 2.05e^{(0.02)(Ht)}$$

where Ht is height in centimeters (2.54 cm/inch) and IBW is ideal weight in kg.

For children **5 feet (152 cm) or taller**

$$IBW \text{ (males)} = 39 + [2.27 (Ht - 60)]$$

$$IBW \text{ (females)} = 42.2 + [2.27 (Ht - 60)]$$

where Ht is height in inches and IBW is ideal weight in kg.

Or,

$$IBW \text{ (males)} = 39 + [0.9 (Ht - 152)]$$

$$IBW \text{ (females)} = 42.2 + [0.9 (Ht - 152)]$$

where Ht is height in centimeters and IBW is ideal weight in kg.

Calculating surface area (SA) in meters² (m²)

For adults, children, and infants⁶

$$SA = W^{0.5378} \times Ht^{0.3964} \times 0.024265$$

where W is weight in kg and Ht is height in centimeters.

Another simpler approach to determining BSA uses the following formula⁷:

$$BSA = \sqrt{\frac{\text{height} \times \text{weight}}{3600}}$$

where height is in cm and weight is in kg.

Calculating Body Mass Index (BMI) for men and women^{8,9,a}**METRIC**

$$BMI = \text{weight (kg)} / [\text{height (m)}]^2 \text{ or } [\text{weight (kg)} / \text{height (m)} / \text{height (m)}]$$

POUNDS AND INCHES

$$BMI = \text{weight (lb)} / [\text{height (in)}]^2 \times 703 \text{ or } [\text{weight (lb)} / \text{height (in)} / \text{height (in)}] \times 703$$

^a BMI is an indicator of bodyfat and bodyfat content is related to the risk of disease and death. People are considered underweight if their BMI is <18.5, normal weight if 18.5 to 24.9, overweight if 25 to 29.9, and obese if ≥ 30. There are limits to the use of BMI, including the potential to overestimate bodyfat in athletes and others who have a muscular build and to underestimate bodyfat in the elderly and in those who have lost muscle mass.

GENERAL PHARMACOKINETIC EQUATIONS

The following equations are used to determine or estimate concentration and other pharmacokinetic parameters. These equations may be manipulated to determine other parameters in the equation when the remaining parameters are known or can be estimated. For example, a dose may be calculated from known or estimated CL, V, or k values by manipulating the applicable equations to solve for dose (D).

1. Concentration at any time t after some initial concentration (C_i):

$$C = C_i \times e^{-kt}$$

2. k from two known drug concentration-time points in the elimination phase:

$$k = \frac{\ln(C_i/C)}{\Delta t}$$

3. Concentration at any time t after a single IV bolus dose:

$$C = \left(\frac{S \times D}{V} \right) e^{-kt}$$

4. Concentration at any time t after an IV bolus dose given every τ hours (at steady state):

$$C = \left(\frac{S \times D}{V} \right) \left(\frac{e^{-kt}}{(1 - e^{-k\tau})} \right)$$

5. Concentration at any time t after the start of an IV infusion at rate R_0 :

$$C = \left(\frac{S \times R_0}{CL} \right) (1 - e^{-kt})$$

6. Concentration at steady state of an IV infusion at rate R_0 :

$$C_{SS} = \left(\frac{S \times R_0}{CL} \right)$$

7. Average steady state concentration of a dose given intermittently (by all dosing methods):

$$C_{SS_{avg}} = \left(\frac{S \times F \times D}{CL \times \tau} \right)$$

or

$$C_{SS_{avg}} = \left(\frac{S \times F \times D}{k \times V \times \tau} \right)$$

8. Concentration at any time t after a single dose requiring absorption:

$$C = \left(\frac{S \times F \times D \times k_a}{V \times (k_a - k)} \right) (e^{-kt} - e^{-k_a t})$$

9. Time to peak (maximum concentration) of a dose requiring absorption after a single dose:

$$t_{peak} = \frac{\ln(k_a/k)}{(k_a - k)}$$

10. Concentration at any time t after a dose requiring absorption during steady state conditions:

$$C = \left(\frac{S \times F \times D \times k_a}{V \times (k_a - k)} \right) \left(\frac{(e^{-kt})}{(1 - e^{-k\tau})} - \frac{(e^{-k_a t})}{(1 - e^{-k_a \tau})} \right)$$

11. Time to peak (maximum concentration) of a dose requiring absorption at steady state:

$$t_{ss_{peak}} = \frac{\ln \left(\left[\frac{k_a (1 - e^{-k\tau})}{k (1 - e^{-k_a \tau})} \right] \right)}{(k_a - k)}$$

12. Concentration at any time T after the end of a single short infusion lasting t' time:

$$C = \left(\frac{S \times D}{k \times V \times t'} \right) (1 - e^{-kt'}) e^{-kT}$$

13. Concentration at any time T after the end of a short infusion lasting t' time given every τ hours:

$$C = \left(\frac{S \times D}{k \times V \times t'} \right) \left(\frac{(1 - e^{-kt'})}{(1 - e^{-k\tau})} \right) (e^{-kT})$$

14. Average steady state concentration of a drug that follows Michaelis-Menten elimination:

$$C_{ss_{avg}} = \left(\frac{\left(\frac{S \times F \times D}{\tau} \right) \times k_m}{V_m - \left(\frac{S \times F \times D}{\tau} \right)} \right)$$

15. Dose to produce desired steady state concentration for a drug that follows Michaelis-Menten elimination:

$$D = \frac{C_{ss_{avg}} \times V_m \times \tau}{S \times F \times (C_{ss_{avg}} + k_m)}$$

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SECTION 1



BASIC CONCEPTS AND SPECIAL POPULATIONS

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3 Renal Drug Dosing Concepts

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RATIONAL USE OF DRUG CONCENTRATION MEASUREMENTS

James P. McCormack

For the vast majority of medications, drug concentration monitoring is unnecessary. In contrast, a thorough efficacy and monitoring plan should be developed for every drug a patient receives. The value of drug concentration monitoring in achieving desired therapeutic outcomes for those drugs where concentration monitoring is generally considered useful is often debated. Some suggest that concentration monitoring is excessive and, when concentrations are measured, they are frequently used inappropriately. Others consider it a routine part of outcome assessment for a number of important drugs with narrow therapeutic ranges.

Clinicians who consider using drug concentration monitoring should always ask themselves the following questions:

- Is the patient already responding appropriately to the drug therapy?
- Is the patient having any toxicity from the drug therapy?
- Is the efficacy and toxicity of this drug better predicted by measuring drug concentrations or evaluating the clinical response?
- Will obtaining a drug concentration change the clinical management of the patient?

Clinicians should also carefully establish goals of therapy and monitor whether or not they are being achieved, even when drug concentrations are used as an adjunct to regimen evaluation.

For drugs where concentration monitoring is fairly routinely used but the desired effect of the drug can be easily and quickly measured clinically, the value of measuring its concentration is limited or even potentially harmful if one spends time measuring concentrations at the expense of proper clinical assessment. Where the signs and symptoms of benefit and toxicity can be assessed easily and quickly (within hours or, in some cases, days), appropriate dosage adjustments can usually be based on the clinical response of the patient rather than on drug concentrations. When drug concentration monitoring adds to the predictability of response over monitoring the patient clinically, a number of key issues should be considered before ordering a drug concentration measurement. **Figure 1-1** is a graphic representation of the decision-making process involved in considering those issues.

EVALUATING THE NEED FOR A DRUG CONCENTRATION MEASUREMENT

Drug selection

Before considering the need for drug concentration monitoring, the first consideration for all drug therapy is appropriateness of the selected drug for obtaining the desired outcome in the specific patient. For instance, evidence suggests the addition of aminoglycosides to other safer antibiotics in patients with sepsis or with febrile neutropenia doesn't improve a patient's outcome but does increase the chance of nephrotoxicity.^{1,2} Clinicians should ask themselves whether there are potentially equally effective, less toxic, or less expensive alternatives that should be considered (e.g., beta-lactams alone instead of in combination with aminoglycosides for infections with susceptible organisms; valproic acid instead of phenytoin for certain types of epilepsy, inhaled corticosteroids instead of theophylline



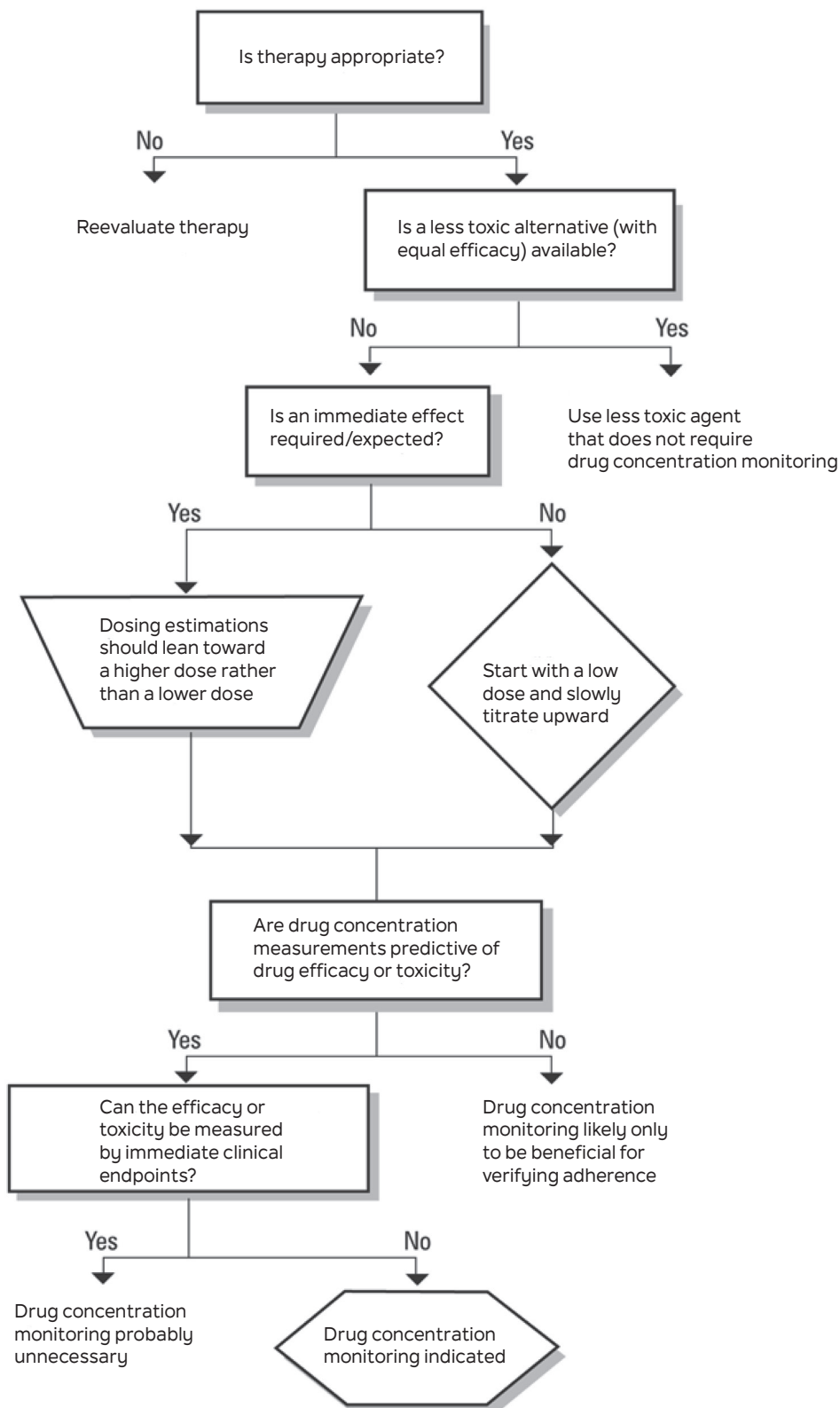


Figure 1-1. Decision-making process for using drug concentration measurements.

for asthma). After it is deemed necessary to use a drug that may require drug concentration monitoring, it is important to determine if efficacy and toxicity are related to drug concentrations in the particular situation. For example, valproic acid in the treatment of infrequent seizures may necessitate the use of concentration measurements, whereas its use for a patient with frequent migraine headaches would not be warranted because assessment should be based on headache frequency changes rather than drug concentrations.

Efficacy concerns

When therapeutic and toxic end points cannot be readily and quickly determined clinically, drug concentration measurements may be useful if research has shown them to be predictive of therapeutic or toxic effects. For instance, in a patient started on an antiepileptic medication for relatively infrequent (every 2–3 months) seizures, improved seizure control may not become apparent for several months. Ensuring that the patient's concentrations are in the generally accepted population therapeutic range may be the best and likely only approach to determining an appropriate dose and schedule.

Clinicians should always ask themselves whether patient outcomes are better predicted by an established “therapeutic range” or by the individual clinical response. If the clinically important event occurs infrequently (e.g., seizures or arrhythmias), is life threatening, or if the beneficial effect of the drug may be delayed (e.g., resolution of depression), the drug concentration found to be effective in similar patients can be used as an initial goal. However, depending on the drug used and the disease state treated, population-based therapeutic ranges may only be weak predictors of therapeutic success because the concentration-effect relationship is variable between individuals. Dosage adjustments should be made based on the clinical response whenever possible, using drug concentrations as a guide.

For many patients, there are likely specific threshold concentrations (assuming the drug will be effective or toxic at some point) above which a desired effect will be achieved and another where toxicities will start to be seen. Some clinicians have recommended measuring the drug concentration associated with therapeutic success to serve as a benchmark for subsequent therapy, and that subsequent failure of therapy could be evaluated based on whether concentrations have fallen below this established benchmark. This approach assumes that the threshold for efficacy does not change with time. Because physiologic and pathophysiologic conditions can change with time, this assumption may not be valid in all cases.

Toxicity concerns

When patients exhibit signs or symptoms of toxicity, the practitioner should first determine if the dosage could likely be decreased or stopped empirically without loss of benefit. If the patient is at risk for toxicity or develops toxicity that is likely caused by the drug rather than other potentially confounding aspects of the patient's diseases or other drug therapies, the dose should be empirically decreased or the drug stopped. If this cannot be done because of concerns over the loss of therapeutic benefit or inability to differentiate potential causes, a drug concentration measurement may help to determine if the drug is the likely cause. This situation is only appropriate if drug concentrations have been shown to predict toxicity.

Drug concentration measurements may also be useful in patients who develop dysfunction in the primary organ of clearance for the drug (e.g., liver or kidney) or in whom an interacting drug was started or stopped after the patient was stabilized on the initial drug. Measurements are not required if empiric reduction or increase in the drug dosage is possible.

Adherence issues

Lack of adherence by patients to medication regimens is a frequently occurring problem. When a patient is suspected of not adhering to his or her medication regimen, drug concentration monitoring may be a useful tool, along with evaluation of pharmacy records or the medication administration record, to

help establish whether or not adherence is an issue. However, if nonadherence is suspected, clinicians need to first explore possible reasons; the patient may be exhibiting intelligent nonadherence because he or she is not getting the desired effect or is having side effects. It is also possible the patient cannot afford to purchase the medication, an issue that would be addressed in another manner.

APPROACHES TO DOSING WITH LIMITED NEED FOR DRUG CONCENTRATION MEASUREMENTS

Immediate effect required or expected

If a patient requires treatment for an immediate life-threatening illness, the initial dosage should be selected based on avoidance of underdosing, not overdosing. The largest dose usually associated with efficacy and acceptable toxicities should be chosen to ensure the greatest chance of a positive outcome. When concentrations are not measured, concern for toxicity, if it occurs acutely, may be assessed clinically (if possible) and evaluated on the basis of the benefits versus risks of continued therapy at the selected dosage.

For drugs such as the aminoglycosides, vancomycin, and phenytoin that may be used for life-threatening illness, severe toxicity usually does not develop until after at least a few days of therapy (e.g., renal/ototoxicity from aminoglycosides/vancomycin) or the acute toxicities are minor (nystagmus, or ataxia with phenytoin). The acute treatment of life-threatening infections with aminoglycosides or vancomycin should be accomplished with dosages known to produce effective clinical results, while concerns over possible toxicity should be relevant but secondary. The initial dosage selected for the life-threatening infection does not have to be the dosage used for continued therapy. Dosage adjustment can be guided by drug concentration measurements, when appropriate, based on all other considerations. However, before clinicians routinely measure concentrations for a particular drug or class of drugs, they should review the available evidence for the therapeutic range. Despite widespread use, the evidence may not be very persuasive when looked at in a systematic and critical way.^{3,4}

Immediate effect not required or expected

For the vast majority of conditions treated with medications, an immediate response is not needed. In these cases, the dosing can be approached in one of two ways.

Titrating the dose up

In conditions that do not require an immediate response, it may be possible to gradually titrate the dose up to the usual recommended starting dose with the understanding that the medicines that can extend or improve a patient's quality of life can also produce a number of side effects. A strategy using one quarter to half the usual starting dose could minimize side effects by identifying the lowest effective dose. This may also provide cost savings to the patient. Such a dose titration approach will likely require more time for the clinician to monitor patient outcomes as well as more time for clinician-patient discussion, because the patient often needs to be made aware of how to monitor for efficacy and toxicity. Patients should be told that the dose titration process takes time and that an immediate effect is not expected or necessary based on selection of this approach. The patient should be made to understand that the time spent in determining the appropriate dose may prevent unnecessary adverse effects and may reduce drug product expense.

Taking this approach may be justified from the perspective that many clinical trials begin with fairly aggressive doses to establish efficacy. Studies are often not conducted on lower doses until after the product has been on the market for a considerable length of time.⁵

Even though theophylline is rarely used today, it serves as a useful example of how clinicians should first use clinical response as the end-point versus measuring a drug concentration. If one wanted to start theophylline in a patient, given the caveat the evidence that theophylline produces a useful

clinical response is at best limited, one could start with a 100-mg sustained release product twice daily for 1 wk, evaluate for any important clinical changes (less shortness of breath, signs and symptoms of toxicity), and then if there is limited or no response after 1 wk the dose should be increased to 200 mg twice daily. Evaluate again in 1 wk. If there has been only limited response, increase the dose to 300 mg twice daily. If there is little or no response at this dose, it is unlikely that there will be any response from further increases, and the drug can just be stopped, assuming that the patient has been adherent to the recommended regimen, there were no identifiable problems with absorption, and the patient was not on a drug that was enhancing the metabolism of the theophylline. If one wished to increase the dose further, measuring concentrations may be useful if for no other reason than to justify doses greater than those typically used. If the concentration comes back and is not consistent with estimates, other reasons for uncharacteristic drug concentrations should be considered (see Introduction). In a similar fashion, low doses of some of the antiepileptic medications could be used initially when these agents are being used for the treatment of chronic neuropathic pain and the dose could be titrated up slowly over a period of a few days to a week. This approach also decreases a clinician's need to worry about potential drug interactions that impact the anticonvulsant's pharmacokinetic parameters, because one is starting with a low dose. However, clinicians need to keep in mind that even low-dose anticonvulsants may still have a clinically important impact on other drugs the patient is receiving. It should be noted that if patients are unable to titrate the dose themselves, a titration approach may require additional visits to a clinician, and the costs of the extra visits would need to be weighed against the potential utility of a drug concentration.

Titration of the dose down

A second approach that may be used to determine the lowest effective dose is to begin therapy with the product monograph recommended dose (empirically adjusted on the basis of kidney and/or liver function and drug-disease interactions), assess response, and gradually reduce the dose according to the response of the patient (weighing beneficial and toxic effects). The advantage of this approach is that an effect will likely be seen more quickly than by titrating upward. However, titrating down may not lead to finding the lowest effective dose, because clinicians and patients may be unwilling to decrease the dose once benefits are being achieved. It is important to remember that higher than necessary doses increase the chance of adverse effects, may increase the frequency of dosing, and may thereby compromise adherence and increase the cost of therapy. Even in the face of drug efficacy without signs of toxicity, there may be value in tapering to the lowest effective dose over time to determine if the correct diagnosis was made, if the disease state is fluctuating, or if nondrug factors, such as lifestyle changes, have made a difference.

The approaches of titrating up or down apply to many medical conditions for which clinical end points are frequent and easily measurable (e.g., asthma and hypertension). However, when the clinical end points are infrequent (e.g., seizures) or life threatening (e.g., arrhythmias), this approach may be of less value.

CONCLUSION

Drug concentration monitoring should only be considered as a tool to supplement proper clinical assessment of patient response. Appropriate drug selection (based on the best available evidence) and proper initial dosage selection, along with the clinical monitoring of response, are the most crucial components of pharmacotherapy.

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ESTIMATING CREATININE CLEARANCE

Robert E. Pachorek

The importance of accurate estimations of glomerular filtration rate (GFR), the principal measure of renal function, cannot be overemphasized. Many drugs or active metabolites are eliminated to some extent by renal excretion, creating the need for dosage adjustments as renal function deteriorates, particularly for drugs with a narrow therapeutic range (see Chapter 3, Renal Drug Dosing Concepts). In general, decreases in the rate of elimination of drugs primarily excreted unchanged by the kidneys are proportional to decreases in the GFR.

Although methods to determine the clearance of inulin and other exogenous compounds are available for such assessment, the renal clearance of the endogenously produced amino acid creatinine is the most commonly used estimate of GFR in hospitalized patients. Creatine, a product of protein metabolism, is primarily produced in the liver, pancreas, and kidneys and is actively transported into muscle tissue where it is stored. Creatinine is produced from creatine in muscle tissue proportionally to muscle mass. It is released at a constant rate (~1.5% of the total pool per day) into the general circulation and is distributed to total body water. The glomerulus passively filters creatinine, although 10% to 40% of the total creatinine found in urine is a result of active renal tubular secretion.¹⁻⁴

The creatinine clearance (CrCl), in milliliters per minute (mL/min), can be directly measured by collecting urine over a period of time (e.g., 24 hr) using the following relationship:

$$\text{CrCl} = \frac{U_{\text{Cr}} \times V_{\text{Cr}}}{S_{\text{Cr}} \times t}$$

where U_{Cr} is the urine creatinine concentration (mg/dL), V_{Cr} is the urine volume collected (mL), S_{Cr} is serum creatinine (mg/dL) measured at the midpoint of the urine collection, and t is the time interval in minutes of the urine collection (e.g., 1,440 min for 24 hr).^{1,2}

FACTORS AFFECTING ESTIMATES OF GLOMERULAR FILTRATION RATE

Because some creatinine found in the urine is due to tubular secretion, CrCl overestimates the GFR at all levels of renal function. Drugs such as amiloride, cimetidine, trimethoprim, salicylate, triamterene, and spironolactone, which inhibit this secretory function, may increase S_{Cr} and decrease the CrCl estimate without actually affecting the GFR.²⁻⁵ As GFR declines, there is a progressive relative increase in creatinine tubular secretion compared to filtration and a progressive disparity between actual GFR and CrCl. In one study, it was noted that when the true GFR was around 100 mL/min, the CrCl overestimates the GFR by about 20%; for a GFR of 60 mL/min, the CrCl was overestimated by about 60%; and for a GFR of 20 mL/min, the CrCl was overestimated by 100% or more.²⁻⁵ In the past this error was partially offset if the laboratory was using an uncorrected Jaffe-based method assay to determine serum creatinine because endogenous serum substances added ~0.2 mg/dL to the creatinine value when measured by this common method.⁵ The new assay reference standard negates the increase in S_{Cr} seen with the Jaffe-based method and thus reintroduces the error of GFR estimate caused by tubular secretion of creatinine (see Creatinine Assay Standardization, below).⁶

Disease states and aging effects on muscle mass affect creatinine production and turnover. The measured 24-hr CrCl is less likely to be affected than estimates using patient demographics and S_{Cr}



to estimate CrCl. Drugs and exogenous or endogenous compounds that interact with the laboratory assays for creatinine may also affect estimates of CrCl. The compounds in **Table 2-1** may positively bias the creatinine concentration by interfering with creatinine assays (dependent on the assay system, methodology, and instrument used).

These compounds all have the potential to interfere with the S_{Cr} assays although the extent of interference is dependent on the given instrument used. If a patient has a potential for a creatinine–laboratory assay interaction, clinicians should check with the laboratory for the specific interference with the instrument used. Judicious timing of the drawing of blood for S_{Cr} determination (at minimal interfering drug concentration) or using an alternate assay method may be advisable.^{2,3,5,7}

TABLE 2-1. COMPOUNDS THAT INTERFERE WITH CREATININE ASSAYS

Jaffe-based Assays	Enzymatic Assays
Acetoacetate	Dopamine
Bilirubin	Dobutamine
Cefoxitin, cephalothin	Flucytosine
Clavulanic acid	Lidocaine
Other cephalosporins (supratherapeutic)	
Furosemide (supratherapeutic)	
Lactulose	
Endogenous serum substances (+ 0.2 mg/dL creatinine prior to assay standardization to isotope dilution mass spectrometry [IDMS] reference method)	

Exogenous creatine supplementation could be thought to affect the creatinine serum concentration because creatine is converted to creatinine. One review of studies of acute and chronic creatine ingestion in young healthy populations found minimal impact on serum creatinine concentrations; however, other more recent studies found an increase in S_{Cr} with a buffered creatine supplement and a creatine ester supplement.⁸⁻¹⁰

CREATININE ASSAY STANDARDIZATION

The National Kidney Disease Education Program (NKDEP) of the U.S. National Institutes of Health (NIH) launched an international program to standardize the creatinine assay calibration in healthcare laboratories. This decreased the former positive bias (up to 20%) of the creatinine assay through laboratory instrument recalibration to agree with an IDMS reference method.^{6,11} This calibration may lead many of the CrCl estimating equations for adults and pediatrics to give higher CrCl estimates than in the past, depending on the previous assay used.¹¹⁻¹³ These differences may not be as clinically important for dosing of a drug with a wide therapeutic index (e.g., cefazolin); however, for drug dosing using pharmacokinetic population estimates in drugs with a narrow therapeutic index (e.g., aminoglycosides) this change may have important clinical implications.

It should be noted that most 24-hr measured CrCl values from the past that were obtained using a non-standardized assay (non-IDMS) would be expected to yield the same value as today because the serum and urine creatinine were usually assayed using the same calibration scheme.¹² This is a result of the creatinine concentration being located in the numerator and the denominator of the 24-hr CrCl equation noted above.¹²

FORMULAS TO ESTIMATE CREATININE CLEARANCE IN ADULTS

Collecting urine for 24 hr for a creatinine measurement is tedious and must be done accurately with no missed collections and accurate measurement of urine volume to properly measure the CrCl. Because this is difficult and time-consuming, formulas have been derived that use the serum creatinine and patient demographics to estimate CrCl.

The many equations for rapid estimation of CrCl published over the last 40 yr generally produce similar values. Two well-validated and commonly used equations for *adult* patients when S_{Cr} is at steady state are the Cockcroft-Gault equation and the Jelliffe equation.¹⁴⁻¹⁶ Cockcroft-Gault is the equation usually included in drug product labeling (package inserts) for individualizing drug dosages for renally cleared drugs when an equation is mentioned.¹⁷ Other more recently developed equations are used to estimate GFR in adult patients with chronic kidney disease (Modification of Diet in Renal Disease [MDRD] Study equation, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation; discussed later); however, at this time their use for drug dosing purposes has been questioned.¹⁷⁻¹⁹

Cockcroft-Gault Equation:

$$CrCl_{(males)}(mL/min) = \frac{(140 - \text{Age})(W)}{(72)(S_{Cr})}$$

$$CrCl_{(females)}(mL/min) = CrCl_{(males)} \times 0.85$$

where S_{Cr} is in milligrams per deciliter (mg/dL) and W is weight (kg). The International Systems conversion is:

$$CrCl_{(males)}(mL/min) = \frac{1.23 \times (140 - \text{Age})(W)}{(S_{Cr})}$$

$$CrCl_{(females)}(mL/min) = CrCl_{(males)} \times 0.85$$

where S_{Cr} is in micromoles per liter ($\mu\text{mol/L}$) and W is weight (kg).

Jelliffe Equation:

$$CrCl_{(males)}(mL/min/1.73m^2) = \frac{98 - [0.8(\text{Age} - 20)]}{(S_{Cr})}$$

where S_{Cr} is in mg/dL.

The International Systems conversion is:

$$CrCl_{(males)}(mL/min/1.73m^2) = \frac{8663 - [70.7(\text{Age} - 20)]}{(S_{Cr})}$$

where S_{Cr} is in $\mu\text{mol/L}$.

$CrCl_{(females)} = CrCl_{(males)} \times 0.9$ for both versions.

Because creatinine is produced in muscle tissue, the weight used in the Cockcroft-Gault equation has commonly been ideal body weight (IBW) or actual body weight (ABW) if it is less than IBW. However,

there are many important considerations in these generalizations (see section on body weight). The original authors used ABW in developing their equation, but other researchers have examined the impact of excessive weight on predictability. IBW is estimated by the following²⁰:

$$\text{IBW (males) (kg)} = 50 + [2.3(H - 60)]$$

$$\text{IBW (females) (kg)} = 45.5 + [2.3(H - 60)]$$

where H is height in inches, or,

$$\text{IBW (males) (kg)} = 50 + [0.9(H - 152)]$$

$$\text{IBW (females) (kg)} = 45.5 + [0.9(H - 152)]$$

where H is height in centimeters (cm).

In the Jelliffe equation, the CrCl is normalized to an average adult body surface area (BSA) of 1.73 m² and the units are mL/min/1.73 m². If the patient does not have a BSA of 1.73 m², then the result needs to be converted to their actual CrCl in mL/min. To calculate the CrCl (in mL/min), the result is multiplied by the patient's BSA and then divided by 1.73. BSA may be determined from the following equation (other approaches to estimating BSA are shown in Chapter 4, Medication Dosing in Overweight and Obese Patients)²¹:

$$\text{BSA (m}^2\text{)} = W^{0.5378} \times H^{0.3964} \times 0.024265$$

where W is weight (kg) and H is height (cm).

The Cockcroft-Gault and Jelliffe equations work reasonably well for most adults with S_{Cr} at steady state because they allow for declining muscle mass (and creatinine production) often associated with reduced weight and advancing age and are adjusted for the average smaller muscle mass of females. The Cockcroft-Gault equation is the most commonly used and recommended equation for CrCl estimation for drug dosing and is discussed in greater detail in the following sections. The Jelliffe equation is still used by some clinicians and is reasonably accurate for use when height and weight are not available in average-sized patients.¹⁶ The accuracy of these equations in predicting CrCl is often limited in patients with various disease states or conditions. These include the elderly, the malnourished, the obese, patients with amputations or spinal cord injuries, those with chronic renal insufficiency, acutely changing renal function, those with liver disease, critically ill patients, and pediatric patients (see specific sections, below.).¹⁻³ Other, possibly more accurate, methods and equations for rapid prediction of renal function will continue to evolve as more patients and larger subgroups are studied.^{22,23}

NKDEP previously recommended using the MDRD Study equation or the CKD-EPI equation for estimation of GFR in adults as a screening tool for kidney disease and encouraged clinical laboratories to report this estimated GFR (eGFR) along with the patient's serum creatinine. The CKD-EPI equation eGFR result may now be reported in this situation, as it does not require the patient's weight. The NKDEP has suggested use of this eGFR or the Cockcroft-Gault equation for drug dosing.¹² In the United States, most of the drugs that have the Food and Drug Administration–approved product labeling for drug dosing in patients with renal dysfunction have dosing guidelines specifically indexed to CrCl, and many note use of the Cockcroft-Gault equation.¹⁷⁻¹⁹ For this reason, use of the eGFR for drug dosing has been questioned, and it was reported in one survey that pharmacy clinicians did not substitute eGFR for CrCl, although this may evolve over time.^{17-19,24}

Abbreviated MDRD Study Equation:

IDMS Laboratory-Calibrated Creatinine¹²:

$$\begin{aligned} \text{GFR (mL/min/1.73 m}^2\text{)} &= 175 \times (S_{\text{Cr}})^{-1.154} \times (\text{Age})^{-0.203} \\ &\times (0.742 \text{ if female}) \\ &\times (1.21 \text{ if African American}) \end{aligned}$$

where S_{cr} is in milligrams per deciliter (mg/dL). For conversion to International Systems using S_{cr} in $\mu\text{mol/L}$, change the S_{cr} equation term to:

$$\left(\frac{S_{cr}}{88.4} \right)^{-1.154}$$

The rest of the equation remains the same.

This equation provides eGFR values that are automatically normalized to $\text{mL/min}/1.73 \text{ m}^2$. When using this equation in very large or very small patients, the NKDEP recommends that the normalized result in $\text{mL/min}/1.73 \text{ m}^2$ should be converted to mL/min .¹² To calculate the actual eGFR (in mL/min), the normalized result is multiplied by the patient's BSA and then divided by 1.73 m^2 .

The MDRD Study equation, although created from a large group of patients, had not been validated in many population groups including children, the elderly (>70 yr), patients with serious comorbid conditions, body size extremes, muscle mass extremes, severe malnutrition, pregnant patients, ill hospitalized patients, amputees, and patients with near normal renal function.^{11,25} The equation is not weight-based but is affected by obesity and other factors that affect creatinine production.^{6,11,25} As noted above, the NKDEP has recommended eGFR (MDRD Study or CKD-EPI equation) reporting by laboratories along with serum creatinine to aid in the detection, evaluation, and management of patients with CKD. For the MDRD Study equation, they had recommended reporting exact actual values for eGFRs of $60 \text{ mL/min}/1.73 \text{ m}^2$ and below, but for values above $60 \text{ mL/min}/1.73 \text{ m}^2$ they recommend reporting it as $> 60 \text{ mL/min}/1.73 \text{ m}^2$ as this equation was found to underestimate measured GFR at higher levels.^{6,12}

The CKD-EPI equation was developed as another option to estimate GFR in adult patients with kidney disease. This equation was derived from over 12,000 patients of various races with and without CKD, diabetes, and kidney transplant.²⁶ The CKD-EPI equation is considered more accurate than the MDRD Study equation for a $\text{GFR} > 60 \text{ mL/min}/1.73 \text{ m}^2$, and appears to be the better equation to estimate GFR for staging of CKD.^{12,27,28} NKDEP suggested this GFR estimating equation for drug dosing, but recent studies have indicated serious limitations.^{12,19,29} Again, when using this equation in very large or very small patients, the NKDEP recommends that the normalized result in $\text{mL/min}/1.73 \text{ m}^2$ be converted to mL/min .¹² To convert eGFR to mL/min , the normalized result is multiplied by the patient's BSA and then divided by 1.73 m^2 .

CKD-EPI Equation¹²:

$$\text{GFR (mL/min}/1.73 \text{ m}^2) = 141 \times \min(S_{cr}/\kappa, 1)^\alpha \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$$

[if female] $\times 1.159$ [if African American]

where:

S_{cr} is serum creatinine in mg/dL ,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

In international units where S_{cr} is in $\mu\text{mol/L}$, the equation would be the same except for the terms below:

S_{cr} is serum creatinine in $\mu\text{mol/L}$,

κ is 61.9 for females and 79.6 for males.

Adjustments in the weight and/or creatinine variables based on a patient's clinical condition are commonly made in the Cockcroft-Gault equation in attempts to improve predictive performance. Clinicians should carefully assess the patient's clinical status and importance of an accurate assessment of renal function and modify these variables or use another more suitable equation or a timed CrCl measurement if necessary. In general, the following subgroup reviews pertain to adult patients (see section on pediatrics for CrCl estimation in children).³⁰⁻⁶⁴

BODY WEIGHT

Creatinine production is dependent on muscle mass, and the use of IBW in the Cockcroft-Gault equation appears to produce reliable results in patients whose ABW is not far from IBW. For patients who are malnourished or cachectic with an ABW less than their IBW, the ABW should be used.^{1-3,20,30,64} For adult patients less than 1.52 m (60 in) tall, use of the lesser of ABW or IBW (males = 50 kg, females = 45.5 kg) has been proposed.³¹ Other methods of predicting IBW are provided in the Introduction and Chapter 4, Medication Dosing in Overweight and Obese Patients.

Obesity (defined as >20% over IBW or BMI > 30) is another factor that affects the Cockcroft-Gault CrCl estimation. Obese patients appear to have a larger muscle mass than would be predicted when using height in the IBW equation. Using IBW is still preferable to using ABW; however, using an adjusted body weight (BW_{adj}) between IBW and ABW may be more accurate. Use of a factor of 40%, 30%, or 20% of the difference between ABW and IBW has been proposed.^{3,22,31,32,64}

$$BW_{adj} = IBW + 0.4 (ABW - IBW)$$

$$BW_{adj} = IBW + 0.3 (ABW - IBW)$$

$$BW_{adj} = IBW + 0.2 (ABW - IBW)$$

A meta-analysis including 13 trials comparing a 24-hr measured CrCl with a Cockcroft-Gault estimation found that use of IBW with Cockcroft-Gault had a lower mean difference (5.2 mL/min) compared to a 24-hr CrCl than using ABW (15.9 mL/min). In a smaller number of trials, the use of no body weight (using 72 in the Cockcroft-Gault equation numerator) or adjusted body weight (0.3 factor) also had a low mean difference.³²

The notion of “correct” weight to use in the prediction equations is an interesting one. As mentioned earlier, Cockcroft and Gault used ABW to develop the equation. Many authors have studied and suggested the use of IBW or one of the BW_{adj} for patients who weigh more than their IBW. Intuitively such approaches seem reasonable because creatinine is produced in muscle, not fat tissue. One suggestion that might help in determining a reasonable weight is to avoid using only standards and to visually examine the patient. For example, a 180 cm (5'11") body builder who weighs 100 kg (220 lb) would clearly be expected to produce more creatinine daily than a sedentary individual of the same height and weight. Both patients would be estimated to have the same IBW, and both are considered obese by definition (ABW > 20% above IBW). It would seem reasonable to anticipate that the former patient should have CrCl estimated using ABW, since the additional weight will be creatinine producing, while the latter would be best estimated using BW_{adj} (or even IBW if they were extremely sedentary with little additional muscle mass associated with the adiposity). Finally, it should be expected that the more the patient differs from the patients used in the studies to develop the equations, the greater the potential that predictions might not match actual measured CrCl.

The Salazar-Corcoran equation (see below) is another method of CrCl estimation that has been useful in the obese patient but is a bit more complicated to use.^{3,22,33} Methods of adjusting body weight in the morbidly obese (BMI > 40) have recently been reviewed, and for this body weight group use of lean body weight (LBW; see equation below) in the Cockcroft-Gault equation may be the most appropriate; however, this practice has been questioned and still needs to be validated.^{34-36,64}

Salazar-Corcoran Equation:

$$CrCl_{(males)} (mL/min) = \frac{(137 - Age) \times \left[(0.285 \times W) + (12.1 \times H^2) \right]}{(51)(S_{Cr})}$$

$$CrCl_{(females)} (mL/min) = \frac{(146 - Age) \times \left[(0.287 \times W) + (9.74 \times H^2) \right]}{(60)(S_{Cr})}$$

where W is weight in kg, H is height in **meters**, and S_{Cr} is in mg/dL.

In international units where S_{Cr} is in $\mu\text{mol/L}$, the equations would be:

$$\text{CrCl}_{(\text{males})}(\text{mL/min}) = \frac{(137 - \text{Age}) \times [(0.285 \times W) + (12.1 \times H^2)]}{(0.58)(S_{Cr})}$$

$$\text{CrCl}_{(\text{females})}(\text{mL/min}) = \frac{(146 - \text{Age}) \times [(0.287 \times W) + (9.74 \times H^2)]}{(0.68)(S_{Cr})}$$

Lean Body Weight Equations (see Chapter 3):

$$\text{LBW}_{(\text{males})}(\text{kg}) = (9270 \times \text{ABW}) / [6680 + (216 \times \text{BMI})]$$

$$\text{LBW}_{(\text{females})}(\text{kg}) = (9270 \times \text{ABW}) / [8780 + (244 \times \text{BMI})]$$

where ABW is in kg, and body mass index (BMI) is in kg per meter².

LOW SERUM CREATININE IN ELDERLY OR UNDERWEIGHT PATIENTS

It is a fairly common practice for clinicians to round measured S_{Cr} concentrations that are less than 0.8 or 0.9 mg/dL to a higher value in elderly or underweight adult patients before using the estimating equations. The S_{Cr} is inversely proportional to CrCl, so using an unrealistically low S_{Cr} value in an elderly or other patient with significantly decreased muscle mass or creatinine production may overestimate the CrCl, leading to the use of higher drug doses. The use of a value of 1 mg/dL as the lower limit of S_{Cr} in these equations has been popular with some clinicians; however, underprediction of CrCl may also occur, and this practice is not recommended.^{19,35} Using 0.8 or 0.7 (or less) as the lower limit of S_{Cr} may be more appropriate.^{37,38} Intuitively, it would seem to make sense that a patient's muscle mass would give some guide to how much "fudging" should be done in setting a lower limit of S_{Cr} . That is, in a patient with obviously limited muscle mass, it might be more reasonable to adjust the S_{Cr} upward than in a patient with average muscle mass. Also, it seems reasonable to assume that the larger the degree of "fudging" of the S_{Cr} upward to some minimum value, the greater the likelihood of poor prediction. That is, changing a measured S_{Cr} from 0.3 to 0.7 might result in a poorer prediction of actual CrCl than changing from 0.6 to 0.7. Further, it also seems logical that the same conditions (elderly with decreased muscle mass) present in a patient with an S_{Cr} of 1 or more would lead to a need to increase the S_{Cr} arbitrarily to avoid overestimating CrCl. However, this has not generally been recommended, and there are few data to support such approaches. The use of a percentage increase in S_{Cr} might be more logical and would be an area for study.

AMPUTATIONS

Estimation of CrCl in patients with amputated limbs poses a dilemma for IBW calculation. A reasonable approach would be to determine the height-based IBW before the amputation, then subtract the percent of the missing limb based on data from a body segment percentage table.³⁹ The weight used would be the lesser of this adjusted IBW or the ABW. The average weight of body segments of a 68-kg (150-lb) man are: upper limb, 4.9%; entire lower limb, 15.6%; thigh, 9.7%; leg (below knee), 4.5%; and foot, 1.4%. This suggested method for IBW calculation in amputees has not been validated for its utility in predicting CrCl in these patients.

SPINAL CORD INJURY

CrCl estimation in patients with spinal cord injury appears to be unpredictable (overprediction) because of the loss in muscle mass that occurs over time after the injury. Accuracy has been reported in some patient populations (paraplegics with good renal function); however, the 24-hr CrCl measurement should be used in patients with spinal cord injuries if accuracy is necessary.^{40,41}

CHRONIC RENAL INSUFFICIENCY

As already noted, with declining renal function S_{Cr} may become a less accurate indicator of renal function (GFR) due to the increasing percentage of tubular secretion of creatinine in relation to the total urinary excretion. That is, as renal function decreases, tubular secretion becomes a larger part of creatinine elimination. In addition, there appears to be an extrarenal route of creatinine elimination via the gastrointestinal tract in uremic patients. These patients may have poor dietary intake and reduced muscle mass as well.^{2,22} Use of oral cimetidine (800 mg every 12 hr for three doses) to inhibit tubular secretion of creatinine prior to urine collection or S_{Cr} measurement has been advocated to improve estimation of GFR.⁴²⁻⁴⁴ Ranitidine and famotidine have not been shown to inhibit the tubular secretion of creatinine and should not be used for this purpose.⁴³ Again, if the CrCl is used to determine doses, it may not be necessary to make such changes for estimating GFR, since drug dosing studies have traditionally used CrCl estimates.

DIALYSIS

Estimating CrCl in patients receiving dialysis is problematic and not recommended. A patient without functioning kidneys has no glomerular filtration. Thus, the S_{Cr} concentration becomes primarily a function of the dialysis procedure rather than the patient's kidney function. Because no urine output indicates no renal function, monitoring residual urine output gives some idea whether the patient's kidneys have any potential role in drug elimination.

LIVER DISEASE

Estimation of renal function in patients with cirrhosis presents certain dilemmas. Estimates of GFR using CrCl estimations (Cockcroft-Gault) and 24-hr CrCl measurements may be unreliable as shown by inulin clearance tests in these patients. The GFR estimating equations (CKD-EPI, MDRD) have also been found to be inaccurate.⁴⁵ These patients should have their drug therapy monitored more carefully, particularly for drugs with a narrow therapeutic index, where drug concentration monitoring is recommended whenever possible.⁴⁶⁻⁵¹

PEDIATRICS

CrCl estimations in children have been shown to reasonably accurately predict GFR. Because a measured 24-hr CrCl is as difficult and time-consuming as in adults, equations have been developed for rapid estimation based on a patient's height and weight. These estimates appear most accurate for patients of average weight for their size. The equations use S_{Cr} and height (body length) to estimate the normalized CrCl (as if BSA was 1.73 m²). The correlation of a child's muscle mass with his or her height helps factor in the relationship between muscle mass and creatinine production. However, these estimations may be less accurate for children who are significantly under- or overweight for their height and in the first week of life when the serum creatinine of an infant still reflects maternal serum creatinine and renal function is immature.⁵²

A commonly used equation (the first equation in Table 2-2) for *children 1–18 yr of age* was developed by Traub and Johnson.⁵³ For *infants, children, and adolescents*, specific equations shown in **Table 2-2** have also been used.⁵² The IDMS creatinine calibration introduces a potentially unacceptable amount

of error (CrCl appears higher than it is) with use of the Jaffe method of analysis. The following equation can be used only if the laboratory is employing the enzymatic assay.^{11,54-56}

Using IDMS Calibrated Creatinine in Children—Enzymatic Assay Only^{11,54-56}

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 0.41 (\text{H}/\text{S}_{\text{Cr}})$$

where S_{Cr} is in mg/dL and H in centimeters.

In international units where S_{Cr} is in $\mu\text{mol/L}$, the equation would be:

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 36.2 (\text{H}/\text{S}_{\text{Cr}})$$

All of these equations provide values that are automatically normalized to 1.73 m^2 . To calculate the actual CrCl (in mL/min), the equation result is multiplied by the patient's BSA and divided by 1.73 .²¹

TABLE 2-2. CREATININE CLEARANCE ESTIMATION IN CHILDREN^{a,11}

Age Range (Years)	Standard Units ^b	International Standardized Units ^c
1 to 18 ⁵³	$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{(0.48)(\text{H})}{(\text{S}_{\text{Cr}})}$	$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{(42.4)(\text{H})}{(\text{S}_{\text{Cr}})}$
<1 ⁵²		
Preterm infant	$\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(0.33)(\text{H})}{(\text{S}_{\text{Cr}})}$	$\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(29.2)(\text{H})}{(\text{S}_{\text{Cr}})}$
Full-term infant	$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{(0.45)(\text{H})}{(\text{S}_{\text{Cr}})}$	$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{(39.8)(\text{H})}{(\text{S}_{\text{Cr}})}$
1 to 12 ⁵²	$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{(0.55)(\text{H})}{(\text{S}_{\text{Cr}})}$	$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{(48.6)(\text{H})}{(\text{S}_{\text{Cr}})}$
13 to 21 (girls) ⁵²	$\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(0.55)(\text{H})}{(\text{S}_{\text{Cr}})}$	$\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(48.6)(\text{H})}{(\text{S}_{\text{Cr}})}$
13 to 21 (boys) ⁵²	$\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(0.70)(\text{H})}{(\text{S}_{\text{Cr}})}$	$\text{GFR (mL/min/1.73 m}^2\text{)} = \frac{(61.9)(\text{H})}{(\text{S}_{\text{Cr}})}$

^aDeveloped using non-IDMS calibrated creatinine assay; results now likely to have a positive bias.

^b S_{Cr} is in mg/dL and H in cm.

^c S_{Cr} is in $\mu\text{mol/L}$ and H in cm.

PATIENTS WITH UNSTABLE RENAL FUNCTION

The discussed equations for CrCl estimation are based on patients with stable renal function with S_{Cr} at steady state. In patients with changing renal function, S_{Cr} may not reflect the current function for several days. Using a value of S_{Cr} that is not at steady state to estimate CrCl may significantly over- or underestimate the patient's renal function and result in inappropriate drug dosing.

ESTIMATING TIME TO STEADY STATE SERUM CREATININE CONCENTRATION

The time to a steady state S_{Cr} value increases as the patient's renal function declines. Using the calculation below, the time to ~90% of steady state (3.3 half-lives) is estimated to be 26 hr, 53 hr, 5.6 days as a patient's renal function rapidly declines to 50%, 25%, and 10% of normal (70 kg, CrCl = 120 mL/min), respectively. It is estimated that if the S_{Cr} increases by more than 0.2 mg/dL in 8–12 hr, steady state probably has not been reached.⁵⁷

Determining a rough estimate of the half-life and time to steady state of creatinine in a specific adult patient may be made by assuming that the Cockcroft-Gault equation is accurate in estimating CrCl, that the patient's volume of distribution (V) of creatinine is ~0.6 L/kg of IBW^{57,58} and making the following calculations:

1. Estimate the patient's CrCl (mL/min) based on the Cockcroft-Gault equation.
2. Convert the patient's CrCl in milliliters per minute (mL/min) to liters per hour (L/hr) by multiplying by 0.06 (because of the following conversion):

$$\frac{60 \text{ min}}{1 \text{ hr}} \times \frac{1 \text{ L}}{1000 \text{ mL}} = 0.06 \text{ (units will cancel appropriately below)}$$

Thus, mL/min $\times$ 0.06 = L/hr.

3. Use the relationship $K = CL/V$ to calculate K, the elimination rate constant, where CL is the creatinine clearance in liters per hour (L/hr), and V is the volume of distribution of creatinine in liters (0.6 L/kg $\times$ IBW).
4. Use $t_{1/2} = 0.693/K$ to estimate the half-life.
5. Approximately 3.3 times the estimated half-life equals time to steady state (90% achieved).

CREATININE CLEARANCE ESTIMATION IN UNSTABLE RENAL FUNCTION

Several equations for use in patients with unstable renal function are available and may be useful for initial drug dosing; however, estimating CrCl in a patient with changing renal function can be problematic and drug concentration monitoring is recommended for drugs with a narrow therapeutic index.^{1-3,57,58} For 24-hr CrCl measurements in patients with changing renal function, use the midpoint (12th hr) S_{Cr} or the average of the S_{Cr} at the beginning and the end of the 24-hr urine collection.⁵⁸ The following equation has been used to estimate CrCl in patients with unstable renal function⁵⁹:

$$\text{CrCl}_{(\text{males})} (\text{mL/min}) = \frac{[[293 - 2.03(\text{Age})] \times [1.035 - 0.01685(S_{Cr1} + S_{Cr2})]] + [49(S_{Cr1} - S_{Cr2}) / \Delta t]}{(S_{Cr1} + S_{Cr2})}$$

where Δt is the change in time in number of days between measurement of S_{Cr1} and S_{Cr2} .

$$\text{CrCl (females)} = \text{CrCl (males)} \times 0.86$$

Other methods of CrCl estimation in unstable renal function using mass balance (estimated creatinine production versus creatinine excretion) may be useful and have been reviewed.⁶⁰⁻⁶³ Various internet

CrCl and GFR calculators are available on line. General principles from the literature noted above and/or institutional protocols, along with documentation of the specific equations and patient factors utilized, should guide the usage of these calculators.

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RENAL DRUG DOSING CONCEPTS

Dean A. Van Loo and Thomas C. Dowling

Chronic kidney disease (CKD) is a progressive consequence of systemic diseases such as diabetes and hypertension as well as localized kidney injury as the result of glomerulonephritis. Over 500,000 patients in the United States have stage 5 CKD, which is also categorized as end-stage renal disease (ESRD). Each year, for the last several decades, up to 100,000 patients have developed ESRD and over 80,000 have died.¹ Chronic renal replacement therapy, whether peritoneal or hemodialysis (HD), was life-sustaining for over 600,000 patients in 2011 at a total cost of over \$49 billion USD. A significant portion of patients who receive a kidney transplant continue on to develop CKD. Most stage 1 to 4 CKD patients are initially identified in primary care clinics, while others are identified in acute care environments. Population-based studies, such as NHANES, report that the prevalence of CKD is increasing dramatically, with more than 50% of U.S. adults aged 30 to 64 expected to develop CKD in their lifetime.²

Kidney failure can also appear abruptly, with some patients presenting with acute kidney injury (AKI) in emergency departments, clinical wards, or intensive care units.³ The majority of AKI cases are attributed to drug therapy or renal hypoperfusion in hospitalized patients, which often requires continuous renal replacement therapies (CRRT). Regardless of the cause of acute or chronic renal impairment, these patients are at increased risk of accumulating drugs, toxic metabolites, and other nephrotoxins. For any drug that relies extensively on the kidney for elimination from the body (i.e., renal clearance > 30% of total clearance) and drug concentrations in blood or plasma are clearly associated with a pharmacodynamic effect (success, failure, or toxicity), dose adjustments are necessary when renal function is considerably reduced. The aim of this chapter is to describe dosing strategies for patients with CKD, AKI, and those receiving renal replacement therapies on an intermittent and/or continuous basis.

CLINICAL ASSESSMENT OF KIDNEY FUNCTION

The indices of glomerular and tubular function most widely utilized clinically include daily urinary protein excretion rate (glomerular), urine albumin-creatinine ratio (glomerular), fractional excretion of sodium (tubular), and serum creatinine concentration (glomerular and tubular). Creatinine is excreted by glomerular filtration and tubular secretion, making creatinine clearance (CrCl) a composite index of renal function that has been strongly associated with the total and renal clearance of many drugs that are eliminated by the kidney and is the primary index of renal drug dosing in FDA product labeling.

In patients with CKD stages 1 through 5 (pre-dialysis), the Cockcroft-Gault (CG) equation (see Chapter 2) is commonly used to estimate CrCl in the presence of stable kidney function. Newer equations that estimate GFR (eGFR), such as the CKD-EPI equations, are most appropriately used for identifying CKD and staging their degree of CKD severity.⁴ Although the Modification of Diet in Renal Disease (MDRD) equation was initially adopted into automated systems for reporting GFR in clinical settings, it has been shown to be largely inaccurate at GFR > 60 mL/min and has since been replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Neither of these eGFR equations has been consistently demonstrated to be equivalent to CG or measured CrCl when adjusting drug doses for renal impairment.^{5,6} Recent studies by the Food and Drug Administration (FDA) and others showed that eGFR equations yield significantly higher estimates of kidney function, and significantly different dose calculations, when compared to CG equation, particularly in elderly individuals and those receiving narrow therapeutic index drugs such as enoxaparin.⁵⁻⁹ Thus, renal dosing practices should remain consistent with the original pharmacokinetic studies of a particular drug in CKD, which to date generally involves estimation of CrCl.



Quantification of renal function in patients with AKI, where renal function and serum creatinine values are rapidly changing, is a challenging situation. Here, numerous equations for estimating CrCl based on two non-steady-state serum creatinine values have been proposed. See Chapter 2 for further discussions of appropriate use of equations to quantify renal function in various situations and patient populations. For critically ill patients with AKI receiving CRRT, estimation of both residual renal function (CrCl) and CRRT clearance are required for dose individualization (see section on dosing strategies).^{10,11}

MECHANISMS OF DRUG CLEARANCE

Renal elimination

The process of renal drug elimination is a composite of glomerular and tubular functions, with the amount of drug cleared by the kidney (A_c) described by the following equation:

$$A_c = A_{\text{filt}} + A_{\text{sec}} - A_{\text{reabs}} \quad (\text{Eq. 1})$$

Initially, unbound drug is filtered through the glomerulus (A_{filt}) into the proximal tubular fluid. When in the tubule, filtered drug may then be passively or actively reabsorbed (A_{reabs}) back into the bloodstream. This reabsorptive process is rare and occurs primarily in distal segments for unionized drugs at low urine flow rates. Drugs may also undergo active tubular secretion (A_{sec}), where unbound drug in plasma is transported into the tubular cell. This process of secreting drugs into the urine is mediated by transporters such as the organic anionic transporter (OAT), organic cationic transporter (OCT), or p-glycoprotein (P-GP). These transporters act in an efflux and uptake manner and are located along the basolateral and apical membranes of the proximal tubule.¹²⁻¹⁴ The pathways work together to form an extremely efficient process of detoxification, resulting in renal clearance values that can exceed GFR, and in some cases approach renal plasma flow, which can be observed with para-aminohippurate and several penicillins. As filtration capacity (measured as GFR) progressively diminishes in CKD, some experimental data suggest that tubular secretory mechanisms may maintain their functionality, thereby providing significant renal clearance for some drugs even in the presence of severe glomerular damage.¹⁵

Kidney diseases can affect both glomerular and tubular function, leading to reduced overall drug elimination. As destruction of nephrons progresses, it has traditionally been believed that the function of all segments of the remaining nephrons is affected equally.¹⁶ Based on this assumption, the rate of drug excretion in the normal or diseased kidney can be estimated by GFR or CrCl, which are predominantly measures of glomerular function.¹⁷ The total renal clearance of a drug from the body also depends on (1) the fraction of the drug eliminated unchanged by the normal kidney, (2) the renal mechanisms involved in drug elimination, and (3) the degree of functional impairment of each of these pathways. The fraction of unchanged drug eliminated renally (f_e) and an assessment of the relationship between renal function and the drug's parameters, such as half-life ($t_{1/2}$), total clearance (CL), and renal clearance (CL_{Renal}), can be used to individualize drug therapy. Ideally, renal drug clearance is determined by quantifying the amount of drug excreted in urine relative to the area under plasma drug concentration versus time curve (AUC) of drug in plasma, and renal function is measured using a GFR method such as iohexol or iothalamate clearance.¹⁸ More commonly, the relationship between CrCl and drug clearance (CL) is evaluated in a large patient population with varying renal function, as follows:

$$CL = (A \times \text{CrCl}) + B \quad (\text{Eq. 2})$$

$$k = (A \times \text{CrCl}) + B \quad (\text{Eq. 3})$$

where A is the slope of the linear relationship between CrCl and either CL or k (the elimination rate constant), and B is the nonrenal CL (CL_{NR}) or nonrenal k (k_{NR}), respectively. This drug-specific information can then be used to design dose adjustment strategies in patients with renal insufficiency to minimize drug toxicity and optimize therapeutic efficacy.

Role of renal drug transporters

All aspects of drug transport in the kidney may be affected by co-administration of other substances, even in patients with normal renal function. First, drugs that cause a change in GFR will alter the CL_R of other renally eliminated drugs, assuming that tubular function remains unchanged. Second, substances may alter the tubular transport of one or more secretory pathways at uptake and efflux sites, such as P-GP, OAT, or OCT, through noncompetitive inhibition or degradation of transport carriers. The most common type of tubular transport interaction occurs when two substances compete for tubular secretion by the same pathway. Clinically significant drug interactions involving renal transport mechanisms, both beneficial and detrimental, have been reported for the OAT, OCT, P-GP, and multi-drug and toxin extrusion (MATE) transporters (Table 3-1).¹⁴

TABLE 3-1. EXAMPLES OF RENAL DRUG TRANSPORTER-INTERACTION STUDIES IN HUMANS^{14,19–23}

Transporter(s) (Gene)	Substrate	Inhibitor	Pharmacokinetic Results
P-GP (ABCB1)	Fexofenadine	Probenecid	44%↓ CL/F; 70%↓ CLR; 53%↑ AUC
	Cimetidine	Itraconazole	26%↓ CL; 30%↓ CLR; 25%↑ AUC ⁶⁶
	Digoxin	Itraconazole	21%↓ CLR; 50%↑ AUC
	Digoxin	Ritonavir	42%↓ CL/F; 21%↓ CLR; 86%↑ AUC
OAT1 (SLC22A6)/ OAT4 (SLC22A11)	Zidovudine	Probenecid	49%↓ CL; 56%↓ CLR; 50%↑ T1/2
	Ciprofloxacin	Probenecid	41%↓ CL; 64%↓ CLR; 74%↑ AUC
OAT3 (SLC22A8)	Benzylpenicillin	Probenecid	78%↓ CLR; 327%↑ AUC
OCT1 (SLC22A1)	Metformin	Cimetidine ^a	50%↓ CL/F; 50%↓ CLR; 57%↑ AUC 37%↓ CL/F; 17%↑ AUC
OCT2 (SLC22A2)	Amantadine	Quinidine	33%↓ CLR
MATE1 (SLC47A1)	Pramipexole	Cimetidine	57%↑ AUC; 40%↑ T1/2

^aInteraction observed only in patients with OCT1 GG genotype.

MATE = multi-drug and toxin extrusion protein, OAT1/4 = family of organic anion transporters 1–4, OCT1 = organic cation transporter 1, OCT2 = organic cation transporter 2, P-GP = p-glycoprotein.

Although the mechanism is not well defined, an interaction between cimetidine and creatinine has been reported.¹⁴ Cimetidine appears to block the OCT, P-GP, or MATE-mediated tubular secretion of creatinine, which then provides for a more accurate assessment of the GFR using a CrCl estimation method. There is increasing evidence to suggest that genetic variability of renal drug transporters, such as OAT1 and OCT1, may be an important determinant of urinary drug excretion. Other transporters such as the peptide transporter and concentrative nucleoside transporters may also contribute to renal drug elimination of drugs such as β -lactam antibiotics and didanosine, respectively.

An example of the beneficial effect of renal interactions is the management of drug toxicity by enhancing urinary excretion of the toxin to reduce serum drug concentrations, or by inhibiting drug uptake in tubules. For example, administration of urinary acidifying agents such as ammonium chloride, reduces the renal tubular reabsorption of weak basic drugs such as xanthines, amphetamine, and phenobarbital, resulting in increased renal elimination. In contrast, urinary alkalinizing agents would reduce the renal elimination of weak basic drugs, which enhances systemic exposure. A known mechanism of cidofovir nephrotoxicity is intracellular localization of the drug in the proximal tubule. The use of probenecid to block cellular uptake of cidofovir provides renal protection, thereby circumventing the development of nephrotoxicity caused by this agent.

NONRENAL MECHANISMS

Metabolism

Biotransformation of drugs by Phase I (oxidative) and Phase 2 (conjugation) reactions generally results in the formation of inactive metabolic products. Decreased intra-renal metabolism, decreased hepatic metabolism, and reduced renal clearance of active or toxic metabolites have all been noted in CKD and may result in significant reductions in drug elimination (**Table 3-2**).²⁴⁻²⁷ The kidney itself plays an important role in the metabolism of many endogenous proteins and small peptides in addition to some drugs. For example, renal dehydropeptidase I, located in high concentrations along the brush border of the nephron inactivates the carbapenem antibiotic imipenem.²⁸ Data from animal models of CKD and evidence in ESKD patients have shown that hepatic CYP activity is reduced by up to 30% in the presence of renal failure, which can significantly impact drug clearance.²⁹⁻³⁰ For example, the nonrenal clearance of reboxetine, which is extensively metabolized by CYP3A and minimally excreted unchanged by the kidneys, was 30% lower in ESKD patients (CKD stage 5) compared to those with mild renal impairment (CKD stage 2-3), and 67% lower than subjects with normal renal function.³¹ Altered stereoselective metabolism may also occur in CKD. For example, a preferential increase in formation of metoprolol R-MAM and OHM was observed in CKD patients relative to normal controls.³² Thus, for drugs where nonrenal clearance is affected by renal disease, appropriate dose adjustments and close monitoring is needed to maintain steady state drug concentrations at values similar to individuals with normal renal and hepatic function.

TABLE 3-2. DRUGS REPORTED TO HAVE REDUCED NONRENAL CLEARANCE IN CKD

Acyclovir ^a	Cyclophosphamide ^c	Nitrendipine ^b
Aztreonam ^a	Didanosine ^a	Nortriptyline ^c
Bufurolol ^b	Encainide ^b	Oxprenolol ^b
Bupropion ^c	Erythromycin ^c	Procainamide ^c
Captopril ^c	Felbamate ^c	Propoxyphene ^{b,c}
Carvedilol ^c	Guanadrel ^b	Propranolol ^c
Cefepime ^a	Imipenem ^a	Quinapril ^a
Cefmetazole ^a	Isoniazid ^c	Raboxetine ^b
Cefonicid ^a	Ketoprofen ^a	Raloxifene ^c
Cefotaxime ^a	Ketorolac ^a	Repaglinide ^c
Ceftibuten ^a	Lidocaine ^c	Rosuvastatin ^a
Ceftriaxone ^a	Lomefloxacin ^a	Roxithromycin ^b
Cerivastatin ^b	Losartan ^c	Simvastatin ^c
Cibenzoline ^b	Lovastatin ^c	Sparfloxacin ^a
Cilastatin ^a	Metoclopramide ^a	Telithromycin ^a
Cimetidine ^a	Minoxidil ^c	Valsartan ^c
Ciprofloxacin ^a	Morphine ^c	Vancomycin ^a
Codeine ^c	Nicardipine ^c	Verapamil ^c
	Nimodipine ^c	Zidovudine ^a

^aIndicates that a renal dose adjustment is required; see Table 3-3 or package insert.
^bIndicates drug not available in United States.
^cIndicates no FDA-approved dose adjustment in CKD provided; use with caution in CKD.

Gastrointestinal absorption

The effect of CKD on gastrointestinal GI absorption of drugs is not well understood and the impact of AKI on GI absorption is unknown. Many patients with diabetes mellitus are known to have decreased gastric emptying; therefore, delayed absorption of some drugs can be expected in the presence of diabetes.

However, the extent of absorption and overall bioavailability are typically unchanged compared to patients without renal disease. Although the bioavailability of a few drugs are reportedly reduced, consistent findings of impaired absorption in CKD patients is lacking. For the majority of drugs that have been evaluated, GI absorption is either unchanged or increased, suggesting that pre-systemic (or first-pass) extraction may be reduced in these patients. The absorption of some drugs such as digoxin, doxycycline, levothyroxine, and fluoroquinolone antibiotics may be impaired due to the concomitant administration of phosphate binders, including sucroferic oxyhydroxide, that are commonly observed in CKD patients.³³⁻³⁵

VOLUME OF DISTRIBUTION

The volume of distribution (V) of many drugs, including aminoglycosides and cephalosporins, has been reported to be significantly increased in CKD patients.³⁶⁻³⁸ Proposed mechanisms of increased V for various drugs include fluid overload, decreased plasma protein binding due to hypoalbuminemia or competitive binding interactions with uremic toxins, or altered tissue binding. Decreased V in patients with ESRD is rare and, if present, is due to reduced binding to tissue proteins. The two primary plasma proteins that bind acidic and basic drugs are albumin and α_1 -acid glycoprotein (AAG), respectively. The protein binding for some acidic drugs such as penicillins, cephalosporins, furosemide, theophylline, and phenytoin, is reduced in patients with renal failure.^{39,40} The binding of basic drugs to AAG is, however, generally unaltered in CKD patients, although increased V has been reported for some drugs such as bepridil and disopyramide.^{41,42} Although changes in plasma protein binding are not usually clinically significant, close monitoring in patients receiving narrow therapeutic index drugs is warranted unless there is clinical confirmation of no associated problem.

DRUG DOSING STRATEGIES FOR CKD PATIENTS

For drugs that rely to a significant degree on the kidneys for total body elimination (i.e., $f_e > 0.3$), dose reductions may be required in patients with CKD to avoid systemic accumulation and adverse drug events. In nearly all cases, the FDA-approved drug product label (i.e., package insert) includes drug dose adjustment guidelines based on the degree of reduction in CrCl.⁴³

It is important to understand the mathematical basis for dose adjustment recommendations. The following approach involves an initial estimation of the drug's CL (or k) based on either literature data or derivation of a regression equation from clinical trial data.^{17,44} The next step is to use the estimates of CL or k to determine the dose adjustment factor (Q):

$$Q = k_R \div k_{\text{norm}} \quad (\text{Eq. 4})$$

$$Q = \text{CL}_R \div \text{CL}_{\text{norm}} \quad (\text{Eq. 5})$$

R = in reduced renal function
norm = in normal renal function

An assumption when using Equation 4 is that V does not change in the presence of renal disease and, for both equations, that the normal values are representative of individuals with CrCl ≥ 120 mL/min.

An alternative approach to calculating Q involves determination of the ratio (KF) of the patient's CrCl to a presumed normal CrCl of 120 mL/min, based on estimation of the fraction of drug eliminated unchanged renally in subjects with normal renal function (f_e), as:

$$Q = 1 - [f_e (1 - KF)] \quad (\text{Eq. 6})$$

Use of this approach is based on the following assumptions:

- elimination of the drug is best described by a linear, first-order process;
- glomerular and tubular function decrease in a parallel fashion in all renal diseases;
- other aspects of drug absorption (bioavailability), distribution (protein binding) and metabolism (nonrenal clearance) remain constant;

- metabolites of the drug are pharmacologically inactive or do not accumulate in renal disease; and
- the pharmacodynamics (i.e., the concentration or dose response relationship) of the drug or metabolites remains unchanged by renal disease.^{17,43}

Once the dosage adjustment factor (Q) for the patient has been estimated, the dosage regimen for that drug can be modified to achieve the desired serum concentration profile. If clinically significant relationships between peak and trough concentrations and efficacy or toxicity have been described then the dosage regimen should be designed to attain and maintain these target values. In all other cases, the goal of dose individualization may be to achieve similar average steady state concentrations (Css_{av}) to those typically observed in patients with normal renal function. If the goal is to maintain the same Css_{av} and the dosage form precludes modification (e.g., time-release capsule), then one must prolong the dosing interval (τ). Conversely, if the standard dosing interval is desired, the dose can be reduced to maintain the desired Css_{av} . The new dosing interval (τ_R) or dose (D_R) for the patient with renal insufficiency can be calculated from the interval (τ_{norm}) and dose (D_{norm}) used in normal renal function as follows:

$$\tau_R = \tau_{norm} \div Q$$

(Eq. 7)

$$D_R = D_{norm} \times Q$$

(Eq. 8)

The strategies shown in Eq. 7 and 8 are designed to achieve the same Css_{av} . However, the resultant steady state peak [Css_{max}] and trough [Css_{min}] concentrations may be markedly different in each case. The reduced dosage strategy (Eq. 8) yields lower Css_{max} and higher Css_{min} compared to the prolonged dosage interval (Eq. 7) approach, which results in values that are similar to the individual with normal renal function. If this approach yields an interval that is impractical, a new dose can be calculated using a fixed, pre-specified dose interval (τ_R), as follows:

$$D_R = [D_{norm} \times Q \times \tau_R] / \tau_{norm}$$

(Eq. 9)

The methods of dosage individualization described above (Eq. 7–9) are applicable to clinical settings where no serum concentration data are available to guide the therapeutic decision making process. These approaches are based on data obtained from clinical pharmacokinetic studies in patients with renal impairment, and serve as the basis for making initial dosing decisions based on renal function (CrCl) as shown in **Table 3-3**. However, when a specific serum concentration-time profile, peak, trough, or AUC is required, measurement of drug concentrations and traditional therapeutic drug monitoring approaches are recommended (see the drug-specific chapters of this book).

TABLE 3-3. PHARMACOKINETIC PARAMETERS AND MAINTENANCE DOSAGES FOR SOME COMMONLY USED DRUGS IN PATIENTS WITH CKD^{46–49,a}

Drug	V (L/kg)	fe	CrCl (mL/min)			
			120–70	70–50	50–10	<10
Acyclovir	0.7	0.4–0.7	5 mg/kg every 8 hr	5 mg/kg every 8 hr	5 mg/kg every 12–24 hr	2.5 mg/kg every 24 hr
Amantadine	4–5	0.9	100 mg every 12 hr	Every 24–48 hr	Every 48–72 hr	Every 7 d
Amphotericin B	4	0.05–0.1	20–50 mg every 24 hr	Every 24 hr	Every 24 hr	Every 24–36 hr
Amoxicillin	0.26	0.5–0.7	250–500 mg every 8 hr	Every 8 hr	Every 8 hr–12 hr	Every 24 hr
Ampicillin	0.17	0.3–0.9	250 mg–2 g every 6 hr	Every 6 hr	Every 6–12 hr	Every 12–24 hr
Apixaban	0.3	0.27	5 mg every 12 hr	100%	50%	Not recommended

TABLE 3-3. CONTINUED

Drug	V (L/kg)	fe	CrCl (mL/min)			
			120–70	70–50	50–10	<10
Atenolol	1.1	0.9	50–100 mg every 24 hr	100% every 24 hr	50% every 48 hr	30%–50% every 96 hr
Aztreonam	0.5–1	0.75	2 g every 8 hr	100%	50%–75%	25%
Benazepril	0.15	0.2	10 mg every 24 hr	100%	50%–75%	25%–50%
Bisoprolol	3	0.5	10 mg every 24 hr	100%	75%	50%
Cefazolin	0.13–0.22	0.75–0.95	1–2 g every 8 hr	Every 8 hr	50% every 12 hr	50% every 18–24 hr
Cefepime	0.3	0.85	2 g every 8–12 hr	Every 12–24 hr	Every 12–24 hr + dose reduction	Every 24 hr + dose reduction
Cefotaxime	0.15–0.55	0.6	1 g every 6 hr	Every 6 hr	Every 8–12 h	Every 24 hr
Cefoxitin	0.2	0.8	1–2 g every 8 hr	Every 8 hr	Every 8–12 hr	Every 24–48 hr
Ceftazidime	0.28–0.4	0.6–0.85	1–2 g every 8 hr	Every 8–12 hr	Every 24–48 hr	Every 48 hr
Ceftaroline	0.37	0.64	600 mg every 12 hr	600 mg every 12 hr	50%–66%	33%
Ceftolozane/ tazobactam	0.19 (C) 0.25 (T)	0.95 (C) 0.8 (T)	1.5 g every 8 hr	100%	25%–50%	750 mg × 1 then 150 mg every 8 hr
Cefuroxime IV	0.13–1.8	0.9	0.75–1.5 g every 8 hr	Every 8 hr	Every 8–12 hr	Every 24 hr
Cephalexin	0.35	0.98	250–500 mg every 6 hr	Every 8 hr	Every 12 hr	Every 12 hr
Cetirizine	0.4–0.6	0.6–0.7	5–20 mg every 24 hr	100%	50%	25%
Cimetidine	0.8–1.3	0.5–0.7	400 mg every 12 hr	100%	50%	25%
Cidofovir	0.3–0.8	0.9	5 mg/kg every 1–2 wk	100%	Avoid	Avoid
Ciprofloxacin IV	2.5	0.5–0.7	400 mg every 12 hr	100%	50%–75%	50%
Clarithromycin	2–4	0.15–0.25	0.5–1 g every 12 hr	100%	75%	50%–75%
Daptomycin	0.1	0.78	6 mg/kg every 24 hr	100%	50%–100%	50%
Didanosine	1	0.4–0.69	200 mg every 12 hr (125 mg if < 60 kg)	100%	150–200 mg every 24 hr (100–150 mg if < 60 kg)	50% every 24 hr 75 mg if < 60 kg
Doripenem	0.24	0.7	500 mg every 8 hr	100%	33%–50%	33%
Enalapril	No data	0.43	5–10 mg every 12 hr	100%	75%–100%	50%
Famciclovir	1.5	0.5–0.65	500 mg every 8 hr	100%	250–500 mg every 24–48 hr	250 mg every 48 hr
Famotidine	0.8–1.4	0.65–0.8	20–40 mg every 24 hr	50%	25%	10%
Fexofenadine	5–6	0.1	60 mg every 12 hr	Every 12 hr	Every 12–24 hr	Every 24 hr
Flucytosine	0.6	0.9	37.5 mg/kg every 6 hr	Every 12 hr	Every 16 hr	Every 24 hr

TABLE 3-3. CONTINUED

Drug	V (L/kg)	fe	CrCl (mL/min)			
			120–70	70–50	50–10	<10
Foscarnet	0.3–0.6	0.85	40 mg/kg every 8 hr	28 mg/kg	15 mg/kg	6 mg/kg
Gabapentin	0.7	0.9	300–600 mg every 8 hr	400 mg every 8 hr	300 mg every 12–24 hr	300 mg every 48 hr
Ganciclovir	0.47	0.9–1	5 mg/kg every 12 hr	Every 12 hr	Every 24–48 hr	Every 48–96 hr
Glipizide	0.13–0.16	0.05–0.07	2.5–15 mg every 24 hr	100%	50%	50%
Glyburide	0.2–0.3	0.5	1.25–20 mg every 24 hr	No data	Avoid	Avoid
Insulin	0.15	None	Variable	100%	75%	50%
Insulin (Lispro)	0.26–0.36	No data	Variable	100%	75%	50%
Itraconazole	10	0.35	100–200 mg every 12 hr	100%	100%	50%
Lamivudine	0.83	0.7–0.8	150 mg every 12 hr	100% every 24 hr	50–150 mg every 24 hr	25–50 mg every 24 hr
Levetiracetam	0.5–0.7	0.66	0.5–1.5 g every 12 hr	0.5–1 g every 12 hr	250–750 mg every 12 hr	0.5–1 g every 24 hr
Levofloxacin	1.1–1.5	0.67–0.87	500 mg every 24 hr	100%	250 mg every 24–48 hr	250 mg every 48 hr
Linezolid	0.57–0.71	0.3	600 mg every 12 hr	100%	100%	100%
Lisinopril	0.13–0.15	0.8–0.9	5–10 mg every 24 hr	100%	50%–75%	25%–50%
Meropenem	0.35	0.65	0.5–1 g every 6 hr	500 mg every 6 hr	250–500 mg every 12 hr	250–500 mg every 24 hr
Metformin ^b	1–4	0.9–1	500–850 mg every 12 hr	50% ^b	25% (avoid) ^b	Avoid ^b
Methicillin	0.31	0.25–0.8	1–2 g every 4h	Every 4–6 hr	Every 6–8 hr	Every 8–12 hr
Metoclopramide	2–3.4	0.1–0.22	10–15 mg every 6 hr	100%	75%	50%
Metronidazole	0.3–0.9	0.2	7.5 mg/kg every 6 hr	100%	100%	50%
Nizatidine	0.8–1.3	0.1–0.15	150–300 mg every 24 hr	75%	50%	25%
Olmesartan	0.24	0.5	20 mg every 24 hr	100%	Use caution when CrCl < 20 mL/min	Use caution when CrCl < 20 mL/min
Oxcarbazepine ^c	0.7–0.8	0.3	300–600 mg every 12 hr	100%	75%	50%
Penicillin G	0.3–0.4	0.6–0.85	0.5–4 MU every 6 hr	100%	75%	20%–50%
Pentamidine	3–4	0.05	4 mg/kg every 24 hr	Every 24 hr	Every 24 hr	Every 24–36 hr
Piperacillin	0.2–0.3	0.75–0.9	3–4 g every 4 hr	Every 4–6 hr	Every 6–8 hr	Every 8 hr
Quinapril	1.5	0.3	10–20 mg every 24 hr	100%	75%–100%	75%
Ramipril	1.2	0.1–0.21	10–20 mg every 24 hr	100%	50%–75%	25%–50%

TABLE 3-3. CONTINUED

Drug	V (L/kg)	fe	CrCl (mL/min)			
			120–70	70–50	50–10	<10
Ranitidine	1.2–1.8	0.8	150–300 mg every 24 hr	75%	50%	25%
Rivaroxaban	0.71	0.36	15–20 mg every 24 hr	100%	75% (avoid if CrCl < 30 mL/min)	Not recommended
Sotalol	1.3	0.6	160 mg every 24 hr	100%	30%	15%–30%
Spironolactone	No data	0.2–0.3	25 mg every 6–8 hr	Every 6–12 hr	Every 12–24 hr	Avoid
Stavudine	0.5	0.4	30–40 mg every 12 hr	100%	50% every 12–24 hr	50% every 24 hr
Tedizolid	0.96–1.14	<0.03	200 mg every 24 hr	100%	100%	100%
Tetracycline	0.7	0.48–0.6	250–500 mg every 6 hr	Every 8–12 hr	Every 12–24 hr	Every 24 hr
Tigecycline	7–9	0.22	50 mg every 12 hr	100%	100%	100%
Topiramate	0.6–0.8	0.7–0.97	200 mg every 12 hr	100%	50%	25%
Trimethoprim	1–2.2	0.4–0.7	100–200 mg every 12 hr	Every 12 hr	Every 18 hr	Every 24 hr
Venlafaxine	6–7	0.05	75–375 mg every 24 hr	75%	50%	50%
Vigabatrin	0.8	0.7	1–2 g every 12 hr	Every 24 hr	Every 48 hr	Every 2–3d

^aThe doses provided are approximations due to overlap in CrCl ranges for each drug. See the FDA approved product label for updates and specific dose recommendations for drugs listed in this table.

^bContraindicated in patients with an eGFR below 30 mL/min/1.73 m². Starting metformin in patients with an eGFR between 30 and 45 mL/min/1.73 m² is not recommended. In patients taking metformin whose eGFR later falls below 45 mL/min/1.73 m², assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/min/1.73 m².

^cMHD, the monohydroxy derivative, is the active metabolite 10,11-dihydro-10-hydroxy-carbazepine (monohydroxy derivative, MHD).

fe = fraction excreted unchanged in the urine, GFR = glomerular filtration rate (the range following GFR indicates the use of the dose that corresponds to that range of GFR in patients not on dialysis), MU = million units, PB = plasma protein binding, V = volume of distribution.

The doses provided are approximations due to overlap in CrCl ranges for each drug. See the FDA approved product label for updates and specific dose recommendations.

HEMODIALYSIS AND CONTINUOUS RENAL REPLACEMENT THERAPY

HD is the predominant modality of renal replacement therapy for over 500,000 individuals who reside in the United States.¹ The medical care environment of free-standing community-centered dialysis units often places them outside of traditional healthcare institutions and, because only a small number of pharmacists practice in this setting, pharmacotherapeutic patient care management is often dependent on the nursing staff. The medication burden of typical HD-dependent patients is extensive: they often are prescribed 12 or more medications and also consume multiple over-the-counter drugs and dietary supplements.⁴⁵ Therefore, it is essential for community pharmacists to recognize the influence of HD on the pharmacokinetics and dynamics of the medications that these patients are receiving. The establishment of a consultant relationship with dialysis centers is one avenue for a pharmacist to participate in the care of these vulnerable patients, just as many pharmacists do for those who reside in skilled nursing facilities.⁵⁰ Finally, because the average age of HD patients is over 65 and they have a significant medication burden, they are prime candidates for the receipt of comprehensive medication reviews as part of the Medicare Part D Medication Therapy Management Program.

This section of the chapter serves as a primer on the impact of renal replacement therapies such as HD and CRRTs on acute and chronic drug therapy regimens and provides clinically useful dosage recommendations for many of the most commonly used medications for this patient population.

Principles of hemodialysis

The removal of a drug by dialysis is dependent on several factors, including the physiochemical and pharmacokinetic characteristics of the drug, the patient’s residual renal function, volume status and acuity of their illness, a myriad of other factors mentioned in the preceding section, and finally the dialysis prescription, which consists of the selection of the dialyzer, the blood and dialysate flow rates, the extent of fluid removal, and the frequency and duration of the procedure.⁵¹⁻⁵³ Drugs that are highly protein bound have low dialysis clearances because α_1 -acid glycoprotein and albumin have molecular weights in excess of 20,000 Daltons (D) and, thus, do not cross the dialysis membrane. Drugs that have a V greater than 2 L/kg are also poorly removed by HD. **Table 3-4** outlines the key factors.

TABLE 3-4. FACTORS AFFECTING THE HEMODIALYZABILITY OF A DRUG

		Impact on Dialyzability
Physicochemical and pharmacokinetic drug properties	Molecular weight	Increases
	< 10,000 Daltons	Increases
	High water solubility	Decreases
	High lipid solubility	Decreases
	Increased ionization—anionic	Decreases
	Large volume of distribution	Decreases
	High protein binding	Decreases
	Lower red blood cell partition	
Mechanical properties of the renal replacement therapy	Larger surface area of dialyzer	Increases
	Higher porosity dialysis membrane	Increases
	Higher dialysate flow rates	Increases
	Higher blood flow rate	Increases

The degree of drug removal by the HD procedure, be it acute for the management of AKI or the typical three-times-a-week regimen for the management of stage 5 CKD, can be dramatically affected by the prescribed dialysis regimen.^{51,53-55} The intensity of the HD prescription for patients who have stage 5 CKD has increased dramatically in the last decade, in part because of increasing blood and dialysate flow rates and the use of new high flux, large surface area, dialysis filters. Dialyzers composed of synthetic materials (e.g., polysulfone, polymethylmethacrylate, or polyacrylonitrile) readily remove drugs with molecular weights between 1,000 and 5,000 D, which in the past were likely to be considered non-dialyzable.^{53,55} Thus, high-molecular-weight drugs such as vancomycin are now extensively cleared by HD. In addition, significant increases in HD clearance of 50%–100% have been noted for many drugs, especially antibacterial agents that have a molecular weight of less than 1,000 D.⁵³

Dosage regimen adjustment strategies for patients receiving hemodialysis

Prospective individualization of drug dosage regimens is recommended for narrow therapeutic range drugs, such as the aminoglycosides, vancomycin, and the multiple others identified in this chapter. Several factors contribute to the complexity of accomplishing this in the CKD patient who is receiving chronic HD. Of considerable importance is the long turnaround time associated with measurement and reporting of serum concentrations in the ambulatory care setting and the delay in implementing a new dosage. Thus, in most ambulatory HD care situations, patients will initially benefit from the

recognition that a drug dosage regimen should be adjusted and the implementation of a best practical dosage regimen based on data derived from prior clinical investigations. The data in the second column of Table 3-5 presents recommendations for dialysis-dependent CKD patients with a residual CrCl <10 mL/min who are receiving intermittent HD on a three times per week schedule. This is the rationale for the every 48–72 hr dosage intervals for many agents included in **Table 3-5**, because drug administration is almost always fixed to be during the last hour of or after the end of the dialysis procedure. These dosage regimens should be used with caution since there is tremendous variability in the clearance efficiency of the over 100 dialysis filters currently available.^{58,59} Dosage recommendations for HD patients derived prior to 1995 likely provide an underestimate of patient needs because of the enhanced clearance with newer, more efficient, dialyzers and more aggressive dialysis prescriptions.

For medications that are commonly individualized on the basis of serum concentration guidance, the primary dosage regimen design issues are to avoid administration in the hours immediately before dialysis to minimize excessive removal of standard doses of the medication and the use of simple consistent administration schedules that minimize the need for variable drug doses being administered on non-dialysis as well as dialysis days. For some drugs, higher doses have been proposed and evaluated to facilitate delivery during dialysis that compensate for the enhanced removal resulting from administration during dialysis.^{59,60} Although this approach may increase medication cost, it may enhance patient compliance and improve the efficiency of the dialysis center. The primary objective for most medications is to design a regimen for administration on dialysis days such that the dose given at the end of dialysis is sufficient to achieve the desired maximum drug concentration. In this setting, the dose to be administered after dialysis (D_{postHD}) can be calculated as:

$$D_{\text{postHD}} = V \times (C_{\text{max}} - C_{\text{postHD}}) \quad (\text{Eq. 10})$$

$$C_{\text{postHD}} = C_{\text{preHD}} \times (e^{-kt} + e^{-k_{\text{HD}}t}) \quad (\text{Eq. 11})$$

where V is the patient's estimated volume of distribution for the drug of interest, e^{-kt} is the fraction of drug concentration (C_{preHD}) remaining at the end of the dialysis procedure as a result of the patient's residual total body clearance ($k_{\text{pt}} = \text{CL}_{\text{pt}} \div V$), and $e^{-k_{\text{HD}}t}$ is the fraction of drug concentration (C_{preHD}) remaining as a result of elimination by the dialyzer ($k_{\text{HD}} = \text{CL}_{\text{HD}} \div V$). The duration of the dialysis procedure in hours is expressed as t . Values for CL_{pt} can be derived from the drug clearance to renal function relationships in the literature or estimated from the information in Table 3-3, while CL_{HD} values for many dialyzers and dialysis procedures will need to be acquired from reliable literature sources.⁵¹⁻⁵³

Alternatively CL_{HD} can be measured for individual patients if a series of serum concentrations are collected using the following approach³⁶:

$$\text{CL}_{\text{HD}} = \left(\frac{C_{\text{art}} - C_{\text{ven}}}{C_{\text{art}}} \right) \times (Q_b (1 - \text{Hct})) \quad (\text{Eq. 12})$$

Where C_{art} is the concentration of the drug in the plasma entering the dialyzer, C_{ven} is the concentration of the drug in the plasma leaving the dialyzer, Q_b is the blood flow through the dialyzer, and Hct is the patient's hematocrit. This information can be used with the measured CL_{pt} using the equation to estimate k_{HD} described in the preceding paragraph to calculate the post HD dose (Eq. 10).

Dosage individualization strategies for patients receiving continuous renal replacement therapies

In contrast to intermittent HD, CRRTs that were developed over the past two decades have proven to be a viable management approach for hemodynamically unstable patients with or without AKI.¹¹ Several variants have been developed, and there are currently two primary techniques employed in most clinical settings Drug removal by continuous venovenous hemofiltration (CVVH) occurs by convection/ultrafiltration, whereas continuous venovenous hemodiafiltration (CVVHDF), which is more efficient, uses convection/ultrafiltration and diffusion as the two predominant means for drug removal.

Optimization of drug therapy for patients with AKI is often quite challenging. Interpretation of the limited literature available on drug removal by CRRT in critically ill patients is complicated by the large variation between hemofilters, the CRRT prescription, and the marked degree of interpatient variability in residual renal function and fluid volume status.^{61,62} This is further challenged by the lack of consistent reporting of CRRT studies in new drug applications submitted to the FDA.⁶³ The essential elements that characterize each of the predominant CRRT variants are well described elsewhere.^{64,65}

Although dosing guidelines based on data derived from *in vitro* experiments or studies in patients with stable stage 5 CKD may not reflect the clearance and V in critically ill AKI patients, this may be the only information available for many drugs. Table 3-5 presents drug dosage recommendations for AKI patients with a CrCl <10 mL/min who are receiving CVVH or CVVHDF compiled from many sources.^{56,57,61,62,65} These recommendations differ from FDA-approved product labeling in those situations where more current clinical information was available in the literature.

TABLE 3-5. DOSAGE RECOMMENDATIONS FOR PATIENTS RECEIVING HEMODIALYSIS, CVVH, OR CVVHDF^a

Drug	Dosage Recommendation ^a		
	HD	CVVH	CVVHDF
Acyclovir	2.5–5 mg/kg every 24 hr	5–10 mg/kg every 24 hr	5–10 mg/kg every 12–24 hr
Amantadine	200 mg every 7 days	100 mg every 24–48 hr	100 mg every 24–48 hr
Amphotericin B	0.25–1.5 mg/kg every 24 hr	0.25–1.5 mg/kg every 24 hr	0.25–1.5 mg/kg every 24 hr
Amoxicillin	250–500 every 24 hr	ND	ND
Amikacin	IND or 5–7.5 mg/kg every 48–72 hr	IND or 7.5 mg/kg every 24–48 hr	IND or 7.5 mg/kg every 24–48 hr
Ampicillin	1 g every 12 hr	1–2 g every 8–12 hr	1–2 g every 6–8 hr
Ampicillin/sulbactam	1.5–3 g every 12–24 hr	1.5–3 g every 8–12 hr	1.5–3 g every 6–8 hr
Atenolol	25–50 mg every 48–72 hr	25–50 mg every 24 hr	25–50 mg every 24 hr
Aztreonam	0.5 g every 12 hr	1–2 g every 12 hr	2 g every 12 hr
Benazepril	2.5–10 mg every 12–24 hr	5–20 mg every 12–24 hr	5–20 mg every 12–24 hr
Bisoprolol	2.5–10 mg every 24 hr	5–15 mg every 24 hr	5–15 mg every 24 hr
Cefazolin	15–20 mg/kg every 48–72 hr	1–2 g every 12 hr	2 g every 12 hr
Cefepime	1–2 g every 48–72 hr	1–2 g every 12 hr	2 g every 12 hr
Ceftazidime	1 g every 24 hr	1–2 g every 12 hr	2 g every 12 hr
Ceftaroline	200 mg every 12 hr	300 mg every 12 hr	300 mg every 12 hr
Ceftriaxone	1–2 g every 24 hr	1–2 g every 12–24 hr	1–2 g every 12–24 hr
Cephalexin	250–500 every 24 hr	ND	ND
Cidofovir	AVOID	2 mg/kg every 7 days	2 mg/kg every 7 days
Cimetidine	300 every 8–12 hr	200 every 12 hr	200 every 12 hr
Ciprofloxacin	0.2–0.4 g every 24 hr	0.2–0.4 g every 12–24 hr	0.4 g every 12 hr
Clarithromycin	Dose after HD	250–500 mg every 12 hr	250–500 mg every 12 hr
Colistin	1.5 mg/kg every 24–48 hr	2.5 mg/kg every 48 hr	2.5 mg/kg every 48 hr
Daptomycin	4–6 mg/kg every 48–72 hr	4 mg/kg every 24 hr	4 mg/kg every 24 hr
Didanosine	100 mg every 24 hr	200 mg every 12 hr	200 mg every 12 hr
Enalapril	5–10 mg every 24 hr	5–10 mg every 12–24 hr	5–10 mg every 12–24 hr
Famciclovir	250 mg after HD	500 mg every 12 hr	500 mg every 12 hr
Famotidine	5 mg every 24 hr	5–10 mg every 24 hr	5–10 mg every 24 hr
Fexofenadine	30 mg every 24 hr	60 mg every 24 hr	60 mg every 24 hr
Fluconazole	0.2–0.4 g every 48–72 hr	0.2–0.4 g every 24 hr	0.8 g every 24 hr

TABLE 3-5. CONTINUED

Drug	Dosage Recommendation		
	HD	CVVH	CVVHDF
Foscarnet	45–60 mg/kg every 48–72 hr after HD	60–80 mg/kg every 48 hr	60–80 mg/kg every 48 hr
Gabapentin	200–300 mg every 48–72 hr	300 mg every 12–24 hr	300 mg every 12–24 hr
Ganciclovir	0.625 (maintenance) to 1.25 (induction) mg/kg every 48–72 hr	1.25 mg/kg every 24 hr	2.5 mg/kg every 24 hr
Gentamicin	IND or 1.5–2 mg/kg every 48–72 hr	IND or 1.5–2 mg/kg every 24–48 hr	IND or 1.5–2 mg/kg every 24–48 hr
Glipizide	1.25–7.5 mg every 24 hr	1.25–7.5 mg every 24 hr	1.25–7.5 mg every 24 hr
Imipenem/ cilastatin	0.25–0.5 g every 12 hr	0.5 g every 8 hr	0.5 g every 6 hr
Lamivudine	1 mg/kg every 24 hr	4 mg/kg every 24 hr	4 mg/kg every 24 hr
Levetiracetam	500–750 every 24 hr	250–750 every 12 hr	250–750 every 12 hr
Levofloxacin	250–500 every 48–72 hr	500 every 24 hr	500 every 24 hr
Linezolid	600 mg every 12 hr	600 mg every 12 hr	600 mg every 12 hr
Meropenem	500 mg every 24 hr	0.5–1 g every 12 hr	0.5–1 g every 8–12 hr
Metformin	AVOID	AVOID	AVOID
Metoclopramide	5 mg every 6 hr	5–10 mg every 6 hr	5–10 mg every 6 hr
Metronidazole	0.5 g every 8–12 hr	0.5 g every 6–12 hr	0.5 g every 6–12 hr
Moxifloxacin	0.4 g every 24 hr	0.4 g every 24 hr	0.4 g every 24 hr
Ofloxacin	100–200 mg after HD	300 mg every 24 hr	300 mg every 24 hr
Piperacillin	2 g every 8 h + 1 g supplemental dose after HD	ND	ND
Piperacillin/ tazobactam	2.25 g every 8–12 hr	2.25–3.75 g every 6–8 hr	3.375 g every 6 hr
Quinapril	2.5 mg every 12–24 hr	2.5–5 mg every 12–24 hr	2.5–5 mg every 12–24 hr
Ramipril	1.25–2.5 mg every 24 hr	2.5–5 mg every 24 hr	2.5–5 mg every 24 hr
Ranitidine	75–150 mg every 24 hr	150 mg every 12–24 hr	150 mg every 12–24 hr
Stavudine	20 mg every 24 hr	40 mg every 12 hr	40 mg every 12 hr
Tetracycline	250–500 every 24 hr	ND	ND
Ticarcillin/ clavulanate	2 g every 12 hr	2 g every 6–8 hr	3.1 g every 6 hr
Tobramycin	IND or 1.5–2 mg/kg every 48–72 hr	IND or 1.5–2 mg/kg every 24–48 hr	IND or 1.5–2 mg/kg every 24–48 hr
Topiramate	50 mg every 12 hr	100 mg every 12 hr	100 mg every 12 hr
Trimethoprim/ sulfamethoxazole	5–15 mg/kg (TMP) every 48–72 hr	2.5–7.5 mg/kg (TMP) every 12 hr	2.5–7.5 mg/kg (TMP) every 12 hr
Vancomycin	IND or 7.5 mg/kg every 48–72 hr	IND or 10–15 mg/kg every 24–48 hr	IND or 7.5–10 mg/kg every 12 hr
Vigabatrin	1–2 g every 48–72 hr	1–2 g every 48 hr	1–2 g every 48 hr
Voriconazole ^a	4 mg/kg every 12 hr	4 mg/kg every 12 hr	4 mg/kg every 12 hr

^aThe amount of drug dialyzed can be highly dependent on conditions such as type of filter, blood filtration and ultrafiltration rates. Therefore, the adjustments in this table are estimates based on best available data. Refer to the FDA approved package insert for specific dose recommendations.

^bIntravenous voriconazole should not be used in CKD (non-dialysis) due to accumulation of the vehicle (sulfobutylether-B-cyclodextrin, SBECD).

IND = individualize because desired concentrations and or pharmacodynamic endpoints may vary markedly, ND = no data available.

When there is a need to tightly control patient exposure to a given drug, either for the enhancement of therapeutic response or the minimization of risk of adverse events, the dosage regimen for patients receiving CRRT can be individually ascertained by adding the estimated or measured drug clearance by CRRT to the patient's residual drug clearance. Once the total clearance is known, the dosage regimen can be projected using the same principles as those described for patients with stable CKD. For example, the dosage regimen for cefepime of a patient receiving CVVHDF will be predicated on the sum of the patient's residual clearance and the clearance associated with CVVHDF, which can be approximated as follows. If a patient with a CrCl of 10 mL/min is receiving CVVHDF with an AN69 filter at blood, ultrafiltrate, and dialysate flow rates of 200, 12, and 33 mL/min, respectively, and is to receive cefepime while on CVVHDF, the patient's residual cefepime clearance (CL_{RES}) can be estimated using the following regression equation relating CrCl and cefepime clearance drawn from the literature.³⁶ The cefepime clearance of a patient with normal renal function (CrCl of 120 mL/min) would be calculated as:

$$CL_{norm} \text{ (mL/min)} = [0.96 \times (\text{CrCl})] + 10.9$$

$$CL_{norm} = [0.96 \times 120] + 10.9$$

$$CL_{norm} = 126.1 \text{ mL/min}$$

This patient's cefepime clearance as the result of his residual CrCl value can be calculated similarly:

$$CL_{RES} \text{ (mL/min)} = [0.96 \times (10)] + 10.9$$

$$CL_{RES} = [0.96 \times (10)] + 10.9$$

$$CL_{RES} = 20.5 \text{ mL/min}$$

The total clearance while on CVVHDF would be the sum of the patient's residual clearance and the cefepime clearance associated with CVVHDF, which can be approximated as follows:

$$CL_{CVVHDF} = [(UFR + DFR) \times f_u] \quad (\text{Eq. 13})$$

(where UFR = ultrafiltrate formation rate, DFR = dialysate flow rate, and f_u = fraction unbound)

$$CL_{CVVHDF} = [(12 + 33) \times 0.97] = 43.7 \text{ mL/min}$$

$$CL_T = CL_{RES} + CL_{CVVHDF} \quad (\text{Eq. 14})$$

$$CL_T = 20.5 \text{ mL/min} + 43.7 \text{ mL/min}$$

$$CL_T = 64.2 \text{ mL/min}$$

The dosage adjustment factor would then be:

$$Q = CL_T / CL_{norm}$$

$$Q = 64.2 \div 126$$

$$Q = 0.51$$

For this patient's situation, the normal regimen of cefepime would be 2,000 mg (D_{norm}) every 12 hr (τ_{norm}). If one wanted to maintain D_{norm} at 2,000 mg, the extended dosing interval, τ_R , would be calculated as:

$$t_R = t_{norm} / Q$$

$$t_R = 12 \text{ hr} / 0.51$$

$$t_R \approx 24 \text{ hr}$$

It is important to monitor these patients on a continual basis as dose adjustments will be required if renal function significantly improves or worsens, if there are prolonged interruptions in the delivery of the CRRT therapy, or if CRRT is discontinued.

CONCLUSION

Patients with AKI or CKD and those receiving intermittent HD or CRRT present many challenges to the clinician as they are at increased risk for adverse events due to accumulation of drugs and/or their active or toxic metabolites. Important therapeutic decisions can be made based on awareness of each patient's functional renal capacity and of the effects of renal disease on drug metabolism, metabolite formation, and renal excretion. Clinicians can play a critical role in providing rational drug therapy to these patients making dose adjustments based on renal function using either traditional TDM or empiric methods, ensuring avoidance of drugs with toxic metabolites, determining the optimal dose to accommodate immediate post dialysis dosing, and taking responsibility for patient outcomes.

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MEDICATION DOSING IN OVERWEIGHT AND OBESE PATIENTS

Brian L. Erstad

The increasing prevalence of obesity, and particularly extreme obesity, is a major public health issue that presents a number of challenges for health professionals caring for these patients. Among these is the difficulty of designing medication dosing regimens that take into account the body composition alterations and disease states associated with excess weight. If these factors are not considered, the patient may incur toxicity when medications are dosed based on mg/kg of actual body weight (ABW) when ABW is not the most appropriate size descriptor to use, or therapeutic failure when some form of adjusted body weight in mg/kg or standard dosing in mg is used. The purpose of this chapter is to describe important considerations for designing dosing regimens for overweight and obese patients. This chapter is not intended to provide dosing recommendations for specific drugs discussed in other chapters in this booklet. Much of the discussion will pertain to patients with more extreme forms of obesity because they are the most difficult to dose given the paucity of published literature.

The terms *overweight* and *obesity* are most commonly defined by body mass index (BMI) calculations. Adult subjects with a value of 25 to 29.9 are considered overweight, while subjects with a value of 30 and above are considered obese.¹ For purposes of this chapter, unless specified otherwise, adult subjects with BMI values above 40 are termed *extremely obese*. BMI calculations can also be used for screening children and teens for weight problems, but the values require adjustment based on growth charts. The calculations and references for other size descriptor terms used in this chapter are listed in **Table 4-1**.

OBTAINING AN ACCURATE WEIGHT

Research has shown that ABW recordings documented in nursing records in both intensive care unit (ICU) and non-ICU settings are frequently inaccurate. Therefore, clinicians should try to ensure that ABW is measured using an accurate and reliable device when feasible and that the measurement is appropriately documented in the patient's medical records. This means that weighing devices must be periodically checked and calibrated to ensure appropriate function and accuracy. Measurement of weight may not be possible in some patients due to the type of injury (e.g., head injury), which may preclude an immediate determination. Although healthcare personnel's estimates of patient weight may be used in such situations, they are often inaccurate. Self-reporting of weight by adult subjects has been shown to be reasonably accurate in some investigations but may not be possible depending on the type of injury or disease state. When multiple weights are documented in medical records, the clinician should look for clues to inaccurate estimates or measurements as might be seen when values vary greatly from day to day in the absence of substantial fluid gains or losses. In light of all of these considerations, the process for obtaining measured or estimated ABW and other size descriptor data should be standardized as much as possible.

BODY COMPOSITION CHANGES ASSOCIATED WITH OBESITY

When accurate recordings of height and weight are available, the subject's body composition is another factor that must be considered when dosing medications. Unfortunately, there is no agreement on a



TABLE 4-1. BODY SIZE DESCRIPTOR EQUATIONS^a

		Units	Intended Age (Sex)	Ref.
<i>General Body Size Descriptors</i>				
BMI =	(ABW in kg) / (height in m) ²	kg/m ²	Adult	4
	(ABW in kg) / (height in m) ² adjust by growth charts for age and sex	percentile	Child	5
BSA =	[(ABW in kg) ^{0.425} × (height in cm) ^{0.725}] × 0.007184	m ²	Adult	6
	SQRT [(height in cm) × (ABW in kg) / 3600]	m ²	Child/adult	7
	[(ABW in kg) ^{0.5378} × (height in cm) ^{0.3964}] × 0.024265	m ²	Infant/child/adult	8
<i>Lean Body Mass Descriptors</i>				
IBW ^b =	50 kg + 2.3 kg [(height in inches) – 60]	kg	Adult (male)	9
	45.5 kg + 2.3 kg [(height in inches) – 60]	kg	Adult (female)	9
	2.05 e ^{0.02} × (height in cm)	kg	Child < 5 feet	10
	39 kg + 2.27 kg [(height in inches) – 60]	kg	Child ≥ 5 feet (male)	10
	42.2 kg + 2.27 kg [(height in inches) – 60]	kg	Child ≥ 5 feet (female)	10
LBW ^c =	[1.1 × (ABW in kg)] – {128 × [(ABW in kg) / (height in cm)] ² }	kg	Adult (male)	11
	[1.07 × (ABW in kg)] – {148 × [(ABW in kg) / (height in cm)] ² }	kg	Adult (female)	11
FFM =	[0.285 × (ABW in kg)] + [12.1 × (height in m) ²] ^d	kg	Adult (male)	12
	[0.287 × (ABW in kg)] + [9.74 × (height in m) ²] ^d	kg	Adult (female)	12
	[9,270 × (ABW in kg)] / [6,680 + (216 × BMI)] ^e	kg	Adult (male)	13
	[9,270 × (ABW in kg)] / [8,780 + (244 × BMI)] ^e	kg	Adult (female)	13
<i>Adjusted Body Size Descriptors</i>				
ABW =	(IBW in kg) + {(ABW in kg) – (IBW in kg)} × 0.2 to 0.6 ^f	kg	Adult	14–16 ^g
Predicted normal weight =	[1.57 × (ABW in kg)] – [0.0183 × BMI × (ABW in kg)] – 10.5	kg	Adult (male)	17
	[1.75 × (ABW in kg)] – [0.0242 × BMI × (ABW in kg)] – 12.6	kg	Adult (female)	17

BSA = body surface area, FFM = fat-free mass, IBW = ideal body weight, LBW = lean body weight.
^aThere are a number of variations of these formulae, but only the most commonly cited and recently introduced versions are listed. This table is for illustration purposes only. Some of the equations are inappropriate or have not been validated for use in more extremely obese patients so the references need to be pulled and reviewed prior to use.
^bAlthough IBW was originally used as a target weight for life insurance tables, it has since been used as a surrogate for lean body mass; but, it should not be used as a surrogate in patients with more severe forms of obesity since it does not take into account the increasing lean weight associated with increasing fat weight.
^cThese equations for LBW are inconsistent in patients with more severe forms of obesity, so should not be used in current practice for estimating LBM.
^dThese equations for FFM were derived in the past using patients with less severe forms of obesity, so they should not be used in current practice for estimating LBM.
^eThese are the preferred equations for calculating LBM.
^fThese are some of the first citations of this formula with a correction factor (i.e., 0.3–0.6), but a number of variations of the correction factor were subsequently studied, so a range is listed in the table.
^gVarious adjustments for various medications have been reported where the adjustment adds 20% to 60% of the difference between ABW and IBW to the IBW for medications not as well distributed into adipose tissue.

reference standard for *in vivo* assessments of fat mass in the clinical setting, and the most accurate approach to determine lipid, water, protein, and mineral composition in the research setting, cadaver analysis, has obvious limitations for widespread use.² So, other indirect approaches for body composition assessment have been developed (e.g., computed tomography/magnetic resonance imaging scanning, neutron activation analysis, underwater weighing, dual energy x-ray plethysmography, bioelectrical impedance), particularly for use in the research setting. The most basic body composition model has two compartments, fat and fat-free mass; but more complex models (atomic, molecular, cellular, functional, and whole body) have been studied.³ Although the simpler models are easier to study and require fewer assumptions, the multi-compartmental model better reflects the human body's complexity and has the potential to yield a better understanding of compositional changes associated with obesity and medication disposition in obese subjects. Of the available technologies for the delineation of fat, lean and water mass in the clinical setting, bioelectrical impedance has been most studied because it is a noninvasive assessment tool that can be performed at the bedside. The importance of body composition is illustrated by a hypothetical example using three patients of the same age, sex, height, and weight. One patient weighing 100 kg has 20 L of excess body fluid from over-resuscitation. A second patient weighing 100 kg has 20 kg of excess fat weight. The third patient weighing 100 kg is a body builder with a very low percentage of body fat. If dosed simply by body weight, it is easy to see how medications with varying physicochemical characteristics could result in substantial pharmacokinetic and pharmacodynamic differences in these three patients.

SIZE DESCRIPTORS

The limitations of using ABW for dosing medications with different physicochemical characteristics in patients with varying body compositions have fostered research in the area of size descriptors.⁴⁻¹⁷ A listing of size descriptors and the equations used to calculate them is contained in Table 4-1. Equations for allometric scaling, which deals with relationships between body function and body size, are not included because the body weight used to develop allometric equations is presumed to be of normal body composition.¹⁸ Note that only a few of the equations in Table 4-1 take into account all the common factors (age, sex, height, and weight) that are likely to be needed in a size descriptor equation used to adjust the dose of a medication for obesity, and none take into account potential factors such as race or genetics that might further improve dose individualization.¹⁹ Of importance, the equations for adults should not be used for infants or children who may have substantially different body composition and medication disposition compared to adults.²⁰

BMI has primarily been used to define subjects at risk from the complications of excess body weight and has not been found to be useful as a size predictor for adjusting medications in obese patients. BSA is commonly used to adjust doses in infants and young children, as well as patients receiving chemotherapy, but BSA has not been validated for dosing medications in obese patients. Of the equations used to estimate lean body mass, the IBW calculation by Devine (and subsequent minor modifications) has been most frequently used in pharmacokinetic investigations and for adjusting loading doses of medications with small volumes of distribution (e.g., < 15 L in an adult) or with limited fat distribution (e.g., digoxin) in the clinical setting. However, IBW calculations do not take into account the increases in lean body mass that occur with increases in fat mass in patients who are overweight or obese, so they likely will underestimate weight-based medication doses in such patients. More recent validated equations with better approximations of fat-free mass in men and women have been evaluated in modeling calculations in patients with obesity.¹³ These newer equations are intended to account for the portion of lean weight that is associated with increases in adipose tissue weight by incorporating weight in addition to the sex and height parameters used in more traditional IBW equations. Further, these newer fat-free mass equations for men and women do not have the inconsistencies noted with older versions of LBW equations when used in patients with more extreme forms of obesity as illustrated by the lean body equation in **Table 4-2**. Strictly speaking, FFM and LBW are not equivalent, because LBW

TABLE 4-2. EXAMPLES OF OUTPUT FROM SIZE DESCRIPTOR EQUATIONS FOR PATIENTS OF DIFFERENT WEIGHTS BUT SIMILAR HEIGHT, AGE, SEX, RACE, AND CO-MORBIDITIES^a

Equation	Extremely Obese	Moderately Obese	Mildly Obese	Overweight	Normal	Ref.
ABW =	160 kg	120 kg	100 kg	80 kg	73 kg	–
BMI =	50.61 kg/m ²	37.96 kg/m ²	31.63 kg/m ²	25.31 kg/m ²	23.1 kg/m ²	4
BSA =	2.66 m ²	2.35 m ²	2.18 m ²	1.99 m ²	1.9 m ²	6
BSA =	2.81 m ²	2.43 m ²	2.22 m ²	1.99 m ²	1.9 m ²	7
BSA =	2.9 m ²	2.48 m ²	2.25 m ²	2 m ²	1.9 m ²	8
IBW =	73 kg	73 kg	73 kg	73 kg	73 kg	9
LBW =	72.35 kg	73.69 kg	69.51 kg	62.09 kg	58.72 kg	11
FFM =	83.85 kg	72.45 kg	66.75 kg	61.05 kg	59.06 kg	12
FFM =	84.22 kg	74.76 kg	68.61 kg	61.05 kg	57.99 kg	13
Adj (20%) =	90.4 kg	82.4 kg	78.4 kg	74.4 kg	73 kg	14–16
Adj (60%) =	125.2 kg	101.2 kg	89.2 kg	77.2 kg	73 kg	14–16
PNWT =	92.51 kg	94.54 kg	88.62 kg	78.05 kg	73.25 kg	17

Adj = adjusted body weight, PNWT = predicted normal weight.
^aEach patient is assumed to be a 70-inch (1.78 meter) tall male. This table is for illustration purposes only; some of the equations are inappropriate or have not been validated for use in more extremely obese patients, so the references need to be reviewed prior to use. Note that PNWT and LBW both begin to decrease above a certain weight (shown here between moderately and extremely obese).

takes into account fat in cell membranes, bone marrow, and central nervous system, but the difference as a percent of ABW is small (usually less than 3% to 5%).¹³ Therefore, from a practical standpoint, the terms can be considered interchangeable when used in the context of medication dosing in the clinical setting, so for the remainder of this chapter the term *lean body weight* (LBW) will be used to refer to FFM and LBW (with the caveat that the preferred equations for estimation are based on a more recent investigation).¹³ In addition to the predictive equations that have been developed for estimating LBM, more accurate estimations are possible with newer technologies (e.g., segmental multi-frequency bioelectrical impedance, dual energy x-ray absorptiometry), but such devices require the equipment and technical expertise to perform and interpret the measurements, in addition to being costly.

Adjusted body weight equations were originally developed in pharmacokinetic investigations of the aminoglycoside antibiotics in extremely obese patients (i.e., patients whose ABW is at least twice their IBW). The equations were subsequently evaluated in the pharmacokinetic dosing of beta-lactam antimicrobials, where it was found that, similar to aminoglycosides, they have distribution volumes based on weight (L/kg) that is best reflected by using an adjusted body size descriptor somewhere between IBW and ABW. There has been little attempt to prospectively evaluate adjusted weight equations for their predictive dosing potential in patients with varying degrees of obesity.

The anticoagulant heparin provides a useful example for illustrating how the choice of size descriptor complicates dosing in a patient with excess weight relative to height. Heparin is commonly dosed by weight-based regimens in hospital settings. Typical recommendations for the treatment of venous thromboembolism include a load of 80 units/kg followed by a continuous infusion of 18 units/kg/hr. This raises the question as to which weight should be used in overweight or obese patients. Table 4-2 illustrates the range of size descriptors available for an assumed 70-inch tall male of various weights even when factors such as age, sex, race and co-morbidities are presumed to be similar. Using data from this table and the heparin dosing guidelines above, a 70-inch tall male could receive an intravenous loading dose of heparin as low as 4,640 units using a fat-free mass weight of 58 kg for a normal-weight 73-kg patient, to a high of 12,800 units using ABW for an extremely obese 160-kg patient. The continuous

infusion dose for these same weights would range from a low value of 1,044 units/hr to a high value of 2,880 units/hr. When deciding which weight to use, the clinician must consider the thromboembolic consequences of under-dosing, such as pulmonary embolism, versus the potentially fatal hemorrhage that can occur with over-dosing.

There is no high level evidence to guide decisions on the most appropriate choice of weight for the extremely obese patient. The previous example of the difficulty of designing a dosing regimen for heparin is common to other medications. Therefore, approaches used to dosing the more severely obese patient require a careful risk/benefit assessment based on data often extrapolated from studies of more normal-weight subjects.

PHARMACOKINETIC CONSIDERATIONS

Obesity is now known to be a chronic inflammatory state that has the potential to affect most major organ systems in the body.²¹ Therefore, you must consider not only the isolated effects of increased body size (along with other traditional covariates such as age and sex) on the body's disposition of medications, but also the effects of any organ dysfunction related to long-term obesity. With respect to pharmacokinetics, potential alterations in the distribution and clearance of administered intravenous medications have been most studied in patients with obesity. Less information is available on the pharmacokinetics of orally administered medications and those injected by intramuscular or subcutaneous routes.

ORAL ABSORPTION

Oral absorption of medications in obese patients does not appear to be substantially affected by obesity based on the results of the limited studies to date most of which were conducted in obese patients undergoing surgical resection procedures of the gastrointestinal tract such as Roux-en-Y bypass. This presumes that the amount of resected intestine is not so large as to preclude medication absorption due to a lack of absorptive surface area (i.e., short bowel syndrome). Short bowel syndrome is most likely to occur when <2–3 m of small intestine remain after resection.

Subcutaneous and intramuscular absorption

Skin thickness is unlikely to be a factor influencing medication absorption from subcutaneous or intramuscular injection sites since variation in epidermis-dermis thickness is relatively unaffected by obesity. Although skin thickness is increased in obese compared to non-obese patients, the difference is small as indicated by relatively narrow 95% confidence intervals for the thickness at any particular site relative to the typical needle length used for a subcutaneous or intramuscular injection.²² Subcutaneous adipose layer thickness is much greater and more variable between adult subjects with obesity as exhibited by one study that found a 4-mm change in subcutaneous thickness for every 10-unit change in BMI.²³ This variation in subcutaneous thickness has implications for subcutaneous and intramuscular injections, since a medication intended for subcutaneous injection may result in unintended intramuscular injection and vice versa. The latter problem has been most studied with insulin where it has been shown that inadvertent intramuscular injection results in increased variability in absorption and possible impaired glucose control in patients with diabetes.²⁴ Another factor that may influence insulin absorption from subcutaneous sites and associated glucose control in obese subjects is related to reductions in subcutaneous tissue blood flow that have been found in obese subjects with type 2 diabetes.²⁵

Volume of distribution

The primary factors affecting the distribution of a medication into fat and fat-free mass are the relative size of the compartments and binding competition between fat, blood, and lean tissues. The binding

competition is a function of the medication's lipophilicity, which determines binding to adipose tissue, and its chemical structure (e.g., polarity and ionization in body fluid pH), which determines binding to lean tissues. Blood flow affects the rate of distribution.²⁶ Importantly, blood volume and flow do not increase in proportion to increasing body weight in obese patients,²⁷ so a 100% increase in body weight due to obesity will result in less than a 100% increase in blood volume or flow. Similarly, but to even a greater extent, cerebrospinal fluid volume and epidural fat disposition are not increased in obese subjects.^{28,29} This is substantiated by the similar doses of intrathecal bupivacaine needed in morbidly obese women (compared to more normal weight) undergoing cesarean delivery.³⁰

The degree of medication lipophilicity is often expressed by the octanol:water partition coefficient or more commonly the logarithm of the partition coefficient ($\log P$). However, a high $\log P$ (e.g., > 2) is not synonymous with extensive adipose tissue disposition as exemplified by a number of basic lipophilic medications such as desipramine ($\log P$ of approximately 4) that have extensive lean rather than adipose tissue binding. From a practical standpoint, this means that the loading doses of medications that are highly lipophilic are not necessarily dosed on ABW. Digoxin is a case in point. Digoxin has a $\log P$ of approximately 2 and a large volume of distribution (V) (6–7 L/kg in patients with normal renal function); however, studies in obese subjects have found that digoxin should be dosed on some form of LBM (not ABW) due to minimal distribution into adipose tissue and no change in clearance compared to normal-weight subjects.³¹ This illustrates the complex nature of the factors affecting distribution.

Although information concerning tissue binding of medications usually must be inferred, changes in plasma protein binding can be measured and have been investigated in obese patients. Unfortunately, few generalizations are possible other than the concentrations of albumin and alpha-1-acid glycoprotein do not appear to be substantially altered in obesity. Although not well studied, binding and displacement changes associated with elevations in free fatty acid and lipoprotein concentrations are possible in obese subjects.³²

Equations have been developed for predicting the volumes of distribution of medications in patients with obesity.³³ These equations take into account the various physicochemical characteristics of both the medication and body tissues. However, the equations are limited by assumptions concerning lean and adipose tissue mass, tissue binding changes, and the inability to find characteristics such as partition coefficients for newer medications. Most importantly, the equations have not been tested prospectively in patients with varying degrees of obesity.

Renal clearance

Since its publication in 1976, the Cockcroft-Gault equation has become the most common method used to predict creatinine clearance (CrCl) for dosage adjustments of renally eliminated medications.³⁴ The choice of weight for use in this equation was controversial since its inception when the authors suggested the use of an IBW or lean weight in patients with excess adipose tissue (or fluid) even though such patients had not been studied in adequate numbers. Five years after publication of the Cockcroft-Gault equation the first study to investigate CrCl estimations in extremely obese subjects was published.³⁵ In addition to age, sex, and serum creatinine both IBW and ABW were evaluated. None of the methods of CrCl estimation was found to be an accurate predictor of measured clearance; furthermore, the use of IBW led to under-estimations and ABW to over-estimations of clearance. During the 5 to 10 years following the publication of the Cockcroft-Gault equation, more widespread availability of assays for aminoglycosides and vancomycin led to pharmacokinetic investigations of potential dosing regimens for extremely obese patients. Although the kidneys primarily eliminate aminoglycosides and vancomycin, results of the latter studies suggested a need for a different approach to dosing recommendations. For the aminoglycosides, V and clearance appeared to increase proportionately to each other, but not to the increase in weight of the extremely obese patients.¹⁴⁻¹⁶ This led to the recommendation for use of an adjusted body weight for dosing aminoglycosides to avoid the under-dosing that would likely occur with the use of an IBW and the over-dosing that would likely occur with the use of ABW. For vancomycin,

clearance, but not V , increased proportionately to ABW as evidenced by the shorter terminal half-life in the extremely obese compared to normal-weight patients.³⁶ The initial V (i.e., volume of the central compartment) was similar as expressed in liters in the extremely obese and normal-weight patients, which suggests that loading doses should not be based on ABW. The apparent proportionality between vancomycin clearance and ABW in patients with more severe forms of obesity is an unusual finding, particularly for medications with a high fraction of renal elimination. Pharmacokinetic studies involving most other antimicrobials for example, have had findings similar to those from the aminoglycoside studies (i.e., increased, but non-proportionate changes in V or clearance relative to ABW).

The inherent inaccuracies associated with CrCl determinations by the Cockcroft-Gault method in obese patients led to the development of predictive equations for male and female subjects based on estimated fat-free body mass. The so-called Salazar-Corcoran equations were developed to predict CrCl and medication clearance in obese male and female subjects.³⁷ These equations were based on the same weight-height formula (i.e., Quetelet's index) used to calculate body mass index. Salazar-Corcoran has been used for CrCl estimations in some important pharmacokinetic studies. For example, it was used to estimate CrCl in extremely obese patients who received vancomycin for severe infections.³⁸ Vancomycin clearance determined by pharmacokinetic parameters derived from measured vancomycin concentrations was found to correlate with ABW ($r = 0.948$, $p < 0.0001$) and was similar to the CrCl calculated by Salazar-Corcoran (197 mL/min vs. 209 mL/min, respectively). This study is important because it confirmed the results of the earlier vancomycin trial that demonstrated a proportional increase in vancomycin clearance relative to ABW in extremely obese patients. As in the earlier vancomycin study, V did not increase proportionately to ABW.

More recent investigations of CrCl by urine collections or glomerular filtration rate measurements using accurate techniques such as inulin clearance or technetium-99m-labelled diethylenetriamine penta-acetic acid (^{99m}Tc DTPA) radionuclide scanning have found that use of lean body weight in Cockcroft-Gault improves predictive accuracy in obese and normal-weight subjects.^{17,39,40} The LBW used in these studies was determined by accurate methods such as bioelectrical impedance or dual x-ray absorptiometry, rather than older IBW equations of unclear origin and limited validation. A study evaluating different size descriptors for estimating CrCl in extremely obese patients gives further support to the use of a lean weight.⁴¹ In this study, the CrCl estimations from eight equations (six variations of Cockcroft-Gault, Salazar-Corcoran, and the Modification of Diet in Renal Disease 4 [MDRD4]) were compared to measured CrCl determinations. The Cockcroft-Gault equations using fat-free weight (FFW) determined by bioelectrical impedance, or lean weight by a more recent equation were the least biased and provided the most accurate estimates of CrCl.

There is no consensus as to which equation should be used for estimating CrCl or which size descriptor should be used in any given equation. Some have argued for more recent versions of the MDRD equation since it is already being used in hospitals to estimate glomerular filtration rate and detect chronic kidney disease. However, the MDRD equations were developed to predict glomerular filtration rate and not CrCl that also takes into account secretion processes in the kidney; furthermore, the MDRD involves standardization based on body surface area, but dosing of medications in pre-approval investigations or in the clinical setting is usually not standardized in this manner. Others have argued for the use of Cockcroft-Gault with a specific type of size descriptor such as lean weight, or a combination of equations depending on the specific patient (e.g., Salazar-Corcoran or Cockcroft-Gault with an adjusted weight for obesity, Cockcroft-Gault with ABW for normal-weight patients). However, there is little prospective evaluation of either of these approaches in obese patients, particularly more severely obese patients. If anything the situation has become even more complicated with reporting of serum creatinine based on an IDMS-traceable standard, which results in results approximately 10% lower than previously used assays.

Until consensus develops, important concepts to apply in the clinical setting for CrCl estimations are practicality and consistency. When a high degree of accuracy of renal function is needed such as glomerular filtration rate determination in potential kidney donors, measurements using gold

standards such as inulin or diethylenetriamine pentaacetic acid should be performed rather than relying on estimations from equations.⁴² Currently, the U.S. Food and Drug Administration (FDA) in its guidance to industry states that Cockcroft-Gault may be used for CrCl estimation in studies although no particular weight is recommended. Therefore, Cockcroft-Gault using ABW is most commonly used for weight-based dosing in pre-approval studies that typically involve more normal-weight patients. Additionally, the Cockcroft-Gault equation is the most common equation used in the clinical setting. Therefore, a strong argument can be made for the continued use of Cockcroft-Gault for estimating CrCl to adjust doses of renally eliminated medications. As for a size descriptor, a good argument can be made for the use of ABW for more normal-weight patients (e.g., within 130% of IBW), because the estimation of CrCl by either lean weight or ABW is likely to be fairly similar and differences are likely to be small in comparison to sources of error such as weight estimation. For more obese patients, an adjusted or lean weight is more likely to reflect actual clearance of renally eliminated medications and is a reasonable approach to use in the clinical setting.

Nonrenal clearance

Much less information is available regarding nonrenal elimination (e.g., liver, lungs, gastrointestinal tract) or mechanisms (e.g., Hofmann degradation, esterase elimination). For many medications, the amount eliminated by the kidneys is determined in pharmacokinetic studies, and the amount not accounted for by renal elimination is considered *nonrenal*—without further investigation—although these pathways might be affected by obesity. Some of the assumptions of nonrenal elimination do not always appear to be accurate when more in-depth investigations are performed. For example, vancomycin is often stated to have 15% to 30% nonrenal elimination, presumably through the liver, which would suggest dose adjustments might be needed for more severe forms of liver dysfunction. But, when this issue was investigated in patients with cancer, liver failure did not influence vancomycin clearance.⁴³ As with renal clearance, the overall effect of obesity on hepatic metabolism appears to be an increase or no change in phase I and phase II metabolic processes.³² The clearance by some hepatic metabolic pathways (e.g., glucuronidation) appears to be more consistently increased than others based on a limited number of medications that have been studied. From a practical standpoint, for the majority of medications that are titrated to clinical effect or that use blood concentration determinations as a surrogate marker, any alterations due to obesity are likely to be mitigated. Perhaps the ability to dose medications cleared by hepatic processes may improve with advancements in pharmacogenomics and body composition assessments.

CONCEPT OF DOSE PROPORTIONALITY

The use of ABW for weight-based dosing of a medication in an obese patient presumes that pharmacokinetic parameters such as V and clearance increase proportionately with the excess weight. In other words, if ABW increases by a certain percent, V and clearance not adjusted for weight will increase by the same percent. However, this is often not the case and should not be assumed, particularly for patients with extreme forms of obesity. Even assuming there are data to suggest dose proportionality with increasing weight for a particular medication, there may be other reasons to avoid the use of ABW for initial dosing. For example, assume that an intravenously administered antihypertensive agent has recently become available that was dosed using ABW in clinical trials involving small numbers of patients with relatively normal body weights. This agent is now being considered for use in a severely obese patient with postoperative hypertension, but no organ dysfunction attributable to the increased pressure. In this example, the risk of hypoperfusion of organs associated with rapid decreases in blood pressure would more than offset the benefit of acute pressure reduction in a patient who does not have a hypertensive emergency. If blood pressure reduction with this new antihypertensive agent was needed more quickly in the case of a hypertensive emergency, other options such as a series of mini-boluses administered over a relatively short period of time may be safer while accomplishing the same

purpose as the administration of one large bolus loading dose. **Table 4-3** illustrates the concept of dose proportionality in two hypothetical patients of the same height, weight, and sex. Note how the values for each of the kinetic parameters may vary between the normal weight and obese patient depending on the units (e.g., V in L/kg vs. L/kg/min). These differences, along with other considerations such as patient co-morbidities, will influence the assessment of proportionality.

TABLE 4-3. ILLUSTRATION OF CONCEPT OF DOSE PROPORTIONALITY IN TWO HYPOTHETICAL PATIENTS OF SAME HEIGHT, WEIGHT, AND SEX

Normal weight (BMI = 24)	Morbidly obese (BMI = 49)
ABW = 80 kg; IBW = 70 kg	ABW = 160 kg; IBW = 70 kg
<i>Pharmacokinetic parameters</i>	<i>Pharmacokinetic parameters</i>
V = 50 L	V = 100 L
V (IBW) = 0.72 L/kg	V (IBW) = 1.43 L/kg
V (ABW) = 0.63 L/kg	V (ABW) = 0.63 L/kg
Clearance = 100 mL/min	Clearance = 200 mL/min
Clearance (IBW) = 1.43 mL/min/kg	Clearance (IBW) = 2.86 mL/min/kg
Clearance (ABW) = 1.25 mL/min/kg	Clearance (ABW) = 1.25 mL/min/kg
Half-life = 5.78 hr	Half-life = 5.78 hr

RECOMMENDATIONS FOR DOSING MEDICATIONS IN OBESE PATIENTS

Product information from the pharmaceutical industry typically lacks details regarding dosing in obese patients, which is not surprising because the investigators in pre-approval clinical trials of a medication usually strive to obtain a homogeneous patient population to ensure internal validity. Subjects in these trials almost always receive fixed doses or mg/kg doses based on ABW, although this is often not explicitly stated in the published methodology. Furthermore, extremely obese subjects are either limited in numbers or specifically excluded. Many pharmacokinetic studies are single-dose evaluations involving small numbers of patients that are unlikely to be obese; nevertheless, they may provide useful information for initiating therapy. Therefore, the first step in developing a dosing regimen for a medication in an obese patient begins with a search of the literature for applicable studies. In the absence of specific investigations or therapeutic alternatives with more dosing-related information, there is little choice but to dose obese patients using available pharmacokinetic and pharmacodynamic data.

Many medications used in adults are not dosed by body weight but rather started at a set dose and titrated to clinical effect (see Chapter 1 for additional discussion of this approach). This is a reasonable approach for dosing non-critically ill adult patients with less severe forms of obesity. Designing a weight-based dosing regimen for hospitalized adults and children with more severe forms of obesity is challenging given the lack of information available in common resources such as manufacturers' product information, and the unstable nature of more severely ill patients, no matter what their weight might be. The latter problem is illustrated by a study of the pharmacokinetics and pharmacodynamics of vancomycin in critically ill patients, where the V was found to be double the usual 0.6–0.7 L/kg often cited in published literature, and standard dosing was found to be inadequate in one-third of patients.⁴⁴

Despite the lack of literature on the most appropriate size descriptor to use for weight-based dosing protocols, the American Society of Clinical Oncology recommends the use of ABW for weight-based cytotoxic chemotherapy.⁴⁵ This recommendation was based on the concern related to under-dosing and

the authors' perception (albeit based on limited evidence) that dose-related toxicities would not increase with full weight-based dosing. Although the available literature does not demonstrate a substantial increase in toxicity with ABW dosing in obese patients, there were relatively few patients in the studies with more severe forms of obesity. Additionally, chemotherapy doses were frequently dosed based on BSA and as illustrated in Table 4-2, a doubling of weight does not result in a doubling of BSA as would occur using more common weight-based (e.g., mg/kg) dosing regimens. Hopefully follow-up efficacy and toxicity studies that include a sufficient number of more severely obese patients will be conducted after the recommendations of these guidelines have been disseminated and presumably followed. A more recent guideline by the American Society for Blood and Marrow Transplantation Practice Guideline Committee concluded that standardized dosing recommendations for conditioning chemotherapy regimens for hematopoietic stem cell transplantation could not be made for obese patients given the lack of high-level evidence.⁴⁶

Loading doses

Given the difficulties in choosing an appropriate size descriptor for weight-based dosing in obese patients, particularly in patients with more severe forms of obesity, the first question to ask is whether a loading dose is needed. For example, many of the vasoactive medications administered to critically ill patients must be given by continuous intravenous infusion due to their onset and offset of effects that often occurs within a few minutes. For such medications, loading doses may be replaced by rapid titration of the infusion to clinical effect. For other medications that take days or weeks to reach therapeutic or steady state concentrations, loading doses may be needed. In these situations, the loading dose is primarily a function of the medication's V, so the literature should be evaluated for evidence that the V increases proportionally to increased ABW before considering ABW for dosing on an mg/kg basis.

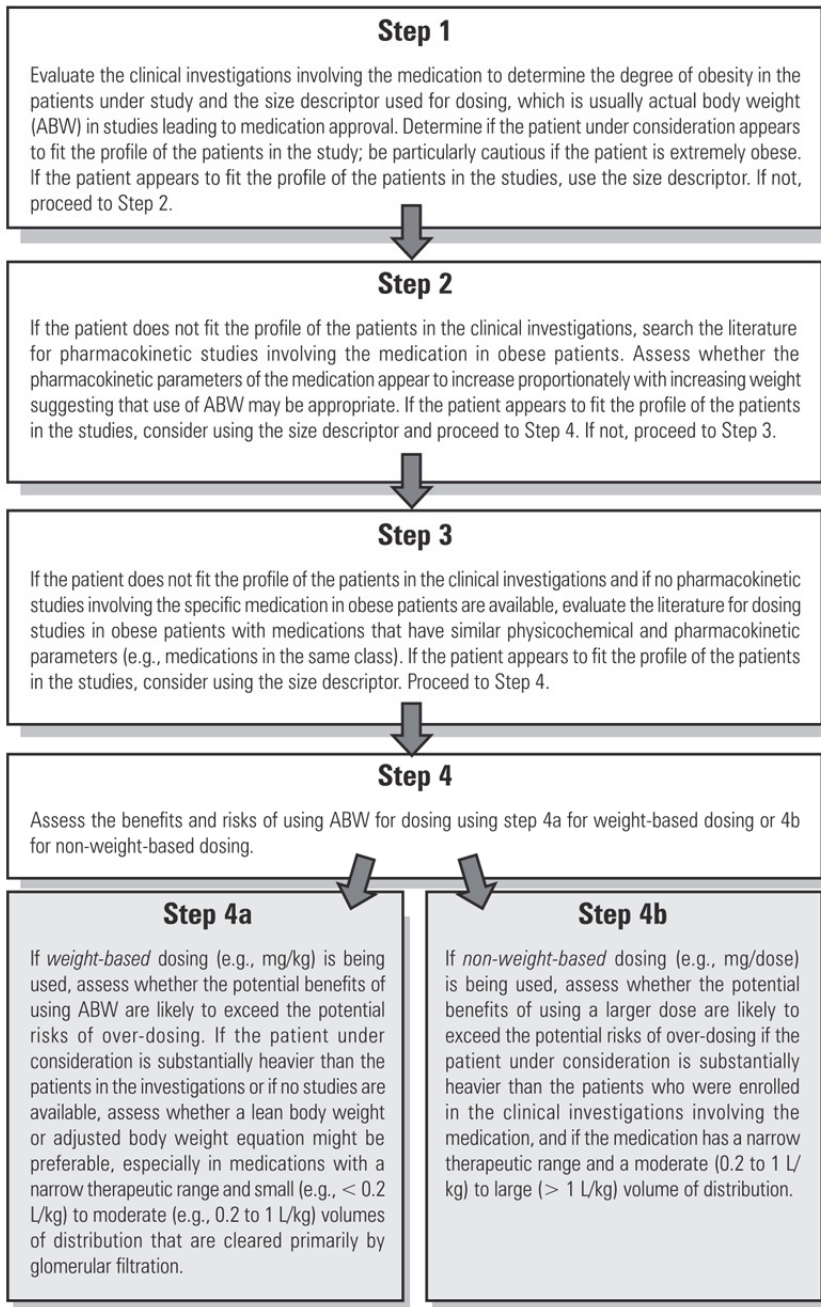
Maintenance doses

Clearance is the more important parameter to assess for dose proportionality in obese patients when starting maintenance regimens of medications given by regularly scheduled intermittent doses or by continuous infusions. With a few notable exceptions (e.g., vancomycin), most hydrophilic medications eliminated by the kidneys do not have clearance increase in proportion to excess body weight, so use of ABW for dosing patients with more severe forms of obesity could lead to toxicity. Even when dose proportionality appears to exist, a risk/benefit assessment of using ABW compared to a lean or other adjusted weight should be performed.

Figure 4-1 provides a conceptual framework for initiating the dosing of medications in obese patients, particularly patients with more severe forms of obesity. The step-by-step process contains the major scenarios likely to be encountered in clinical practice, but cannot account for every possible scenario and does not replace sound clinical judgment backed by available evidence. Furthermore, pharmacokinetic parameters may change relatively quickly, which may necessitate dosing adjustments in any patient in settings such as the intensive care unit. When feasible, it is preferable to titrate a medication to desired clinical effect, possibly in conjunction with pharmacokinetic monitoring, rather than relying solely on estimated pharmacokinetic parameters derived from previous studies of drug monitoring to predict a dosing regimen.

GENETIC AND GENOMIC CONSIDERATIONS

Pharmacogenetic and pharmacogenomic information have the potential to provide more patient-specific medication dosing regimens for overweight and obese patients. Genetic technologies that have been approved by the FDA include tests for predicting the metabolism of medications that are CYP isoenzyme substrates and for identifying adverse reactions to antipsychotic agents.⁴⁷ Future testing will hopefully be available for a number of other medications such as opioids that have demonstrated



^aAlways take into account potential co-morbidity confounders such as renal or liver dysfunction when determining dosing regimens.

Figure 4-1. Conceptual framework for dosing medications in obese patients.^a

heritability of common adverse effects.⁴⁸ Epigenetics is another area of increasing research focus because it involves inherited forms of gene expression that change during life and may be modified by medications.⁴⁹

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THE ROLE OF PHARMACOGENOMICS IN PHARMACOKINETICS

Cheryl D. Cropp

INTRODUCTION

Recent advances in personalized medicine have demonstrated that genetic variations in genes encoding for drug metabolizing enzymes (DMEs) and drug membrane transporters (DMTs) can have an important impact on drug disposition and efficacy. These variations are integral to the explanation of differences in drug disposition between and within populations. This chapter provides a general review of the role of pharmacogenomics and its established importance in the safe and effective dosing of medications.

BASIC DEFINITIONS

Highlighted fields of study related to drug disposition and therapeutic outcomes include:

- **Pharmacodynamics:** What the drug does to the body. It is the science of how the drug and drug-target interact and result in a biological effect.
- **Pharmacogenetics:** The study of genetic causes of individual DNA variations in drug response.
- **Pharmacogenomics:** A genome-wide analysis (DNA, RNA level) of the genetic determinants of drug efficacy and toxicity.
- **Pharmacokinetics:** What the body does to the drug. Pharmacokinetics relates to how drug concentrations of a medication change over a dosing interval. It involves the dynamics of how the drug is absorbed, distributed, metabolized, and eliminated (ADME) by the body.
- **Pharmacology:** An investigation of the drug action's impact on biological systems including an understanding of chemical properties, mechanism of action, therapeutic response, and biological transformation.

Overall, the pharmacokinetics, pharmacodynamics, pharmacogenetics, and pharmacogenomics related to a drug interact biologically to influence efficacy and/or toxicity and serve as a framework for improving the understanding of pharmacology and drug development in the creation of more advanced and novel approaches to treat disease and provide precision therapies for individual patients (see **Figure 5-1**).

Pharmacogenomic variation within human populations can impact pharmacokinetics by altering a drug's expected ADME profile. For example, the final bioavailability (F) of a substrate medication is significantly impacted by the interplay of influx transporters such as organic acid transporters (OAT) and organic cation transporters (OCT) and efflux transporters (e.g., P-glycoprotein; P-gp) with DMEs present in the gastrointestinal tract and the liver (e.g., CYP3A4 and CYP2C9). The presence and/or absence of environmental factors (e.g., diet, disease) may also contribute. For example, the overexpression of P-gp and CYP2C9 in a given individual would lead to a lower F because of increased efflux transport back into the lumen of the gut and enhanced first-pass metabolism.



Pharmacokinetics and Pharmacodynamics

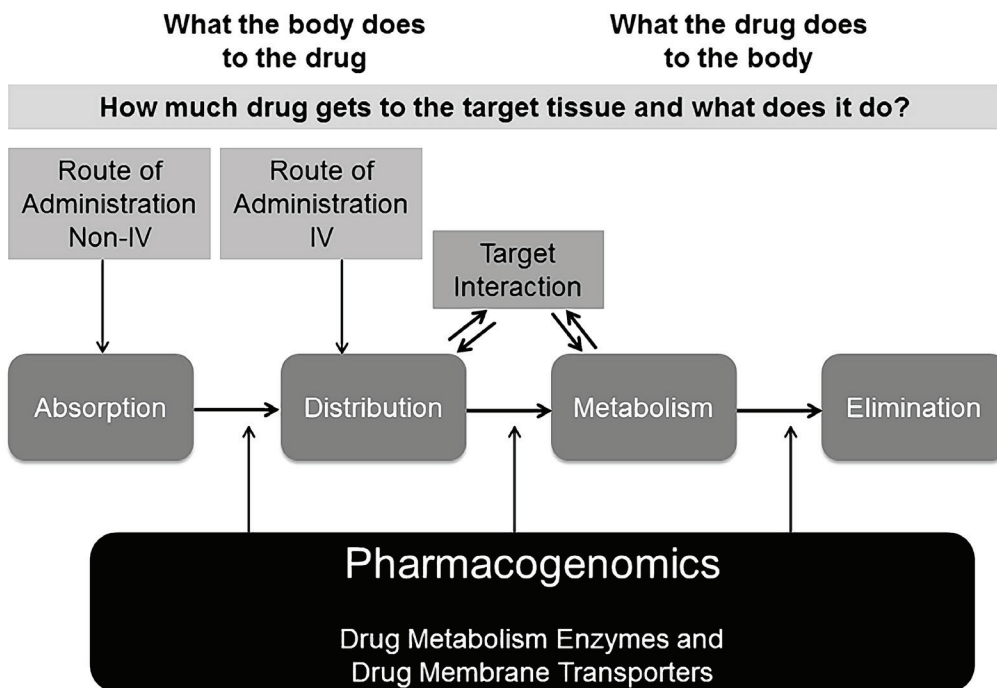


Figure 5-1. Interplay of pharmacokinetics, pharmacodynamics, and pharmacogenomics.

HISTORY OF PHARMACOGENETICS AND PHARMACOGENOMICS

Pharmacogenetics was first described in the scientific literature in the 1930s, when it was theorized that adverse drug reactions that occurred only in some patients taking a drug could be possibly explained through biochemical differences among individuals. Phenylthiocarbamide, which tests for inter-individual differences in tasting capacity, and the clinical observation of primaquine-induced hemolytic anemia that occurred in African American soldiers during World War II are among the first reports delineating the connection between genetic variation and drug disposition.^{1,2} Vogel was the first to use the term *pharmacogenetics* in the scientific literature in 1959.³ Later key discoveries in genetic variation included differing drug profiles with debrisoquine⁴ and differences in drug disposition between heterogeneous populations.^{5,6} These led to the eventual recognition that variation in drug response was not limited to a single or a few genes, but instead was due to assorted factors including variation in many genes and environmental factors such as age, weight, diet, smoking, concomitant drugs, and occupational exposures. It also led to the evolution of pharmacogenetics into the field of pharmacogenomics, which not only attempts to elucidate the reasons for changes in drug response but also drug-induced changes in gene function (e.g., drug–drug interactions).

The work on, and completion of, the mapping of the human genome in 2003⁷⁻⁹ has resulted in major advances in recent decades in genotyping and sequencing technologies, bioinformatics, and pharmacogenomic epidemiology that have enabled a more refined understanding of the integral role of pharmacogenomics in drug disposition, development, and discovery.

Currently, there are clinically relevant examples of the importance of pharmacogenomic considerations in the appropriate selection of a medication to provide the greatest efficacy with minimal risk in a given patient. Approximately 140 drugs approved by the U. S. Food and Drug Administration (FDA) have pharmacogenomic information on the drug label, and some have recommendations for pharmacogenomic testing (see <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>).^{10,11} The PharmGKB websites <https://www.pharmgkb.org/view/vips.jsp> and <https://www.pharmgkb.org/> are useful to follow for updates to knowledge about recent discoveries in pharmacogenomics.

CYTOCHROME P450 ENZYMES AND SOLUTE CARRIER TRANSMEMBRANE PROTEINS

Cytochrome P450 (CYP) enzymes are a superfamily of enzymes responsible for the metabolism and clearance of a diverse assortment of endogenous and exogenous substances through various organs through the body including the liver and gastrointestinal tract. Such substances include xenobiotic compounds from many therapeutic categories (e.g., conventional and targeted oncology, cardiology, and neurology). A superfamily of transmembrane protein transporters, including ATP-binding cassette (ABC) and solute carrier (SLC) superfamilies, also work together to play a vital role in the pharmacokinetic (by mediating drug absorption, distribution, and elimination) and pharmacodynamic impact of targeted drug therapy. Transmembrane proteins are also responsible for the influx and efflux of numerous endogenous and clinically relevant xenobiotics in the liver and kidney.

Research in personalized medicine involves the development of novel or improved drugs to target specific molecular structures and to test for inherited drug metabolism mutations in cytochrome P (CYP) 450 enzymes in the liver and membrane transporters (ABC and SLC super-families) primarily in the liver and kidneys. Of note, it is well documented that three polymorphic liver enzyme genes (*CYP2C9*, *CYP2C19*, and *CYP2D6*) are major CYP genes with variants that result in the observance of individuals who either do not respond or are deemed intolerant to medications that are substrates for these DMEs. Inherited mutations in CYP enzymes may result in significant impact on the disposition of conventional and targeted medications.

Membrane transporters are also determinants of resistance to, or limited effect from, various medications. An early and well-known example that refined understanding of resistance of cancer to conventional chemotherapeutic agents is attributed to the membrane transporter *ABCB1*. This transporter encodes for P-gp, which is also known as multidrug resistance (MDR) protein, leading to resistance to doxorubicin chemotherapy.¹²⁻¹⁴ Membrane transporters have also been implicated in the development of adverse drug reactions. For example, genetic mutations of the SLC transporter *SLCO1B1* have been significantly associated with statin-induced myopathies.¹⁵⁻¹⁸ **Table 5-1** provides examples of various transporters in the liver and kidney as well as select substrates.

IMPACT OF THE BLOOD–BRAIN BARRIER

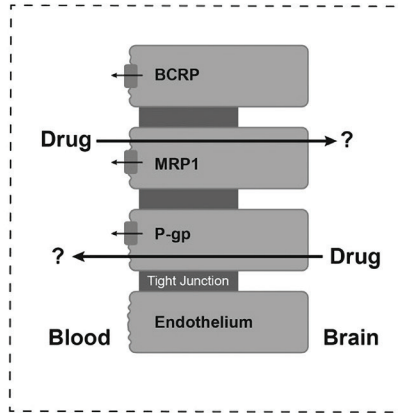
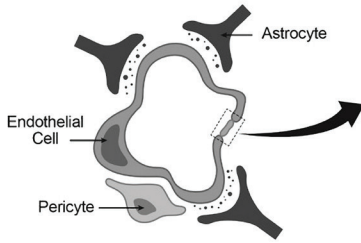
The blood–brain barrier (BBB) restricts the passage of most molecules into the brain. One of the challenges in applying precision medicine to neurological cancers such as glioblastoma, a type of brain tumor, is adequate delivery of the drug to the brain. Clinicians and researchers must make decisions on the feasibility of a clinical trial for drugs targeting brain tumors with consideration of whether the drugs can cross the BBB and get into the brain. Factors impacting these decisions include whether the drug is lipophilic or hydrophilic, whether it requires a transporter to cross, and whether the drug is an efflux pump substrate or efflux pump inhibitor.^{19,20} **Figure 5-2** illustrates factors that impact whether or not a drug can cross the BBB and **Table 5-2** shows the transporters and metabolizing enzymes important to the BBB.

TABLE 5-1. REPRESENTATIVE ABC AND SLC TRANSPORTERS IN THE LIVER AND KIDNEY TRANSPORTERS

Gene	Symbol Name	Full Protein Name	Location	Representative Substrate(s)
<i>Influx</i>				
SLC22A1	OCT1	Organic cation transporter 1	Liver	Metformin, oxaliplatin
SLC22A2	OCT2	Organic cation transporter 2	Kidney	Metformin, varenicline
SLC22A4	OCTN1	Novel organic cation transporter 1	Kidney	Gabapentin
SLC22A5	OCTN2	Novel organic cation transporter 2	Kidney	Carnitine
SLC22A6	OAT1	Organic anion transporter 1	Kidney	Adefovir, tenofovir
SLC22A7	OAT2	Organic anion transporter 2	Liver and kidney	Cyclic GMP, zidovudine
SLC22A8	OAT3	Organic anion transporter 3	Kidney	Furosemide, cefotaxime
SLC22A11	OAT4	Organic anion transporter 4	Kidney	Bumetanide, uric acid
SLC22A12	URAT1	Urate anion exchanger 1	Kidney	Uric acid, oxypurinol
SLCO1A2	OATP1A2	Organic anion transporting polypeptide A	Kidney	Methotrexate, fexofenadine
SLCO1B1	OATP1B1	Organic anion transporting polypeptide C	Liver	Pravastatin, repaglinide
SLCO1B3	OATP1B3	Organic anion transporting polypeptide 8	Liver	Paclitaxel
SLCO2B1	OATP2B1	Organic anion transporting polypeptide B	Liver	Atorvastatin, benzylpenicillin
SLC47A1	MATE1	Multidrug and toxin extrusion 1	Kidney	Paraquat, topotecan
SLC47A2	MATE2-K	Multidrug and toxin extrusion 2	Kidney	Metformin, topotecan
<i>Efflux</i>				
ABCB1	P-gp	P-glycoprotein	Liver and kidney	Etoposide, fexofenadine
ABCB11	BSEP	Bile salt export pump	Liver	Paclitaxel, sitaxsentan
ABCC1	MRP1	Multidrug resistance-associated protein 1	Kidney	Methotrexate
ABCC2	MRP2	Multidrug resistance-associated protein 2	Liver and kidney	Doxorubicin, cisplatin
ABCC3	MRP3	Multidrug resistance-associated protein 3	Liver and kidney	Etoposide, methotrexate
ABCC4	MRP4	Multidrug resistance-associated protein 4	Liver and kidney	Methotrexate, folic acid
ABCC6	MRP6	Multidrug resistance-associated protein 6	Liver and kidney	Anthracyclines
ABCG2	BCRP	Breast cancer resistance protein	Liver	Mitoxantrone, doxorubicin

THE BLOOD–BRAIN BARRIER

The blood–brain barrier (BBB) restricts the passage of most small molecules into the brain.



Does the drug penetrate the BBB?

Experimental evidence

Predictive models

Efflux pump substrate?

Efflux pump inhibitor?

Figure 5-2. Interplay of drug disposition and membrane transporters in the blood–brain barrier.

TABLE 5-2. REPRESENTATIVE DRUG MEMBRANE TRANSPORTERS AND DRUG METABOLIZING ENZYMES OF THE BLOOD–BRAIN BARRIER

Gene	Symbol Name	Full Protein Name
Drug Membrane Transporters		
ABCB1	P-gp	P-glycoprotein
ABCC1	MRP1	Multidrug resistance-associated protein 1
ABCG2	BCRP	Breast cancer resistance protein
SLC6A13	GAT2	γ -aminobutyric acid (GABA) transporter 2
SLC7A5	LAT1	Large neutral amino acids transporter small subunit 1
SLC19A3	THTR2	Thiamine transporter 2
SLC22A3	OCT3	Organic cation transporter 3
SLCO2B1	OATP2B1	Organic anion transporting polypeptide B
SLC26A2	DTD	Diastrophic dysplasia protein
SLC47A2	MATE2-K	Multidrug and toxin extrusion 2
Drug Metabolizing Enzymes		
CYP1B1	CYP1B1	Cytochrome P450, Family 1, Subfamily B, Polypeptide 1
CYP2J2	CYP2J2	Cytochrome P450, Family 2, Subfamily J, Polypeptide 2
CYP2U1	CYP2U1	Cytochrome P450, Family 2, Subfamily U, Polypeptide 1

SPECIAL POPULATIONS

Pharmacokinetic and pharmacodynamic differences of drugs that are substrates of DMEs or are transported by DMTs can impact the pharmacologic effects observed between ethnic groups. Differences may be attributed to variations in genetic and/or environmental factors. Determining the impact of genetic differences in metabolism and transporter activity on drug disposition and response is

challenging. Although there have been numerous pharmacogenomic studies assessing the effects of genetic polymorphisms in DMEs on drug disposition, studies of genetic variants in DMEs, DMTs, and the interaction effects of polymorphisms in DME and DMTs on treatment outcome in underserved and underrepresented groups are needed. Elucidation of these relationships in different ethnic groups could have a powerful impact on understanding why the treatment outcome of disease varies among human populations. Through genotyping and/or sequencing of metabolism and membrane transporter candidate genes, investigators can identify the genetic variants that play a role in the success or failure of treatments in various therapeutic areas including cancer, cardiology, and psychiatry. This could improve efficacy and safety prediction of currently available medications and contribute to future drug development. This knowledge may help improve ability to reduce morbidity and mortality that sometimes exists at greater rates in underserved and minority subpopulations.

PHARMACOGENOMIC EXAMPLES IN THERAPEUTICS

Oncology

The impact and benefit of pharmacogenomics in oncology is well-recognized. Inherited genetic alterations and/or mutations that develop throughout life can lead to alterations in normal cell growth and regulation that may lead to cancer. To date, most cancer pharmacogenomics studies analyze either hereditary mutations or somatic variants for optimal cancer chemotherapy selection, but not both mutation types simultaneously. Identifying the coexistence of inherited and tumor-specific variants may correlate better with optimal drug delivery, positive therapeutic response, and favorable outcomes including prevention of cancer recurrence and survival (e.g., DME and DMT polymorphisms examined in combination with genetic aberrations found in an individual's tumor type).

Cardiology

Clopidogrel and CYP2C19. Genetic polymorphisms in CYP2C19 affect the balance of therapeutic effectiveness versus side effect profile (i.e., bleeding) of the prodrug clopidogrel, an antiplatelet used to prevent clot formation in cardiovascular disease.²¹ The variant *CYP2C19**2 leads to a loss of metabolizing capability and has been associated with decreased clopidogrel bioactivation and reduced antiplatelet activity, leading to an increased risk of negative cardiac events including myocardial infarction and stroke, which may not have occurred with normal CYP2C19 metabolizing function.²²⁻²⁷ It should be noted that some reports have not replicated these findings in carriers of *CYP2C19**2.^{28,29} *CYP2C19**17 has been characterized as a variant with enhanced metabolic activity. Individuals who carry the *17 variant may experience increased risk of bleeding as a result of greater than expected platelet inhibition.^{30,31} Due to the pharmacogenomic variability associated with CYP2C19 polymorphisms and the safety and efficacy profile of clopidogrel, the FDA requires that its label include a black box warning.

VKORC1, CYP2C9, and warfarin. CYP2C9 and VKORC1 play an important role in changing the clinical response to the anticoagulant effect of warfarin's (S)-enantiomer. Carriers of common CYP2C9 single-nucleotide polymorphisms that reduce enzymatic activity require lower average warfarin dose requirements.^{32,33} Loss of metabolic function polymorphisms *CYP2C9**2 and *CYP2C9**3 are associated with decreased clearance of warfarin leading to a higher risk of bleeding and lower warfarin dosing requirements in individuals carrying these alleles.^{34,35}

The vitamin K epoxide reductase subunit 1 (*VKORC1*) gene encodes for a protein that interacts with warfarin to produce the drug's anticoagulant effect. Certain populations (e.g., Asian and European ancestry) that carry genetic polymorphisms in this gene's promoter region have reduced warfarin dose requirements to achieve therapeutic anticoagulation and to decrease the risk of bleeding.³⁶⁻³⁸ Other groups (e.g., African descent) have different *VKORC1* promoter mutations necessitating increased warfarin doses to prevent a thrombotic event.^{39,40} It has been reported that the wide variation in the therapeutic efficacy and safety of warfarin witnessed in the clinical setting can be explained by clinical factors and common variants in CYP2C9 and VKORC1. Despite this knowledge, standardized

pharmacogenetic testing for these CYP2C9 and VKORC1 genotypes prior to initiating warfarin has not been universally adopted into standard clinical practice.

Psychiatry

Antiepileptic Drugs

It is estimated that there is limited efficacy of both old and new generation antiepileptic drugs (AEDs) in >60% of patients, and adverse drug reactions are prevalent among patients treated with these agents.⁴¹ Due to these challenges in personalized AED dosing, polymorphisms in *CYP2C9* and *CYP2C19* are of interest in the metabolism of a variety of AEDs. Genetic variation that results in altered expression of these metabolic enzymes can lead to either poor metabolism (PM) or extensive metabolism (EM) of diazepam and mephenytoin (both *CYP2C19*) and phenytoin (*CYP2C9*). Up to a two-fold difference in the hepatic clearance of phenytoin, a narrow therapeutic index drug, has been observed between individuals who are phenotypically labeled as *CYP2C9* PM versus EM, often necessitating more vigilant therapeutic monitoring and dosing adjustments in individuals carrying these phenotypic genetic mutations.⁴²⁻⁴⁴

Antidepressants

Major depressive disorders (MDD) is a leading contributor to overall disease burden in the United States.⁴⁵ Despite ubiquitous prescribing of antidepressants to treat depression, only one-third of treated patients achieve sustainable remission of their depressive symptoms.⁴⁶ Thus, the role of precision medicine toward the development of more targeted initial selection of the best antidepressant for patients afflicted with depression is of intense research interest. Although genome-wide association studies of antidepressant response have yet to demonstrate consistent and replicative results, DMEs and DMTs are among a small collection of candidate genes including *ABCB1*, *CYP2D6*, *CYP2C19*, and *SLC6A4*, a serotonin reuptake transporter, that have facilitated an enlightened understanding of genetic variation and biological pathways involved in efficacy of antidepressants.⁴⁷⁻⁵¹ Genotyping and sequencing analysis studies are currently ongoing to convert advanced knowledge of antidepressant pharmacogenomics into improved MDD clinical outcomes.

SUMMARY

The role of pharmacogenetics and pharmacogenomics in improving understanding drug disposition (i.e., pharmacokinetics) and drug response (i.e., pharmacodynamics) is indisputable. There has been useful integration of personalized pharmacogenomic information directed toward improving drug therapy. However, the full impact of potential benefits is not yet fully realized. Additionally, there are recommendations that pharmacogenomic studies should move more toward less-understood parts of the human genome including RNA, gene expression, proteomics, and epigenetics (e.g., methylation).^{52,53} These noncoding aspects of the human genetic code are increasingly recognized as playing a role in disease risk and drug efficacy and safety.

Acknowledgment

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DRUG DOSING IN PEDIATRIC PATIENTS

Vinita B. Pai and Milap C. Nahata

Pediatric patients have been labeled *therapeutic orphans* because of the lack of pharmacokinetic, pharmacodynamic, efficacy, and safety data necessary to provide safe and effective drug therapy to this population. Efficacy and safety trials of new drugs are initially conducted in adult patients, most often excluding infants, children, and pregnant women. Many drugs routinely used in pediatric patients do not have pediatric labeling. Rather, safety and efficacy data may come from trial and error approaches with use of these drugs.

Children of all ages should not be considered miniature adults; adult doses scaled down based on body weight may not be as safe or effective in the pediatric population as in adults. Further, as neonates develop into toddlers and then young adolescents, physiologic events occur that change the body composition and organ function. Changes in body water, body fat, plasma proteins, hormonal composition, and renal and hepatic function all occur and influence drug disposition.

Table 6-1 shows the classification of the pediatric population into distinct age groups and provides selected birth age terminology.^{1,2} However, physiological changes resulting in growth and development of a human body do not strictly occur within these age-related boundaries and are often not linearly related to age. Drug disposition in pediatric patients may change due to certain intrinsic factors such as sex, race, heredity, inherited diseases, and certain extrinsic factors such as acquired diseases, diet, and prior exposure to drug therapy. To provide safe and effective drug therapy to pediatric patients, it is important to gain knowledge of the pharmacokinetic and pharmacodynamic properties of each drug and the effect of development on its disposition. Within the pediatric population, neonates (especially premature neonates) exhibit marked differences in body composition and organ function when compared to each other and to the rest of the pediatric population. This chapter focuses on the influence of growth and maturation on drug disposition and pharmacodynamic response to drugs in the pediatric population, ranging from neonates to adolescents.

TABLE 6-1. AGE GROUPINGS OF CHILDREN AND BIRTH AGE

Terminology	Age Grouping
Neonates	Birth to 4 weeks of age
Premature neonate	Gestational age <37 weeks at birth
Full-term neonate	Gestational age 39–40 weeks at birth
Post-term neonate	Gestational age ≥38 weeks at birth
Infant	1 to <12 months of age
Child	1–12 years of age
Adolescent	13–18 years of age
Pediatric	Birth to 18 years of age
Birth Age Terminology	
Gestational age (GA)	Number of weeks from the first day of the last normal menstrual period to birth
Postnatal age or chronological age	Age since birth
Postconceptional age or postmenstrual age	Gestational age + postnatal age, in weeks



GENERAL PHARMACOKINETIC INFORMATION

Table 6-2 lists physiologic changes that occur with aging in children and some examples of the pharmacokinetic consequences that can result from the changes.

Physiologic Variability	Neonate	Infant	Child	Adolescent	Pharmacokinetic Consequence
Absorption					
Gastric pH	(>5)	(2–4)	(2–3)	↔	Increase in bioavailability of acid-labile drugs, e.g., penicillin G in neonates and infants compared to children and adults; decreased bioavailability of weak organic acids, e.g., phenobarbital ^{3,4}
Gastric and intestinal emptying time	↑	↑	↔	↔	Specific examples influencing drug pharmacokinetics not available.
Biliary function	↓	~ ↔	↔	↔	Reduced absorption of fat and fat-soluble vitamins D and E in neonates compared to infants and children. ⁵
Pancreatic function	↓	~ ↔	↔	↔	Reduced hydrolysis and bioavailability of oral liquid ester formulations of clindamycin and chloramphenicol in neonates compared to infants and children. ⁶
Gut microbial colonization	↓	~ ↔	↔	↔	Increased bioavailability of digoxin in neonates and infants compared to adults due to lack of microbial gut colonization with an oral digoxin-reducing anaerobic bacteria. ⁷
Intramuscular absorption (rate and extent)	↓	↑	↑ to ~ ↔	↔	Benzathine penicillin G more rapidly absorbed in children compared to adults since no measurable activity was detected in children 18 days after the injection. ⁸
Skin permeability and percutaneous absorption	↑	↑ (extent)	~ ↔	↔	EMLA should be used with caution in patients <3 months of age due to risk of methemoglobinemia from increased percutaneous absorption of prilocaine and decreased methemoglobin reductase, especially in combination with other methemoglobinemia-inducing agents. ⁹
Distribution					
Total body water and extracellular water	↑	↑	↓ ~ ↔	↔	Increase in mean apparent volume of distribution (V) for hydrophilic drugs, e.g., gentamicin in neonates and infants. ^{10,11}
Total body fat	↓	↓	Increases by ages 5–10 yr	↔	Mean apparent V for lipophilic drugs increases from infants to adults, e.g., diazepam. 1.3–2.6 L/kg in infants vs. 1.6–3.2 L/kg in adults. ¹²
Total plasma proteins	↓	↓ or ~ ↔	↔	↔	Increase in V and unbound phenytoin fraction in infants and children. ¹³
Renal Elimination					
Glomerular filtration	↓	↔	↔	↔	Famotidine—renal clearance reduced in neonates but equivalent to adults by 1 yr of age. ¹⁴

Tubular secretion and
tubular reabsorption ↓

~ ↔

↔

↔

Penicillins—increased half-life due to decreased excretion both by glomerular filtration and tubular secretion, therefore, lengthened dosing interval in infants compared to children and adolescents.⁶

↔ = similar to adult capacity, ~ ↔ = near adult capacity, ↑ = increased compared to adult capacity, ↓ = decreased compared to adult capacity, EMLA = eutectic mixture of local anesthetics lidocaine and prilocaine.

Absorption—oral

Most drugs administered by the oral route are absorbed by passive diffusion. Gastric pH, gastric and intestinal motility, pancreatic enzyme activity, bacterial colonization of the intestines, bile salt production, blood flow to the gastrointestinal (GI) tract, and the surface area of absorption affect the rate and extent of GI absorption.^{15,16} These factors undergo considerable maturational changes as a neonate grows into an adult. Newborns of <32 weeks GA rarely have any gastric acid production, while the gastric pH in a newborn at term is alkaline (pH 6–8) but becomes acidic over the next 24 hr (pH 1.5–3).^{17–20} Over the next few months of life, gastric acid production may remain low. The volume and acid concentration of the gastric fluid are dependent on age and approach the lower limit of normal adult values by 3 months of age; but reach adult values only after 2 years of age.^{6,18} The rate and extent of absorption for drugs that are weak acids or bases may depend on their partition coefficients and gastric/intestinal pH. Gastric pH may change with ingestion of certain foods. For example, orange juice, cranberry juice, and carbonated beverages decrease the gastric pH causing acidic drugs such as itraconazole to be absorbed more readily (increased bioavailability) since an acidic gastric pH is necessary for complete absorption. H₂-antagonists such as ranitidine can raise pH and reduce absorption of drugs such as itraconazole. Absorption of acidic drugs may decrease when given with milk or infant formula due to increases in gastric pH.²¹

Gastric emptying rate is considerably delayed in infants, only reaching adult capacity by 6–8 months of age.^{22,23} Because most drugs are absorbed in the small intestine, the rate of drug absorption may be decreased due to delayed (lengthened) gastric emptying time, but bioavailability of the drugs may increase due to slower intestinal transit. The rate and extent of drug absorption may be significantly altered in patients with acute changes in the GI tract. Decreased and delayed absorption of ampicillin and nalidixic acid was observed in infants and children treated with these drugs for acute shigellosis. In another study involving use of ampicillin in the treatment of gastroenteritis in children, mean concentrations of ampicillin were lower in the children with gastroenteritis than in children without the malady, possibly due to malabsorption.²⁴ In infancy and beyond, differences in GI maturation and absorption between the different age groups may not be significant enough to impact oral dosing recommendations for most drugs.²⁵

Pancreatic enzymes increase the bioavailability of oral drug dosage forms that require intraluminal hydrolysis in the GI tract prior to absorption such as oral liquid ester formulations of clindamycin and chloramphenicol palmitate.⁶ Pancreatic enzyme activity is low at birth.²⁶ Amylase activity remains low (approximately 10% of adult values) even after the first month of life.⁶ Lipase activity is present by 34 to 36 weeks GA and increases 5-fold during the first 7 days of life to 20-fold during the first 9 months after birth but remains less than in adults. Trypsin secretion in response to pancreozymin and secretin is decreased at birth but develops during the first year of life.^{25–27} Bile salts may influence the absorption of certain fat-soluble drugs and nutrients. Bile salt metabolism matures postnatally within the first few months of life and continues to mature during the first year of life.²⁸ After infancy, neither pancreatic enzymes nor bile salts activity should be expected to affect dosing recommendations in normal children.

Composition and rate of GI colonization by bacterial flora depend more on diet than on age; however, the effect of bacteria on intestinal motility and drug metabolism is not completely known.⁵ For example, the GI bacterial flora approaches adult composition by 4 years of age, and intestinal colonization by oral digoxin-reducing anaerobic bacteria approaches adult values by 2 years of age; however, the reduction

of digoxin by these bacteria that is observed in adults may not be achieved until adolescence.⁷ Therefore, when compared to adults, higher digoxin bioavailability can be anticipated in infants and children below 2 years of age. An additional factor that can influence plasma concentration of drugs including digoxin is efflux transporters such as P-glycoprotein (P-gp). Expression of P-gp as a drug efflux transporter is also dependent on age.²⁹ P-gp is present in many parts of the body including intestine, liver, kidney, and brain. Rifampin, an inducer of P-gp, has been shown to decrease plasma concentration and the area under the curve (AUC) of digoxin following oral administration.³⁰ Underdevelopment of P-gp in the brain may limit the ability of neonates to efflux opioids such as morphine back into the systemic circulation, increasing the potential for central nervous system depression.³¹ The exact period to achieve full development of P-gp at various sites after birth has not been fully characterized.

Absorption—intramuscular

The surface area over which the injected drug volume can be distributed, blood flow to the injection site, ease of penetration through the endothelial capillary walls, and muscle activity may all influence the absorption of drugs after intramuscular (IM) administration. IM absorption is variable in premature newborns as they have a small percentage of body weight that is skeletal muscle and subcutaneous fat compared to older infants, children, and adults. Circulatory insufficiency, hypoxia, and exposure to a cold environment may also decrease the rate or extent of IM absorption in newborns, particularly those who are premature. For example, the IM administration of aminoglycosides in premature neonates is discouraged due to inconsistent serum concentrations, but it may be employed in full-term, otherwise healthy, infants. Drugs administered by this route are generally well absorbed in infants and children. Obviously, IM injections can be a painful route of administration and should be used only when oral administration is not indicated or intravenous (IV) access is unavailable. The IM route is more commonly used for administration of vaccines.

Absorption—percutaneous

Greater skin hydration, thinner and/or immature stratum corneum, and greater body surface area to weight ratio increase percutaneous drug absorption in pediatric patients.³² Percutaneous absorption is pronounced in the premature neonate because the epidermal barrier is thin and often poorly developed.^{33,34} Toxic effects have been reported with topical agents such as EMLA (eutectic mixture of lidocaine and prilocaine) and hexachlorophene solution.^{9,35} Topical drugs with limited safety experience in neonates should be employed cautiously. Because percutaneous absorption is increased through damaged skin, application of high-potency corticosteroids to diaper rashes with severe perianal inflammation should be avoided.³⁶

Absorption—rectal

With proper formulation, the rectal route of administration is a useful alternative when oral, IV, or IM administration is not possible (e.g., nausea, vomiting, seizures, preparation for surgery, lack of injectable products). Due to limitations in availability of different doses, suppositories are often impractical for drugs with narrow therapeutic ranges since dosing requirements in neonates are often based on body weight. In addition, cutting suppositories may result in an unpredictable dose because the drug is not always uniformly dispersed throughout the preparation. The rate and extent of absorption of certain drugs such as diazepam may be improved when solutions are used rather than suppositories for rectal administration.³⁷ For example, diazepam concentrations attained after rectal administration of solution have been comparable to those attained after IV administration. However, rectal administration is often erratic or incomplete compared to oral or IV administration. Delay in onset of action and failure to reach minimal effective concentrations for some drugs can make the rectal route of administration inferior to the oral and IV routes.

DISTRIBUTION

Factors such as the relative proportion of body water and body fat and differences in protein binding determine the differences in drug distribution between infants and adults. The total body water decreases from approximately 92% of body weight in a premature newborn, to 75% in a full-term newborn to 60% (25% is extracellular water and 35% is intracellular) by 1 yr of age.^{6,38} Total body water approaches adult values of 50%–60% (20% extracellular and 40% intracellular) by 12–13 years of age.

Hydrophilic drugs such as the aminoglycoside antibiotics and linezolid largely distribute into the extracellular fluid and thus have larger volumes of distribution relative to body weight (i.e., L/kg) in neonates compared to older infants and children.^{10,11,39} Larger volumes of distribution relative to body weight require larger milligram-per-kilogram doses of aminoglycosides to achieve similar peak concentrations. However, caution should be exercised in using actual body weight in calculating aminoglycoside doses in obese children due to the relatively lower percentage of extracellular water in obesity.

On average, total body fat increases from 12% to 16% of body weight at full-term to 20% to 25% at 1 yr of age. It then increases between 5 and 10 years of age, followed by a decrease in boys around age 17. At puberty, there is a rapid increase in percent body fat in females, approaching twice the value compared to males.^{38,40} Lipophilic drugs will have a larger volume of distribution relative to body weight in children and adults than neonates and infants due to higher percentage of body fat.¹² Obesity in any age group will generally increase volume of distribution of lipophilic compounds compared to normal weight patients.

The binding of drugs to circulating plasma proteins depends on multiple factors such as total amount of proteins, the number of binding sites, the binding affinity, and the presence of pathophysiologic conditions (e.g., change in blood pH) or endogenous compounds (e.g., bilirubin, free fatty acids) that may alter the drug-protein interaction. Albumin, alpha-1-acid glycoprotein, and lipoproteins are the important drug-binding proteins; albumin comprises an average of 58% of all plasma proteins.⁴¹ The plasma protein binding of various drugs is less in the neonate compared to other patient populations because of lower total plasma protein concentration and lower drug-protein binding capacities.⁴² Total protein concentration, including serum albumin and alpha-1-acid glycoprotein, as well as their function and binding capacity approach adult values by the first year of age and remain consistently stable in healthy children between 2 and 18 years of age.^{12,43} Conditions that decrease plasma proteins may increase the free, active fraction of highly protein-bound drugs, which can lead to enhanced effect or toxicity.

Acidic and neutral drugs such as beta-lactam antibiotics, warfarin, and phenytoin exhibit great binding affinity for albumin; basic compounds such as propranolol and alprenolol bind to alpha-1-acid glycoprotein, lipoproteins, and beta-globulins.⁴⁴ Several endogenous substances such as bilirubin and free fatty acid compete for the albumin binding sites and influence the drug-protein binding capacity. For example, bilirubin is often increased in neonates secondary to increased red cell destruction and limited liver capacity to conjugate it. The binding capacity of bilirubin to plasma albumin is decreased in newborn infants but approaches adult values by 5 months of age. Drugs highly bound to the plasma proteins, such as the sulfonamides, may displace bilirubin and contribute to kernicterus in neonates.⁴⁵

ELIMINATION

Most drugs or their water-soluble metabolites are excreted through the kidneys. Glomerular filtration, tubular secretion, and reabsorption all impact the renal elimination of drugs. The anatomical development of nephrons (nephrogenesis) in a fetus continues until 36 weeks GA with significant glomerular maturation occurring between 34 and 36 weeks GA.⁴⁶ After 36 weeks GA, the increase in renal mass is predominantly due to renal tubular growth. The overall functional capacity of the kidney increases with age up to early adulthood.

Glomerular filtration of drugs depends on the functional capacity of the glomerulus, the integrity of renal blood flow, and the extent and strength of drug-protein binding. The glomerular filtration rate (GFR) increases as renal blood flow increases and decreases with increasing protein binding of a drug. There is a positive correlation between GA and GFR in newborns between 27 and 43 weeks of GA. Renal blood flow approaches adult values by approximately 5–12 months of age.^{3,4} The GFR dramatically increases from birth and approaches adult values by approximately 3–5 months of age.⁴⁷ The GFR undergoes postnatal increases ranging from 10–15 mL/min/1.73 m² in a full-term newborn to 20–30 mL/min/1.73 m² by 1–2 weeks of life and approaches adult values of 73–127 mL/min/1.73 m² by 3 months of age.^{47–49}

GFR can be assessed by determining or estimating creatinine clearance (CrCl). Determining CrCl requires a 24-hr urine collection that is difficult to obtain in infants and children wearing diapers. Incomplete collections will lead to inaccurate results; complete collection may require catheterization of the patient, making the process more invasive. CrCl may not be the most accurate estimate of GFR, especially in neonates and infants since creatinine is not only filtered by the glomerulus but also secreted by the renal tubules.⁵⁰ In the early postnatal period, the serum creatinine value reflects maternal values. Nomograms or mathematical formulas are used to estimate CrCl from single serum creatinine values, which are most convenient but potentially less accurate (see Chapter 1).⁵¹ The Schwartz formula is commonly used to determine CrCl in the pediatric population. It uses serum creatinine (S_{cr}) as a surrogate marker of GFR and the concept of body height or length as a measure of body muscle mass. The formula is $GFR (mL/min/1.73 m^2) = k \times (L/S_{cr})$, where L is height or length in centimeters, S_{cr} is in mg/dL, and k is an empirical constant. This constant is determined by comparing L/S_{cr} ratio against measured GFR. The value of k is 0.45 for term infants through the first year of life, 0.55 for children and adolescent girls, and 0.7 for adolescent boys.⁵¹ However, this method of CrCl measurement invariably overestimates GFR in children, especially in those with mild-to-moderate chronic kidney disease (CKD). The k values used in this formula are more specific to the colorimetric method used to assay S_{cr} . However, at the end of 2010, all U.S. clinical laboratories switched to the new standardized Isotope Dilution Mass Spectrometry (IDMS) method to measure serum creatinine.⁵² The IDMS method appears to underestimate S_{cr} when compared to older methods and hence increases estimates of CrCl by 20 to 30%. A new equation has been developed taking into account this change in assay methodology. This new equation was developed in children with CKD with a median GFR of 41.3 mL/min/1.73 m² using iohexol plasma disappearance measurements as gold standard.⁵³ The bedside formula recommended in this group of patients is $GFR (mL/min/1.73 m^2) = 0.413 \times (L/S_{cr})$, where L is height or length in centimeters and S_{cr} is in mg/dL. This formula has not been evaluated in children with normal renal function and additional studies are required. GFR determined by the original and the updated Schwartz formula were compared to GFR measured using the technetium 99 diethylenetriaminepentaacetic acid as gold standard.⁵⁴ These measurements were conducted in pediatric patients prior to their hematopoietic stem cell transplantation and had a mean ($\pm$ standard deviation) GFR of 107 ± 28 mL/min/1.73 m². Only 53% of the GFR values estimated using the original Schwartz formula were within 30% of the corresponding DTPA-Tc99m determined GFR, compared to 77% of the GFR values estimated using the updated Schwartz formula. The updated formula classified normal GFR as reduced. Hence, the updated formula performed marginally better compared to the original formula but may not be accurate enough for routine use. The updated formula was developed for pediatric patients with mild-to-moderate CKD; however, the patients in this study had near normal GFR. In patients receiving aminoglycosides, renal clearance of the aminoglycoside approximates creatinine clearance, because >90% of the dose is filtered through the glomeruli and minimal excretion occurs in the form of tubular secretion.^{55,56} Because of this, aminoglycoside clearance has also been used to estimate GFR in patients receiving aminoglycosides. In general, the bedside Schwartz equation is a convenient and noninvasive method of determining CrCl and, hence, renal function in pediatric populations between 1 and 16 years of age.

Significant anatomical and functional immaturity of the renal tubules exists at birth. This affects passive reabsorption, active secretion, and active reabsorption processes. The tubular secretory

function does not mature at the same rate as the GFR because the proximal convoluted tubules are small relative to their corresponding glomeruli at birth.⁵⁷ Tubular function approaches adult values by 1 yr of life, thus affecting drugs eliminated by tubular secretion in addition to glomerular filtration. The renal tubules of a neonate have less surface area and urine concentrating ability and pH is lower compared to infants, children, and adults.⁵⁸

Dosing recommendations for renally excreted drugs, especially those with a narrow therapeutic range, should be based on the patient's renal function to avoid toxicity due to decreased elimination and increased accumulation when renal function decreases. Monitoring parameters such as urine output, creatinine clearance, and serum creatinine can help in the assessment of renal function. However, urine output varies with fluid intake, hydration status, renal solute load, and urine concentrating capabilities and may not accurately reflect renal clearance of drugs primarily excreted through the kidneys, especially drugs eliminated by tubular secretion rather than glomerular filtration.

METABOLISM

Drug metabolism primarily occurs in the liver; however, the kidneys, intestines, lungs, and skin may also be involved.⁵⁹ Most drugs that are metabolized are converted to more water-soluble compounds for excretion from the body by the kidneys. Active parent compounds may be transformed into inactive or active metabolites and pharmacologically inactive compounds, or prodrugs may be converted to their active moiety.

Hepatic blood flow, extraction efficiency, binding affinity, and enzyme activity can affect hepatic drug metabolism. Of these factors, enzyme activity is greatly dependent on patient age. Two primary enzymatic processes, phase I (nonsynthetic) reactions and phase II (synthetic) reactions, are involved in drug biotransformation. Phase I reactions include oxidation, reduction, hydrolysis, and hydroxylation. These reactions introduce or reveal a functional group within the substrate that will serve as a site for a phase II conjugation reaction.

The activity of the oxidizing enzymes is greatly reduced at birth, resulting in prolonged elimination of drugs such as phenytoin and diazepam.^{15,16,60,61} The hepatic mono-oxygenase system approaches and exceeds adult capacities by approximately 6 months of age.⁶² Alcohol dehydrogenase activity, detectable at $\leq 3\%$ to 4% of adult activity at 2 months of age, approaches adult capacity after 5 years of age.⁶³ Demethylation activity may not be seen until 14–15 months of age and may increase thereafter. Hydrolytic activity reaches adult values within the first few months of life. Quantitatively, cytochrome P450 isoforms are the most important phase I enzymes with CYP1, CYP2, and CYP3 genes important in human drug metabolism (see **Table 6-3**).

In phase II reactions, the substrate may be conjugated with endogenous agents such as sulfate, acetate, glucuronic acid, glutathione, and glycine, resulting in a more polar, water-soluble compound that can be eliminated easily by the renal and/or biliary systems. The phase II enzymes consist of glucuronosyltransferases, sulfotransferases, arylamine *N*-acetyltransferases, glutathione *S*-transferases, and methyltransferases, all of which play an important role in biotransformation of drugs (**Table 6-4**). Important differences exist between children and adults, and phase II enzymes do not all follow the same developmental patterns.

FACTORS INFLUENCING DRUG DISPOSITION

Asphyxia⁷⁷⁻⁷⁹

The elimination of aminoglycosides, phenobarbital, and theophylline in neonates asphyxiated at birth is markedly reduced due to decreased renal and liver perfusion during severe hypoxia. The Apgar score, used as a measure of viability in the newborn, is the total score of five objective neonatal assessment signs performed at different time intervals shortly after delivery (maximum score is 10 and scores < 3

TABLE 6-3. AGE-DEPENDENT DIFFERENCES IN ACTIVITY OF IMPORTANT DRUG METABOLIZING PHASE I ENZYMES AND DRUG METABOLISM

Enzyme	Fetus	Neonate	Infant	Child	Adolescent	Pharmacokinetic Consequences
CYP1A2	No activity	↓	↓ 50% of adult activity by age 1 yr	↔ after 1 yr of age	↔	Theophylline has a long half-life and low systemic clearance in newborns. ⁶⁴⁻⁶⁶
CYP2C9	10% of adult activity	30% of adult activity	↔ (reached by age 1–6 months)	↑ (peak activity at age 3–10 years)	↔ (decreases to adult value at puberty)	V _m values for phenytoin decreased from 14 mg/kg/day in infancy to 8 mg/kg/day in adolescence as a function of progressively decreasing CYP2C9 activity. ⁶⁷
CYP2C19 ⁶⁶	10% of adult activity	30% of adult activity	↔ (reached by age 6 months)	↑ (peak activity at age 3–4 years)	↔ (decreases to adult value at puberty)	Diazepam half-life increased in young infants (25–100 hr) compared to children (7–37 hr) and adults (20–50 hr) due to decreased oxidative activity. ⁶¹
CYP2D6	Minimal activity	↓ 30% of adult activity ⁶²	Maturation completed by 1 yr of age ⁶⁸	↔	↔	O-demethylation of codeine to morphine decreased in infants resulting in lack of efficacy and poor pain control. ⁶⁹
CYP2E1	10%–30% of adult activity ⁷⁰	No data	30%–40% of adult activity ⁷⁰	↔ by 10 years of age ⁷⁰	↔	Caffeine, acetaminophen, and certain toxic substances such as cigarette smoke and alcohol metabolized by this pathway. ⁷⁰
CYP3A4	10% of adult activity	↓ 30%–40% of adult activity ⁶⁶	Adult pattern (by age 1 yr) ⁶⁵	↑ (between age 1–4 yr then progressively decreases)	↔ (at puberty)	Midazolam systemic clearance and metabolism to one of its primary metabolites 1'-hydroxy-midazolam reduced in premature infants but increases 5-fold by 3 months of age. ^{71,72}

↔ = similar to adult capacity, ~ ↔ = near adult capacity, ↑ = increased compared to adult capacity, ↓ = decreased compared to adult capacity, V_m = maximum rate of metabolism.

reflect severe respiratory depression). In neonates with Apgar scores of <3 at 1 or 5 min or with cardiac and respiratory arrest requiring resuscitation, concentrations of drugs with narrow therapeutic ranges should be closely monitored. Dosage requirements for some drugs might need to be decreased by up to 50%. Because the duration of this effect is not well established, close follow-up is warranted.

Asphyxiated neonates receiving phenobarbital or theophylline can be initially empirically dosed with half the usual maintenance dose, followed by drug concentration monitoring for dosage adjustment (no adjustment is needed for loading doses). For neonates receiving aminoglycosides or vancomycin, urine output should be evaluated to assess the need for dosing interval adjustments. Urine output can serve as an early indicator of decreased renal clearance due to hypoxia.

TABLE 6-4. AGE-DEPENDENT DIFFERENCES IN ACTIVITY OF IMPORTANT DRUG-METABOLIZING PHASE II ENZYMES AND DRUG METABOLISM

Enzyme	Fetus	Neonate	Infant	Child	Adolescent	Pharmacokinetic Consequences
Uridine 5'-diphosphate glucuronosyl transferase	10% to 20% of adult activity ⁷³	↓	25% of adult activity by 3 months of age ⁷⁴	↔ present by age 6 months to 3 yr	↔	The ratio of glucuronide conjugate to sulfate conjugate of acetaminophen increases with age as the enzyme system matures; newborn 0.34; child (3–10 yr) 0.8; adolescent 1.61; and adult 1.8–2.3. ⁷⁵
N-acetyl-transferase-2	↓	↓	↓	↔ past 1 yr of age	↔	Decreased acetylation of sulfapyridine (sulfasalazine metabolite) results in increased side effects of nausea, headache, and abdominal pain. ⁷⁶
Methyltransferase		↑	↔	↔	↔	Specific drug example not available.
Sulfotransferase		↓	↑ for specific substrates	↑ for specific substrates	↔	Specific drug example not available.

↔ = similar to adult capacity, ~ ↔ = near adult capacity, ↑ = increased compared to adult capacity, ↓ = decreased compared to adult capacity.

Exchange transfusion⁸⁰⁻⁸²

Information regarding the effect of exchange transfusions on concentrations of drugs commonly administered to neonates is limited and often controversial. Drug loss has varied from 1% to 55%, depending on the medications, study design, and timing and frequency of procedures. The magnitude of the decline in drug concentrations is greatest when the procedure is performed shortly after dose administration (because concentrations are higher) and can be considered clinically inconsequential at the end of the dosing interval. The number of blood volumes exchanged (on the same dose) and the rate used augments the effect.

When exchange transfusions are at the beginning of the dosing interval and a drop in concentration might be clinically consequential, drug concentrations may be obtained to assess drug loss and to calculate a “replacement” dose. Concentrations obtained following exchange transfusions should not be employed for routine pharmacokinetic calculations because they do not reflect steady state conditions.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) provides prolonged cardiopulmonary bypass and thus, supports infants with life-threatening cardiac and/or respiratory failure. The following factors influence drug disposition during ECMO: (1) priming volume of the circuit that may exceed the blood volume of the neonates and lead to an increased V for water soluble drugs; (2) membrane oxygenator and polyvinyl chloride (PVC) tubing that provides a large surface area for drug adsorption and subsequent leakage (binding occurs to a greater extent with a new circuit and declines when the circuit has been used over several days); (3) site of administration (administration post-reservoir minimizes the effects of ECMO on drug disposition but bypasses the benefit that occurs with pre-reservoir administration of bolus injections—the trapping of air bubbles that can lead to cerebral emboli); and, (4) flow rate <250 mL/min that can lead to drug pooling at the reservoir for medications administered pre-reservoir. As

a result of these physiologic and mechanical variables, determining pharmacokinetic parameters and appropriate dosing regimens during ECMO is difficult.

In neonates on ECMO, the apparent volume of distribution for gentamicin is increased, and the elimination half-life is prolonged as compared to values observed off ECMO, as well as when compared to term neonates.⁸³⁻⁸⁶ For an infant on ECMO, a gentamicin dose of 2.5–3 mg/kg administered every 18–24 hr to achieve a peak serum concentration between 5–10 mg/L and trough serum concentrations of 0.5–1 mg/L is empirically recommended.⁸⁴ Similar modification in extension of dosing interval can be made for other aminoglycosides such as tobramycin and amikacin. For vancomycin, the data are conflicting.^{87,88} Most studies report similar variability in pharmacokinetic parameters among neonates on or off ECMO and thus suggest no need for vancomycin dosing adjustments. Others suggest extending the interval to ensure troughs within the therapeutic range. Pharmacokinetic studies of midazolam used for sedation in neonates on ECMO offer conflicting data and interpretation.^{89,90} The studies reported a significant increase in volume of distribution and a prolonged half-life from the onset of ECMO. However, one study reported a 3-fold increase in the clearance of midazolam and 1-hydroxymidazolam in the first 5 days after start of ECMO.⁹⁰ At the end of 3 hours only 0.62% of the original amount of midazolam remained in the circuit. The clearance of hydroxymidazolam glucuronide, the metabolite, remained constant. A constant 10% of sedation was provided by 1-hydroxymidazolam, but sedation provided by hydroxymidazolam glucuronide increased from 12% to 34% over the course of 7 days, due to rising concentrations. The authors of this study recommend increasing the infusion rate of midazolam after 5–7 days to compensate for the increased clearance of midazolam and 1-hydroxymidazolam to achieve a target midazolam concentration of 400 mcg/L. The authors of the second study believe that the initial increase in V is due to the ECMO circuit's reversible sequestration of midazolam.⁸⁹ Therefore, increased plasma concentrations of midazolam during the later phases of ECMO were observed. Hence, the need for a higher initial dose of midazolam followed by a decrease in dose rate to prevent high concentrations is recommended. Both studies found large interpatient variability in V and clearance; thus careful dose titration based on sedation scores and adverse effects is recommended. These studies were conducted using silicone membrane oxygenators instead of the currently used polymethylpentate (PMP) membrane oxygenators (MO). The PMP MO were developed to provide efficient gas exchange with less flow resistance requiring smaller priming volumes. The reported midazolam data may not be applicable when using PMP MO. Ex-vivo studies using PMP MO exhibited that at the end of 24 hours only 18.5% of midazolam remained in the circuit.⁹¹ Dosing during ECMO should take into account the site of administration and flow rate and individualized based on drug concentrations.⁹² An increased V and prolonged elimination rate with large interpatient variability was noted when bumetanide was administered to neonates on ECMO.⁹³ Extensive non-renal elimination of bumetanide was hypothesized to be mainly due to drug loss in the ECMO circuit. A pronounced diuresis was observed during the early period after drug administration (6 hr). Due to insufficient data, specific dosing and interval recommendations cannot be made; however, additional doses of the drug may be needed to offset the shorter duration of action. Higher doses of morphine and fentanyl were required in neonates on ECMO to induce prolonged sedation and analgesia.⁹⁴⁻⁹⁷ The reason for increased dose requirement during ECMO is unclear. Clearance also increases once the infants are taken off ECMO, which may result in opioid withdrawal. Despite a possible higher dose requirement in these infants, both drugs should be initiated at standard doses and titrated as needed to obtain pain control and sedation without toxicity. A slow taper can prevent opioid withdrawal after discontinuation of ECMO.

Patent ductus arteriosus⁹⁸⁻¹⁰⁰

In fetal circulation, the ductus arteriosus (DA) connects the pulmonary artery to the descending aorta allowing blood to bypass the lungs. At birth, with clamping of the umbilical cord and aeration and expansion of the lungs, the ductal PaO₂ rises to approximately 100 mmHg. Concurrently, the amount of circulating prostaglandin (PG) and the sensitivity of the ductus to the circulating PG is lowered and the DA constricts and closes. When the DA fails to close, it is called patent ductus arteriosus (PDA).

Significant differences in V (depending on whether the ductus arteriosus is open or closed) have been shown for several drugs including gentamicin, indomethacin, and vancomycin. The calculated V decreases after PDA closure, potentially changing dosing requirements that were previously adequate. When using indomethacin for the pharmacological closure of the PDA, its nephrotoxic effects may decrease renal clearance of aminoglycosides, digoxin, and vancomycin.

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease, predominantly seen in the Caucasian population, affecting approximately 30,000 children and young adults in the United States and 70,000 worldwide.¹⁰¹ About 1,000 new cases are diagnosed each year in the United States with 70% diagnosed by 2 years of age. More than 50% are ≥ 18 years of age, and the median predicted age of survival is almost 40 years. Mutation of a single gene on chromosome 7 encoding the CF transmembrane conductance regulator leads to abnormalities affecting multiple organs; this mutation impacts all aspects of drug disposition.¹⁰² Factors such as lower rate of absorption, larger apparent V , and greater metabolic and renal clearances may alter drug disposition and will result in lower drug concentrations after administration of age-appropriate doses of many drugs in patients with CF when compared to normal patients.

Drug absorption in patients with CF may be decreased due to altered GI physiology such as gastric acid hypersecretion, bile acid malabsorption, and proximal small intestinal mucosal injury.^{103,104} However, changes do not always occur.

Alteration in protein binding of drugs due to hypoalbuminemia and hypogammaglobulinemia in patients with CF can alter the distribution volume.¹⁰⁵ The choice of units using body surface area (L/m^2) and body weight (L/kg) may affect the apparent V because body weight is affected much earlier than would be expected from linear growth during the course of CF. A higher V has been reported for cloxacillin, theophylline, and ceftazidime in patients with CF compared to healthy individuals when expressed by units of body weight.¹⁰⁶⁻¹⁰⁹ For drugs such as methicillin and ticarcillin, the distribution volume was not significantly different when expressed per unit of body surface area (BSA).¹⁰⁸ It has been recommended that V should be normalized by lean body mass rather than BSA in CF patients.^{109,110} However, the appropriateness of one approach over another is still unknown.

Hepatobiliary dysfunction, increases in hepatic enzymes, and reduced synthesis of proteins is reported in approximately 30% to 40% of patients with CF.^{111,112} Hepatic clearance of drugs is largely influenced by the hepatic blood flow and activity of liver enzymes. Evidence of an increase in portal venous blood flow in CF patients is conflicting. Age, severity of CF disease, and extent of hepatic dysfunction may influence the hepatic blood flow.

Hepatic biotransformation of drugs by phase I and II reactions may either be increased or remain unchanged in patients with CF compared to healthy individuals. Disease-specific alterations in hepatic biotransformation in patients with CF are not limited to the mono-oxygenase system. Ibuprofen is mainly metabolized by glucuronosyltransferase to a glucuronide conjugate for example.¹¹³ A significant increase in the apparent total clearance of ibuprofen was observed after oral administration in children with CF compared with healthy children, suggesting that glucuronidation is enhanced in CF.¹¹⁴ Both in vitro and in vivo data showed increased metabolic clearance of unbound sulfamethoxazole to *N*-4-acetylsulfamethoxazole and thus confirmed that the intrinsic activity of *N*-acetyltransferase (NAT1) was significantly increased in patients with CF.^{115,116}

Results from studies measuring renal function, i.e., GFR and tubular clearance, are conflicting with both parameters either increased or unchanged in patients with CF. These conflicting results are possibly attributed to differences in age and severity of the CF disease, e.g., glomerulomegaly and hyperfiltration. The renal clearance of ceftazidime was significantly increased in patients with CF compared to healthy adults due to increased glomerular filtration.^{117,118} Aminoglycosides are primarily eliminated by glomerular filtration; however, they are also reabsorbed by the proximal tubule. Studies comparing renal clearance of amikacin to inulin and tobramycin to iothalamate indicated that the

glomerular filtration of aminoglycosides is not altered in patients with CF.^{119,120} Therefore, a decrease in tubular reabsorption and/or clearance into the respiratory tract was speculated as the cause of increased plasma clearance of the aminoglycosides. Despite faster clearance in the pediatric CF population, extended interval once daily dosing of aminoglycosides is a recommended option for treatment of acute pulmonary exacerbations.¹²¹ In tobramycin naïve patients, a starting dosage of 10 mg/kg/day given once daily may be appropriate.¹²² The therapy should be individualized for the patient by drawing two tobramycin concentrations; one drawn at least 2 hours after the dose has been administered followed by the second measurement drawn 8 to 12 hours after the dose. These concentrations can be drawn after the first or second dose. Dose recommendations should be made to achieve extrapolated peak concentrations of 20–30 mg/L, troughs of less than 1 mg/L or AUC of 100 mg × hr/L. In amikacin naïve patients, therapy can be started at 30–35 mg/kg/day given once daily. Extrapolated peak amikacin concentrations of 73 to 121 mg/L, trough less than 1 mg/L and area under serum concentration-time curve of 235–287 mg × hr/L can be expected with such doses. If the patient has received aminoglycosides with doses given every 8 hours and pharmacokinetic dosing adjustments in the past, that total daily dose can be administered as a single daily dose.¹²² Tubular secretion of penicillin derivatives such as cloxacillin, methicillin, and ticarcillin that are primarily eliminated renally by tubular secretion was significantly higher in patients with CF compared to healthy individuals.^{108,123,124} Beta-lactams have also been administered using extended duration of infusion or as continuous infusion in general and specifically in the CF population. They exhibit time-dependent killing with bactericidal activity of the drug coinciding with the duration the serum drug concentration that is above the minimum inhibitory concentration (MIC) for the organism. Pharmacodynamic (PD) exposure is measured by determining the duration (percentage) of the dosing interval during which the drug concentration remains above the MIC. Bacterial resistance of gram negative organisms to anti-pseudomonal beta-lactams and carbapenems is increasing in CF patients.¹²⁵ Administering IV beta-lactams as continuous infusions or prolonged infusions have shown to improve the PD exposure. Pharmacokinetics of meropenem administered as a 3-hr infusion has been reported in CF children.¹²⁶ When compared to non-CF children, the clearance when adjusted for body weight was slightly greater in the CF patients.¹²⁷

Altered drug disposition in patients with CF can impact drugs with a narrow therapeutic index and drugs that demonstrate a large degree of variability in their pharmacokinetic parameters. Therefore, the normal age-appropriate drug doses may need to be altered in CF patients based on the results of measured drug concentrations.

PHARMACOGENOMICS IN CHILDREN

Pharmacogenomics, the influence of DNA sequence variation on drug effect, can result in clinically relevant differences in drug absorption, metabolism, and elimination ultimately affecting drug efficacy and safety. Atomoxetine, codeine, pimozide and tramadol are examples of drugs which have a U.S. Food and Drug Administration advisory or black box warnings regarding their use or dose in pediatric patients.^{128–132} These warnings were secondary to increased adverse effects due to genetic differences in CYP2D6 enzyme activity. Atomoxetine and pimozide doses should be decreased to prevent toxicity in children who have decreased CYP2D6 activity (poor metabolizers). Tramadol has a safety alert for its use in children 17 years of age or less due to the risk of slowed or difficult breathing, especially when used in ultra-rapid metabolizers for tonsillectomy/adenoidectomy pain. In ultra-rapid metabolizers an increased amount of O-desmethyltramadol, an opioid metabolite of tramadol, is formed resulting in the adverse effect. Similarly, there is a boxed warning against the use of codeine in children who are ultra-rapid metabolizers for treatment of post tonsillectomy/adenoidectomy pain due to increased risk of respiratory and central nervous system depression and death. These toxicities are seen in genetically ultra-rapid metabolizers of codeine via the CYP2D6 enzyme activity that results in increased morphine concentrations. Advances in the field of pharmacogenomics are likely to contribute to achieving optimal efficacy, safety, and quality of life for the pediatric population in the future.

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THERAPEUTIC DRUG MONITORING IN THE GERIATRIC PATIENT

Susan W. Miller

The complex process of aging is characterized by progressive loss in the functional capacities of organs, a reduction in mechanisms of homeostasis, and altered response to receptor stimulation.¹ These changes combine to increase the susceptibility of elderly individuals to environmental and physical stressors as well as the effects of medications. The prevalence of diseases increases with advancing age, and this increase is accompanied by an increase in the use of medications.² Medication therapy is among the most widely used and highly valued interventions for acute and chronic diseases of older adults, yet the use of drug therapy in the geriatric patient is one of the most difficult aspects of patient care.^{3,4} The unexpected or exaggerated response to drug therapy exhibited by a geriatric patient compared with a younger patient of the same sex and body weight can frequently be explained through pharmacokinetic or pharmacodynamic changes.⁵ Older patients take more medications than younger persons, yet major drug studies are performed primarily on individuals younger than 55 years of age.

The effects of aging on drug metabolism are complex and difficult to predict.⁶ These effects depend on the pathway of drug metabolism in the liver, on environmental factors, and on cardiac function.⁷ Although many irreversible changes occur with aging, it is now well recognized that individuals age at different rates (chronological and biological age are not necessarily synonymous). Frailty, a biological syndrome in the geriatric patient, is recognized as a confounding factor when considering the impact of aging on drug disposition.^{2,8} The frailty of a geriatric patient can alter drug metabolism, and this effect appears to vary from drug to drug. The frail elderly (those that are vulnerable and are at the highest risk for adverse health outcomes) have been shown to have reduced drug metabolism.⁹ Frail older adults are identifiable as those at high risk for dependency, institutionalization, falls, injuries, acute illness, hospitalizations, slow recovery from illness, and mortality.¹⁰ Markers for inflammation, such as tumor necrosis factor, interleukin-6, and C-reactive protein, may serve as biochemical markers for frailty and may prove to be a method to characterize an individual's biological age.¹¹ Because of the frailty of elderly patients, it is important that the first medication prescribed be the most effective choice for the best chance at an optimal clinical outcome.¹² To make the most effective choice, clinicians should take into consideration both personalized pharmacokinetic changes in drug metabolism and pharmacodynamic responses of individual patients, when selecting drug therapies for geriatric patients.

Pharmacokinetic studies comparing young and older adults are often difficult to accomplish due to the problems associated with recruiting healthy older individuals to compare with healthy younger individuals; however, they are increasing in number.¹³⁻²⁹ Problems have been identified with the selection of patient participants and reporting of the clinical trials results to assess age-related pharmacokinetic differences in drugs.³⁰ Often, participants are the healthy (younger) geriatrics and not the very old (over the age of 85 and/or frail) geriatric patients. The extrapolation of dosages and possible side effects in the very old population may or may not be appropriate.³⁰ Physiological differences, pathophysiological changes, altered protein binding, and/or concomitant use of medications may account for the altered pharmacokinetics displayed by older patients.³¹

The following examples illustrate the variability of changes that occur in the elderly. There is evidence to show that increased age may delay absorption of transdermal *opioids* but not affect the maximum and steady state concentrations.³² An infusion of morphine into older patients showed a rapid distribution, followed by a slower elimination when compared to younger patients.³³ Pharmacokinetic studies



have reported no need for dosage changes in the elderly for proton-pump inhibitors, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.³⁴⁻³⁶ Data show that the angiotensin converting enzyme inhibitors (ACEIs) *trandolapril* and *moexipril* should be initiated at lower doses in geriatric patients, but no overall dosage modifications are necessary.³⁷ Other data show that, in the presence of renal impairment, plasma concentrations of ACEIs increase and doses should be adjusted based on renal function.³⁸ The selective estrogen receptor modulators have variable pharmacokinetic changes associated with aging, with *tamoxifen* and *toremifene* exhibiting increased plasma concentrations with increased age; tamoxifen greater than toremifene; however, neither drug has accompanying package insert recommendations for dosage alterations. No age-related differences in *raloxifene* pharmacokinetics have been identified, but cautionary dosing is advised in both moderate-to-severe renal impairment and in hepatic impairment.³⁹ Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reduced renal clearance in the presence of renal impairment.⁴⁰

Decreased clearance and prolonged half-life of sertraline suggest that steady state concentrations would be higher and achieved later during long-term administration to geriatric patients.⁴¹ A reduced clearance for fosphenytoin, ticlopidine, and ropinirole has been shown in geriatric patients, with the clinical significance of this reduced clearance unknown.⁴²⁻⁴⁴ The fluoroquinolone antibacterials, including ciprofloxacin, and levofloxacin require dosage adjustments based on their predominant renal elimination.⁴⁵ The antiepileptic drugs, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, and topiramate, all exhibit a decrease in apparent oral clearance in elderly patients when compared to non-elderly adult controls.⁴⁶ Studies in geriatric patients also show reduced clearance of pregabalin, lacosamide, and retigabine due to less efficient metabolism and/or impaired renal function.⁴⁷ Studies measuring the pharmacokinetics of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine in geriatric patients report some changes in pharmacokinetic parameters, but these are not considered clinically significant and no dosage changes are suggested unless patients are in severe renal impairment (galantamine and creatinine clearance <9 mL/min).⁴⁸

Studies reporting data on hypnotic drug disposition and effects in geriatric patients indicate that this population may have reduced metabolic clearance of hypnotic medications, leading to increased plasma concentrations of these agents and/or increased sensitivity to hypnotic medications. Recommended doses of sleep-inducing medications such as triazolam and zolpidem for geriatric patients are generally lower than for non-geriatric patients.⁴⁹

Information regarding dosage alterations based on the pharmacokinetic profiles of drugs in geriatric patients is very important to the clinician as current dosing in geriatric patients is often based on broad generalizations such as “use one-third to one-half the usual dose,” or anecdotal data—not on solid pharmacokinetic or pharmacodynamic studies. Pharmacokinetic and/or pharmacodynamic differences in older patients may account for either the toxic or subtherapeutic response that often occurs.

Adverse drug reactions or events (ADEs) and drug-drug interactions (DDIs) occur more frequently in geriatric patients, in part because this population is most likely to be using complex drug therapies.⁵⁰⁻⁵⁶ The estimated annual rate of ADEs for individuals aged 65 years or older has been measured at more than twice the rate for those younger than 65 years of age.⁵⁷ Additional data have shown that for persons 65 years of age and older, the estimated annual rate of ADEs requiring hospitalization was nearly seven times the rate for persons younger than 65 years. Although considerable evidence suggests that an ADE will not occur simply because a patient is elderly, pharmacokinetic and pharmacodynamic changes in the elderly may significantly alter drug disposition and must be considered as contributing to ADEs.⁵⁸⁻⁶⁰ Symptoms of ADEs can be extremely subtle in an elderly patient and may be manifested by increased frequency of falls, increased confusion, excessive sedation, constipation, urinary retention, decreased oral intake, or a general failure to thrive.⁶¹

Significant ADEs are most likely observed with drugs having a narrow therapeutic index or saturable hepatic metabolism (e.g., *phenytoin*, *warfarin*, and *theophylline*) or when elimination is via a single mechanism or pathway. A study of emergency department visits for ADEs showed that drugs that

commonly require regular outpatient monitoring to prevent toxicity (*antidiabetic agents, warfarin, several anticonvulsants, digitalis glycosides, theophylline, and lithium*) were involved in the most unintentional overdoses.⁵⁷ The patients most at risk usually have multiple disease states or compromised organ function, and they receive multiple drug therapy. Complicated drug therapy, poor compliance, and altered pharmacokinetics are among the many possible causes of ADEs and DDIs.^{50,51,55,60-62}

PHYSIOLOGIC CHANGES

Absorption, distribution, metabolism, and excretion

The processes of absorption, distribution, metabolism, and excretion determine the amount of drug present at any given time within the body’s various tissue and fluid compartments.

Pharmacokinetic parameters represent a composite of both genetic and environmental effects.⁶³⁻⁶⁶ The physiologic changes produced by aging that may have important implications for altered pharmacokinetics are summarized in **Table 7-1**.

Age-related physiologic changes in the gastrointestinal (GI) tract include elevated gastric pH, delayed gastric-emptying, and decreases in GI motility, intestinal blood flow, and absorptive surface area. Reduced gastric secretion of acid can reduce tablet dissolution and decrease the solubility of basic drugs.⁶⁷

TABLE 7-1. PHYSIOLOGIC CHANGES WITH AGING THAT MAY AFFECT PHARMACOKINETICS^{7,65}

Process	Physiologic Effect
Absorption	Reduced gastric acid production
	Reduced gastric-emptying rate
	Reduced GI motility
	Reduced GI blood flow
	Reduced absorptive surface
Distribution	Decreased total body mass
	Increased percentage of body fat
	Decreased percentage of body water
	Decreased plasma albumin
	Disease-related increase in alpha-1-acid glycoprotein
Metabolism	Altered relative tissue perfusion
	Altered protein binding
	Reduced liver mass
	Reduced liver blood flow
	Reduced hepatic metabolic capacity
Excretion	Reduced enzyme activity
	Reduced enzyme induction
	Reduced renal blood flow
	Reduced glomerular filtration
	Reduced renal tubular secretory function
Tissue sensitivity	Alterations in receptor number
	Alterations in receptor affinity
	Alterations in second messenger function ^a
	Alterations in cellular response
	Alterations in cellular nuclear response

^aA chemical (e.g., cyclic AMP or Ca⁺⁺) inside the postsynaptic neuron released by a first messenger (e.g., a neurotransmitter) and responsible for downstream regulation of a pathway or gene expression.

The delay in gastric emptying allows more contact time in the stomach for the following:

- Potentially ulcerogenic drugs such as the NSAIDs and bisphosphonates
- Antacid drug interactions due to an increased opportunity for binding
- Increased absorption of poorly soluble drugs

A higher incidence of diarrhea and a delay in onset action of weakly basic drugs also result from this physiologic effect.

One study reported a three-fold increase in *levodopa* availability in the elderly due to reductions in intragastric and hepatic first-pass metabolism.⁶⁸ Differences in gastric emptying might help explain the unpredictable and inconsistent responses to *levodopa* in individual patients.⁶⁹ The increased degradation of *levodopa* by dopa-decarboxylase occurs when *levodopa* is used alone (not in combination with a dopa-decarboxylase inhibitor such as *carbidopa*). *Levodopa* is only used in combination therapy as an anti-Parkinson agent.

Clorazepate, a benzodiazepine, is converted by acid hydrolysis in the GI tract to an active metabolite, desmethyldiazepam, that has reported lower concentrations in both elderly and patients with gastrectomies compared with younger adults. This decrease in active metabolite levels is presumed to be a result of a decreased conversion from the parent drug.⁷⁰

Age influences the active transport mechanisms involved in the absorption of nutrients such as sugars, vitamins (e.g., *thiamine* and *folic acid*), and minerals (e.g., *calcium* and *iron*). In elderly patients, this absorption is often reduced.⁷¹ Age-related physiologic changes alone apparently do not influence the passive transport mechanisms by which most drugs are absorbed.

Some drugs with high intrinsic clearance in the liver are metabolized during their passage from the portal vein through the liver to the systemic circulation, thus reducing their oral bioavailability. Drugs with potentially *increased* bioavailability in the elderly, presumably due to a decrease in first-pass metabolism, are shown in **Table 7-2**.^{72,73}

Drugs that undergo first-pass metabolism and may have *decreased* bioavailability in older patients include *clorazepate*,²³ *digoxin*,⁷⁴ and *prazosin*.⁷⁵ The decrease in bioavailability may be the result of a combination of reduced blood flow to the hepatic system and slowed GI motility that allows for drug degradation in the GI tract prior to absorption.

Although the total amount of absorbed drug reaching the systemic circulation is affected for only a few drugs, age-related physiologic changes can alter the absorption rate, resulting in an erratic and sometimes inconsistent pharmacologic response. The clinical effect is a delay in the time to peak or maximum concentration, which is more problematic with therapies where a high peak or short time to peak is important. Clinical factors such as acute congestive heart failure (CHF), achlorhydria, and unusual dietary patterns may occasionally necessitate the intravenous route of administration because of the incomplete absorption via oral and intramuscular routes. The absorption of intramuscularly administered drugs decreases in bedridden elderly patients, perhaps because of changes in regional blood flow. In geriatric patients, percutaneous absorption of transdermal medications can be affected by reductions in the water and lipid layers of the aged skin. Lipophilic medications such as *testosterone*, *estradiol*, and *fentanyl* have shown reduced absorption in geriatric patients.⁷⁶ Considerations involved in using controlled-release dosage formulations include age-related changes in GI transit time, motility, and pH.⁷⁷

Binding proteins

Age can alter the distribution of drugs throughout the body and to target organs. Although total protein generally is unaffected by aging, the plasma albumin portion has been shown to decrease from 4 g/dL in young adults to approximately 3.5 g/dL in patients over 80.⁷⁸ The mean serum albumin of nursing facility residents has been found to be 3 g/dL or lower.⁷⁹ The two major plasma proteins to which medications can bind are albumin and alpha-1-acid glycoprotein (AAG), and concentrations of these

TABLE 7-2. DRUGS WITH INCREASED BIOAVAILABILITY IN THE ELDERLY

Amitriptyline	Lidocaine
Chlordiazepoxide	Metoprolol
Cimetidine	Metronidazole
Desipramine	Propranolol
Imipramine	Quinidine
Labetalol	Trazodone
Levodopa	Verapamil

proteins may change with concurrent pathologies seen with increasing age. Plasma protein binding is a major determinant of drug action, particularly for drugs that are highly protein bound and changes in protein binding can have clinical implications.³¹ If albumin is decreased, a compensatory increase in unbound (active) drug occurs if the percentage of the bound drug is 90% or more; however, this is often compensated by increased distribution or clearance, so little or no clinical effect is experienced. In addition to age, disease states such as cirrhosis, renal failure, and malnutrition can lower albumin concentrations.

AAG, an acute phase reactant, binds mostly to lipophilic basic drugs and tends to increase with age and in response to acute illness. The binding of drugs to AAG increases during acute illness and can return to normal after several weeks or months when the acute stress passes and AAG decreases.^{80,81} Medications that bind to AAG and are commonly associated with adverse effects in geriatric patients are *lidocaine*, *meperidine*, and *propranolol*.³¹ Though protein binding may be altered in aging, physiological changes and pathophysiological disorders also occur and these changes usually have greater clinical significance than changes in drug plasma protein binding.³¹

Increased unbound (free) fraction

Increases in the free fraction of *naproxen*, *diflunisal*, and *salicylates* have been found in the elderly, presumably as a result of the decrease in albumin protein binding.⁸² Increased concentrations of NSAIDs have been associated with a higher incidence of gastric bleeding from peptic ulcers.⁸³ Whether the increase in gastric bleeding is due to changes in protein binding or the increased drug concentration is not known.

Decreased protein binding (as well as the resultant increased free fraction) is also seen with *phenytoin*, which is cleared from the plasma more rapidly because of an increase in free phenytoin.⁸⁴ Seizure control may be seen at lower measured total (bound plus unbound) phenytoin concentrations in the elderly whose unbound fraction has increased. Although the increase in the free fraction of phenytoin with age is statistically significant, it is unlikely to warrant a compensatory change in dose unless the patient has a total phenytoin concentration that is near the upper limit of the therapeutic range and/or that is sufficient to saturate metabolizing enzymes. With *meperidine*, binding to red blood cells decreases with age, thus increasing the amount of free meperidine available in the elderly patient.⁸⁵ Meperidine is considered an inappropriate drug for use in the elderly.⁸⁶⁻⁸⁹

Although higher concentrations and the resulting therapeutic effects of some drugs may be beneficial, the accompanying risks of toxicity are problematic in the geriatric patient. Doses of most highly protein-bound drugs (>90% protein bound) should be reduced initially and increased slowly if there is evidence of decreased serum albumin (i.e., <3.5 g/dL). If several highly protein-bound drugs are used together, the chance of a drug interaction increases. **Table 7-3** shows the impact of age on the protein binding of select drugs.

Lean body weight to fat ratio

Changes in the ratio of lean body weight to fat also can alter drug distribution leading to changes in pharmacologic response. In the average elderly patient, total body water is decreased and total body

TABLE 7-3. EFFECTS OF AGE ON PLASMA PROTEIN BINDING OF SELECT DRUGS IN GERIATRICS⁸²

Drugs with decreased protein binding (increased free fraction)	
Acetazolamide ^b	Lorazepam ^{a,b}
Carbenoxolone	Meperidine ^{a,b}
Ceftriaxone ^a	Naproxen ^b
Clomethiazole ^a	Phenytoin ^a
Desipramine ^{a,b}	Salicylate ^a
Desmethyldiazepam	Temazepam ^b
Diazepam ^{a,b}	Theophylline ^b
Diflunisal ^b	Tolbutamide
Fluphenazine ^b	Triazolam ^{a,b}
Flurazepam	Warfarin ^a
Lidocaine ^a	
Drugs with increased protein binding (decreased free fraction)	
Amitriptyline ^{a,b}	Flurazepam ^b
Benazepril	Haloperidol ^{a,b}
Ceftriaxone ^a	Ibuprofen ^{a,b}
Chlorpromazine ^{a,b}	Lidocaine ^a
Disopyramide ^{a,b}	Naproxen ^b
Enalaprilat	Nortriptyline ^{a,b}
Etomidate	Propranolol ^a
Select drugs with no change in protein binding	
Alprazolam ^b	Metoprolol
Amitriptyline ^{a,b}	Midazolam
Atropine ^b	Nadolol
Caffeine ^b	Nitrazepam ^{a,b}
Chlordiazepoxide ^b	Nortriptyline ^{a,b}
Chloroquine	Oxazepam ^b
Desipramine ^{a,b}	Penicillin
Desmethyldiazepam	Phenobarbital
Diazepam ^{a,b}	Phenytoin ^a
Disopyramide ^{a,b}	Piroxicam ^b
Donepezil	Propranolol ^{a,b}
Etodolac ^b	Quinidine ^b
Fentanyl	Risperidone ^b
Furosemide	Salicylate ^a
Haloperidol ^{a,b}	Sotalol ^b
Ibuprofen ^{a,b}	Sulfadiazine
Imipramine ^b	Sulfamethoxazole
Lorazepam ^{a,b}	Thioridazine ^b
Maprotiline ^b	Triazolam ^{a,b}
Meperidine ^{a,b}	Trimethoprim
Methadone	Vancomycin
Methotrexate	Verapamil ^b
	Warfarin ^a

^aConflicting data have been reported.
^bDrugs considered to be inappropriate for use in the elderly.

fat is increased. These changes influence the onset and duration of action of highly tissue-bound drugs (e.g., *digoxin*) and water-soluble drugs (e.g., *alcohol*, *lithium*, and *morphine*). The dosages of most water-soluble drugs are based on estimates of lean or ideal body weight. If a patient's actual weight is less than the estimated lean body weight, the actual weight should be used in most dosage calculations.

Between ages 18 and 85, total body fat increases on average in both females and males; lean body mass eventually decreases in both groups as well. With increasing age, the volume of distribution of lipophilic drugs may increase as a result of diminished protein binding and an increased fat to lean muscle ratio. Fat-soluble drugs (e.g., most *tricyclic antidepressants*, *barbiturates*, *benzodiazepines*, *calcium channel blockers*, and *phenothiazines*) may have a delayed onset of action and can accumulate in adipose tissue, prolonging their action sometimes to the point of toxicity.^{67,90} All of these drugs are considered inappropriate in the elderly due to safer alternatives.⁸⁶⁻⁸⁹

DRUG ELIMINATION

Drugs are primarily cleared from the body by metabolism in the liver, excretion by the kidneys, or some combination of the two processes. A decrease in total body clearance results in higher drug concentrations and an enhanced pharmacologic response, which can lead to toxicity.⁹⁰

Metabolism

For some drugs, hepatic metabolism is highly dependent on blood flow. Liver blood flow can decrease significantly with increasing age and is further compromised in the presence of CHF. With drugs that are highly dependent on hepatic metabolism (e.g., most *beta-blockers*, *lidocaine*, and *narcotic analgesics*), a decrease in hepatic clearance can increase the drug concentration and lead to toxicity.

In addition to altering hepatic blood flow, age influences the rate of hepatic clearance by causing changes in the intrinsic activity of selected liver enzymes. This age-related process has been found in the Phase I enzymatic pathway. Common drugs using this pathway and having the potential for metabolism influenced by age include the longer acting benzodiazepines such as *diazepam*, *chlordiazepoxide*, and *clorazepate*. The enzymatic demethylation of *nortriptyline*,⁹¹ *imipramine*,⁹² *thioridazine*,⁹³ and *theophylline*⁹⁴ also decreases in the elderly. All of these drugs are considered inappropriate for use in the elderly except *imipramine*.⁸⁶⁻⁸⁹

Drugs that undergo hepatic Phase II enzymatic biotransformation (e.g., *lorazepam*, *oxazepam*, and *temazepam*) do not appear to be adversely affected by age; therefore, they are preferred agents for older patients.

At all ages, drug metabolism can be affected by genetics, smoking, diet, gender, comorbid conditions, and concomitant drugs. The cytochrome P (CYP) 450 enzyme system, primarily a part of the Phase I hepatic metabolism pathway, can be affected by many drugs. Of the more than 30 CYP 450 isoenzymes identified to date, the major ones responsible for drug metabolism include CYP3A4, CYP2D6, CYP1A2, and the CYP2C subfamily. Newer evidence in geriatric patients has shown a reduction in CYP2C19 activity, no reduction in CYP2D6 activity, and marked variability with little change in the CYP1A2, CYP2C9, CYP2E1, and CYP3A4 isoenzymes.^{76,95} CYPs are increasingly being identified in extrahepatic organs such as the intestine, kidney, brain, and skin. The full effect of aging on these enzyme systems is yet to be determined.⁹⁶ Unlike renal function, no accurate laboratory tests directly measure liver function for drug dosage adjustment. Nonspecific tests to monitor liver function include alanine aminotransferase, plasma albumin, and prothrombin time.

The effect of aging on P-glycoprotein (Pgp) function throughout the body is yet to be reported. Pgp is found in the intestine, among other sites, and it has been implicated in the efflux of many medications that could account for variability in drug metabolism. Altered expression of Pgp with increasing age may be the cause of drug interactions and altered drug effects in geriatric patients.⁹⁵

Renal clearance

Consistent with the behavior of many drugs, pharmacokinetic data from elderly patients are similar to that of patients with mild renal compromise, in that most age-related declines in drug clearance can be explained by reductions in renal function.⁹⁷ Age-related physiologic changes in the kidneys influence drug response and elimination more than hepatic changes in the geriatric patient. Between ages 20 and 90, the glomerular filtration rate (GFR) may decrease as much as 50% (average decline of 35%). The average CrCl of elderly nursing facility residents has been found to be about 40 mL/min.⁹⁸ Serum creatinine is frequently used to monitor kidney function, but this test alone is of limited utility in estimating the geriatrics patient’s GFR. Serum creatinine does not increase significantly unless kidney function deteriorates greatly. The production of creatinine, which is dependent on muscle mass, decreases in the elderly; therefore, an apparently normal serum creatinine in a geriatric patient may not be a valid predictor of renal function and drug elimination. Blood urea nitrogen also is not a useful predictor of renal function because it can be affected by hydration status, diet, and blood loss.

The most accurate, readily available estimation of GFR in the elderly is creatinine clearance (CrCl), which correlates well with both GFR and tubular secretion. The CrCl can be estimated using a standard equation that considers age, body weight, and serum creatinine in patients with stable renal function (see Chapter 2). Of course, mathematical equations are simply estimates of an individual’s actual renal function. Even the best methods for estimating creatinine clearance may result in suboptimal dosing for many elderly patients. For geriatric patients with low serum creatinine <1 mg/dL, (88.4 μM/L SI), the practice of rounding the serum creatinine to 1 mg/dL (88.4 μM/L SI) may result in underestimation of creatinine clearance and suboptimal dosing.⁹⁹

Dosages of drugs that are primarily renally excreted should generally be adjusted if the patient has lost more than 50% of kidney function. If creatinine clearance is less than 50 mL/min, major dosage adjustments may be necessary to avoid drug toxicity. Some common drugs with a narrow therapeutic range that are excreted primarily unchanged by the kidneys are shown in **Table 7-4**.

TABLE 7-4. SELECT DRUGS WITH PRIMARY RENAL EXCRETION THAT HAVE A NARROW THERAPEUTIC RANGE IN THE ELDERLY

Acetazolamide ^a	H2-antagonists (e.g., cimetidine)
ACE inhibitors	Lithium
Amantadine	Metformin
Aminoglycosides	Methotrexate
Chlorpropamide ^a	Procainamide ^a
Digoxin	Quinidine ^a
Disopyramide ^a	Vancomycin
Ethambutol	

^aConsidered inappropriate for use in the elderly.

AGE-RELATED PHARMACODYNAMIC CHANGES INFLUENCING DRUG RESPONSE

With increasing age, the tolerance to drugs decreases as a result of altered pharmacodynamic responses at target organs. Pharmacodynamics governs the type, intensity, and duration of drug action. The clinical manifestation of this altered sensitivity may range from an insignificant response, to an adverse drug reaction, or to therapy failure.

Qualitative differences in drug response also may occur. Pharmacodynamic alterations are often unpredictable and can lead to toxicity. Altered response may be due to changes in receptor number or

affinity, depletion of neurotransmitters, disease, or physiologic changes. With aging, there is evidence of the following:

- Decreased acetylcholine, dopamine, and serotonin
- Decreased enzymatic degradation of monoamine oxidase
- Impaired baroreceptor response to blood pressure changes
- Decreased responsiveness of beta-adrenergic receptors
- Increased pain tolerance
- Decreased antibody response to vaccination
- Decreased *insulin* sensitivity
- Decreased cortisol suppression
- Enhanced responsiveness to the anticoagulants *warfarin* and *heparin*
- Enhanced responsiveness to thrombolytics

Altered end organ sensitivity may result in exaggerated pharmacologic response, as seen with *barbiturates* and *benzodiazepines*, or diminished pharmacologic response, as seen with *beta-blockers*, *beta-agonists*, and *calcium channel blockers*. Other affected drug classes include the *narcotic analgesics*, *antihypertensive agents*, *antiparkinson drugs*, *phenothiazines*, and *antidepressants*. The incidence and irreversibility of tardive dyskinesia are increased in the elderly and may be due to age-related imbalances in neurotransmitters.¹⁰⁰ The newer oral anticoagulant apixaban, has not been shown to exhibit altered pharmacodynamic responses when the pharmacodynamic assessments of international normalized ratio, modified prothrombin time, and anti-Xa activity were measured.¹⁰¹

Dosing adjustments are usually necessary because many of these drugs are also influenced by age-related physiologic changes, especially drug distribution and elimination. The net effect in an individual patient is often difficult to predict. For example, elderly patients have increased bioavailability of *beta-blockers* but decreased responsiveness at the receptor site level (a variable effect is seen with *propranolol*). Another example is that *theophylline's* inotropic effect increases with age, but its bronchodilator effect decreases.¹⁰² Drugs that may exhibit an increased pharmacologic response in the geriatric population include *halothane*, *hydroxyzine*, *metoclopramide*, *warfarin*, and the *calcium channel blockers*.¹⁰² Age-related peripheral and central pharmacokinetic changes may contribute to age-related sensitivity to both first- and second-generation *antipsychotic agents*, but pharmacodynamic mechanisms may play the most significant role in a geriatric patient's response to any dose of an antipsychotic agent.¹⁰³

More than one in six elderly patients is taking prescription drugs that are not suited for geriatric patients and may lead to physical or mental deterioration and possibly death.¹⁰⁴ Strategies have been developed in attempts to foster appropriate prescribing of medications in the geriatric population overall. The Beers Criteria—explicit criteria for determining elderly patients' potentially inappropriate medication use—were originally published in 1992 and have undergone three subsequent updates.⁸⁶⁻⁸⁹ The criteria are now known as the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.⁸⁹ The current criteria are divided into three groupings: Potentially Inappropriate Medication Use in Older Adults, Potentially Inappropriate Medication Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome, and Potentially Inappropriate Medications to Be Used with Caution in Older Adults. Portions of these criteria are listed in **Table 7-5**.⁸⁹

These criteria were developed through a panel of experts in geriatric care, geriatric pharmacology, geriatric psychopharmacology, and nursing home care. These experts reached agreement on criteria defining inappropriate drug use in nursing home residents. The criteria relate to certain drugs that should not be used and doses and durations of therapy of some drugs that should not be exceeded in the older patient who is a resident of a nursing facility.⁸⁷ These criteria have since been applied and

evaluated in geriatric patients in various levels of care, including assisted living facilities, community dwelling, office-based physician practices, and emergency departments.¹⁰⁵⁻¹¹²

A study of use of these medications in a very large group of hospitalized senior patients showed that about half of geriatric patients received a medication deemed inappropriate according to Beers List criteria.¹¹³ Practitioners may extrapolate these recommendations to the geriatric patient population at large, keeping in mind that they are not meant to regulate practice in a manner to which they supersede the clinical judgment and assessment of the practitioner.⁸⁵ Refined Beers Criteria, to include preferred medications for use in geriatric patients or those with the greatest benefit-to-risk ratio for use in geriatric patients, are in development.¹¹⁴

Additional listings of medications that are problematic in the geriatric patient and subsequent recommendations of preferred medications to use in geriatric patients have been published. Two of the more useful lists are the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria.^{115,116} The American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults was published in October 2015 and for the first time, includes a listing of alternatives to the medications that the Beers Criteria deems risky for geriatric patients.¹¹⁷

TABLE 7-5. EXPLICIT CRITERIA FOR INAPPROPRIATE MEDICATION ORDERS⁸⁶⁻⁸⁹

Medications That Should (Generally) Be Avoided in Geriatric Patients

Sedative or hypnotic agents	
<i>Non-benzodiazepines</i>	
Eszopiclone	
Zaleplon	
Zolpidem	
<i>Long-acting benzodiazepines</i>	
Clorazepate	Chlordiazepoxide
Diazepam	Flurazepam
Quazepam	
<i>Short- and intermediate-acting benzodiazepines</i>	
Alprazolam	Estazolam
Lorazepam	Oxazepam
Temazepam	Triazolam
Antidepressants	
Combination antidepressants-antipsychotics	
Doxepin (> 6 mg/day)	
Tricyclic antidepressants	
Antihypertensive agents	
Clonidine	Doxazosin
Methyldopa	Nifedipine (short-acting)
Prazosin	Reserpine (> 0.1 mg/day)
Spironolactone (> 25 mg/day)	
Terazosin	
Nonsteroidal anti-inflammatory drugs	
Indomethacin	
Ketorolac (includes parenteral)	
Oral hypoglycemic agents	
Chlorpropamide	
Glyburide	
Analgesic agents	
Meperidine	
Pentazocine	
Antithrombotics	
Dabigatran (use with caution)	
Dipyridamole (oral, short-acting)	

Muscle relaxants or antispasmodic agents

Carisoprodol	Chlorzoxazone
Cyclobenzaprine	Metaxalone
Methocarbamol	Orphenadrine

Antispasmodic agents

Belladonna alkaloids combination
Dicyclomine
Metoclopramide (unless for gastroparesis)

Antiarrhythmics

Amiodarone	Disopyramide
Dronedarone	Procainamide
Quinidine	Sotalol

Anticholinergics and antihistamines

Chlorpheniramine	Cyproheptadine
Dexchlorpheniramine	Diphenhydramine (oral)
Hydroxyzine	Promethazine
Tripolidine	

Non-COX-selective NSAIDs, oral (unless other alternatives are not effective and the patient can take gastroprotective agent)

Aspirin > 325 mg/day	Diclofenac
Diflunisal	Etodolac
Fenoprofen	Ibuprofen
Ketoprofen	Meclofenamate
Mefenamic acid	Meloxicam
Nabumetone	Naproxen
Oxaprozin	Piroxicam
Sulindac	Tolmetin

Other agents

Thioridazine
Digoxin (> 0.125 mg/day)
Trimethobenzamide
All barbiturates (except phenobarbital)
Amphetamines and anorexic agents
Nitrofurantoin
Methyltestosterone
Testosterone
Megestrol
Insulin, sliding scale
Mineral oil
Dessicated thyroid
Estrogens (with or without progestins)

SUMMARY OF CHANGES

Appendix 7-A is a compilation of the pharmacokinetic and pharmacodynamic literature available on the dosing of drugs in the geriatric population. However, dosing of any drug in a specific patient should be based on that patient's response and ability to clear the drug.¹¹⁸⁻¹¹⁹

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APPENDIX 7-A

Pharmacokinetic Parameters and Average Doses of Drugs Commonly Used in Geriatric Patients^{114,118,119}

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Acarbose	?	D	?	?	?	?	75–300	Use is not recommended in significant renal dysfunction ($S_{Cr} > 2$ mg/dL); avoid intensive glucose control ($HbA_{1c} < 6.5\%$)
Acetaminophen	D	D	I	?	D	?	1500–3000	Hepatic metabolism not significantly altered; no dosage adjustment necessary unless patient is taking chronic high doses
Albiglutide	NC	NC	NC	NC	NC	?	30–50 sub-Q once weekly	No dosage adjustment necessary
Alendronate	D	?	?	?	?	?	10	No dosage adjustment necessary in elderly; use not recommended in $CrCl < 35$ mL/min
Alprazolam	D	D	I	NC	D	**	0.75–2	
Amantadine ^c	D	?	I	?	?	?	200	Dosage reduction in renal impairment
							$CrCl$ (mL/min/1.73 m ²)	Dose
							≥80	100 mg twice daily
							60–79	200 mg/100 mg on alternate days
							40–59	100 mg once daily
							30–39	200 mg twice weekly
							20–29	100 mg three times weekly
							10–19	200 mg/100 mg alternating every 7 days
Amikacin ^c	I	D	I	?	?	?	***	Dose conservatively based on $CrCl$ and measured concentrations
Aminophylline	I	NC	I	NC	?	?	0.4 mg/kg/hr	Maximum dose of 507 mg/day, equivalent to theophylline 400 mg/day

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Amitriptyline	I	D	I	D*	I	?	10–150	Prolonged half-life; evaluation of therapeutic effect to be delayed; increased bioavailability
Amlodipine	NC	D	I	?	?	**	2.5–10	Geriatrics may experience greater hypotensive response and no significant CNS effects
Amoxicillin ^c	?	?	?	?	?	?	750–1500	Dosage reduction in moderate to severe renal impairment
Ampicillin ^c	NC	D	I	?	I	?	500–2000	Dosage reduction in moderate to severe renal impairment
Apixaban	NC	NC	NC	NC	NC	?	10	Patients with $S_{cr} > 2.5$ mg/dL or CrCl < 25 mL/min were excluded from trials
Aripiprazole	?	?	?	?	?	?	10–15	Dosage adjustments not routinely indicated on basis of age, gender, race, or renal or hepatic impairment
Aspirin	I	D	I	I*	I	?	1300–4000	No dosage adjustment necessary
Atenolol	I	D	I	?	?	?	25–150	No dosage adjustment necessary
Azathioprine	?	D	I	I	?	?	1.5–2.5	If CrCl < 50 mL/min give 75% of dose; if CrCl < 10 mL/min, give 50% of dose
Azithromycin ^c	NC	NC	NC	NC	?	?	250–500	If CrCl < 10 mL/min, use with caution
Benazepril	NC	I	NC	NC	NC	?	5–40	Preferred class in comorbid CHF, DM, HTN
Bleomycin	NC	*	I	*	?	?	5–10 units/m ²	If CrCl < 50 mL/min give 75% of dose; if CrCl < 10 mL/min, give 50% of dose. Incidence of pulmonary toxicity increases with age > 70 yr and in cumulative lifetime dose of 400 units.
Bupropion	?	D	?	?	?	?	100–300	SE profile allows use in patients intolerable to TCAs. A pharmacokinetic study suggested that accumulation of bupropion and its metabolites may occur in the elderly.

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Bupirone	NC	D	I	NC	NC	I	10–60	Slow titration to avoid side effects in hepatic failure; reduced sedation advantageous
Busulfan	NC	?	?	D	?	?	1.8 mg/m ²	No dosage adjustment necessary
Candesartan	?	?	?	?	?	?	8–32	Use lower doses in mildly impaired hepatic and renal function; stronger effect on blood pressure at any dose
Captopril	?	D	I	?	?	I	12.5–250	In renal impairment monitor K ⁺ ; see benazepril
Cefadroxil ^c	?	?	I	NC	NC	?	1–2 g/day	Base dose on renal function and severity of infection
Cefaclor ^c	NC	D	I	NC	NC	?	750–1500	If CrCl < 50 mL/min, use 50% of dose twice daily
Cefamandole ^c	NC	D	I	NC	NC	?	4–12 g/day	If CrCl < 50 mL/min, reduce dose and increase dosage interval
Cefazolin ^c	NC	D	I	?	?	?	3–4.5 g/day	Dosage reduction in renal impairment; all adults receive loading dose of 500 mg
							CrCl (mL/min)	Dose
							≥55	Usual adult dose
							35–54	Usual adult dose every 8 hr
							11–34	One-half usual adult dose every 12 hr
							≤10	One-half usual adult dose every 24–48 hr
Cefdinir ^c	NC	NC	NC	NC	NC	?	300–600	Reduce dose by 50% in renal impairment
Cefepime ^c	NC	D	I	NC	NC	?	0.5–4 g/day	Base dose on renal function and severity of infection
Cefixime ^c	NC	D	I	NC	NC	?	400	If CrCl 21–60 mL/min, give 75% of usual dose; if ≤ 20, give 50%

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Cefoperazone ^c	NC	D	I	NC	NC	?	2–12 g/day	Reduce dose in hepatic failure; sodium content is 1 g (1.5 mEq)
Cefotaxime ^c	I	D	I	NC	NC	?	2–12 g/day	If CrCl = 10–50 mL/min, give every 8–12 hr; if <10 mg/min, give every 24 hr; a significantly greater increase in t _{1/2} and decrease in CL is reported in patients > 80 yr of age
Cefotetan ^c	NC	D	I	NC	NC	?	1–6 g/day	If CrCl <30 mL/min, increase dosing interval
Cefoxitin ^c	I	I	I	D	?	?	3–8 g/day	Dosage reduction in severe renal impairment (may need to give every 12–48 hr)
Cefpodoxime ^c	NC	D	I	NC	NC	?	200–800	If CrCl <30 mL/min, give every 24 hr
Cefprozil ^c	I	D	I	NC	NC	?	500–1000	Administer for ≥10 days
Ceftazidime ^c	D	D	I	D	NC	?	3–6 g/day	*Base on renal function; minimum interval is 12 hr
Ceftriaxone ^c	D	D	I	I	?	?	500–2000	No dosage reduction with impaired renal or hepatic dysfunction; in severe renal impairment or in both hepatic and substantial renal impairment (maximum dosage of 2 g daily)
Cefuroxime ^c	NC	D	I	NC	NC	?	O: 250 mg–1 g/day P: 3–6 g/day	If CrCl < 20 mL/min, reduce dose
Celecoxib	?	?	?	?	?	?	200–400	Use lowest recommended dose in patients weighing <50 kg
Chlorambucil	NC	*	*	*	*	?	0.1–0.2 mg/kg/day	Start at lowest end of dosage range
Chlordiazepoxide	I	D	I	NC*	?	?	10–40	Not a drug of first choice in the elderly
Chlorpromazine	I	D	I	D	?	?	10–800	Maximum dose of 33% to 50% of usual dose

APPENDIX 7-A (cont'd)

Drug	Volume of		Clearance	Half-Life	PB (%) ^a	Time		Dynamics	Dose (mg/day) ^b	Comment
	Distribution	Distribution				to Peak	to Peak			
Chlorpropamide	NC	NC	NC	I	NC	NC	NC	NC	100–750	Reduce initial dose to 100–125 mg; titrate upward after 5–7 days. Inactive metabolite excreted via urine; avoid in elderly
Cholestyramine	Not absorbed*	*	*	*	*	*	?	?	16–24 g/day	No dosage adjustment in renal failure
Cimetidine	D	D	I	I	NC	NC	NC	NC	300–1200	If CrCl < 30 mL/min/1.73 m ² , 300 mg every 12 hr (IV or oral); further dosage reduction in concomitant hepatic impairment. Half-life dependent on urine pH. Caution use in geriatrics due to risk of confusion and other CNS effects.
Ciprofloxacin ^c	NC	D	I	I	NC	NC	NC	NC	1000–1500	If CrCl = 30–50 mL/min/1.73 m ² , 250–500 mg every 12 hr (IV or O); if CrCl = 5–29 mL/min/1.73 m ² , 250–500 mg (O) every 18–24 hr or 200–400 mg (IV) every 18–24 hr
Cisapride	NC	NC	NC	NC	NC	NC	?	?	40–80	Css higher but no clinical effect; use restricted due to QTc/torsades de pointes
Cisplatin	*	*	*	*	*	*	?	?	50–100 mg/m ² every 4 weeks	Hydrate to prevent toxicity. If CrCl < 50 mL/min, give 75% of dose; if CrCl < 10 mL/min, give 50% of dose
Citalopram	*	D	I	I	*	I	I	I	20–40	Maximum dose in ≥ age 60 is 20 mg/day due to increased exposure and risk of QT prolongation; avoid in CrCl < 20 mL/min
Clarithromycin ^c	NC	D	I	I	NC	NC	I	I	500–1000	Systemic exposure increased in ≥ age 60; if CrCl < 30 mL/min, give 50% of dose or every 24 hr
Clonidine	?	D	?	?	?	?	?	?	0.1–1.2	Potential for adverse CNS effects
Colestipol	Not absorbed*	*	*	*	*	*	?	?	13–30 g/day	No dosage adjustment in renal failure
Clorazepate	I	D	I	I	I	I	**	**	15–30	Not a drug of choice in geriatrics due to long-acting metabolite; use associated with falls

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Cyclophosphamide	I	D	I	?	?	**	O: 1–5 mg/kg/day; P: 40–50 mg/kg over 2–5 days	If CrCl < 10 mL/min, give 75% of dose; risk of hemorrhagic cystitis
Dabigatran etexilate	NC	NC	I	NC	NC	**	300	No dosage adjustment necessary in renal failure, but monitor closely; trend toward increased bleeding in age ≥ 75 receiving 150 mg/day
Dapagliflozin	NC	NC	NC	NC	NC	NC	5	Correct volume depletion prior to initiation; no dosage change based on age; increased ADRs in age > 65 yr based on volume depletion or renal impairment/failure
Dalbavancin	NC	NC	NC	NC	NC	NC	1000 mg single initial dose; then 500 mg single dose 1 week later	If CrCl < 30 mL/min: P: 750 mg as single initial dose, followed by P: 375 mg as single dose 1 week later
Daunorubicin	NC	NC	NC	NC	NC	NC	45 mg/m ²	Reduce dose by 33% in age ≥ 60 to 30 mg/m ²
Desipramine	?	I	I*	?	?	?	20–150	Prolonged half-life; evaluation of therapeutic effect to be delayed; start at lower end of dosage range and titrate based on tolerance and response
Diazepam	I	D	I	I*	?	**	2–20	Oral absorption more reliable than IM; not a drug of choice in geriatrics due to long-acting metabolite; use associated with falls
Diclofenac	NC	NC	NC	NC	NC	?	50–150	High risk for GI bleed or CNS effects; reduce dose in CrCl < 50 mL/min; use lowest recommended dose and frequency
Diflunisal	NC	D	I	NC	NC	?	500–1500	High risk for GI bleed or CNS effects; use lowest recommended dose and frequency
Digoxin	D	D	I	NC	NC	?	0.125–0.25	Conservative dosing based on IBW and CrCl
Diltiazem	NC	D	I	?	?	**	120–480	Initiation with low dose because of significantly reduced clearance; see amlodipine

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution		Clearance	Half-Life	PB (%) ^a	Time to Peak		Dynamics	Dose (mg/day) ^b	Comment
Diphenhydramine	D		D	I	?	?	I	I	25–50	Elderly more sensitive to anticholinergic and sedative effects
Donepezil	I		NC	I	NC	NC	NC	NC	5–10	No dosage adjustments suggested
Doxepin	?		?	I	?	?	?	?	25–150	Prolonged half-life; evaluation of therapeutic effect to be delayed
Doxorubicin	NC		NC	NC	NC	NC	?	?	60 mg/m ²	Dose limiting cardiotoxicity
Doxycycline	NC		D	I	?	?	?	?	50–100	Tetracycline drug of choice in severe renal impairment
Droxidopa	NC		NC	NC	NC	NC	?	?	300	Caution when GFR < 30 mL/min
Dulaglutide	NC		NC	NC	NC	NC			0.75–1.5 sub-Q	Once weekly dosing; avoid intensive glucose control (HbA _{1c} < 6.5%)
Edoxaban	NC		NC	NC	NC	NC			CrCl (mL/min)	Dose
									>50	Usual adult dose 50–60 mg
									15–50	30 mg daily
Empagliflozin	NC		NC	NC	NC	NC	?	?	10–25	Assess for volume depletion prior to initiation; avoid intensive glucose control (HbA _{1c} < 6.5%)
Enoxaparin	NC		D	NC	?	NC	?	?	40–60 sub-Q	Increase in risk of injection associated bleeding; age associated serious adverse reactions; adjust dose in renal impairment; may omit IV bolus in age ≥ 75; caution in patients < 45 kg
Eprosartan	NC		NC	NC	NC	NC	?	?	400–800	Monitor BP and volume status
Erythromycin ^c	NC		D	I	NC	NC	?	?	1–4 g/day	Geriatrics at increased risk of torsades de pointes, ototoxicity
Escitalopram	NC		NC	I	NC	NC	?	?	10	34% increase in maximum concentration; 50% increase in area under the curve

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Esomeprazole	NC	NC	NC	NC	NC	?	20–40	No dosage adjustment in renal insufficiency or mild to moderate hepatic dysfunction; maximum dose of 20 mg in severe hepatic dysfunction; increased risk of fractures of hip, spine, or wrist
Ethanol	D	NC	NC	NC	NC	?	600–700 mg/kg	Increased concentrations due to lowered volume of distribution; additive effects with other sedatives
Etodolac	NC	NC	NC	NC	NC	I	400	High risk for GI bleed or CNS effects; increased sensitivity to antiprostaglandin effects; consider dosage adjustment
Ezetimibe	NC	NC	NC	NC	NC	?	10	Plasma concentrations higher in geriatric patients in one study. Bioavailability increased in severe renal and hepatic impairment
Famotidine	NC	NC	NC	NC	NC	?	40	Maximum recommended length of therapy
							CrCl (mL/min)	Dose
							>60	Usual adult dose 40 mg
							30–60	20 mg
							<30	10 mg
							<10 mg	4 mg
Fentanyl	NC	D	I	NC	?	I	20–30 mcg every 30–60 min	Increased age may delay absorption from transdermal system
Felodipine	NC	NC	NC	NC	NC	**	2.5–10	In hepatic impairment, use initial dose of 2.5 mg/day; avoid doses >10 mg/day; see amlodipine; geriatrics may experience a greater hypotensive response
Fenoprofen	NC	NC	NC	NC	NC	**	1.2–4 g/day	Higher risk for GI bleed or CNS effects; use lowest recommended dose and frequency

APPENDIX 7-A (cont'd)

Drug	Volume of		Clearance	Half-Life	PB (%) ^a	Time		Dynamics	Dose (mg/day) ^b	Comment
	Distribution					to Peak				
Fexofenadine	NC	NC	I	NC	NC	NC	?		60–180	Peak plasma concentrations 99% higher in elderly; however, no adverse effects observed
Fluorouracil	NC	NC	NC	NC	NC	NC	?		500 mg/m ²	Use lowest effective dose
Fluoxetine	NC	NC	NC	NC	NC	NC	**		20–40	May require initial dose of 10 mg/day; SE profile allows use in patients who cannot tolerate TCAs; use with caution in history of hyponatremia and SIADH
Flurazepam	NC	NC	I	I	NC	NC	**		15	Dose-related drowsiness from drug accumulation; increased fall risk associated with use
Flurbiprofen	NC	NC	NC	NC	NC	NC	**		200–300	High risk for GI bleed or CNS effects
Flutamide	*	*	*	*	*	*	*		450	Gynecomastia; antiandrogenic
Fluvastatin	NC	NC	NC	NC	NC	NC	?		2–10	No dosage reduction in reduced CrCl
Fondaparinux	NC	C	I	NC	NC	NC	?		2.5–10 sub-Q	Continue according to guidelines until anticoagulant effect is therapeutic
Fosphenytoin	NC	D	NC	NC	NC	NC	?		4–6 mg phenytoin equivalents/kg	Lower and less frequent dosing required
Fosinopril	NC	I	NC	NC	NC	NC	**		5–40	See benazepril
Furosemide	D	D	I	NC	NC	NC	**		40–2000	Increase dose slowly to desired response
Gabapentin (and gabapentin enacarbil)	NC	D	NC	NC	NC	NC	NC		900–3600	Dosage reduction in renal impairment; base dose on calculated CrCl
									CrCl (mL/min)	Dose
									30–60	200–700 twice daily
									16–29	200–700 daily
									15	100–300 daily
									<15	Dose conservatively

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Gemfibrozil	NC	NC	NC	NC	NC	?	1200	Drug of choice for hypertriglyceridemia and hypoalphaproteinemia in geriatrics
Gentamicin ^c	I	D	I	NC	NC	**	4–7 mg/kg	Conservative dosing based on weight and CrCl or measured concentrations; interpatient variation
Glimepiride	NC	NC	NC	NC	NC	**	1–8	Rapid and prolonged hypoglycemia >12 hr reported; avoid intensive glucose control (HbA _{1c} < 6.5%)
Glyburide	I	NC	I	NC	NC	**	2.5–20	Reduce dose in CrCl < 10 mL/min/1.73 m ² ; conservative initial and maintenance doses to avoid hypoglycemia; do not titrate to maximum dose; avoid intensive glucose control (HbA _{1c} < 6.5%)
Haloperidol	NC	NC	I	D*	NC	?	0.25–4	Elderly more susceptible to side effects; prolonged half-life
Heparin	NC	NC	NC	?	?	**	***	Increased age may increase risk of major bleeding; may experience exaggerated response during maintenance dosing; geriatric women more likely to have bleeding complications
Hydralazine	NC	NC	NC	NC	NC	**	20–200	Use lower initial doses due to vasodilating effects; titrate to response
Hydrochlorothiazide	NC	I	NC	NC	NC	?	12.5–50	Not effective in CrCl < 30 mL/min; minimal increase in response and more electrolyte disturbances in doses > 50 mg/day
Hydrocodone	I	D	I	NC	NC	I	10–30	Enhanced CNS effects and constipation noted
Hydroxyurea	NC	*	*	*	*	I	50–100 mg/kg	If CrCl < 50 mL/min give 50% of dose; if CrCl < 10 mg/min, give 20% of dose; advance dose slowly with monitoring of renal function
Ibuprofen	NC	NC, D	NC	NC	NC		800–3200	High risk for GI bleed or CNS effects; consider reduced initial dosage in debilitated or frail; use lowest recommended dose and frequency

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution		Clearance	Half-Life	PB (%f) ^a	Time to Peak		Dynamics	Dose (mg/day) ^b	Comment
	NC	NC				NC	NC			
Imipramine	NC	NC	NC	I	NC	NC	I	I	25–100	Prolonged half-life; evaluation of therapeutic effect to be delayed; risk of orthostatic hypotension
Indomethacin	NC	NC	NC	I	NC	NC	I	I	50–200	Other NSAIDs preferable due to efficacy and lower toxicity; use lowest effective dose
Irbesartan	NC	NC	NC	NC	NC	NC	?	?	75–300	Monitor BP and volume status; initiate dose at 75 mg in volume depleted patients
Isoniazid ^c	D	D	D	NC	NC	NC	?	?	200–300	Dosage adjustment in slow acetylators
Isradipine	NC	NC	NC	NC	NC	NC	**	**	5–10	Geriatrics may experience greater hypotensive response but no significant CNS effects
Ketoprofen	I	D	D	I	NC	NC	?	?	150–300	Decrease dose in > 75 years; suggested at 33% to 50% reduction in initial dose; consider renal function in dosing; use lowest effective dose and frequency
Ketorolac	NC	D	D	I	NC	NC	?	?	15–60	High risk for GI bleed or CNS effects; reduce dose because of decreased clearance; consider renal function in dosing; use lowest effective dose and frequency
Labetalol	NC	D	D	I	NC	NC	D	D	200–2400	Initiation with lower doses because of increased bioavailability with age; titrate to response
Lamotrigine	NC	*	*	NC	NC	NC	?	?	100–500	If CrCl 10–50 mL/min, give 75% of dose; if CrCl < 10 mL/min, give 100 mg every other day
Lansoprazole	NC	D	D	I	NC	NC	NC	NC	15–30	No dosage reduction in reduced CrCl
Levetiracetam	NC	NC	NC	I	NC	NC	?	?	1000–3000	Essential to base dose on calculated CrCl
									CrCl (mL/min)	Dose
									50–80	500–1000 every 12 hr
									30–50	250–750 every 12 hr
									<30	250–500 every 12 hr

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Levodopa and carbidopa	NC	NC	I (with controlled/extended release formulations)	NC	I	I (levodopa)	300/75–1000/100	Increased bioavailability (levodopa alone)
Levofloxacin ^c	NC	D	I	NC	NC	?	250–500	Dosage reduction based on renal impairment. If CrCl = 20–49 mL/min/1.73 m ² , 250 mg every 24 hr (after initial dose of 500 mg). If CrCl 10–19 mL/min/1.73 m ² , 250 mg every 48 hr (after initial dose of 250 mg for renal infections and 500 mg for others)
Lidocaine	I	D	I	D	?	**	L: 1–1.5 mg/kg; M: 1–4 mg/min	Decreased clearance in presence of CHF or liver disease
Linagliptin	NC	NC	NC	NC	NC	?	5	Avoid intensive glucose control (HbA _{1c} < 6.5%)
Lisinopril	NC	D	I	NC	NC	I	2.5–40	Consider low initial dose and titrate to response; preferred class in comorbid CHF, DM, HTN
Lithium	NC	D	I	NC	NC	I	150–900	One-half initial dose because of susceptibility to volume depletion; dose based on drug concentrations (0.4–0.7 mEq/L)
Loratadine	NC	NC	*	NC	NC	?	10	Wide variation in half-life is a consideration in initiating dosing
Lorazepam	D	D	I	I*	**		1–3	Dose at low end of dosage range; preferred agent in geriatrics
Losartan	NC	NC	I	NC	NC	?	25–100	Monitor BP and volume status
Lovastatin	NC	NC	NC	NC	NC	?	20–80	Age > 65 risk for myopathy
Maprotiline	NC	NC	NC	NC	NC	I	25–75	Titrate slowly to response; not a drug of first choice due to sedation and anticholinergic effects

APPENDIX 7-A (cont'd)

Drug	Volume of		Clearance	Half-Life	PB (%) ^a	Time		Dynamics	Dose (mg/day) ^b	Comment
	Distribution					to Peak				
Meclofenamic acid	NC	NC	NC	NC	NC	NC	?	?	150–400	High risk for GI bleed or CNS effects; consider reduced initial dosage in debilitated or frail; use lowest recommended dose and frequency
Mefenamic acid	NC	NC	NC	NC	NC	NC	?	?	1000	High risk for GI bleed or CNS effects; consider reduced initial dosage in debilitated or frail; use lowest recommended dose and frequency; maximum therapy of 1 week
Melphalan	?	D	I	I	?	?	?	?	6	If CrCl < 50 mL/min, give 75% of dose; if CrCl < 10 mL/min, give 50% of dose
Metformin	NC	D	I	I	NC	NC	?	?	850–2500	Lower dosages and frequent monitoring are recommended; dose conservatively and avoid maximum dose; avoid intensive glucose control (HbA _{1c} < 6.5%)
Methotrexate	NC	D	I	I	NC	NC	?	?	5–10 mg/week	For rheumatoid arthritis; if CrCl < 50 mL/min, give 50% of dose; if CrCl < 10 mL/min, avoid; refer to specific disease protocols for neoplastic disease
Methyldopa	NC	D	I	I	NC	NC	?	?	250–3000	May be inappropriate due to side effect profile; initiate therapy at lower end of dosage range
Metoclopramide	NC	D	I	I	I	NC	I	I	10–20	Geriatrics more likely to develop dyskinesias
Metoprolol	NC	NC, I	NC, I	NC, I	NC	D	**	**	25–300	Consider lower initial doses and titrate to response
Miglitol	NC	NC	NC	NC	NC	NC	?	?	75–300	Titrate to response; avoid intensive glucose control (HbA _{1c} < 6.5%)
Mirabegron	NC	NC	NC	NC	NC	NC	**	**	25–50	Max dose of 25 mg/day in CrCl = 15–29 mL/min; useful in patients who poorly tolerate anticholinergic effects of other overactive bladder therapies
Mirtazapine	?	D	I	I	?	?	I	I	15–45	Dosage reduction in mild to moderate hepatic and renal impairment

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Misoprostol	?	?	I	?	?	?	0.1–0.4	Routine use as prophylaxis not justified; not a first line agent in geriatrics
Moexipril	NC	NC	NC	NC	NC	I	3.75–30	Initiate at lower dose; no overall reduction in total daily dose
Morphine	D	D	D	?	?	I	20–100	Dosage reduction because of increased sensitivity; elderly more susceptible to side effects; use with caution
Nabumetone	NC	NC	NC	NC	NC	I	1–2 g/day	High risk for GI bleed or CNS effects; reduce dose if CrCl < 50 mL/min; use lowest recommended dose and frequency; do not exceed 2 g/day
Nadolol	NC	NC	NC	NC	NC	**	20–320	Consider lower initial doses and titrate to response; adjust dose in renal impairment
Naproxen	I	D	I	I	I	I	500–750	High risk for GI bleed or CNS effects; use lowest recommended dose and frequency; avoid use in CrCl < 30 mL/min
Nateglinide	?	?	?	?	?	I	60–360	Titrate to response; avoid intensive glucose control (HbA _{1c} < 6.5%)
Nefazodone	NC	D	I	NC	NC	?	100–400	Initiate dose at 50 mg/day; gradual titration to response; conflicting pharmacokinetic data reported in single-dose vs. multiple-dose studies
Nicardipine	NC	D	NC	?	?	**	30–60	Geriatrics may experience greater hypotensive response and no significant CNS effects
Nifedipine	NC	D	I	?	?	**	30–120	Geriatrics may experience greater hypotensive response and no significant CNS effects
Nisoldipine	?	D	I	?	?	**	10–40	Geriatrics may experience greater hypotensive response and no significant CNS effects
Nitroglycerin	I	NC	I	NC	NC	I	10–104	Pharmacokinetics independent of age. Increased sensitivity to drug requires lower dosages; monitor for hypotension

APPENDIX 7-A (cont'd)

Drug	Volume of		Clearance	Half-Life	PB (%f) ^a	Time		Dynamics	Dose (mg/day) ^b	Comment
	Distribution					to Peak				
Nizatidine	NC	D	I	I	NC	NC		Exaggerated	150–300	Preferred agent in class; adjust dose based on CrCl; maximum recommended length of therapy
Nortriptyline	I	D	I	I	D*	NC	I	I	30–50	Prolonged half-life; evaluation of therapeutic effect to be delayed; preferred agent of class
Olanzapine	NC	D	I	I	NC	NC	?	?	2.5–10	Slowly titrate to response with monitoring of BP
Olmesartan	NC	NC	NC	NC	NC	NC	?	?	20–40	For patients with possible depletion of intravascular volume (diuretic therapy or impaired renal function), initiate under close supervision and consider lower starting dose
Omeprazole	NC	D	I	I	NC	NC	?	?	20–40	Bioavailability slightly increased; however, no dosage adjustment required. No dosage reduction in reduced CrCl
Oxaprozin	NC	NC	NC	D*	NC	NC	?	?	1200	Dual elimination (renal and hepatic) leads to decreased t½ in chronic dosing; high risk for GI bleed or CNS effects; use lowest recommended dose and frequency
Oxazepam	I	D	I	I	NC	I	**		10–60	Upward titrate dose slowly to evaluate sensitivity
Oxybutynin	NC	NC	I	I	NC	NC	NC		5–15	Lower doses improve tolerability
Oxycodone	I	D	I	I	I	NC	I		10–20	Enhanced CNS effects and constipation noted
Pantoprazole	NC	NC	NC	NC	NC	NC	?	?	40	No dosage adjustment required in elderly; increased risk of fractures of hip, spine, or wrist
Paroxetine	D	NC	I	I	NC	NC	?	?	10–40	Half-life and steady-state concentration increase disproportionately to dose with single and multiple dosing; use with caution in history of hyponatremia and SIADH
Penicillin G ^c	NC	NC	I	I	NC	NC	?	?	1–2 g/day	Dosage reduction in moderate to severe renal impairment

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Perindopril	NC	?	?	NC	NC	I	4–8	Preferred class in comorbid CHF, DM, HTN
Phenobarbital	NC	D	I	NC	NC	I	30–60	Start at lowest recommended dose; dose administration at bedtime to avoid excessive sedation; tolerance within a few weeks; discourage use as a sedative-hypnotic agent
Phenytoin	NC	D	I*	NC	NC	?	200–300	Decreased serum albumin concentrations may increase clearance; monitor free phenytoin concentrations
Peramivir ^c	NC	NC	NC	NC	NC	?	600 as a single dose	Dose based on renal function
							CrCl (mL/min)	Dose
							30–49	200 mg (single dose)
							10–29	100 mg (single dose)
Pioglitazone	NC	NC	NC	NC	NC	?	15–30	No dosage adjustment required; avoid intensive glucose control ($HbA_{1c} < 6.5\%$)
Piroxicam	D	D	I	NC	D	I	10–20	Avoid due to long half-life (60–70 hr) and higher GI bleed risk; use lowest recommended dose and frequency
Pravastatin	NC	D	NC	NC	NC	?	10–40	Age > 65 risk for myopathy
Prazosin	I	D	I	NC	NC	?	2–10	Consider lower initial doses and titrate to response
Propranolol	D	D	I	D*	NC	**	O: 10–320	Consider lower initial doses and titrate to response; adjust dose in renal impairment
Quetiapine	NC	D	NC	NC	NC	?	25–200	Use 40% to 80% lower doses in elderly as compared to younger patients; increased mortality in geriatrics with dementia related psychosis

APPENDIX 7-A (cont'd)

Drug	Volume of		Clearance	Half-Life	PB (%f) ^a	Time		Dynamics	Dose (mg/day) ^b	Comment
	Distribution					to Peak				
Quinapril	NC	D	I	I	NC	NC	I	I	2.5–40	Consider lower initial doses and titrate to response; preferred class in comorbid CHF, DM, HTN
Quinidine	?	D	I	I	NC	?	?	?	600–3600	Dosage reduction because of decreased clearance; dose based on side effects, therapeutic response, and concentrations (2–6 mg/L)
Rabeprazole	NC	NC	NC	NC	NC	NC	?	?	20	No dosage adjustment necessary; increased risk of fractures of hip, spine, or wrist
Ramipril	NC	D	I	I	NC	NC	I	I	1.25–10	Consider lower initial doses and titrate to response; preferred class in comorbid CHF, DM, HTN; dose based on renal function
Ranitidine	D	D	I	I	NC	NC	?	?	150–300	Prolonged half-life; if CrCl < 50 mL/min, 150 mg every 24 hr orally or 50 mg every 18–24 hr intramuscularly or by intravenous intermittent slow infusion or direct injection; preferred agent in class; adjust dose based on CrCl; maximum recommended length of therapy
Repaglinide	?	?	?	?	?	?	?	?	1–16	Has not been studied extensively in the elderly; avoid intensive glucose control (HbA _{1c} < 6.5%)
Risedronate	NC	NC	NC	NC	NC	NC	?	?	5 every/day; 35 every/week; 150 every/month	Not recommended for use in severe renal impairment (CrCl < 30 mL/min); no dosage adjustment necessary in CrCl at least 30 mL/min or in elderly; consider risk vs. benefit
Risperidone	NC	D	I	I	I	NC	?	?	0.5–2	Titrate slowly to avoid ADRs; use 40% to 80% lower doses in elderly as compared to younger patients; increased mortality in geriatrics with dementia related psychosis
Rivaroxaban	I	D	I	I	NC	NC	?	?	10–20	Administer with food; avoid use in CrCl < 30 mL/min
Rivastigmine	?	D	I	I	?	?	?	?	3–12	Titrate dose to tolerance

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Ropinirole	NC	D	I	?	?	?	0.75–24	Slow titration dose required; clinical significance of reduced clearance unknown; titrate dose to clinical response
Rosiglitazone	NC	NC	NC	NC	NC	?	4–8	No dosage adjustment; avoid intensive glucose control ($\text{HbA}_{1c} < 6.5\%$)
Sertraline	D	D	I	I	NC	?	25–50	Preferred agent of class; use with caution in history of hyponatremia and SIADH
Simvastatin	NC	NC	NC	NC	NC	?	5–40	Maximum effectiveness achieved with dose of ≤ 20 mg/day; age > 65 risk for myopathy
Spirolactone	NC	NC	I	NC	NC	?	50–100	Dosage reduction in significant renal impairment; avoid doses > 25 mg/day; monitor potassium; use with caution
Sulindac	?	NC	NC	NC	NC	?	400	Hepatic metabolism to active metabolite; high risk for GI bleed or CNS effects
Suvorexant	NC	NC	NC	NC	NC	?	10–20	Administer dose 30 min prior to HS; use lowest effective dose; titrate to response
Tedizolid ^c	?	?	?	?	?	?	200	Insufficient studies in geriatrics
Telmisartan	NC	NC	NC	NC	NC	?	40–80	Monitor BP and volume status
Temazepam	NC	NC	NC	I	NC	**	7.5–30	Dose at bedtime; increased fall risk associated with use
Terazosin	NC	D	D	NC	NC	?	0.5–10	Dose depends on indication; consider lower initial doses; dry mouth and urinary incontinence are common
Tetracycline ^c	NC	I	NC	NC	NC	?	1000–2000	Rarely drug of choice
Theophylline	D	D	I	I	?	**	0.2–0.4 mg/kg/hr	Elderly more susceptible to side effects; CHF or liver disease decreases clearance; dose based on serum concentrations (7.5–15 mg/L)

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Thioridazine	NC	I	NC	NC	NC	?	10–800	Elderly more susceptible to side effects: prolonged half-life; proarrhythmic effect; increased mortality in geriatrics with dementia related psychosis
Ticagrelor	NC	NC	NC	NC	NC	?	180	Administer with low-dose aspirin; use with caution in geriatrics; monitor closely during initiation; no dosage adjustment necessary in renal impairment
Tigecycline ^c	NC	NC	NC	NC	NC	?	100	No significant PK differences in healthy older adults
Timolol	NC	NC	NC	NC	NC	**	20–60	Titrate to response
Tinzaparin	NC	NC	NC	?	NC	I	50–175 anti-Xa units/kg	Consider risk vs. benefit in age ≥ 70 with CrCl ≤ 30 mL/min or age > 75 with CrCl ≤ 60 mL/min
Tobramycin	NC	D	I	NC	NC	?	***	Dose conservatively based on weight and CrCl or measured concentrations
Tolazamide	NC	NC	NC	NC	NC	?	100–500	Avoid intensive glucose control (HbA _{1c} < 6.5%)
Tolbutamide	D	D	I	I	NC	?	250–3000	Inactive metabolite excreted via urine; avoid intensive glucose control (HbA _{1c} < 6.5%)
Tolmetin	NC	NC	NC	NC	NC	?	1200–1800	Use lowest recommended dose and frequency; consider renal function decline with increased age
Tolterodine	NC	D	I	NC	NC	?	2–4	High risk for GI bleed or CNS effects; consider reduced initial dosage in debilitated or frail; use lowest recommended dose and frequency
Topiramate	NC	NC	NC	NC	NC	?	50–400	Dose conservatively based on CrCl; initial dose of 25 mg daily and titrate at 25 mg daily at weekly intervals; not a drug of first choice in geriatrics
Toremifene	I	NC	I	NC	NC	?	60	No dosage reduction required

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Tramadol	NC	D	I	NC	NC	?	200–300	Dose cautiously; initiate dose at lower end of range; max dose of 100 mg daily in CrCl < 30 mL/min
Trandolapril	I	?	?	?	I	?	1–4	Initiate at lowest dose; use lowest doses in CrCl < 30 mL/min
Trazodone	NC	NC	I	NC	D	NC	25–150	Prolonged half-life; evaluation of therapeutic effect to be delayed; very sedating with few anticholinergic effects
Triamterene	NC	D	I	D	NC	?	50–100	More effective in combination with thiazide diuretic; avoid in patients with CrCl < 30 mL/min; consider lower initial doses; titrate to response; monitor potassium
Triazolam	NC	D	I	I*	I	**	0.125–0.25	Dose at bedtime; increased fall risk associated with use; not a drug of first choice in this class
Trimethoprim-sulfamethoxazole ^c							320/1600–640/3200	Dosage reduction based on degree of renal impairment, severity of infection, and susceptibility of causative organisms; monitor potassium; consider risk vs. benefit
							CrCl (mL/min)	Dose
							15–30	One-half usual adult daily dose
							<15	Conflicting data (recommend reduced dose or no use at all)
Trosipium	NC	I	NC	NC	NC	?	20–40	Base dose on tolerability. Increased incidence of anticholinergic side effects in > 75 yr of age
Valsartan	NC	NC	NC	NC	NC	?	80–320	Monitor BP and volume status
Valproic acid	NC	D	I	NC	NC	?	10–15 mg/kg/day	When used for treatment of agitation associated with dementia, note: serum concentrations do not correlate with behavior response; initiate with lower dosages and slowly titrate to response

APPENDIX 7-A (cont'd)

Drug	Volume of Distribution	Clearance	Half-Life	PB (%) ^a	Time to Peak	Dynamics	Dose (mg/day) ^b	Comment
Venlafaxine	NC	D	I	NC	NC	?	50–375	Decrease dose by 25% in CrCl 10–70 mL/min. Decrease dose by 50% in hepatic impairment; use with caution; geriatrics more prone to SSRI/SNRI induced hyponatremia; useful agent in geriatrics
Verapamil	I	D	I	NC	NC	**	120–480	Geriatrics may experience greater hypotensive response and no significant CNS effects; consider lower initial doses and titrate to response
Vilazodone		NC	NC	NC	NC	**	20–40	No dosage adjustment necessary in renal impairment; area under the curve decreased by 50% in fasting state; geriatrics more prone to SSRI/SNRI induced hyponatremia
Vortioxetine	NC	NC	NC	NC	NC	?	5–20	No dosage adjustment necessary in renal impairment; titrate to response
Warfarin	I	D	I	I*		**	***2–5 mg	Increased age and female sex may increase risk of bleeding; 40% dosage reduction
Ziprasidone	NC	NC	NC	NC	NC	?	40–80	Does not require dosage modification in geriatrics; initiate dose at lower end of dosage range; no additional benefit noted from doses above 20 mg twice daily; increased mortality in geriatrics with dementia related psychosis; monitor for diabetes
Zolpidem	NC	NC	I	NC	NC	**	5–12.5	Lower dosages in females; No dosage adjustment necessary in renal impairment, but monitor closely; take dose immediately before bedtime; only administer if ≥ 4 hours of sleep remaining; increased incidence of hypotension and falls

APPENDIX 7-A (cont'd)

^aPB (%f) = protein binding alterations (percent free fraction).

^bDose in mg/day except where specifically noted as different (e.g., g/day).

^cAdminister for maximum days in dosing range.

^dInformation unknown or not reported.

* = conflicting data reported; ** = age-related alterations in sensitivity reported; and *** = dose to be individualized for particular patients. BP = blood pressure, CNS = central nervous system, CSS = steady state concentration, CNS = central nervous system; D = decreased; dynamics = pharmacodynamics; dose = recommended daily dosage for geriatric patients; DM = diabetes mellitus, GI = gastrointestinal; HTN = hypertension, I = increased; IBW = ideal body weight, IM = intramuscular, I = loading dose; M = maintenance dose; NC = no change; O = oral; P = parenteral; PK = pharmacokinetics, QT = QT interval, SE = side effects, SIADH = syndrome of inappropriate antidiuretic hormone secretion, SSRI/SNRI = selective serotonin reuptake inhibitor/selective norepinephrine reuptake inhibitor; sub-Q = subcutaneous; t_{1/2} = half-life.

SECTION 2



SPECIFIC DRUGS AND DRUG CLASSES

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15	Unfractionated Heparin, Low Molecular Weight Heparin, and Fondaparinux	A. Joshua Roberts and William E. Dager
16	Lidocaine	Toby C. Trujillo
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AMINOGLYCOSIDES

John E. Murphy and Kathryn R. Matthias

Aminoglycoside antibiotics have been available for the treatment of infections for over 65 years. They are active against a variety of aerobic Gram-negative and some aerobic Gram-positive bacteria. Agents currently available or that have been studied include amikacin, arbekacin, dibekacin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin, spectinomycin, streptomycin, tobramycin, and trospectomycin. Pharmacokinetic monitoring is generally focused on amikacin, gentamicin, and tobramycin and will be emphasized in this chapter. Use of these agents has diminished with the advent of newer antibiotics that cover similar organisms, do not require therapeutic drug monitoring, and are generally safer. However, use of aminoglycosides continues for a variety of infections and appropriate use is necessary.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

After adjustment to achieve desired concentrations, aminoglycoside dosing regimens vary widely because of interpatient (and to some extent inpatient) variation in pharmacokinetics. Average adult gentamicin and tobramycin doses of 80 mg every 8 hr (smaller dose-short interval [SDSI] dosing) produce low peak concentrations in many patients.^{1,3} Dosing schedules where the entire dose is given at one time or a larger dose is given every 24 or 48 hr (or even at longer intervals) are used frequently now, but these regimens are not included in current prescribing information in package inserts. These large dose-extended interval (LDEI) dosing approaches are generally considered at least equally effective and may be less toxic when used appropriately, as compared to SDSI where smaller doses are given every 8 or 12 hr. LDEI approaches are generally the standard for most patients now, although certain patient types should still not be dosed in this manner. Continuing development of consensus on who should not be candidates for LDEI is warranted.^{4,5}

Because the kidneys eliminate aminoglycosides, decreased renal function affects the dosage interval used, but has less effect on the size of individual doses since high peak and low trough concentrations are generally desired. However, in patients with renal dysfunction the benefit of high peak concentrations depends somewhat on infection type and organism minimum inhibitory concentration (MIC) to the aminoglycoside. The associated risk of toxicity based on individual doses and corresponding 24-hour area under the curve (AUC_{24}) should be evaluated in this context. Both the dose and dosing interval may need to be adjusted in certain patients with renal dysfunction.

Loading dose

Loading doses (**Table 8-1**) are used in SDSI approaches for gentamicin and tobramycin. Amikacin doses are approximately 2–4 times these amounts.

In neonates, a first dose of 2.5 mg/kg generally produces a peak of less than 6 mg/L.^{8,10} The therapeutic implications of a low first-dose peak in this population, particularly early in life for presumed infections, are not clearly established.^{11–14} In adults, treatment failures may occur secondary to a low first-dose peak concentration.

There is minimal accumulation with traditional SDSI aminoglycoside regimens from the first dose to steady state concentration achievement due to the use of dosing intervals of three or more times



TABLE 8-1. LOADING DOSES FOR STANDARD DOSE-STANDARD INTERVAL APPROACHES⁶⁻⁹

Age	SDSI Loading Dose (mg/kg) ^a
Neonates	2.5–4
Infants	2.5–3
Children	2–2.5
Adolescents, adults, geriatrics	1.5–2

SDSI = standard dose, standard interval.
^aSee Dosing Strategies to determine dosing weight.

the half-life. Thus, the usual reason for loading doses, rapid achievement of concentrations closer to goal steady state concentrations in situations where accumulation is extensive, does not hold. Rather, some individuals have recommended loading doses to ensure achievement of a higher first-dose peak concentration. This may enhance the potential for therapeutic success due to the concentration-dependent killing of organisms by aminoglycosides, although some suggest that there is little evidence of a relationship of peak concentration to therapeutic outcome.³

Loading doses are not administered in the LDEI approach because it is generally expected that the concentration reaches zero or very near zero before the next dose is given. Little or no accumulation therefore occurs and high peak concentrations are achieved, negating the need for a loading dose with LDEI approaches.

Maintenance dose

LDEI and traditional SDSI maintenance doses for gentamicin and tobramycin are shown in **Table 8-2**. Amikacin doses are approximately 2–4 times these amounts. Arbekacin doses are similar to gentamicin and tobramycin.¹⁰ For LDEI, amikacin doses have tended to be 15 mg/kg for adults and 20 mg/kg in neonates. Uncomplicated urinary tract infections and infections with organisms with low aminoglycoside MIC may respond to lower doses in all patients.

Reduced renal function necessitates increases in length of the dosing interval, in some cases beyond usual recommendations. Some clinicians may use the higher end of the dosing range for more severe infections and vice versa. However, others use target concentrations or the usual averages. The Dosing Strategies section later in the chapter provides more in-depth dosing guidelines.

DOSAGE FORM AVAILABILITY⁹

Although these drugs are distributed as the sulfate salts, the manufacturers express the doses in terms of drug equivalence; thus, **S = 1** for calculations.

Pharmacokinetic monitoring of aminoglycosides is generally reserved for intramuscular (IM) and intravenous (IV) dosage forms. Irrigations or implanted bone cement with aminoglycosides have resulted in nephrotoxicity and ototoxicity; however, size of dose used, site, contact time, and degree of denuding present are all factors that affect the amount systemically absorbed. One study found very high wound concentrations (median 304 mg/L), but peak serum concentrations tended to be quite low in comparison (median 2.1 mg/L).²⁹ Caution should be exercised when using high doses in localized sites for long periods and serum concentration measurement may be warranted. When used as an intratympanic injection in the treatment of Meniere disease, ototoxicity may occur, although serum concentrations are negligible and the incidence is similar to standard medical measures.^{30,31} Toxicity has been reported, but topical dosage forms (creams, ointments, and solutions) of gentamicin and tobramycin do not appear to require pharmacokinetic monitoring.

Inhalation dosing of aminoglycosides, particularly tobramycin, is used in patients with cystic fibrosis. There have also been studies on inhalation dosing of tobramycin for treatment of *Pseudomonas*

TABLE 8-2. LARGE DOSE-EXTENDED INTERVAL AND STANDARD DOSE-STANDARD INTERVAL MAINTENANCE DOSES AND DOSING FREQUENCIES^{9,11-22}

Age	LDEI Dosage (mg/kg)	SDSI Dosage (mg/kg)
Neonates	3.5–5 every 24–48 hr ^a	2–2.5 every 2–24 hr
Infants	4–6.5 every 24–48 hr	2–2.5 every 8–12 hr
Children	4–8 every 24–48 hr ^b	2–2.5 every 8 hr
Adolescents	4–7.5 every 24–48 hr ^b	1.5–2.5 every 8 hr
Adults	3.5–7 every 24–48 hr ^b	1–1.7 every 8 hr ^c
Younger geriatrics	4–5 every 24–48 hr ^d	1–1.7 every 8–12 hr ^d
Older geriatrics	4–5 every 24–48 hr ^d	1–1.7 every 12–24 hr ^d

LDEI = large dose, extended interval.

^aData from a study of neonates 24–42 weeks' gestation indicated that 4 mg/kg/24 hr of gentamicin resulted in 13% with troughs ≥ 2 mg/L (primarily in gestational ages ≤ 36 weeks) and 30% of 1–<2 mg/L, whereas 4 mg/kg/36 hr led to no troughs above 2 mg/L, only 5% ≥ 1 mg/L, and 75% <0.5 mg/L. With 4 mg/kg every 48 hr all but 5% had troughs <0.5 mg/L.²³

^bUp to 15 mg/kg of tobramycin and 35 mg/kg of amikacin have been used in patients with cystic fibrosis.^{24,26}

^cEvery 8 or 12 hr initially for amikacin.

^dAlthough larger doses have been used, reduced renal function with aging and the potential for therapy with other toxins should probably lead to a more conservative approach.^{27,28}

aeruginosa infections in patients without cystic fibrosis, although the studies were too small or of too short a duration to recommend this approach.³²⁻³⁴ Studies have shown differences in delivery and bioavailability depending on the inhalation devices and concentrations used.³⁵⁻⁴⁰ This dosing, although generally safe in that it usually produces low serum concentrations, has been described in a case report to result in higher concentrations in the presence of renal dysfunction and positive pressure ventilation,⁴¹ and in other cases it has been associated with acute renal failure.^{42,43}

Because injectable gentamicin, tobramycin, and amikacin are available in different concentrations (i.e., pediatric and adult), care must be taken to avoid dosing confusion. Neonates have received overdoses when the dose volume for the 10-mg/mL dosage form was inadvertently used with a 40-mg/mL vial.⁴⁴ For IM injection of amikacin, gentamicin, and tobramycin, the most concentrated forms are recommended. Short IV infusions (0.5–1 hr) and IV bolus injections yield pharmacokinetic profiles similar to IM administration.⁴⁵ These aminoglycosides have also been administered as intrathecal and intraventricular injections, with the latter generally preferred. **Table 8-3** shows the available dosage forms of amikacin, gentamicin, and tobramycin.

TABLE 8-3. AVAILABLE DOSAGE FORMS

Drug ^a	Dosage Form
Amikacin sulfate	Injection for IV and IM use
Gentamicin sulfate	Injection for IV and IM use (with and without preservative) Injection for IV infusion—premixed in normal saline Premixed bone cement
Tobramycin sulfate	Injection for IV and IM use Injection for IV infusion—premixed in normal saline Injection for IV infusion—lyophilized powder Preservative-free solution for inhalation Premixed bone cement

^aAll available from multiple sources at present.

GENERAL PHARMACOKINETIC INFORMATION

Absorption

Information on the bioavailability of various dosage forms and administration methods is given in **Table 8-4**.

TABLE 8-4. BIOAVAILABILITY OF DOSAGE FORMS	
Dosage Form	Bioavailability Percent and Comments
Intravenous	100% (F = 1)
Intramuscular ^{9,46,47}	Assumed complete (100%), although absorption rate may vary with diminished muscle mass and poor circulation; peak at 30–90 min after dosing
Oral ^{48,49}	≤5% with absorption usually being ≤1%; diseases of the bowel such as ulcers and inflammatory bowel disease may lead to enhanced absorption.
Intraperitoneal ^{50,51}	55% (F = 0.55) with absorption being variable; duration of exposure and inflamed peritoneum may affect bioavailability
Intrathecal	Assumed complete (100%); passes into systemic circulation
Intratympanic ³¹	Assumed complete (100%); risk of ototoxicity
Topical irrigations ^{9,52}	Significant with absorption dependent on site and degree of denuding present (e.g., burns, wounds, ulcers, and sinus)
Bladder irrigations ⁵³	Bladder irrigations in children of 14 mg of gentamicin once or twice daily did not result in detectable serum concentrations
Inhalation or nebulization ^{35,38-40,54-57}	Negligible, but may lead to absorption of 30% of a dose (concentrations average 1 mg/L). Peak amikacin concentrations of 5.2–10.2 mg/L after nebulization of high dose amikacin (40–60 mg/kg) were reported in one study ⁵⁷
Polymethylmethacrylate beads ⁵⁸⁻⁶⁰ or cement ⁶¹⁻⁶⁵ and collagen-gentamicin implants ⁶⁶	High concentration at site with variable effect on serum/plasma concentration dependent on a variety of factors of the implanted material such as drug concentration, shape, viscosity, total amount of drug, and combination of antimicrobial agents in implanted material along with patient factors such as renal function. Significant changes in renal function, including acute renal failure, have been reported after implantation. Higher systemic exposure usually occurs in first 72 hr post-implantation; low systemic exposure can be prolonged (>6 months post implantation)
Hypodermoclysis ⁶⁷	100% (F = 1) with time to peak approximately 1.5 hr, peak decreased compared to IM
Liposome encapsulated aminoglycosides ⁶⁸⁻⁷⁰	Delivered inhaled, IV, or locally; with IV, concentration in liver and spleen high; renal accumulation similar to normal dosing; persists much longer and leads to higher concentrations but does not appear to increase toxicity
F = bioavailability.	

Distribution

Aminoglycosides exhibit three-compartment distribution when given by IV bolus.⁴⁸ The central compartment volume is quite small at approximately one-third to one-half of the volumes used for general dosing with one-compartment approaches. The first distribution phase, during the first hour, is generally not detected because it is masked by the infusion time (0.5–1 hr) or absorption after an IM dose. Initial distribution does not impact peak-sampling schedules: 0.5 hr after a 30-minute infusion or at the end of a 1-hour infusion for IV, 1 to 1.5 hr after IM injection, or 0.5 to 1 hr after IV bolus).

The late distribution phase involves slow distribution into and redistribution from tissues. This phase has been associated with nephrotoxicity. The final phase half-life, averaging approximately 150

hr, is generally not detected without analysis of urine collected during therapy and for a week or more after therapy is completed.

The volume of distribution (V) values for aminoglycosides are based on population studies. Although some researchers have found subtle differences among the aminoglycosides, the same volume estimate is suggested for each drug. Amikacin, gentamicin, and tobramycin are generally considered to distribute into the extracellular fluid volume. Dehydration, overhydration, and ascites affect V. Patients who are dehydrated may have a smaller actual V, whereas edematous patients may have a larger V than predicted. Seriously ill adult patients are reported to have larger V per body weight. The average V by age group and by different body weights are provided in **Table 8-5**.

TABLE 8-5. VOLUME OF DISTRIBUTION BY AGE GROUP

Age	V (mean $\pm$ SD) ^{a,b}
Neonates ^{8,23,71-74}	0.45 $\pm$ 0.1 L/kg ^{c,d,e}
Infants ⁷⁵	0.4 $\pm$ 0.1 L/kg ^d
Children ^{76,77}	0.35 $\pm$ 0.15 L/kg ^f
Adolescents ^{76,77}	0.3 $\pm$ 0.1 L/kg ^f
Adults and geriatrics ^{28,78-81}	0.3 $\pm$ 0.13 L/kg ^g

V = volume of distribution; L = liter; kg = kilogram; LBW = lean body weight; IBW = ideal body weight; ABW = actual body weight.

^aThe values used for volumes approximate those in the original studies but are rounded off. Due to the variability in the ages studied, some of these age ranges and values are extrapolated or rounded off from those given in the original studies.

^bStudies are inconsistent in the reporting of V relative to body weight. V may be related to actual (ABW), ideal (IBW), lean (LBW), or an adjusted dosing weight (BW_{adj}); many studies have patients both above and below IBW. See the Dosing Strategies section of this chapter to estimate a patient's dosing weight and V.

^cPremature neonates tend to have a larger V^{7,8,82} (nearer 0.5–0.55 L/kg and perhaps even larger), whereas full-term neonates tend to have smaller values (nearer 0.4–0.45 L/kg).^{6,7,23}

^dTo estimate the V for neonates and infants, ABW should be used.

^eOne report indicates that the presence of sepsis increases V approximately 14%.⁷⁴

^fFor children and adolescents, IBW is suggested for estimating V, although one study found that an BW_{adj} might need to be used in obese children (see Dosing Strategies section for determining BW_{adj}).⁸³

^gFor adults and geriatrics (and perhaps older children), dosing weight for use in V estimates is determined according to the instructions in the Dosing Strategies section.

The calculated V per body weight can vary depending on dosing body weight selected. Pai and colleagues evaluated 2,073 adult patients (without a diagnosis of cystic fibrosis) of varying body weights with stable renal function who had received tobramycin or gentamicin with three to four serum concentrations obtained within a dosing interval.⁸¹ Using a one-compartment model, the volume (in L) increased across the BMI groups. When LBW was used (see LBW estimation method of Janmahasatian et al. in Chapter 4) to determine V in L/kg, the V averaged 0.45 L/kg across all patient groups (underweight, normal weight, overweight, and obese).

Protein binding

Amikacin, gentamicin, and tobramycin are essentially not bound to plasma proteins. No adjustments in dosing or monitoring are necessary based on changes in plasma proteins.

Elimination

The aminoglycosides are eliminated by glomerular filtration in the kidney. Studies indicating some nonrenal elimination were affected by describing the pharmacokinetics assuming a one-compartment model and the occurrence of early tissue accumulation of drug. Aminoglycoside clearance correlates reasonably well with glomerular filtration rate (GFR), actual creatinine clearance (CrCl) by urine sample, or CrCl estimated by the Cockcroft-Gault, modification of diet in renal disease (MDRD), or chronic kidney disease-epidemiology (CKD-EPI) equations.⁸¹

The clearance values provided in **Table 8-6** are based on approximately average renal function for each age group. Reduced renal function in any age group results in decreased clearance. When renal function is decreased, prediction of aminoglycoside clearance from renal function is recommended over using average clearance values.

TABLE 8-6. AVERAGE CLEARANCE IN PATIENTS WITH NORMAL RENAL FUNCTION	
Age	Clearance (Mean ± SD) ^a
Neonates ^{6,23,71,84,85}	0.05 ± 0.01 L/hr/kg ^{b,c}
Infants ⁸⁶	0.1 ± 0.05 L/hr/kg
Children ^{76,77,86-88}	0.13 ± 0.03 L/hr/kg
Adolescents ^{76,77,86,88}	0.11 ± 0.03 L/hr/kg
Adults ⁸⁹	0.08 ± 0.03 L/hr/kg
Geriatrics ^{89,90}	0.06 ± 0.03 L/hr/kg

^aThese values have been rounded off and approximate those found in the original studies.
^bIn newborns, renal function increases rapidly; the glomerular filtration rate tends to double during the first 14 days of life.
^cIn premature or low birth weight neonates, clearance is decreased compared to normal gestation and weight newborns. For this group, the clearance value given minus one standard deviation may be used initially for prediction. One study of extremely premature neonates (post-conception age 27.8 ± 1.8 weeks and weight 1.07 ± 0.34 kg) showed clearances of 0.007 to 0.013 L/hr/kg at 24 and 30 weeks post conception.⁸²

Half-life and time to steady state

The half-lives shown in **Table 8-7** are associated with calculations that assume one-compartment distribution. The half-life of aminoglycosides may increase by 10% to 20% as therapy continues, although in newborns it may decrease because of the natural rapid maturation of renal function in the first few weeks of life.

TABLE 8-7. HALF-LIFE AND TIME TO STEADY STATE BY AGE GROUPING		
Age or Condition	Half-Life (Mean ± SD)	Time to Steady State ^a
Neonates ^{23,48,71,91}	6 ± 2 hr ^b	20–40 hr
Infants ^{c,76}	4 ± 1 hr	15–25 hr
Children ^{77,86,88,92}	1.5 ± 1 hr	3–12 hr
Adolescents ^{7,88,93}	1.5 ± 1 hr	3–12 hr
Adults ^{89,94}	2 ± 1 hr	5–15 hr
Younger geriatrics ^{89,94}	3.5 ± 2 hr	8–27 hr
Older geriatrics ^{89,94}	4 ± 2 hr	10–30 hr
Renal failure ⁹⁵⁻⁹⁷	40–60 hr ^d	8–12 days
During peritoneal dialysis ^{98,99}	10–20 hr ^d	
During hemodialysis ⁹⁵⁻⁹⁷	4.2 ± 2.3 hr	
During continuous renal replacement therapy ^{100,101}	4.5–6.5 (median) hr ^e	

^aTime to steady state assuming five half-lives using +1 SD and –1 SD of the mean half-life (t_{1/2}).
^bPremature neonates would tend to have t_{1/2} = mean +1 SD (8 hr).²³
^cIn infants and children, half-life tends to decrease with advancing age.
^dApproximate range.
^eApproximate range. One patient had a t_{1/2} of 280 hr.

DOSING STRATEGIES

There are several approaches to determining the initial dose and interval for treating patients with aminoglycosides. These range from use of a standard dose and interval for age (using either LDEI or SDSI approaches), to adjusting standard doses and/or intervals based on the patient's renal function, to estimating the pharmacokinetic parameters of the aminoglycoside in the specific patient using population predictors and then determining the dose and interval to produce desired peak and trough concentrations. Many studies have evaluated population values and dosage prediction techniques for the aminoglycosides. One review of SDSI concluded that individualized dosing using Sawchuk-Zaske techniques or Bayesian analysis after monitoring of drug concentrations (particularly with parameters based on the monitored patient population) provided the best predictive performance.¹⁰² In this section, predictive approaches will be discussed.

Estimating pharmacokinetic parameters—dosing weight and volume of distribution

For *adults and geriatrics (and perhaps older children)*, the following algorithm may be followed to determine dosing weight and population volume of distribution.

To determine dosing weight:

Step 1. Patient's ABW in kilograms is determined.

Step 2. Patient's IBW in kilograms is determined.

Step 3. ABW is compared to IBW:

- (a) For a patient whose ABW/IBW ratio is $0.9 < \text{ratio} < 1.2$, use of ABW is suggested for dosing weight.
- (b) For a patient whose ABW/IBW ratio is ≥ 1.2 (classified as overweight/obese), calculate and use adjusted body weight (BW_{adj}) for dosing weight.^{79,103}

$$BW_{\text{adj}} (\text{kg}) = \text{IBW} + 0.4 (\text{ABW} - \text{IBW})$$
- (c) For a patient whose ABW/IBW ratio is $> 0.75 < \text{ratio} < 0.9$, IBW is used for dosing weight.¹⁰⁴
- (d) For a patient whose ABW/IBW ratio is ≤ 0.75 (emaciated), the patient's ABW is multiplied by 1.13 and used for the dosing weight.⁷⁹

To estimate volume of distribution (V)(in liters):

Step 4. The estimated V is determined for all patients *except* emaciated, severely ill, overweight, obese, or trauma patients using:

$$V = 0.3 \text{ L/kg} \times \text{dosing weight (kg)}$$

Another option is $V = 0.48 \text{ L/kg} \times \text{LBW (kg)}$ for all weight categories.⁸¹

Step 5. The estimated V is determined for emaciated, severely ill, obese, overweight, or trauma patients^{79,81,105-108}:

$$V = 0.35 \text{ L/kg} \times \text{dosing weight (kg)} \text{ (emaciated patients)}$$

$$V = 0.4 \text{ L/kg} \times \text{dosing weight (kg)} \text{ (severely ill and trauma patients; some studies show even larger V in this group)}$$

Estimating pharmacokinetic parameters—clearance, elimination rate constant, and half-life

Many methods for estimating the clearance and half-life of aminoglycosides have been evaluated. These methods usually relate the patient's actual or estimated CrCl to the parameter being considered (i.e., the aminoglycoside clearance [CL_{ag}] or the elimination rate constant [k]) and use one-compartment approaches to dosing.¹⁰² Although newer methods to estimate GFR have been developed (see Chapter 1), the use of these GFR estimates to predict drug concentrations have not been studied sufficiently

to recommend their use for drug dosing at this time. New methods for calibrating and standardizing serum creatinine measurements have been adopted that are expected to decrease variability in assay results among laboratories but also to decrease values 10% to 20% on average, with resulting increases in estimates of CrCl compared to when many of the studies relating CrCl to drug clearance were conducted. When CrCl estimates are used in the predictors below, it might be assumed that actual aminoglycoside clearance will be slightly less and half-life slightly longer than what is predicted and, therefore, concentrations may be slightly higher than predicted (on average). Drug dosing guidance has been provided for use of estimated CrCl by the National Institutes of Health at <http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx>.

Estimating clearance

The following equation has been used to relate CL_{ag} to $CrCl$ ¹⁰⁹:

$$CL_{ag} = CrCl$$

Estimating the elimination rate constant (k)

The elimination rate constant can be estimated using two different approaches:

1. CL_{ag} is determined as above and then k is determined using the following equation:

$$k = \frac{CL_{ag}}{V}$$

where CL_{ag} and CrCl are in liters per hr (L/hr), k in hr^{-1} , and V in liters (L). CrCl is converted from milliliters per minute to L/hr by multiplying by 0.06 (i.e., $CrCl [L/hr] = CrCl [mL/min] \times 0.06$).

2. CrCl is related to k using the equation below¹¹⁰:

$$k = (0.0024 \times CrCl) + 0.01$$

where k is in units of hr^{-1} and CrCl in mL/min.

Estimating half-life

After determining k using either approach above, half-life ($t_{1/2}$, in hr) is then estimated by:

$$t_{1/2} = \frac{0.693}{k}$$

Using estimated pharmacokinetic parameters to determine dose and interval

The parameters (k and V) estimated above are next inserted into the appropriate formula describing the dosing pattern. For example, when multiple short infusions are used, the equation in the Introduction to this book (and below) describing this approach to dosing can be manipulated to solve for the dose to provide a target peak concentration after the appropriate interval has been chosen.

$$C = \left(\frac{S \times D}{k \times V \times t'} \right) \left(\frac{(1 - e^{-kt'})}{(1 - e^{-k\tau})} \right) (e^{-kT})$$

Standard approaches, nomograms, and algorithms—SDSI and LDEI

Average SDSI doses frequently produce concentrations outside of the accepted traditional therapeutic range.^{1,2,111-113} In adults and geriatrics, 1-mg/kg doses often result in steady state peak concentrations

of less than 6 mg/L. Use of larger doses reduces the incidence of low peak concentrations but can also increase the incidence of elevated troughs if intervals are not simultaneously lengthened. Individualized dosing using Sawchuk-Zaske¹¹⁴ or Bayesian dosing methods produce desired concentrations more reliably due to the use of measured concentrations for feedback.¹⁰²

Traditional SDSI approaches—doses and dosing intervals

The dosing interval in all patients receiving SDSI should be approximately two to three times the half-life. The usual doses/intervals are shown in Table 8-2. Obviously, this interval value must be rounded off to a logical time (e.g., 6, 8, 12, 16, 18, 24, 36, or 48 hr). Note that the intervals can be as long as those used in LDEI approaches when patients have poor renal function. Clinicians generally do not use less than 8-hour dosing intervals for aminoglycosides, even in patients with excellent elimination, although in the past some have used 6-hour intervals in patients with very high clearance (e.g., burn patients).¹¹⁴ Intervals such as 16, 18, and 36 hr should be avoided if possible as they can cause confusion in scheduling. The correctness of dosing times should be verified when these unusual schedules are ordered.¹¹⁵

When traditional doses of 2.5 mg/kg are used in newborns, dosing intervals may be based on birth weight, gestational age, or post-conception age.²³ For example, one approach based on weight is as follows: 1,000 g or less, interval of 24 hr; 1,001–2,000 g, interval of 18 hr; and over 2,000 g, initial interval of 12 hr.⁹¹ An approach using gestational age and weight suggests 2.5-mg/kg doses with intervals of 24 hr if the newborn is ≤ 34 weeks of gestation and $< 1,000$ g, 18 hr if ≤ 34 weeks of gestation and $> 1,000$ g, and 12 hr if ≥ 35 weeks of gestation.⁸

LDEI dosing initially was not used in certain populations (e.g., ascites, total body surface area burns $> 20\%$, pregnancy, enterococcal endocarditis, end-stage renal disease including dialysis, granulocytopenia, or cystic fibrosis).^{19,116} Increasingly, studies have examined its safety and efficacy in more patient types.^{18,26–28,117–125} However, several populations including enterococcal endocarditis (LDEI not recommended), pregnancy, burns, renal failure, meningitis, and osteomyelitis may require additional caution when receiving this dosing.⁴ A simulation study suggested that many burn patients are not candidates for once-daily LDEI because of pronounced variability in the length of the aminoglycoside-free period (i.e., the time when concentrations are essentially zero). The authors suggested monitoring aminoglycoside concentrations if LDEI is used in burn patients to ensure that the aminoglycoside-free period is not extensive.¹²⁶ Although efficacy studies comparing LDEI and SDSI generally show fairly similar results for many older children and adolescents, additional monitoring may also be necessary as these patients are expected to have a short aminoglycoside half-life.⁶ Patients on long-term therapy with aminoglycosides are at particular risk for toxicity, whatever dosing approach is chosen, and should be monitored very carefully and appraised of the risks.

LDEI dosing—doses and dosing intervals

There are essentially four approaches to LDEI dosing found in the literature:

1. The first, and most common in studies, is to give the usual total daily dose (e.g., 80 mg or 1.5 mg/kg given every 8 hr for gentamicin and tobramycin) as a single dose every 24 hr (e.g., 240 mg or 4.5 mg/kg every 24 hr). In some cases, the dose or interval is adjusted based on measured concentrations.
2. The second approach is to give a large dose (e.g., 7 mg/kg of gentamicin or tobramycin) designed to produce a certain peak to anticipated MIC ratio (e.g., 10:1), or simply a high concentration. The initial dosing interval is based on the patient's estimated or measured renal function and $t_{1/2}$ (either by using CrCl for adults and children or by gestational age in neonates) and the dose is based on estimated V. Intervals are usually 24, 36, or 48 hr, although some protocols may allow even longer. In some approaches it is suggested that the interval be adjusted as needed based on measured concentrations.
3. The third approach is to adjust the LDEI dose used in patients with normal renal function downward based on estimated or actual CrCl, giving the dose every 24 hr in all cases.

4. The fourth approach is individualized dosing that targets desired peak and trough concentrations. This is similar to traditional SDSI approaches except that desired peaks are higher and troughs usually lower.

LDEI dosing in adults

For *adults*, there are many examples in the literature of the first approach to LDEI dosing where the total daily dose is given as a single dose.¹²⁷ Studies of these methods generally show equal efficacy and in some cases reduced toxicity to multiple daily dosing. In some cases, a trough concentration might be monitored and the interval extended if the concentration is not below 2 mg/L. One suggested method simply decreases the starting dose by half if the trough is above 1 mg/L.¹²⁸

The authors of the Hartford method (an example of the second approach described earlier) suggest the initial use of 7 mg/kg of gentamicin or tobramycin (or 15 mg/kg of amikacin) with the interval determined as follows¹⁹:

CrCl is ≥ 60 mL/min	Interval = 24 hr
CrCl is 40–59 mL/min	Interval = 36 hr
CrCl is 20–39 mL/min	Interval = 48 hr

The dosing weight is the patient’s actual body weight unless >20% above IBW (ABW/IBW ratio is >1.2), where the weight would be determined as in Step 3b in the Dosing Strategies section on determining dosing weight and V.

In 2,184 patients treated with this method, 77% were dosed every 24 hr, 15% every 36 hr, 6% every 48 hr, and 2% >48 hr.¹⁹ The monitoring approaches and a dosing interval adjustment nomogram for this method can be found in this chapter in the section on Therapeutic Monitoring.

Two examples of the third approach described earlier—keeping the dosing extended interval (every 24 hr) and simply adjusting the dose downward based on renal function—are shown in **Table 8-8**.

TABLE 8-8. LARGE DOSE-EXTENDED INTERVAL DOSING METHODS, DOSE BASED ON CREATININE CLEARANCE

CrCl, mL/min, Estimated or Actual	Method A ²⁰ Dose, mg/kg ^a	Method B ²¹ Dose, mg/kg ^b
≥80	5.1	4
61–80	3.9	3.25
51–60	3.6	3.25
30–50	3	2.5
<30	Not used	2

^aDoses are based on ABW unless ABW/IBW ratio is ≥1.35, then an adjusted body weight (BW_{adj}) is used. See Step 3b in the Dosing Strategies section on determining dosing weight and volume (V) for determination of BW_{adj}.
^bDoses based on ABW.

An example of the fourth approach, individualized dosing, is found in a study by Rybak and colleagues.¹²⁹ Target peak concentrations in this study were 16–20 mg/L for gentamicin and tobramycin for patients with respiratory infections (60–80 mg/L for amikacin) and 10–12 mg/L for patients with other infections (40–60 mg/L for amikacin). Target trough concentrations were <1 mg/L (<4 mg/L amikacin).

A study evaluating predicted concentrations derived from the pharmacokinetic parameters of 116 patients and applied to the Hartford,¹⁹ Example A,²⁰ and Example B²¹ methods (the latter two shown in Table 8-8), yielded the following results.⁹² Peak concentrations were ≥10 mg/L in 100% of patients given the 7 mg/kg dose of the Hartford method, whereas 92% and 81% of those dosed with the Example

A and B methods, respectively, achieved these peaks. Trough concentrations were >1 mg/L in 17%, 14%, and 13% of patients using Hartford, Example A, and Example B dosing approaches, respectfully. Thus, there appears to be a good chance of desirable high peaks and low troughs with all the methods, but some patients might still benefit from concentration monitoring, particularly for lengthier regimens.

LDEI dosing in neonates

A review by the Cochrane Neonatal Group of the National Institute for Child Health and Human Development on once versus multiple daily dosing of gentamicin for suspected or proven sepsis in neonates found that there was, “insufficient evidence from the currently available randomized controlled trials (RCTs) to conclude whether a ‘once a day’ or ‘multiple doses a day’ regimen of gentamicin is superior in treating proven neonatal sepsis.”¹³⁰ However, the authors concluded that the pharmacokinetic outcomes of LDEI were superior (higher peaks and avoidance of “toxic” trough concentrations) and that there is no difference in nephrotoxicity or auditory toxicity. They concluded that LDEI may be superior in treating neonatal sepsis in neonates more than 32 weeks in gestation.

The following are five of the dosing methods proposed for neonates.

Method 1—The LDEI dosing recommendations shown in **Table 8-9** were generated from pharmacokinetic data from tobramycin dosing studies in a large group of neonates.¹³¹

TABLE 8-9. METHOD 1 DOSING GUIDELINES FOR NEONATES¹³¹

Gestational Age (wk) ^a	Dose (mg/kg)	Interval (hr)
<32	4	48
32–36	4	36
>36	4	24

^aThese authors had originally suggested a slightly different dosing approach (the only difference being modification of the every 36 hr dosing to be gestational age 32–37 weeks).¹³²

Using the recommendations in Table 8-9 and data from two studies, extrapolated predictions found that peaks greater than 5 mg/L would occur in more than 90% of the neonates. Troughs above 2 mg/L would be very rare, and troughs <1 mg/L would occur in the majority (more than 70%).^{131,132}

Method 2—The authors of Method 2 (shown in **Table 8-10**) suggest using decreasing mg/kg doses and shortening the interval based on a newborn’s (first week of life) gestational age.¹³³ The authors of method 1 questioned the validity of certain modeling approaches for development of Method 2.¹³⁴

TABLE 8-10. METHOD 2 DOSING GUIDELINES FOR NEONATES¹³³

Gestation Age (wk)	Dose (mg/kg)	Interval (hr)
<30	5	48
30–34	4.5	36
>34	4	24

Method 3—The authors of Method 3 (shown in **Table 8-11**) suggest lower mg/kg doses compared to Method 2 with the same dosing intervals based on gestational age.¹³⁵ When these two methods were compared, the number of peak gentamicin concentrations within the target range of 5–12 mg/L was higher with Method 3. Peaks would be higher using Method 2 due to the higher doses recommended.

TABLE 8-11. METHOD 3 DOSING GUIDELINES FOR NEONATES¹³⁵

Gestation Age (wk)	Dose (mg/kg)	Interval (hr)
<30	4.5	48
30–34	3.5	36
>34	3.5	24

Method 4—The issue of dosing in very low birth weight neonates (600 g–1500 g) was evaluated in 58 first-week-of-life newborns.¹³⁶ The authors tested 24-hour regimens with lower doses and 48-hour regimens with larger doses and found that the optimal interval for producing desired concentrations was the 48-hour regimen. The 48-hour interval doses studied were 5 mg/kg in 1,001–1,500 g babies and 4.5 mg/kg in 600–1,000 g babies. The authors cautioned that a 36-hour interval might be more appropriate for some neonates since 13% of those on 48-hour interval dosing had troughs <1 mg/L for over 24 hr before the next dose, suggesting the need for measuring concentrations in these groups.

Method 5—Another group proposed a gentamicin dosing algorithm for *neonates* in the first 10 days of life that targets an AUC₀₋₂₄ of 87.5 mg/L × hr.¹³⁷ The algorithm was based on pharmacokinetic data from 139 neonates given gentamicin. The daily dose is determined by the equation:

$$24\text{-hr gentamicin dose (mg)} = [0.441 + (0.0945 \times \text{gestational age})] \times \text{birth weight}$$

where gestational age is in weeks and birth weight in kg.

A study using pharmacokinetic data from 293 newborns ≤1 week of age to simulate peak and trough gentamicin concentrations from the dosing recommendations for each of the five methods above concluded that all “would likely yield acceptable peak concentrations as well as trough concentrations of ≤1 mg/L for at least 50% of patients.”¹³ They suggested that it might be sufficient to monitor only trough concentrations when these protocols were used. Simulated peaks were ≥5 mg/L in at least 97% of patients for all the methods, while method 4 had the greatest percentage of troughs ≥2 mg/L (17%), compared to 8% or less for the others.

LDEI dosing in children

A meta-analysis of 24 eligible studies of LDEI versus SDSI use in children found consistent trends favoring LDEI in terms of lower clinical failure rate, microbiological failure rate, and combined clinical and microbiologic failure rate, but the differences were not statistically significant.¹⁶ No significant differences were found in primary nephrotoxicity (increased serum creatinine or decreased CrCl) although LDEI was significantly better in avoiding secondary nephrotoxicity outcomes (urinary excretion of proteins or phospholipids). Finally, even though reporting on ototoxicity outcomes was somewhat incomplete in the studies, the rates were very low in both arms (LDEI and SDSI), and there was no significant difference noted.¹⁶ A letter to the editor discussing these outcomes pointed out that there are remaining gaps in knowledge that should be addressed before the authors could “confidently recommend universal change.”¹³⁸ The gaps suggested included knowledge about “(1) the incidence of ototoxicity, (2) the appropriate dose (which varied from 4 to 7.5 mg/kg per 24 hr in included trials), and (3) the role and appropriate mode of therapeutic drug monitoring with EIAD [extended interval aminoglycoside dosing].”¹³⁸

The authors of the meta-analysis disagreed that the evidence did not support universal change and pointed out that the original SDSI dosing approaches were developed based on no evidence as well.¹³⁹ They also noted that there was no evidence suggesting that SDSI is indicated in any subgroups (e.g., cystic fibrosis, neonates) either and that “perpetuating emphasis on spurious subgroup differences is likely to inappropriately delay the wider adoption of single daily dosing.”¹³⁹ Finally, they noted “single daily dosing translates to lower trough values and should simplify the need for monitoring.”

In children there have been a number of LDEI regimens suggested and studied. One method from a study of 90 patients 1 month to 12 years of age with urinary tract infections and gentamicin dosed every 24 hr is shown in **Table 8-12**.¹⁴⁰

TABLE 8-12. LARGE DOSE-EXTENDED INTERVAL DOSING GUIDELINES FOR CHILDREN¹⁴⁰

Age	Dose (mg/kg)	Interval (hr)
1 mo–<5 yr	7.5	24
5–10 yr	6	24
>10 yr (to 12 yr)	4.5	24

A review of 13 studies describing extended interval (every 24 hr) dosing of gentamicin in infants and children found that, based on concentrations that resulted, these approaches were theoretically more efficacious with no higher toxicity than standard dosing approaches.¹³⁶ The daily dose used was 4 to 5 mg/kg in 11 of the studies and 7.5 mg/kg in one. The thirteenth study was the method shown in Table 8-12.¹⁴⁰ As would be expected, peaks are higher and troughs lower in the once-daily groups.¹⁴¹ Troughs exceeded 2 mg/L in 5% to 55% of the standard three times daily dosing studies as compared to 0% to 24% of the once-daily groups. The latter result of up to 24% with troughs greater than 2 mg/L in the LDEI approach is a reminder that some patients will need concentration monitoring.

LDEI dosing summary

LDEI dosing approaches may provide rapidly effective concentrations that can maximize the killing of bacteria without enhancing the risk of toxicity and may minimize or prevent the development of adaptive resistance in the bacteria. They may also reduce the need for concentration monitoring, decreasing these and other costs associated with more frequent dosing (e.g., additional administration costs).¹⁴² Further, LDEI approaches can make treatment at home or at day treatment facilities more feasible, allowing some patients to leave hospital settings. LDEI approaches should not be used in all patient types until evidence supports at least equal efficacy and safety.

The variation in individual pharmacokinetic outcomes with LDEI approaches and the variation in suggestions for dosing and intervals suggest that doses may still need to be individualized using concentration monitoring, particularly for extended treatment regimes.

THERAPEUTIC RANGES

SI units have been reported for several aminoglycosides but their use worldwide is rare. Thus, all drug (serum or plasma) concentrations are expressed in milligrams per liter (mg/L) in this chapter.

Traditional SDSI approaches to dosing (i.e., 1 to 1.5 mg/kg every 8 or 12 hr) are used less frequently. When traditional SDSI approaches are used for the treatment of *pneumonia*, peak concentrations of gentamicin or tobramycin—drawn approximately 30 min after a 30-minute infusion or at the end of a 1-hour infusion—should be greater than 7 mg/L.¹⁴³ Trough concentrations—drawn approximately 0.5 hour or less before the next dose—should be 1–2 mg/L.¹⁴⁸ With amikacin, peak concentrations should be greater than 28 mg/L,¹⁴¹ and trough concentrations should be 4–8 mg/L.¹⁴⁸ For *other infections*, gentamicin and tobramycin peak concentrations of greater than 5 mg/L¹⁴⁴ and trough concentrations between 0.5 and 2 mg/L have been recommended.¹²⁶

With LDEI dosing approaches, the peak concentration desired varies. Doses most often recommended in adults range from 4–7 mg/kg, which would produce peak concentrations of approximately 13–23 mg/L in average patients. Recommendations for children have been similar with a range of 4–8 mg/kg every 24 hr.^{16,118} Patients with cystic fibrosis have received 15-mg/kg doses that produce peaks as high as 40 mg/L.²⁴ Although some authors advise against use of LDEI in cystic fibrosis patients,¹¹⁸ one RCT showed equal efficacy and perhaps less nephrotoxicity (in children) with LDEI dosing.¹²⁵

The desired trough concentration varies depending on the approach. The Hartford method assumes that the aminoglycoside concentration drops to zero 4 hr or more before the next dose.¹⁹ Others suggest less than 1 mg/L.¹²⁹ For neonates receiving LDEI doses of 3.5–5 mg/kg of gentamicin and tobramycin

every 24 hr, the trough may not go below 1 mg/L for many patients.^{13, 23,132,136,145,146} It is unknown whether this presents a greater risk of toxicity, although at least one study showed no apparent increase in risk.¹⁴⁷ However, the often brief duration of therapy for neonates and adults (5 days or less) may obscure the potential for toxicity that could occur if these doses are continued for a longer period. Greater caution should always be used in patients who will receive aminoglycosides longer than 5 days, so it is prudent to ensure the lowest possible trough concentrations. Conversely, in low birth weight newborns given 4.5–5 mg/kg every 48 hr, a small percentage of patients (13%) may be below 1 mg/L for more than 24 hr.¹³⁶ Whether this represents a higher risk of therapeutic failure or not needs to be examined as the post-antibiotic effect seen with aminoglycosides is 6 hr or less.

In SDSI approaches, patients of very advanced age (and consequent reduced renal function) and those with diminished renal function due to other causes, may have received every 24-hr dosing of traditional-sized aminoglycoside doses to keep peaks of 5 to 8 mg/L and troughs of <2 mg/L. If these same patients are given LDEI and the interval is not extended beyond 24 hr, the risk of toxicity increases.²⁸ This issue is critical with LDEI dosing approaches, particularly if the interval is fixed at every 24 hr no matter what the patient's renal function might be. The advantages seen in some studies with LDEI in terms of decreased toxicity may have been due to having very low to nonexistent troughs.¹⁴⁸ Extrapolating the benefits of LDEI with every 24-hr dosing to those who would have received traditional doses at extended intervals should probably not be done.

It has been suggested for traditional dosing approaches that the peak aminoglycoside concentration to MIC ratio should be greater than 4:1 and preferably greater than 8:1.^{149,150} The likelihood of success appears to increase with higher values since the aminoglycosides demonstrate concentration-dependent killing. This characteristic of aminoglycosides is exploited in LDEI dosing approaches. When a favorable peak to MIC ratio cannot be attained, synergistic agents or another antibiotic with good organism sensitivity should be used.

The Hartford LDEI dosing approach using 7 mg/kg for gentamicin and tobramycin was based on the assumption of need for a 10:1 peak to MIC ratio for best results and assumes an MIC of 2 mg/L for organisms.¹⁹ Others have made similar dosing suggestions.¹¹⁸ The success of other LDEI approaches using lower doses and the fact that some organisms have lower MICs should lead clinicians and researchers to consider regimens that take advantage of knowledge of the actual MIC to adjust dose size. Because organisms sometimes demonstrate different levels of susceptibility to the various aminoglycosides, it is also conceivable that using the aminoglycoside to which the organism is most susceptible could allow for use of lower doses. The total dose exposure appears to relate to toxicity, so the use of the lowest effective dose is desirable.

THERAPEUTIC MONITORING

Suggested sampling times and effect on therapeutic range

Peak aminoglycoside concentrations usually should be drawn 30 min after a 30-min infusion or less than 15 min after a 1-hour infusion for consistency of evaluation among patients, sites, and studies. The true peak occurs precisely at the end of the infusion. However, to avoid possible predistribution values and unrelated problems in blood drawing times, these recommendations have been generally adopted. If doses are given as bolus injections, *peak* concentrations should generally be drawn 1 hr after the injection to be consistent with other approaches.

The true *trough* aminoglycoside concentration occurs precisely at the end of the dosing interval and before the next infusion, bolus, or IM injection is initiated when appropriately scheduled (i.e., if dosage interval is 12 hr, the trough concentration would occur at 12 hr after start of previous dose but prior to next dose). Trough aminoglycoside concentrations are usually scheduled for 30 min or less before a dose assuming that previous dose and next dose are administered per prescribed dosing interval (i.e., if the next dose is administered 3 hr late a concentration measured at 30 min prior to that

dose would be lower than the trough concentration on the regular schedule). Again, unrelated delays in sample collection and the need for consistency in the evaluation of efficacy and toxicity lead to the recommendation to check the trough approximately 30 min before the next dose.

When peak and trough concentrations are not measured at the correct time, the concentrations that would have occurred at the correct times should be estimated using the measured concentrations to determine whether the dosing regimen is meeting desired concentration goals.

Drug concentration measurements should be collected approximately one half-life apart for improved accuracy (to reduce the impact of any assay error). A number of studies have examined the accuracy of using four, three, two, or one concentration measurement.¹⁵¹⁻¹⁵³ Recommendations vary (three, two, or one) and cost considerations as well as patient discomfort are obviously important. For SDSI dosing, two concentrations continue to predominate monitoring suggestions, while for LDEI most recommendations are for one measurement. Others suggest more traditional approaches for LDEI where a peak is drawn at some point in the hour or so after a dose (fairly similar to traditional peak measurements) with a second concentration measured approximately two estimated half-lives later (usually 6 to 12 hr depending on estimated renal function or 8 to 10 hr for prediction of AUC_{0-24}).¹⁵⁴ Doses and intervals may then be individualized to ensure achievement of a trough concentration at or near zero. Others suggest no concentration measurements when LDEI is used in patients with normal renal function who do not have confounding factors.^{131,155}

Bayesian approaches tend to enhance the accuracy of subsequent dose adjustments when fewer concentrations are measured. However, inaccurate information about dose and sample collection timing can make any concentration report problematic. Varying the definition of when peak concentrations are to be drawn will affect the desired concentrations. These times must be standardized to ensure appropriate and consistent dosing within and among various institutions.

Concentration measurement frequency

Monitoring of aminoglycoside concentrations helps to ensure therapeutic peak concentrations (though of reduced necessity when large doses are used), which enhances the likelihood of clinical response, and to reduce the risk of toxicity. When SDSI approaches were the norm, it was argued that aminoglycoside concentrations were monitored too soon and too often based on the number of patients who have short-term therapy (4 days or less), who do not exhibit toxicity despite elevated aminoglycoside concentrations, and who survive despite concentrations below goal.¹⁵⁶ Many authors still support the value of measurements, while some deny the value, and others suggest reducing the number of measurements around a dose or the total frequency of measurement.^{19,157-159} One study found an association between pharmacist-managed aminoglycoside therapy and improvements in healthcare and economic outcomes for Medicare patients receiving these drugs.¹⁶⁰ This suggests that monitoring concentrations and adjusting doses to achieve desired concentrations improves these outcomes.

Certain patients may not derive benefit from having aminoglycoside concentrations measured, and clinicians should evaluate the cost to benefit for each patient.^{158,161,162} In a patient whose risk of death from infection is significant or the risk of toxicity is high, the assurance of adequate concentrations would appear to be worthwhile.

Initial concentration measurement

If a course of SDSI aminoglycoside therapy is planned (3 or more days), peak and trough concentration determinations can enhance the potential for adequate therapy. These measurements should be obtained early in treatment (first or second day) to ensure adequate peak concentrations or to allow for early dosage adjustment to achieve target concentrations. A study of burn patients demonstrated rapid achievement of therapeutic steady state concentrations when first dose measurements were used to guide therapy.¹⁶³ Patients also had fewer dosing changes than with conventional dosing where concentrations were not measured early in therapy. Thus, early assessment has utility if it is known

that a full course of therapy is fairly certain. Unless a patient has considerably reduced renal function or their intervals are shorter than 8 hr, steady state conditions are usually in place by the second dose.

A study in neonates showed that early measurements after a loading dose led to fewer dose adjustments, fewer concentration measurements, and more rapid attainment of desired concentrations than with standard dosing protocols where concentrations were measured later.¹⁶⁴ In neonates it has also been shown that pharmacokinetic parameters do not change substantially between day 2 of life compared to days 3 or 4, so early monitoring in a course of therapy for these patients is acceptable when a full course of therapy is planned.⁸⁵ It is unknown whether other approaches to monitoring would lead to similar therapeutic outcomes and fewer measurements of concentrations.

Several studies have evaluated the use of a single concentration obtained in neonatal populations to determine dosing interval.¹⁶⁵⁻¹⁶⁸ The use of a 22-hour post dose concentration to determine LDEI dosing interval in neonates has been evaluated: in neonates beyond the first week of life (gestational age 24–36 weeks with postnatal ages of 8–95 days), Dersch-Mills and colleagues evaluated gentamicin doses of 5 mg/kg.¹⁶⁶⁻¹⁶⁷ If the 22-hour gentamicin concentration was reported as <1.2 mg/L, every 24-hour dosing interval was recommended while every 36- or 48-hr dosing intervals were recommended if concentration was 1.3–2.6 mg/L or 2.7–3.5 mg/L, respectively. Although 30% of the obtained concentrations were undetectable (<0.4 mg/L), a predicted peak concentration of 5–12 mg/L and 12.1–15.7 mg/L were reported in 87% and 13% of patients after the second or third dose, respectively.¹⁶⁶ Similar results were reported when the same group evaluated 22-hour concentrations in neonates in the first week of life (gestational age 23 weeks to full term) with average extrapolated peak concentrations of 10.55 mg/L.¹⁶⁷ Because extrapolated peak and trough concentrations are based on neonatal population volume of distribution values, actual peak and trough concentrations may vary in patients with significantly different volume of distribution. Alshaikh and colleagues evaluated this method in 33 neonates at 28 weeks or less gestation.¹⁶⁸ Based on 22-hour concentrations after gentamicin 5 mg/kg, every 36-hour dosing interval was recommended in 61% of patients while every 48-hour dosing interval was used in the other 39%.

As shown in **Figure 8-1** and **Figure 8-2**, two nomograms (for desired trough less than 0.5 mg/L and 1 mg/L) were developed for neonates less than one week old to predict gentamicin dosing interval after one gentamicin concentration is obtained between a suggested sampling time of 15 and 21 hr post-infusion of previous dose (4 mg/kg) using a fixed V of 0.45 L/kg.¹² Based on the pooled data from three retrospective studies, these nomograms predicted the correct interval in 81% to 93% of the concentrations evaluated.

Plot the measured concentration–time point on the graph. If the concentration falls in the 24-hour area, the neonate should be given 4 mg/kg every 24 hr. If the time points falls in another zone, that interval should be used. If the concentration falls in the >48-hour zone, a second concentration should be measured at 48 hr to determine if the concentration is above the desired trough value, in which case the dose should be withheld for an additional period of time, depending on how high the concentration reported was, and further doses should be administered cautiously.

Recommendations for initial monitoring of LDEI dosing generally suggest measurements on the first or second day of treatment. As mentioned previously, it has also been suggested that no monitoring is necessary if the patient has normal renal function, no confounding factors, and therapy will be for 5 days or less.¹⁵⁵ A study evaluating the utility of therapeutic drug monitoring in neonates given LDEI in the first week of life demonstrated no improvement in prediction of final dosing interval over model-based predictions, leading the authors to suggest that there is little value in monitoring concentrations.¹³² Conversely, another study with a fairly small sample size showed that patients on LDEI who were monitored and had doses adjusted had decreased nephrotoxicity.¹⁶⁹

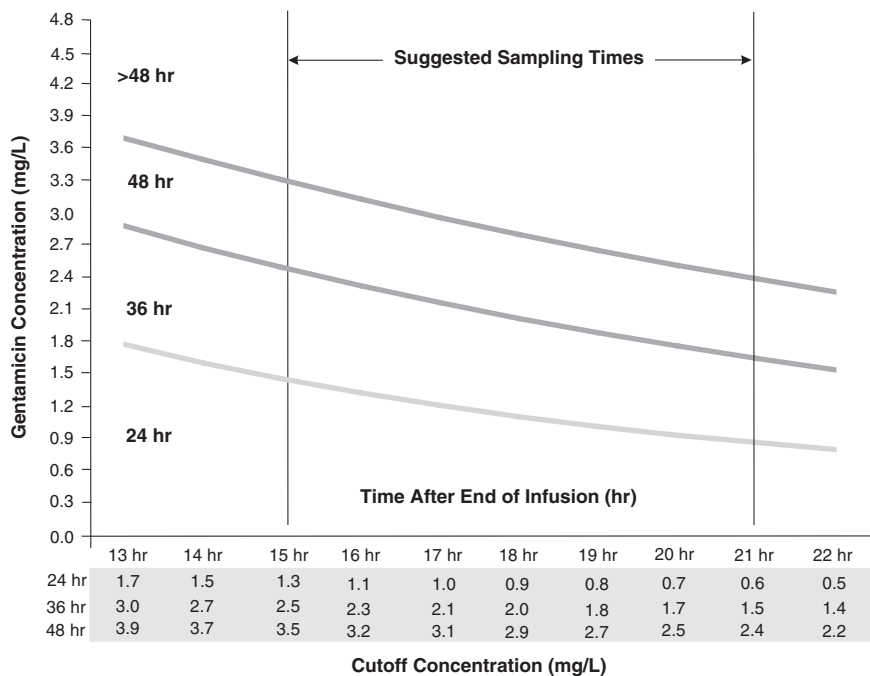


Figure 8-1. Once-daily gentamicin 0.5-mg/L nomogram for neonates.
Source: Originally published in Murphy JE, Roether AM, Two nomograms for determining extended-dosing intervals for gentamicin in © 2008, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission.

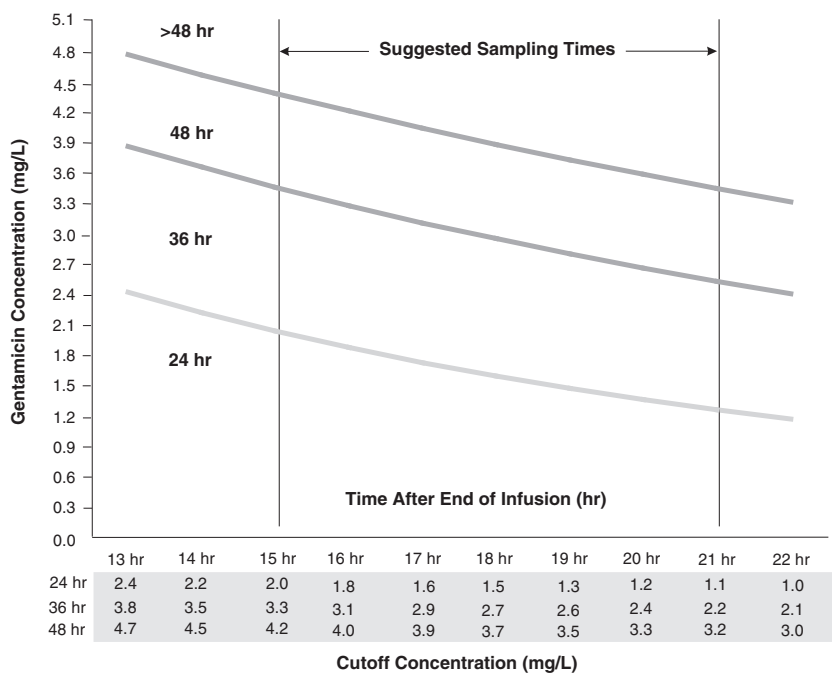


Figure 8-2. Once-daily gentamicin 1-mg/L nomogram for neonates.
Source: Originally published in Murphy JE, Roether AM, Two nomograms for determining extended-dosing intervals for gentamicin in © 2008, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission.

Follow-up concentration measurements

The need to recheck aminoglycoside concentrations depends on several factors:

- The duration of therapy is extended.
- Serum creatinine (or other measure of significant change in renal function) rises or falls considerably.
- More aggressive dosing (e.g., shorter intervals with higher troughs or very high peaks) is used or initial troughs do not reach target concentrations on LDEI. Rechecking of the trough (at least) would be necessitated by a small rise in serum creatinine (e.g., approximately 20%) in these cases. However, if the targeted trough based on initial serum concentrations were approximately 1 mg/L or less for traditional dosing, small changes in serum creatinine would not usually indicate significant increases in the trough concentration so the need for dosage adjustment would not be as likely.
- Unexpected values result. In health systems without well-developed procedures for ensuring the correct timing of concentration measurements, the potential for error is high, particularly if the dose times and collection times are not reported to the clinician. Peaks that are drawn late will be lower than anticipated, and troughs drawn early will be higher. The times of dose administration and blood sampling are important. When unexpected results are obtained and the need to know the concentrations is considered to be high, concentrations should be redrawn with strict instructions as to the time of dose, duration of infusion, and sampling times for both the peak and trough. If only one concentration appears inaccurate, it should be the one to be repeated. As a rule, all orders for aminoglycoside concentration measurements should be written with strict timing instructions unless a scheduling service is provided for ordered drug concentrations.

Other approaches to monitoring

After initiating therapy using the Hartford method (explained in Dosing Strategies section), a single concentration measured between 6 and 14 hr after a dose is plotted on **Figure 8-3**.¹⁹ The concentration result suggests adjustments to therapy if the place it falls does not represent the current dosing interval.

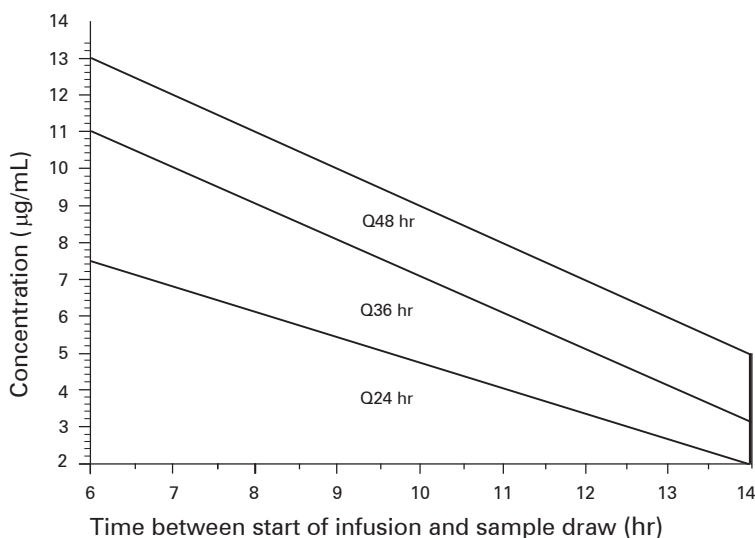


Figure 8-3. Nomogram for concentration monitoring and interval adjustment of gentamicin and tobramycin at 7 mg/kg.

Source: Reproduced with permission from American Society of Microbiology and Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrobial Agents Chemother.* 1995;39(3):650-5.

In a follow-up report, the authors suggested discontinuation of monitoring concentrations in their institution for “patients: (a) receiving 24-hr dosing regimens, (b) without concurrently administered nephrotoxic agents (e.g., amphotericin, cyclosporine, vancomycin), (c) without exposure to contrast media, (d) not quadriplegic or amputee, (e) not in the intensive care unit, and (f) <60 years old.”¹⁵⁵ Adoption of these suggestions at their institution yielded extrapolated savings of >\$100,000/year (value in 1995 dollars) for their 600-bed, tertiary-care hospital and did not demonstrate an increase in nephrotoxicity (ototoxicity was not evaluated).¹⁵⁵

In one evaluation of monitoring of LDEI dosing using 24-hour intervals, the author suggested that there is little evidence that can stand up to critical appraisal for differences in outcomes or toxicity between LDEI and SDSI and that extrapolation of need for peak concentration monitoring from SDSI to LDEI is not valid based on evidence.¹⁷⁰ The author further suggested that there is little evidence to suggest a need for a peak of 10 times the MIC and concluded with some recommendations. First, monitor the patient for efficacy (e.g., temperature, white blood cell count, how the patient feels) and toxicity outcomes, particularly auditory and vestibular as they are the most life-altering for patients. Second, tell patients who are to receive the drugs for more than a couple of days about the ototoxicity risks and explain the early symptoms such as “tinnitus, loss of hearing, a sense of fullness in the ears, headache, nausea and vomiting, giddiness, lightheadedness, vertigo, nystagmus and ataxia.”¹⁷⁰ (p. 1526) Clinicians should then ask the patient about these daily and discontinue the aminoglycoside if at all possible if the symptoms occur and cannot be attributed to another cause. Third, serum creatinine can be monitored to assess whether renal toxicity is occurring; and finally, “every attempt should be made to minimize the duration of aminoglycoside therapy.”¹⁷⁰ (p. 1526)

Assay issues

Although assay quality for aminoglycosides is good, some variation exists between methods, and laboratory quality should be evaluated.¹⁷¹ Assay errors may be more important when the trough (i.e., low) concentration is used to adjust doses, leading some to suggest sampling earlier in the interval.¹⁷² Other factors can affect assay results. One study showed differences in peak (but not trough) concentrations of gentamicin and tobramycin when serum concentrations were compared to samples collected with sodium citrate (12% decrease primarily due to dilution), ethylenediaminetetraacetic acid (EDTA) (5% decrease), and heparin (17% to 22% depending on heparin concentration).¹⁷³ These interactions might be more important in LDEI situations. Although not an assay issue per se, one report documented the potential for erroneously high tobramycin concentrations when samples were taken by finger stick in a patient whose hands were contaminated with drug after inhalation of nebulized tobramycin.¹⁷⁴

Summary of aminoglycoside concentration monitoring

It seems reasonable to assume that patients treated appropriately using either larger doses for SDSI or LDEI approaches with adjustment of dosing interval based on renal function will have sufficiently high aminoglycoside peak concentrations to improve the chance of therapeutic success, unless the organism is resistant. This assumption should reduce the need to monitor peak concentrations. Thus, suggestions to avoid measuring concentrations early in therapy for such patients who have normal renal function seem reasonable. However, serum creatinine should be followed in such a setting. For therapy that will be extended beyond a few days, an aminoglycoside concentration measurement is suggested. Confounding factors such as concomitant nephrotoxins, impaired physiology (e.g., ascites, burns, advanced age, or early age), or changing serum creatinine should signal the need for more aggressive monitoring.

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

Much of the work on concentration-related efficacy occurred when the aminoglycosides were given using SDGI approaches (i.e., every 8 or 12 hr). Moore and colleagues determined that patients with bacteremia responded better when peak gentamicin or tobramycin concentrations were above 5 mg/L and when peak amikacin concentrations were above 20 mg/L.¹⁴⁴ They also found that peaks of all three agents needed to be higher for patients with Gram-negative pneumonia (7 mg/L for gentamicin and tobramycin and 28 mg/L for amikacin).¹⁴³ Binder and colleagues found a 71% response rate in febrile immunocompromised patients with hematologic malignancies whose gentamicin or tobramycin peak was >4.8 mg/L but only 30% response if the peak was ≤4.8 mg/L.¹⁷⁵

Deziel-Evans and colleagues showed that peak concentration-to-MIC ratios might be a better predictor of success.¹⁴⁹ Ratios of 4:1 or more improved survival rate. Others have shown improvement if the ratio is at least 3:1 for infections with Gram-negative organisms.¹⁷⁶

Moore and colleagues also observed a graded dose-response effect with peak-to-MIC ratios and showed that the likelihood of success increased as the peak-to-MIC ratio increased.¹⁵⁰ With a ratio of less than 2:1 as unity, the relative odds of clinical response were 4.35 times higher at a peak-to-MIC ratio of 6:1 to 8:1 and 8.41 times higher at a ratio of 10:1 or more. These results were supported by a study of patients with nosocomial pneumonia where a 10:1 ratio in the first 2 days of treatment predicted a 90% probability of temperature and leukocyte reduction.¹⁷⁷

Per the Clinical and Laboratory Standards Institute recommendations for antimicrobial susceptibility testing, MIC values of 16 mg/L or higher for gentamicin and tobramycin and 64 mg/L or higher for amikacin are considered resistant.¹⁷⁸ It has been suggested that organisms should be considered resistant at gentamicin and tobramycin MICs of 4 mg/L or higher and amikacin MICs of 16 mg/L or higher.^{150,151} However, if a peak-to-MIC ratio of at least 4:1 is desired, gentamicin and tobramycin peak concentrations of 16 mg/L would be required for an organism with an MIC of 4 mg/L. Prior to LDEI dosing, clinicians would have been hesitant to use aminoglycoside doses that could produce such concentrations. Because the goal of some LDEI methods is a 10:1 ratio, a peak of 40 mg/L would be required, which represents a value beyond the majority of LDEI dosing approaches. The use of additional antibiotics with synergistic effect may enhance the potential for successful outcome when organisms are relatively resistant to aminoglycosides.

Concentration- or exposure-related toxicity

Aminoglycosides cause nephrotoxicity, ototoxicity (vestibular and cochlear), and neuromuscular toxicity. It is possible that LDEI is less toxic than SDGI due to saturable uptake of aminoglycosides in the proximal renal tubule cells and the inner ear. One study showed that enzyme markers of nephrotoxicity were lower with LDEI versus SDGI despite higher daily doses.¹⁷⁹ It is not clear, however, whether LDEI is less ototoxic than SDGI.¹⁸⁰

Nephrotoxicity has been associated with a number of factors, including excessive trough concentrations, daily AUC₀₋₂₄ exposure, prolonged drug exposure (including low-dose), higher baseline GFR, and co-administration with other nephrotoxic agents.^{41,129,181-184} The exact relationship has been vigorously debated, but it is generally accepted that in SDGI approaches, troughs of gentamicin and tobramycin should be as low as possible (<2 mg/L) and that troughs of amikacin should be <8 mg/L, if possible. With a number of LDEI dosing approaches, the goal is to have the trough reach <0.1 mg/L for several hr before the next dose is given.

Increased rates of nephrotoxicity were reported in one study with LDEI twice-daily dosing versus every 24 hr dosing (15.4% versus 0%, respectively) potentially due to the increased AUC₀₋₂₄.¹²⁹ Factors that appeared to increase nephrotoxicity are shorter dosing interval, concomitant vancomycin, and AUC₀₋₂₄.¹²⁹

Renal function must be monitored in patients receiving aminoglycosides. Factors such as decreased renal function and concomitant treatment with other nephrotoxins increase the incidence of nephrotoxicity. Fortunately, most nephrotoxicity resolves after therapy is discontinued due to the ability of the kidneys to regenerate tubules.¹⁸⁵ Serum creatinine should be monitored at the beginning of therapy and routinely throughout treatment. The frequency of monitoring varies according to the patient's stability.

Although not generally considered an appropriate reason to recommend therapeutic drug monitoring, litigation associated with aminoglycoside therapy may be prevented or at least reduced by monitoring serum creatinine and aminoglycoside concentrations and by dosage adjustment to provide target concentrations in the generally accepted therapeutic range. More importantly, patients may have a greater likelihood of successful treatment without toxicity.

In general, serum creatinine should be monitored daily in any aminoglycoside patient whose serum creatinine varies by about 25% or more between measurements. For patients with stable measurements, serum creatinine may be monitored approximately every 3 days. Renal dysfunction associated with aminoglycosides can take several days to manifest as rising serum creatinine; therefore, it may be useful to check serum creatinine 2–3 days after treatment is completed in some cases. Because reductions in renal function tend to improve, however, this is unnecessary for most patients. In the presence of other factors that may affect renal function (e.g., treatment with other nephrotoxins or hypotensive episodes), it is suggested that serum creatinine should be monitored more frequently (daily to every other day).

Various urine tests and blood urea nitrogen (BUN) also can be used to monitor renal function. Although not suggested for routine monitoring, urine can be tested for, among other things, decreasing specific gravity (indicating reduced ability to concentrate urine), excretion of protein, cells, and casts and fractional excretion of sodium, potassium, magnesium, and uric acid.¹⁸⁶ Although an increase in BUN may indicate decreasing renal function, it can also be caused by other factors. Diminished urine output over time relative to intake of fluid may also be a sign of decreasing renal function.

One study of LDEI dosing showed timing of dosing as an independent risk factor for nephrotoxicity.¹¹⁶ Patients receiving their dose during midnight to 7:30 a.m. had a higher incidence of nephrotoxicity. These findings have led some authors to suggest that after the first dose, which must be given as soon as possible in sick individuals even if it must be given during the night (or resting period), further LDEI doses should be switched to administration in the morning or early afternoon (active period).¹⁸⁶ There is evidence that liver disease and biliary obstruction are associated with increased potential for nephrotoxicity.^{187,188}

Ototoxicity has been related to prolonged drug exposure and can be monitored by vestibular and auditory tests.^{189,190} These tests are, however, notoriously difficult to use in many settings. Symptoms of ototoxicity include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss. When practical, patients should be questioned regarding such symptoms periodically. Deafness is usually irreversible and may evolve after therapy is concluded. One study found that 33 of 33 subjects with permanent ototoxicity complained of symptoms of vestibular toxicity within 1 to 3 weeks of initiation of gentamicin, yet clinicians did not recognize vestibular toxicity prior to discharge in 32 of 33 subjects.¹⁹⁰ Peak and trough concentrations did not correlate with ototoxicity nor did observance of safe dosage ranges, although all but one of the patients received long-term therapy. The authors of this study recommended frequent monitoring and attention paid to signs and symptoms of ototoxicity since early identification may reduce risk, informing all patients about the risks of ototoxicity, and using other agents whenever feasible.¹⁹⁰

It has been suggested that the choice of aminoglycoside can play an important role in the risk of ototoxicity, although prolonged duration of therapy is probably the most frequently cited factor. Older age, bacteremia, poor physical condition, fever, liver and renal impairment, and the combination with another ototoxic agent are also often reported.^{27,119,191} Genetic predisposition may also play a role (see below in Pharmacogenomic Implications).¹⁹² Iron chelators and radical scavengers have been reported to prevent ototoxicity in guinea pigs, but these have not been adopted for human use.¹⁹³

Neuromuscular toxicity also has occurred with the aminoglycosides; they should be used with caution in patients receiving neuromuscular blocking agents and in patients with muscular disorders such as myasthenia gravis and Parkinsonism. The risk of neuromuscular blocking problems is likely enhanced with use of LDEI approaches in these patients.¹⁹⁴

Other symptoms of toxicity that occur to a minor extent (less than 3% incidence) include hypersensitivity, headache, nausea and vomiting, and abnormal liver function tests. Some brands of aminoglycosides may contain sodium bisulfite, which can cause allergic reactions including anaphylaxis in certain individuals. A syndrome of endotoxin-like reactions was reported with the use of gentamicin for LDEI dosing.^{195,196} One product apparently contained enough endotoxin that the large dose led to pyrogenic adverse consequence for patients, leading two companies' to voluntary withdrawal of the products due to possible association with this adverse event; clinicians should watch for similar reactions when LDEI approaches are used.

In a study of 61 metabolic and respiratory stable preterm neonates who received gentamicin for suspected infection, higher peak serum gentamicin concentrations were associated with an increased incidence of microalbuminuria, natriuresis, and calciuria.¹⁹⁷ Due to these potential complications in neonates, it is recommended that urine albumin/urine creatinine, urine calcium/urine creatinine, and fractional excretion of sodium and potassium be monitored if monitoring gentamicin concentrations are not feasible.¹⁹⁸

DRUG–DRUG INTERACTIONS^{9,48,143}

In vitro sensitivity studies have found that the administration of beta-lactams, extended-spectrum penicillins, or vancomycin with an aminoglycoside can have a synergistic effect, improving the response to therapy. However, in vitro studies also have shown that concomitant administration of carbenicillin, mezlocillin, and ticarcillin decreases aminoglycoside concentrations. The time between collection of blood and concentration determination should be as short as possible when the agents are used to treat patients receiving aminoglycosides. Samples should be refrigerated until analyzed.

In vitro studies have indicated that a precipitate may form when aminoglycosides are administered concomitantly with cefoperazone and cephalothin or in vitro inactivation may occur with various beta-lactams. These agents should not be mixed together for infusion. A study of piperacillin-tazobactam and gentamicin showed no interaction.¹⁹⁸

In vivo studies indicated that concomitant administration of beta-lactam or extended-spectrum penicillin agents might decrease the half-life and increase clearance of the aminoglycosides, especially in patients with renal failure. Although an interaction has been suggested to be more likely in patients with reduced renal function, it appears that there is no need to consider separating gentamicin and ampicillin dosing times.¹⁹⁹ In vivo studies also have found an increase in aminoglycoside toxicity when administered concomitantly with other nephrotoxic agents or potent diuretics like acyclovir, amphotericin B, carboplatin, bacitracin, capreomycin, cisplatin, colistin, furosemide, ethacrynic acid, mannitol, vancomycin, urea, other aminoglycosides, and possibly some cephalosporins.

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

The following disease states or conditions influence certain aspects of aminoglycoside pharmacokinetics.

- *Ascites*^{200,201}—The volume of distribution may increase by as much as 25%.
- *Burns*²⁰²⁻²⁰⁵—Clearance and volume of distribution may increase while half-life may increase or decrease.
- *Cirrhosis*²⁰⁶—Critically ill patients with cirrhosis and sepsis may have 40% larger volume (L/kg) and 38% lower clearance than similar patients without cirrhosis.

- *Cystic fibrosis*^{24,25,207-212}—The volume of distribution or clearance may increase. Larger doses have been recommended for both LDEI and SDSI approaches. LDEI dosing is as effective in patients with cystic fibrosis as SDSI and may be less toxic in children.
- *Dialysis—hemodialysis, peritoneal dialysis*^{99,180,213-219}—Clearance increases and half-life decreases compared to values obtained when patient is not on dialysis. Studies of the use of a LDEI of aminoglycosides intraperitoneally differ on whether it provides appropriate coverage.^{51,218,219} During peritoneal dialysis, efficiency of removal can be affected by various solutes in the dialysis solution and by the integrity of the peritoneal membrane. During hemodialysis, drug removal is affected by numerous variables including dialysate and blood flow rates, efficiency of dialyzer, positive and negative pressures, and length of dialysis. Aminoglycoside concentrations demonstrate a rebound phenomenon after hemodialysis, where the concentration increase may be due to redistribution from tissue. Therefore, sampling should be delayed approximately 2 hr after dialysis to avoid the possibility of dosing errors based on this phenomenon.⁹⁸ Several pharmacokinetic studies have been published evaluating different hemodialysis dosing methods (pre-dialysis, during dialysis, and post-dialysis). Although most studies have evaluated the use of post-dialysis aminoglycoside dosing, this dosing strategy can lead to higher aminoglycoside AUC₀₋₂₄ exposure between hemodialysis sessions since a patient's aminoglycoside concentrations remains fairly stable between sessions if there is no renal function. To decrease AUC₀₋₂₄ exposure between sessions, lower aminoglycoside doses are administered that are potentially subtherapeutic. Another strategy is to either administer a dose during the beginning of a hemodialysis session or 2 to 6 hr prior to a scheduled hemodialysis session to mimic renal clearance with dialysis.²¹⁵⁻²¹⁷ This strategy may allow higher doses to be administered, increasing the probability of achieving goal peak concentration while minimizing AUC₀₋₂₄ between hemodialysis sessions. A concern for using this dosing strategy relates to the potentially high aminoglycoside exposure if the hemodialysis session was not completed as scheduled.²¹⁵⁻²¹⁷
- *Febrile neutropenia*²²⁰—The use of SDSI versus LDEI dosing methods has been evaluated in a few studies. There are potential concerns about LDEI monotherapy if extended periods of time are allowed with low aminoglycoside concentrations.
- *Intensive care setting/severely ill patients*^{105,106,110,221-223}—Patients may have a 25% to 50% higher V than normal and increased clearance. Peak concentrations may be lower based on a specific mg/kg dose in critically ill patients compared to noncritically ill patients.
- *Hepatic dysfunction*²²⁴—Serum cystatin C may be a better predictor of GFR for aminoglycoside dosing due to potential for overestimating GFR with the Cockcroft-Gault equation in hepatic dysfunction.
- *Hypothermia (therapeutic)*²²⁵⁻²²⁷—Patients may have a larger V and longer half-life.
- *Malnutrition or underweight (<90% IBW) or frailty in older patients*^{81,228,229}—For underweight patients with serum creatinine <1 mg/dL, estimated CrCl may overestimate aminoglycoside clearance. An adjustment factor of 0.69 has been proposed.
- *Meningitis*²³⁰—Minimal concentrations of aminoglycosides have been reported in cerebrospinal fluid after intravenous administration but may be increased slightly in patients with meningitis.
- *Obesity*^{81,103}—See Dosing Strategies section on dosing weight and determination of V.
- *Pancreatitis*²³¹—V may increase by as much as 25%.
- *Patent ductus arteriosus*²³²—Clearance may decrease by ~11% and V may increase by ~13%.
- *Postoperative, mechanical ventilation*²³³—V increases.
- *Postpartum*²³⁴—V is increased over normal; 1.5 times the IBW for dosing weight can be used in estimations of V. A study showed that use of BW_{adj} (similar to use in obese patients) provided a good prediction of V.²³⁵ The first approach is slightly more aggressive in patients who were close to IBW prior to pregnancy.

- *Pregnancy*^{9,48}—Certain aminoglycosides are known to cause fetal harm (e.g., streptomycin- and kanamycin-induced ototoxicity) when administered during pregnancy.^{9,48} It is not known whether amikacin, gentamicin, and tobramycin cause fetal harm or whether LDEI approaches would increase risk. One study of LDEI versus SDSI dosing in 38 laboring women found peak concentrations of 13 to 25 mg/L after a 5.1 mg/kg dose in the mothers and extrapolated mean peak cord blood concentrations of 6.9 mg/L in the newborns (compared to 2.9 mg/L for SDSI) and no noted adverse effects.⁴⁸ As always, the benefits should outweigh the risks, and patients should be warned of potential hazard to the fetus, particularly with longer duration therapy.
- *Prematurity*²³⁶⁻²³⁹—Decreases in renal tubular function after administration of aminoglycosides may be more pronounced in premature neonates.
- *Spinal cord injury*²⁴⁰—V is generally increased in patients with decreased muscle mass and increased extracellular fluid. Traditional methods of estimating CrCl may not be accurate in patients with spinal cord injury based on actual weight. Mean absorption times of IM aminoglycosides may be prolonged.

PHARMACOGENOMIC IMPLICATIONS OF AMINOGLYCOSIDE USE

Genetic implications of the effect of aminoglycosides have focused on mutations that may increase the risk of adverse events such as ototoxicity. The A1555G mutation in the 12S ribosomal RNA gene (mitochondrial) along with other variants such as C1494T have been associated with an increased risk of aminoglycoside-induced deafness.^{241,242} A maternal family history of aminoglycoside-associated ototoxicity may be associated with increased risk of hearing loss with aminoglycoside use in certain patient populations. Although molecular screening for the specific polymorphisms in the mitochondrial 12S ribosomal RNA in larger populations for potential future aminoglycoside exposure is controversial, testing in certain patients with higher rates of aminoglycoside exposure such as patients diagnosed with cystic fibrosis or neonates admitted to neonatal intensive care units has occurred.^{242,243}

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ANTIDEPRESSANTS

Patrick R. Finley

Antidepressants have been prescribed for the treatment of mood disorders for almost 60 years. However, it has only been within the last two decades that the popularity of this class of medications has increased dramatically. In 2011, for instance, the Department of Health and Human Services reported that approximately 10% of all adults living in the United States received a prescription for an antidepressant, and data suggest that antidepressants have joined opioid analgesics and lipid-lowering agents as the three medication classes most commonly prescribed in contemporary practice. The popularity of antidepressant medications can be attributed to an enhanced awareness of the prevalence of depression, as well as the discovery and release of newer agents perceived to be safer than tricyclic alternatives. An additional benefit of prescription antidepressants is their clinical utility and effectiveness in the treatment of a wide range of illnesses, ranging from the Food and Drug Administration (FDA)-approved indications such as major depression, anxiety disorders, and smoking cessation, to unapproved uses such as insomnia, premature ejaculation, and weight management.¹

Given the popularity of the antidepressant drug class, concerns about their collective potential for causing drug interactions and potentially serious side effects are well-founded. As depression has been strongly associated with a wide variety of common medical conditions that are chronically treated with medications (e.g., heart disease, diabetes, Parkinson disease), concerns about drug-drug and drug-disease interactions are particularly salient.²

Although the practice of therapeutic drug monitoring (TDM) has been well described for tricyclic antidepressants (TCAs), their use has steadily declined in favor of selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), and norepinephrine reuptake inhibitors (NRI).³ The benefits of TDM are not as apparent for these newer agents. However, an appreciation for the pharmacokinetic disposition of *all* antidepressants is vital to ensure the safe and efficacious use of these medications across a broad and diverse patient population.

In general, the successful incorporation of pharmacokinetic principles into the clinical use of antidepressants requires slightly different considerations than with many other drug classes. For instance, many patients who receive adequate or optimal antidepressant therapy may have drug concentrations that are considerably different than values considered normal or therapeutic based on population-based studies. Ultimately, in clinical practice antidepressant dosages are titrated to desired effect rather than attempting to achieve a plasma concentration that has been determined a priori.⁴⁻⁶ Also, it should be kept in mind that assumptions about the pharmacokinetics and pharmacodynamics of these drugs are based on concentrations achieved in the plasma rather than concentrations determined from the actual site of action in the central nervous system, where sampling is impractical. Nonetheless, the pharmacokinetic parameters of the antidepressants will often be a factor in determining safe and appropriate therapy.

In this chapter, the population parameters, metabolic fate, and monitoring concerns for all antidepressants currently marketed in the United States are summarized. It should be noted that, although there are other psychotropic compounds prescribed for the treatment of depression (e.g., lithium, buspirone, lamotrigine, ketamine, and second-generation antipsychotics), a complete discussion of the wide variety of medications is beyond the scope of this chapter. The disposition of most antidepressants has not been well studied in certain patient populations such as children and adolescents. Thus, the primary focus of this chapter will be on adult pharmacokinetic parameters.



Similarly, the impact of other medical conditions and impairments has not been well described for most antidepressants. At the end of the chapter a theoretical discussion of conditions that may influence antidepressant disposition is provided as well as specific recommendations about drug dosing and therapeutic monitoring.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS^{6–8}

The respective dosage ranges for all antidepressants in the treatment of major depression are summarized in **Table 9-1**. Antidepressant dosing practices for other indications may vary considerably from these ranges. For example, the use of SSRI for obsessive-compulsive disorder (OCD) or panic disorder requires small initial doses to avoid excessive activation (e.g., fluoxetine 5–10 mg daily). Maintenance doses, however, are often greater for the treatment of these anxiety disorders than for major depression, (e.g., 40–80 mg daily of fluoxetine).^{1,9}

The typical initial and daily doses listed in Table 9-1 are generally consistent with those approved for adults by the FDA. Because steady state concentrations can vary more than ten-fold with empiric dosing recommendations and there are substantial inherent differences in pharmacodynamic sensitivity, some patients may require doses greater or less than those listed in the table. For example, daily doses of venlafaxine often exceed the FDA-recommended maximum of 225 mg. Although higher doses are associated with an increased risk of hypertension and tachycardia, clinicians often find that doses greater than 225 mg daily are necessary to achieve complete remission of symptoms. Ultimately, the therapeutic effects and toxicities observed will effectively determine prescribed maintenance doses, so routine and thorough patient monitoring is vital.

DOSAGE FORM AVAILABILITY

Antidepressant medications are currently available in a wide variety of oral dosing formulations (e.g., tablets, capsules, and solution). An injectable preparation of amitriptyline is suitable for intramuscular administration and a transdermal patch of the monoamine oxidase inhibitor (MAOI) selegiline is available. **Table 9-2** provides the available dosage forms.

GENERAL PHARMACOKINETIC INFORMATION

The major pharmacokinetic parameters for commercially available antidepressants in healthy adults are summarized in **Table 9-3**.⁸ Antidepressants are generally highly lipophilic compounds, permitting their passage across the blood brain barrier into the central nervous system. They are usually basic amines with pK_as ranging from 7–10. Many of the antidepressants exist in a racemic formulation with one enantiomer conveying greater pharmacological effects or metabolic inhibition. Important examples of this phenomenon include fluoxetine, citalopram, bupropion and mirtazapine.

Most antidepressants are rapidly and completely absorbed in the small intestine but undergo extensive presystemic elimination in the liver (i.e., high first pass effect). This characteristic makes plasma concentrations highly variable among patients receiving identical doses. The extent of extraction by the liver classifies these drugs as moderate-to-high clearance, with extraction ratios of 0.5–0.8. The presence of food in the gastrointestinal tract does not alter the extent or rate of absorption for most antidepressants, which is important because patients are generally instructed to ingest their antidepressants during or shortly after meals to minimize nausea. One exception to this pattern can be found with sertraline, where the presence of food in the gastrointestinal (GI) tract has been demonstrated to increase the area under the curve (AUC) by 65%. The clinical significance of this finding is unclear.

TABLE 9-1. ORAL DOSAGE RANGES FOR ANTIDEPRESSANT CLASSES

Drug	Initial Daily Dosage ^a	Usual Daily Dosage
Tricyclic and Tetracyclic		
Amitriptyline	25 mg	100–300 mg
Imipramine	25 mg	100–300 mg
Clomipramine	25–50 mg	75–250 mg
Doxepin	25 mg	100–300 mg
Nortriptyline	25 mg	50–150 mg
Desipramine	25 mg	100–300 mg
Protriptyline	15 mg	15–60 mg
Trimipramine	25 mg	50–300 mg
Amoxapine	50 mg	100–600 mg
Maprotiline	25 mg	75–225 mg
SSRIs		
Fluoxetine	10–20 mg	10–40 mg
Sertraline	25–50 mg	25–100 mg
Paroxetine	10–20 mg	10–40 mg
Fluvoxamine ^b	50 mg	100–300 mg
Citalopram	10–20 mg	20–40 mg
Escitalopram	5–10 mg	10–20 mg
SNRIs		
Venlafaxine	37.5 mg	150–300 mg
Desvenlafaxine	50 mg	50–100 mg
Duloxetine	20–30 mg	60–120 mg
Levomilnacipran	20 mg	40–120 mg
NRIs		
Bupropion	200 mg	300–450 mg (divided)
Bupropion sustained release	150 mg	300–400 mg (divided)
Bupropion extended release	150 mg	300–450 mg
MAOIs		
Phenelzine	15 mg	30–60 mg
Tranylcypromine	10 mg	20–40 mg
Selegiline (transdermal)	6 mg	6–12 mg
Miscellaneous		
Mirtazapine	15 mg	15–45 mg
Trazodone	50 mg	150–600 mg
Vilazodone	10 mg	20–40 mg
Vortioxetine	10 mg	10–20 mg

^aIn geriatric patients, the starting dose is generally less than for younger adults.

^bThe dosage given is for obsessive-compulsive disorder. Labeling for treatment of depression has not been approved in the United States.

TABLE 9-2. DOSAGE FORM AVAILABILITY

Drug	Dosage Form	Brand Name(s)
Amitriptyline	Tablets: 10, 25, 50, 75, 100, and 150 mg	Elavil
	Parenteral injection: 10 mg/mL	Elavil
Amoxapine	Tablets: 25, 50, 100, and 150 mg	Asendin
Bupropion	Tablets: 75 and 100 mg	Wellbutrin
	Tablets (sustained release): 100, 150, and 200 mg	Wellbutrin SR, Zyban
	Tablets (extended release): 150 and 300 mg	Wellbutrin XL
Citalopram	Tablets: 10, 20 and 40 mg	Celexa
	Oral solution: 10 mg/5 mL	
Clomipramine	Capsules: 25, 50, and 75 mg	Anafranil
Desipramine	Tablets: 10, 25, 50, 75, 100, and 150 mg	Norpramin
	Capsules: 25 and 50 mg	Pertofrane
Desvenlafaxine	Tablets (extended release): 50 and 100 mg	Pristiq
Doxepin	Capsules: 10, 25, 50, 75, 100, and 150 mg	Adapin, Sinequan
	Oral solution: 10 mg/mL	Sinequan
Duloxetine	Capsules: 20, 30, and 60 mg	Cymbalta
Escitalopram	Tablets: 5, 10, 20 mg	Lexapro
	Oral solution: 5 mg/5 mL	
Fluoxetine	Tablets: 10, 20 mg	Prozac
	Capsules: 10, 20, and 40 mg	Prozac, Sarafem
	Capsules (delayed-release): 90 mg	Prozac Weekly
	Oral solution: 20 mg/5 mL	Prozac
Fluvoxamine	Tablets: 25, 50, and 100 mg	Luvox
	Capsules (extended release): 100 and 150 mg	Luvox CR
Imipramine	Tablets: 10, 25, and 50 mg	Tofranil
	Capsules: 75, 100, 125, and 150 mg	Tofranil-PM
Levomilnacipran	Capsules (extended release): 20, 40, 80, 120 mg	Fetzima
Maprotiline	Tablets: 25, 50, and 75 mg	Ludiomil
Mirtazapine	Tablets: 15, 30, and 45 mg	Remeron
	Tablets (orally disintegrating) 15, 30, and 45 mg	
Nortriptyline	Capsules: 10, 25, 50, and 75 mg	Aventyl, Pamelor
	Oral solution: 10 mg/5 mL	Aventyl, Pamelor
Paroxetine	Tablets: 10, 20, 30, and 40 mg	Paxil, Pexeva
	Oral solution: 10 mg/5 mL	Paxil
	Tablets (controlled release): 12.5, 25, 37.5 mg	Paxil CR
Phenelzine	Tablets: 15 mg	Nardil
Protriptyline	Tablets: 5 and 10 mg	Vivactil
Selegiline	Transdermal patch: 6, 9, 12 mg	Emsam
Sertraline	Tablets: 25, 50, and 100 mg	Zoloft
	Oral solution: 20 mg/mL	
Tranylcypromine	Tablets: 10 mg	Parnate
Trazodone	Capsules: 50, 100, 150, and 300 mg	Desyrel
Trimipramine	Capsules: 25, 50, and 100 mg	Surmontil
Venlafaxine	Tablets: 25, 37.5, 50, 75, and 100 mg	Effexor
	Capsules (sustained-release): 37.5, 75, and 150 mg	Effexor XR
Vilazodone	Tablets: 10, 20, 40 mg	Viibryd
Vortioxetine	Tablets: 5, 10, 15, 20 mg	Trintellix

TABLE 9-3. PHARMACOKINETIC PARAMETERS FOR ANTIDEPRESSANTS IN HEALTHY ADULTS^{4,5,11,14}

Drug	Bioavailability (%) ^a	Clearance (L/hr) ^b	Volume of Distribution (L/kg)	Half-Life (hr)
Amitriptyline	30–60	19–72	6–36	9–46
Amoxapine	46–82	42–73 ^c	8–14	6–16
Bupropion	>90	126–140	27–63	9–21
Citalopram	95	23–38	14	23–45
Clomipramine	36–62	23–122	9–25	15–62
Desipramine	33–51	78–168	24–60	12–28
Desvenlafaxine	80	210	3.4	9–15
Doxepin	13–45	41–61	9–33	8–25
Duloxetine	^c	114	11–50	9–19
Escitalopram	80	36	12–26	27–32
Fluoxetine	>70	5–42	12–42	26–220
Fluvoxamine	53–84	33–320	>5	9–28
Imipramine	30–70	32–102	9–23	6–28
Levomilnacipran	92	24–29	55–68	12
Maprotiline	70–90	17–34	16–32	27–50
Mirtazapine	50	^c	4.5	13–34
Nefazodone	>20	^c	0.2–1	2–8
Nortriptyline	46–70	17–79	15–32	18–56
Paroxetine	>90	15–92	3–28	7–37
Phenelzine	^c	^c	^c	11.6
Protriptyline	75–90	8–23	15–31	54–198
Selegiline	25–30	16	^c	10
Sertraline	>44	96	>20	22–36
Tranlycypromine	^c	^c	1.1–5.7	1.5–3.5
Trazodone	70–90	7–12	1–2	3–14
Trimipramine	18–63	40–105	17–48	16–40
Venlafaxine	92	40–129	2–23	2–11
Vilazodone	72	20–25	8.6	25
Vortioxetine	75	33	39	66

^aValues are generally low for many of these drugs due to extensive presystemic elimination.

^bValues approach or exceed hepatic blood flow due to an inherent artifact in calculating clearance from oral dose data.

^cReliable values are not available in the literature.

Most antidepressants are highly bound to plasma proteins (>80%), with the notable exceptions of venlafaxine (27%), escitalopram (56%), and levomilnacipran (22%). Volumes of distribution greatly exceed body weight, implying that antidepressants accumulate in tissues, and concentrations are much higher in this compartment than in the plasma. Since as little as 3% of the total body burden of some antidepressants resides in the circulating plasma, extracorporeal methods of drug elimination (hemodialysis and hemoperfusion) have little benefit in the treatment of overdose.¹⁰ Fortunately, the most popular class of antidepressants (SSRI) appears to be less toxic in overdose than the older TCAs.^{8,11–13}

All FDA-approved antidepressants undergo hepatic biotransformation prior to excretion. For the most part this is a Phase 1 reaction and with several of the antidepressants the primary metabolic pathway produces an active metabolite.^{8,15} Examples include amitriptyline (nortriptyline), imipramine (desipramine), fluoxetine (norfluoxetine), venlafaxine (o-desmethylenlafaxine), bupropion (hydroxybupropion) and selegiline (amphetamine). The clinical importance of these metabolites can be quite profound. For instance, demethylation of fluoxetine produces a moiety with comparable activity (relative to the parent compound), but it has a much longer half-life (7–15 days versus 1–4 days) and concentrations exceed those of fluoxetine once steady state is achieved. Similarly, the activity of hydroxybupropion is roughly half that of the parent compound, but concentrations at steady state are 7–10 times higher.¹⁶ There are also phenotypic variations in the hepatic transformation of antidepressants that may be clinically relevant. Pharmacogenetic studies with paroxetine, for instance, have determined that patients who are ultra-rapid metabolizers at the cytochrome P450 2D6 (CYP2D6) isoenzyme are unlikely to achieve quantifiable plasma concentrations and are not good candidates for this agent. Conversely, patients receiving citalopram who exhibit poor metabolizer status for CYP2C19 will achieve much higher concentrations of the compound and lower dosages are advised. Other antidepressants that may have clinically relevant phenotypic variations in metabolism include sertraline, venlafaxine, mirtazapine, and vortioxetine.

The terminal half-lives of many antidepressants are approximately 24 hours or less (See Table 9-3). Therefore, steady state concentrations would be achieved within roughly 4 days. The pharmacologic half-life of these medications in the central nervous system is probably much longer, as evidenced by the delayed onset of therapeutic effects commonly observed (e.g., 1–2 weeks). Similarly, the pharmacologic actions of these medications may persist for weeks after discontinuation. For example, the effects of irreversible MAO inhibitors (such as phenelzine, selegiline, and tranylcypromine) may be evident for as long as 2 weeks, necessitating a relatively long washout period before the risk of drug and dietary interactions has diminished.

The metabolic fate of the various antidepressants is shown in **Table 9-4**. The primary isoenzymes metabolizing the parent drug and the primary metabolite(s) are listed.

DOSING STRATEGIES

Dosing and titration methods for antidepressants vary considerably from patient to patient and medication to medication. With the SSRI, for instance, there is no mention made of titration methods in the manufacturers' package inserts (PI), yet many clinicians find it a worthwhile practice to initiate treatment at lower doses (e.g., 5 mg fluoxetine daily) in the interest of improving adherence and ultimately treatment outcomes.¹⁹ With SNRI, NRI, and TCAs, there are more specific recommendations found in the PI, which are designed to minimize the risk of adverse effects while the clinician advances treatment toward a therapeutic dose. The rationale and recommendations associated with these respective approaches can be found below.

As a rule, loading doses are generally not practical or useful for antidepressants available at the present time. Side effects are quite common with the initiation of most antidepressants, and higher initial doses would be poorly tolerated. Fortunately, most of these side effects are transient and less severe with lower doses (e.g., GI and insomnia associated with SSRI and SNRI) and will abate with continued treatment.

TABLE 9-4. METABOLIC FATE OF ANTIDEPRESSANTS^{17,18}

Drug	CYP450 Isoenzyme ^a	Primary Active Metabolite(s) ^b
Amitriptyline	1A2, 2C19, 3A4	Nortriptyline (2D6), hydroxy amitriptyline
Amoxapine	2C19>1A2, 2D6, 3A4	7-Hydroxy amoxapine, 8-hydroxy amoxapine
Bupropion	2B6	Hydroxy-bupropion (2D6)
Citalopram	2C19>3A4	Desmethyl-citalopram (2D6), didesmethyl-citalopram (2D6)
Clomipramine	2C19, 1A2	<i>N</i> -Desmethyl-clomipramine (2D6)
Desipramine	2D6	Hydroxy-desipramine
Desvenlafaxine	UDGPT>3A4	Desvenlafaxine-glucuronide
Doxepin	2D6>1A2, 2C9, 2C19, 3A4	Desmethyl-doxepin
Duloxetine	1A2>2D6	Hydroxy-duloxetine
Escitalopram	2C19	Desmethyl-escitalopram (2D6), Didesmethyl-escitalopram (2D6)
Fluoxetine	2C19, 2D6	Norfluoxetine (2D6)
Fluvoxamine	1A2, 2D6	None
Imipramine	1A2>2C19, 3A4; 2D6	Desipramine (2D6), 2-hydroxy-imipramine
Levomilnacipran	Renal>3A4	None
Maprotiline	2D6	Desmethyl-maprotiline
Mirtazapine	3A4>2D6>1A2	Desmethyl-mirtazapine
Nefazodone	3A4	Hydroxy-nefazodone, <i>m</i> -chlorophenylpiperazine (2D6)
Nortriptyline	2D6	10-Hydroxy-nortriptyline
Paroxetine	2D6>COMT	None
Protriptyline	2D6	Desmethyl-protriptyline
Selegiline	2B6	Desmethyl-selegiline, L-methamphetamine, L-amphetamine
Sertraline	2C19	Desmethyl-sertraline
Trazodone	3A4	<i>m</i> -Chlorophenylpiperazine (2D6)
Trimipramine	2D6	Desmethyl-trimipramine
Venlafaxine	2D6	<i>o</i> -Desmethyl-venlafaxine (2D6)
Vilazodone	3A4>2C19 >2D6	None
Vortioxetine	2D6	None

^aWhen multiple pathways are shown, the > symbol indicates greater importance relative to isoenzymes that follow. Other non CYP pathways include renal elimination (Renal), uridine diphosphate glucuronosyl transferase (UDPT), and catechol O-methyl transferase (COMT).

^bIsoenzyme responsible for the metabolism of primary metabolite is indicated in parentheses.

Because the onset of therapeutic benefit is usually not evident for 1–2 weeks after initiation, and maximum benefit may require 3–4 weeks, the rate of titration is most strongly influenced early on by tolerability rather than efficacy. Recommended titration methods for bupropion are more specific to account for the risk of seizures that have been linked to total daily doses as well as aggressive initiation. For most antidepressants, titration is designed to improve general tolerability and is left to the prescriber's discretion.

Other factors that may influence titration include the severity of target symptoms and the treatment setting (inpatient versus outpatient). As most patients are prescribed antidepressants for mild-to-moderate symptoms and are seen in an ambulatory care setting, slow titration is often preferred and is usually associated with increased medication adherence. It should be noted that the elderly often

respond more slowly to the pharmacological effects of antidepressants, and therapeutic trials may be considerably longer in this population (6–8 weeks versus 3–4 weeks in the general population).²⁰

When an effective dose is identified, it may be advisable to assess drug concentrations for certain antidepressants that possess experimental evidence of an effective therapeutic range (i.e., certain of the tricyclics). With antidepressants such as the SSRI and SNRI, efficacy and toxicity have not been closely correlated with drug concentrations, and therapeutic drug monitoring is only recommended under uncommon circumstances such as hepatic or renal insufficiency, supra-therapeutic doses, or history of poor compliance. Although a recommended therapeutic range for bupropion has not been determined, concerns about the accumulation of the active metabolite (hydroxybupropion) and subsequent seizures may warrant plasma concentration monitoring in patients with hepatic or renal impairment.

For TCAs, a variety of dosing strategies have been proposed. For instance, several methods use a concentration determined shortly after the initial dose to select a constant dosage for reaching a targeted concentration at steady state. These methods, which have been thoroughly reviewed elsewhere, have acceptable accuracy and probably have been underutilized.²¹ They require use of a previously established mathematical relationship between the drug concentration determined one or more times after a single dose and the concentration produced at steady state following constant dosing. The use of this type of predictive approach with a new patient assumes that the patient's drug disposition pattern will be similar to that of the previously tested population.

Several concentrations determined after the first dose can be used to estimate clearance and to predict a dosage for a targeted steady state with simple mathematical relationships. Nomograms are also available for this purpose. The most applicable drug for prospective dosing methods is nortriptyline with its widely accepted therapeutic range.²¹

For most patients, linearity can be assumed in drug disposition with most antidepressants, and dosage can be adjusted using proportionality (concentrations change proportional to dose changes). Dosage changes made to achieve a new concentration should always be guided by feedback from acute and chronic pharmacological effects (presence or lack of side effects and therapeutic effects). Nonlinearity may be encountered occasionally and can be manifested by an exaggerated pharmacologic response to a dosage increase,²² which is attributed to a disproportional increase in the concentration of a drug and/or metabolites. For example, a doubling of the daily dose of paroxetine has been shown to increase steady state plasma concentrations five-fold in some patients.²³ Non-linearity in the dose–concentration relationship has also been described for fluoxetine. Although the clinical significance of nonlinearity is debatable, this pharmacokinetic anomaly may suggest that smaller dose increments should be used during titration.⁸

THERAPEUTIC RANGE

The effective and appropriate dosing recommendations for many psychotropic medications are often different than those found in the manufacturers' package insert. With antidepressants, the effective maintenance doses are often *lower* than the FDA-approved package insert for several reasons. For instance, dose-ranging or fixed-dose studies are usually conducted among study subjects with moderate-to-severe symptoms and little if any medical comorbidity (and corresponding potential for drug interactions). However, most patients treated with antidepressants have mild-to-moderate symptoms and are concurrently suffering from other medical illnesses and receiving other medications that may interact with antidepressants or alter patients' sensitivity to their effects.

An additional reason that the manufacturers often endorse a higher dosing range is associated with preclinical study designs. By including higher doses in clinical trials, researchers may be able to demonstrate a larger effect size, which allows for a smaller study population. Effective therapeutic doses may also contrast with published recommendations for pharmacokinetic reasons. For instance, huge interindividual variations in clearance values have been reported for many of the antidepressants.

Steady state concentrations can vary 10-fold with fluoxetine at fixed dosages and 40-fold variations have been reported with tricyclic agents. Much of this variability can be attributed to differences in the genetic expression of liver enzymes (e.g., genetic polymorphism of the CYP 2D6 isoenzyme). Genetic variability may also influence the activity of transport proteins, such as p-glycoprotein, which regulate CNS concentrations, leading to further variability in patient response.

The antidepressants with the best established therapeutic ranges are nortriptyline, imipramine, desipramine, and amitriptyline.²⁴ The SSRI and other antidepressants have not been reported to have a concentration range correlated with clinical response or adverse events.²⁵ Average steady state concentrations from usual doses have been reported, which may be useful in assessing medication adherence or the presence of drug-drug interactions, but are not necessarily predictive of response.

The lack of rigorously defined therapeutic ranges complicates the use of drug concentrations to determine adequate dosages for antidepressants. Furthermore, the variability of patient response to various concentrations (i.e., pharmacodynamic variations) also complicates the use of average dosage ranges with the cyclic antidepressants. Due to the vast differences in pharmacokinetic parameters among various patient populations, clinical response continues to be the best indicator of adequate dosage.

Tricyclic antidepressants

Several studies confirmed that a curvilinear therapeutic window exists for nortriptyline and the best antidepressant response is frequently obtained with a concentration of 50–150 mcg/L.^{4,26,27} The recommended therapeutic range for nortriptyline (or other TCAs) in children has not been determined but clinical experience suggests that safe and effective concentrations are comparable to or slightly lower than those achieved by adults.²⁸ It should be noted, however, that the effects of tricyclics on cardiac conduction and blood pressure parameters can be considerably different in children than mature adults and electrocardiogram (EKG) monitoring is always advised.

The combined plasma concentration of imipramine and its demethylated metabolite, desipramine, is frequently 180–350 mcg/L when optimal antidepressant response is observed.²⁴ However, the dose-response curve is thought to be more linear compared to that of nortriptyline, and the upper limit of the range is less distinct. Desipramine concentrations of 115–250 mcg/L are frequently therapeutic.

It is rarely justified for imipramine plus desipramine concentrations to exceed 350 mcg/L. However, an occasional patient will have excessive concentrations from usual doses, probably due to genetically determined poor hepatic hydroxylation ability. A combined concentration >500 mcg/L should prompt great concern as TCAs can slow cardiac conduction in a concentration-dependent manner. Concentrations approaching 500 mcg/L may result in serious EKG abnormalities such as QT prolongation or asystole. A concentration of 1,000 mcg/L for any tricyclic antidepressant may herald extreme toxicity (seizures, arrhythmias, coma) and is sometimes used to define an overdose. Unfortunately, some side effects of TCAs can occur at any concentration and cannot be used to reflect the drug concentration.²⁸

Evidence for amitriptyline's therapeutic range is not as strong.²⁹ On the lower end, combined concentrations of amitriptyline plus nortriptyline that are less than 100–200 mcg/L tend not to be therapeutic except in a small number of patients. Concentrations greatly exceeding this range (e.g., >450 mcg/L) have been associated with anticholinergic delirium.

Other antidepressants

Efforts to predict therapeutic response from drug concentrations with newer agents have not been quite as fruitful. Research investigations in recent years have begun to focus more intently on genetic differences in metabolic capacity rather than traditional clinical pharmacokinetic domains. The therapeutic ranges listed in **Table 9-5** reflect the steady state concentrations observed in pooled populations of responsive patients, as opposed to genuine therapeutic ranges identified from rigorous

TABLE 9-5. POTENTIAL THERAPEUTIC CONCENTRATIONS OF ANTIDEPRESSANTS

Drug	Average Steady State Concentrations (Css _{ave}) with Therapeutic Doses (mcg/L) ^a
Amitriptyline ⁴³⁻⁴⁵	120–250 ^{b,c}
Amoxapine ⁴⁶	200–600 ^d
Bupropion ^{35,47}	20–50, <100 ^e
Citalopram ⁷	40–300
Clomipramine ⁴⁸⁻⁵⁰	100–250 ^{b,f}
Desipramine ⁵¹	>115–250
Desvenlafaxine	N/A
Doxepin ⁵²	>110–250 ^{b,d}
Duloxetine	N/A
Escitalopram	N/A
Fluoxetine ³⁴	75–450 ^g
Fluvoxamine ⁷	20–500
Imipramine ^{53,54}	180–350 ^{b,c}
Maprotiline ⁵⁵	200–600 ^{b,d}
Mirtazapine ⁷	20–40
Nefazodone ⁷	150–1000
Nortriptyline ^{24,56}	50–150 ^h
Paroxetine	10–600
Phenelzine	N/A
Protriptyline ^{57,58}	75–250 ^d
Selegiline	N/A
Sertraline	20–200
Tranylcypromine	N/A
Trazodone ^{59,60}	500–1500
Trimipramine ⁶¹	100–300 ^d
Venlafaxine ⁷	50–150

NA = data not available.

^aApplies to treatment of major depression. Concentration monitoring may be particularly helpful in situations of overdosage, inadequate response, diagnosis of noncompliance, and investigation of drug interactions.

^bParent drug plus desmethyl metabolite.

^cTherapeutic range is less established than for nortriptyline. Concentrations >450 mcg/L frequently correlate with delirium and anticholinergic toxicity. Some responders occur below this range.

^dNo established therapeutic range; responders are frequently in this range.

^eLimited data are available but suggest that high parent drug concentrations (>100 mcg/L) may be disadvantageous; one small study suggested that high hydroxylated metabolite concentrations correlated with the lack of antidepressant response.

^fParent drug concentrations. Metabolite concentrations may be somewhat higher. Therapeutic range is not well established.

^gSparse data are available. Metabolite concentrations may fall in the same range as for the parent drug but persist longer after discontinuance of dosing due to a prolonged half-life.

^hClear therapeutic window with curvilinear response. Many patients with concentrations greater than 150 mcg/L show a poor response; a better response occurs if the dose is decreased to produce concentrations within the range.

controlled trial conditions. Responders may exist outside of the ranges listed, and some nonresponders may have steady state concentrations within the desired ranges. Nonetheless, drug concentration measures may be useful in verifying adherence, documenting drug interactions, and monitoring safety in special populations such as the elderly, children, or patients with renal or hepatic impairment.

Although there have only been a limited number of studies examining the relationship of plasma concentrations of SSRI with therapeutic response, recent international consensus guidelines from Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) indicated there was sufficient evidence of this association to support routine therapeutic drug monitoring practices.³⁰

Among the individual SSRI, fluoxetine is perhaps the best studied.^{31,32} Multiple reports found no relationship between drug concentrations and clinical effects. However, other data suggest the existence of a possible therapeutic window where high concentrations of the metabolite, norfluoxetine, are associated with nonresponse. Overall, the best response appears when the combined fluoxetine plus norfluoxetine concentration is less than 500 mcg/L.

A small flexible dose study with sertraline reported a significant correlation between drug concentrations and effectiveness as maintenance treatment.³³ A relatively low concentration of 25–50 mcg/L was adequate for maintaining therapeutic effects, but this association has not been replicated in a larger study population. Naturalistic studies with citalopram, fluoxetine, and sertraline reported large differences in inter-individual concentrations with therapeutic doses and lower apparent clearance values for women and the elderly.^{25,34} Correlations between drug concentrations and response or toxicity were not found.

Multiple studies have examined the value of monitoring bupropion concentrations.^{35–37} Data have suggested that hydroxymetabolite concentrations exceeding 860 mcg/L were required to optimize therapeutic benefit but that concentrations greater than 1,200 mcg/L may undermine response. For bupropion alone, concentrations associated with clinical response appear to be in the 20–50 mcg/L range, but it is unclear what the contribution of the parent compound is to clinical effects as plasma concentrations of the active metabolite are 10–13 times greater at steady state. AGNP Guidelines determined that this constituted Level 2 evidence and recommended therapeutic drug monitoring. There have also been attempts to demonstrate an association with venlafaxine concentrations and clinical response.^{38,39} Although authors have reported a very wide range of concentrations relative to dose and little evidence of a true therapeutic range, venlafaxine was still deemed to have sufficient evidence to recommend therapeutic monitoring (i.e., Level 2 evidence).

More recently, researchers have employed positron emission tomography to study the correlation between the occupancy of serotonin reuptake sites by SSRI/SNRI in the brain and daily dosages, drug concentrations, and patient response.⁴⁰ They reported a nonlinear relationship, with occupancy rates greater 80% correlated with positive outcomes and that there was little gained from further dosage increases (i.e., a therapeutic plateau). Interestingly, the researchers confirmed that doses generally prescribed for treatment response were also associated with achievement of this 80% threshold (fluoxetine 20 mg daily; sertraline 25 mg daily; paroxetine 20–40 mg daily; citalopram 20–40 mg daily; and venlafaxine 75 mg daily). Two published reports have linked trazodone concentrations with observed clinical effects.^{41,42} A therapeutic threshold concentration of 650 mcg/L was reported but, as this medication is only rarely used for its antidepressant properties due to potent sedating effects, the clinical utility of this association is limited.

THERAPEUTIC MONITORING

Suggested sampling times

Accurate interpretation of drug concentrations requires the achievement of steady state conditions. For most of these drugs, the minimum time to steady state is 3–4 days. Exceptions are protriptyline and fluoxetine. Because of the long half-life of the drug or metabolite, at least 2 weeks of constant dosing with protriptyline and up to 4 weeks for fluoxetine may be required before steady state conditions occur. For antidepressants with relatively short half-lives such as venlafaxine and duloxetine, steady state concentrations of the parent drugs may be reached in 2 days. When concentration monitoring is indicated, an accepted standardized time for drawing blood is approximately 12 hours after the previous dose, usually in the morning. Trough concentration measurements are acceptable. If therapeutic monitoring of antidepressants is indicated for a given patient, no established frequency has been recommended. Concentration monitoring may be advisable when: (1) a significant dosage change occurs, (2) a patient is exhibiting serious symptoms of toxicity at doses within the therapeutic range,

(3) a medication is ineffective and/or noncompliance is suspected, (4) a potential drug interaction may be present, (5) pharmacogenetic testing indicates high or low metabolism potential, or (6) renal or hepatic function significantly changes.

FURTHER CONSIDERATIONS FOR SAMPLING

Analytical methods used to quantify antidepressant concentrations in plasma vary in their expense, sensitivity, reliability, and ease of operations. Currently employed methods include radioimmunoassay, high performance liquid chromatography, gas chromatography, and enzyme and fluorescence immunoassay methods (EMIT and TDX). All are sensitive enough to provide reliable data for routine monitoring purposes, but the laboratory must maintain an internal and external quality control program. Recently, NMR spectroscopy has been employed to estimate antidepressant concentrations in the brain. With fluoxetine and norfluoxetine, researchers reported that CNS concentrations were roughly 10 times those reported in the periphery. It is hoped that these efforts to quantify antidepressant concentrations in the effective compartment (the brain) will inspire future efforts to explore correlations with efficacy and/or toxicity.⁶²

PHARMACODYNAMIC MONITORING

Drug–drug interactions

The CYP450 isoenzyme inhibitory potential of the various antidepressants is summarized in **Table 9-6**. The capacity for some newer drugs to inhibit isoforms of the cytochrome P450 (CYP450) system in recent years has stimulated much research in this field and identified a wide variety of potential interactions. Although much can be learned about the inhibitory effects of these medications from *in vitro* investigations or small controlled studies of healthy volunteers, the potential for and severity of observed drug interactions remains largely unpredictable. This may be due to phenotypic variations among the liver enzymes (e.g., CYP2C19, CYP2D6), as well as differences in study design (single dose versus steady state, dosing strength, sampling methods, etc.). More in-depth discussions of this phenomenon have been published elsewhere.^{63–67}

Among the SSRIs, fluoxetine and paroxetine strongly inhibit CYP2D6 *in vitro*. Fluoxetine also has been shown to be a mild inhibitor of CYP2C9; its metabolite, norfluoxetine, is a potent inhibitor of CYP3A4, which may be of clinical relevance as steady state concentrations of the metabolite usually exceed the parent compound. Fluvoxamine is unique among the SSRIs in its potent inhibition of CYP1A2. It also inhibits CYP2C9 and CYP3A4. Sertraline is a mild inhibitor of CYP2D6 and CYP2C9. Citalopram and escitalopram are mild inhibitors of CYP2D6.

Although bupropion has only a mild affinity for the CYP2D6 isoenzyme *in vitro*, subsequent *in vivo* studies have revealed a potent inhibitory effects on this enzyme and clinically significant drug interactions have been reported.^{68,69} Duloxetine has also demonstrated potent inhibitory effects on the metabolism of CYP2D6 substrates.⁷⁰ Venlafaxine and mirtazapine do not appear to have a significant potential for inhibiting CYP450 isoenzymes.

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

Adolescence

Milligram per kilogram dose requirements may be higher in adolescents compared with adults due to more efficient hepatic elimination and differences in body composition (e.g., lower percentage of body fat). Chronic therapy may require relatively higher doses to maintain the same concentration.⁷¹ Divided doses may be necessitated by shorter half-life as well.

TABLE 9-6. INHIBITORY POTENTIAL OF SELECTED ANTIDEPRESSANTS^a

Medication	CYP 1A2	CYP 2C9	CYP 2C19	CYP2D6	CYP3A4
Bupropion	---	---	---	+++	---
Citalopram	---	---	---	+	---
Desvenlafaxine	---	---	---	---	---
Duloxetine	---	---	---	+++	---
Escitalopram	---	---	---	+	---
Fluoxetine	+	+	+	+++	+
Fluvoxamine	+++	+++	+++	---	+++
Paroxetine	---	---	---	+++	---
Sertraline	+	---	+	+	+
Venlafaxine	---	---	---	+	---
Levomilnacipran	---	---	---	---	---
Vilazodone	---	---	---	---	---
Vortioxetine	---	---	---	---	---

^a --- = minimal, + = mild, ++ = moderate, +++ = strong.

Advanced age

Geriatric patients (age > 65 years) have decreased ability to metabolize many medications, including antidepressants. Drug concentrations are often higher at steady state due to lower clearance values and lower initial dosages are often recommended. This is particularly relevant for antidepressants such as citalopram, desvenlafaxine, and mirtazapine. Conversely, some elderly will show no apparent impairment in clearance compared to younger patients because the activity of CYP450 enzymes does not decrease uniformly with age.^{20,72} CYP2D6 is still preserved in the elderly while total P450 content decreases markedly after age 70 years.⁷⁰ Plasma half-lives are considerably longer in the elderly due to decreased clearance as well as larger volumes of distribution secondary to higher body fat composition. The pharmacodynamic action of psychotropic medications may also be inherently different in the elderly and they may consequently be more sensitive to cognitive or sedating effects. This sensitivity may be attributed, in part, to changes in the integrity of the blood-brain barrier that occur with age and ultimately permit increased CNS penetration of lipophilic agents.⁷³ As a result of these physiological distinctions, the elderly should empirically receive smaller initial doses of all antidepressants (e.g., one-third to one-half reduction).

Alcoholism, alcoholic liver disease

The usual result of alcoholic liver disease is impairment of drug metabolism accompanied by a longer half-life and higher steady state concentrations. An increase in the severity of adverse drug reactions is possible.⁷⁴ Further, patients commonly report an increased sensitivity to the subjective effects of alcohol when antidepressants are concurrently administered with subsequent impairment in motor and cognitive function. Alcohol dependence or abuse may also dampen or reverse the therapeutic benefits of antidepressants.

Cardiac disease

Little data exist on alterations of pharmacokinetic parameters in cardiac disease. Orthostatic hypotension may become worse, especially with tricyclic antidepressants and trazodone. Caution is also required due to tachycardia and anticholinergic effects of tricyclics. TCAs may be relatively

contraindicated in severe conduction defects, while the SSRIs and bupropion appear to be relatively safe in patients with cardiac disease, and there is evidence that SSRIs may improve cardiac outcomes in the depressed population.^{75,76}

SNRIs and bupropion have been associated with small but statistically significant elevations in blood pressure and/or heart rate, and routine monitoring is advisable when these medications are prescribed.

Hepatic insufficiency

As the liver metabolizes virtually all antidepressants, significant hepatic compromise may lead to accumulation of the parent compound(s) and some metabolites. Similarly, liver dysfunction may lead to a decrease in first pass metabolism and an increase in apparent bioavailability. In general, hepatic compromise will affect drugs undergoing phase I reactions (such as oxidative metabolism) to a greater extent than phase II reactions (conjugation).⁷⁶ Most psychotropic medications undergo phase I metabolic processes. For example, the disposition of duloxetine is dramatically affected by even moderate liver impairment (e.g., 5-fold increase reported in AUC). As a result, empiric dosage reduction and/or increases in dosing intervals are encouraged for all antidepressants whenever significant liver damage is evident. Antidepressants with narrow therapeutic indices or those that possess potentially toxic metabolites (e.g., bupropion) should be avoided.

Inflammatory disease states

Protein binding may be altered due to increases in alpha-1-acid glycoprotein. As the blood-brain barrier is relatively impermeable to bound drug, increases in plasma protein binding may theoretically decrease the free concentration of antidepressant in the plasma, leading to a decrease in cerebrospinal fluid (CSF) concentrations. However, the clinical importance of protein binding changes has not been demonstrated.

Nutritional status

Severe malnutrition may alter protein binding and potentially impact therapeutic outcomes. Although literature documentation is limited, caution is warranted.

Renal insufficiency

Parent drug concentrations of most cyclic antidepressants are not greatly affected, but conjugated water-soluble metabolites can show excessive accumulation in renal insufficiency. In moderate-to-severe renal failure (i.e., CrCl = 10–50 mL/min), adverse consequences may be more likely to occur with normal doses so initial doses should be decreased by 50%–75% for antidepressants such as bupropion, mirtazapine, paroxetine, venlafaxine, and levomilnacipran.⁷⁷

Smoking status

Smoking has an inductive effect on hepatic microsomal enzymes responsible for metabolizing cyclic antidepressants. More rapid drug elimination and decreased steady state concentrations may result. This effect is best described for medications metabolized via the CYP1A2 isoenzyme, but other pathways may be affected. Due to the high interindividual variability in clearance values, empiric changes in dosing recommendations for smokers are not endorsed at this time.

Thyroid disease

Documentation of effects of thyroid disease on the pharmacokinetics of antidepressants is lacking. Hypothyroidism may mimic depression and result in a lack of antidepressant response until the underlying problem is treated. L-Triiodothyronine (T₃) is sometimes used as an adjunct to antidepressant therapy in relative nonresponders.⁷⁸

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ANTIEPILEPTICS

Jacquelyn L. Bainbridge, Pei Shieen Wong, and Felecia M. Hart

See Chapters 12, 14, 18, 19, and 21 for other antiepileptics and anticonvulsants.

Sixteen antiepileptic drugs (AEDs) have been approved by the Food and Drug Administration (FDA) over the last two decades, with several more in development. These drugs differ in structure and mechanism of action from the older AEDs (phenytoin, carbamazepine, phenobarbital, primidone, and valproic acid). Unlike the earlier AEDs, many of these newer agents have fewer undesirable drug–drug interactions and less significant adverse effects. In addition, the pharmacokinetic profiles are generally more predictable. In 2008, the International League Against Epilepsy issued an updated guideline for the therapeutic drug monitoring (TDM) of AEDs in view of the many new agents that were added to the epilepsy armamentarium.¹

There is considerable interpatient variability in the concentration that an AED will produce optimal therapeutic responses. In comparison with the older agents, the newer AEDs have a wider therapeutic margin. Thus, identifying an individual's therapeutic concentration may be especially relevant with the use of these agents. This is defined as the range of concentrations that have been empirically found to produce optimal response in the individual, taking into account seizure control and concentration-dependent adverse effects. As elucidated in the guideline, routine monitoring of AED concentrations is not recommended. However, application of TDM may be clinically useful for dose adjustment in the extremes of ages, renal and hepatic impairment and pregnancy, as well as for adherence assessment and diagnosis of clinical toxicity. Understanding the pharmacokinetic characteristics of these newer agents will be useful to guide dosing and therapy optimization. Therapy with these agents is generally started at a low dose and titrated to patient response. High initial doses and rapid dose escalation have been shown to significantly increase the incidence of side effects with lamotrigine, tiagabine, topiramate, zonisamide, lacosamide, vigabatrin, clobazam, and perampanel. **Table 10-1** provides the dosage forms and brand names of the 16 drugs in order of their FDA approval.

FELBAMATE

Felbamate blocks the glycine receptor on the *N*-methyl-d-aspartate (NMDA) complex, thereby inhibiting the response to NMDA neuronal excitation. Felbamate may also prevent seizure propagation by blocking voltage-dependent sodium channels, calcium channels, and bursting from kainic acid, as well as affecting the gamma-aminobutyric acid (GABA) system. It is structurally related to meprobamate, but dependency does not develop, and there are no withdrawal effects.² Felbamate is approved for use in patients with refractory partial or generalized seizures and in patients with Lennox-Gastaut syndrome at doses of up to 3.6 g/day in adults and up to 45 mg/kg/day in children. Due to an increased risk of aplastic anemia and liver failure, the FDA currently limits the use of felbamate to patients who are refractory to other antiepileptic agents and places the following restrictions on its use: (1) full hematological evaluations should be performed before therapy, frequently during therapy, and for a significant time after discontinuing therapy, and (2) liver function tests (AST, ALT, and bilirubin) should be done before therapy is started and at frequent intervals while the patient is taking felbamate, although the exact monitoring schedule is left to the clinical judgment of the prescriber.



TABLE 10-1. DOSAGE FORMS OF NEWER ANTIEPILEPTIC DRUGS

Felbamate (Felbatol)	400- and 600-mg tablets 600-mg/5-mL suspension
Gabapentin (Neurontin)	100-, 300-, and 400-mg capsules 600- and 800-mg tablets 250-mg/5-mL oral solution
Lamotrigine (Lamictal)	25-, 100-, 150-, and 200-mg tablets 2-, 5-, and 25-mg chewable, dispersible tablets ^a 25-, 50-, 100-, 200-, 250-, and 300-mg extended-release tablets 25-, 50-, 100-, and 200-mg orally-disintegrating tablets
Tiagabine (Gabitril)	2-, 4-, 12-, and 16-mg tablets
Topiramate (Topamax, Qudexy XR, Trokendi XR)	25-, 50-, 100-, and 200-mg tablets 15- and 25-mg sprinkle capsules ^b 25-, 50-, 100-, 150-, 200-mg extended-release capsules
Levetiracetam (Keppra)	250-, 500-, 750-, and 1,000-mg tablets 100- mg/mL oral suspension 500- mg/5 mL IV injection 500- and 750-mg extended-release tablets
Oxcarbazepine (Trileptal, Oxtellar XR)	150-, 300-, and 600-mg tablets 150-, 300-, and 600-mg extended-release tablets 300 mg/5 mL oral suspension
Zonisamide (Zonegran)	25-, 50-, and 100-mg capsules
Pregabalin (Lyrica)	25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg capsules 20-mg/mL solution
Lacosamide (Vimpat)	50-, 100-, 150-, 200-mg tablets 10-mg/mL oral solution 200-mg/20-mL IV injection
Rufinamide (Banzel)	200- and 400-mg tablets 40-mg/mL oral suspension
Vigabatrin (Sabril)	500-mg tablet 500-mg powder for solution ^c
Ezogabine (Potiga)	50-, 200-, 300-, 400-mg tablets
Clobazam (Onfi)	10-, 20-mg tablet 2.5-mg/mL oral suspension
Perampanel (Fycompa)	2-, 4-, 6-, 8-, 10-, 12-mg tablets
Eslicarbazepine (Aptiom)	200-, 400-, 600-, 800-mg tablets

IV = intravenous.

^aMay be swallowed, chewed, or diluted with 5 mL of water or fruit juice and taken immediately.

^bMay be swallowed whole but not chewed.

^cMust be mixed with water before dose is given.

Table 10-2 provides various pharmacokinetic parameters and general dosing guidelines for felbamate. The drug displays linear pharmacokinetics, and available oral products are rapidly absorbed. Food does not affect the absorption of the tablet dosage form, and the apparent bioavailability is estimated to be complete ($F = 1$). Felbamate is distributed to a variety of organs including the liver, kidney, heart, lung, spleen, muscle, gonads, eyes, and brain, and protein binding (mainly albumin) is limited.³ Approximately 40% to 50% of a given dose will be excreted unchanged in the urine with the rest undergoing liver metabolism. Felbamate is a substrate for CYP3A4, CYP2E1, and uridine-diphospho-glucuronyltransferase (UDPGT). The half-life is decreased in patients taking enzyme-inducing drugs such as carbamazepine and phenytoin as compared to drug-naïve patients. Felbamate concentrations

in children are less than the concentrations in adults receiving comparable mg/kg doses, suggesting a more rapid elimination in the pediatric population.^{3,4} Elderly subjects require a lower initial dose and slower rates of titration.⁵ Gender does not affect the pharmacokinetics of felbamate, nor does race, renal function, or liver function.^{4,6} The effects of pregnancy on the pharmacokinetics of felbamate are unknown at this time.⁷

Felbamate inhibits CYP2C19, increases the half-life, and decreases the clearance of phenobarbital, phenytoin, and valproic acid, and probably affects the pharmacokinetics of other drugs extensively metabolized by this enzyme. Interestingly, felbamate decreases the concentration of carbamazepine but increases the concentration of the active 10, 11-di-epoxide metabolite. The doses of phenobarbital, phenytoin, carbamazepine, and valproic acid should be decreased by 30% to 50% when felbamate is added.^{8,9}

In contrast to other antiepileptic drugs, felbamate is associated with central nervous system (CNS) stimulation. Side effects include insomnia, decreased appetite, and weight loss.⁴ At least 32 cases of aplastic anemia and 16 cases of hepatic failure had been reported prior to 2002. Aplastic anemia may be the result of the formation of an uncommon but toxic metabolite.⁴ The incidence of aplastic anemia is higher in women with a history of autoimmune disease. Patients taking felbamate should have frequent complete blood counts and liver function tests.¹⁰

TABLE 10-2. PHARMACOKINETIC AND DOSING SUMMARY FOR FELBAMATE

Bioavailability (F)	100% (F = 1)
t _{max}	3–5 hr
t _{1/2}	16–23 hr (drug-naïve patients)
	11–16 hr (when receiving enzyme-inducing antiepileptics)
V	0.7–0.8 L/kg
Clearance	1.6 ± 0.2 L/hr/kg
Protein binding	20% to 35%
Elimination	50% renal, 50% hepatic
Therapeutic range	30–60 mg/L ^{7,11}
Usual dose	Adults: Initiate at 1,200 mg/day (in three to four divided doses) then increase by 1,200 mg/day weekly to a maximum dose of 3,600 mg/day
	Pediatrics: Initiate at 15 mg/kg/day (in three to four divided doses) then increase by 15 mg/kg/day weekly to 45 mg/kg/day
	Maximum dose: 3,600 mg/day
Pregnancy	Unknown

GABAPENTIN

Although gabapentin was designed to potentiate GABA at neuronal receptor sites, it does not work at either GABA A or GABA B receptors. It interacts with a specific high-affinity binding site that is an auxiliary protein subunit of voltage-gated calcium channels. It also causes a dose-proportional nonsynaptic release of GABA, which increases the concentration of GABA in the brain. Gabapentin may also slightly increase GABA by enhancing its rate of synthesis from glutamate. It may decrease the concentration of glutamate, and it inhibits sodium channels by mechanisms different than phenytoin and carbamazepine. Gabapentin readily crosses the blood–brain barrier and concentrates in brain tissue by an active transport process that may saturate at higher plasma concentrations.¹²

Gabapentin is indicated as adjunctive therapy for patients with partial seizures with or without secondary generalization.¹³ It is widely used in the treatment of pain and also for anxiety, panic attacks, migraine headaches, and other CNS disorders. The initial dose is 900 mg/day, given in 3–4 divided doses that are usually titrated upward over 3 days; the dose is then titrated to the patient's response.¹⁴ The initially approved dose of up to 3.6 g is inadequate for many patients, and doses up to 10 g have been reported. Because the CNS side effects do not seem to be dose-dependent, gabapentin can be rapidly titrated to response.

Following oral administration, gabapentin binds to a sodium-independent L-like amino acid transport system that facilitates transport across the gut into the bloodstream and across the blood–brain barrier to the site of activity in the brain.¹⁵ However, binding to the L-amino acid transport system becomes saturated, and the bioavailability of gabapentin decreases with increasing dose (see **Table 10-3** for pharmacokinetic parameters and general dosing guidelines).¹⁶ Because of the dose-dependent bioavailability, achieved concentrations are not proportional to increasing doses. Bioavailability may be increased by giving the drug more frequently (i.e., four times a day rather than three).¹⁷ Absorption is somewhat delayed with peak concentrations occurring 2–4 hr after an oral dose. Food does not affect the absorption rate, but a high-protein meal will increase overall absorption.^{18,19} Absorption appears to vary more between subjects than within a single subject.²⁰ The bioavailability of gabapentin given orally in a capsule and in a solution is comparable, although it is not well absorbed after rectal administration.²¹ Gabapentin has a bitter taste when put into solution.

Gabapentin does not undergo liver metabolism and is excreted unchanged in the urine with a half-life of 5–9 hr.²² Its clearance is proportional to creatinine clearance, and young children (< 5 yr) have higher and more variable clearances than older children. On a mg/kg dose basis, 33% larger doses would be required in children < 5 yr of age compared to older children.^{23,24} Age-related decreases in renal function decrease gabapentin clearance, and the dose should be decreased in patients with renal impairment.²⁵ Gabapentin is removed by hemodialysis, and a replacement dose of 200 to 300 mg for each 4 hr of dialysis has been suggested.²⁶ Gender, race, and hepatic function do not affect the pharmacokinetics, and there are no apparent pharmacogenetic or pharmacogenomic issues for dosing noted to date. The effects of pregnancy on the pharmacokinetics of gabapentin are unknown at this time.

Gabapentin does not undergo liver metabolism and is poorly protein bound, so it is not associated with many significant pharmacokinetic drug interactions. Concurrent administration with antacids may decrease absorption by 20%; therefore, it is recommended that gabapentin be taken at least 2 hr after an antacid.²⁷ Cimetidine may decrease clearance by 10%.²⁶ Dosage adjustments are usually not necessary.

Gabapentin is generally well tolerated, with CNS effects such as fatigue, somnolence, dizziness, ataxia, nystagmus, tremor, and diplopia noted at the onset of therapy. As tolerance develops, the CNS side effects seem to plateau.²⁸ Other side effects include weight gain, edema, and behavioral abnormalities.²⁹⁻³² Rash is uncommon. The consequences of overdose appear to be minimal.³³ Withdrawal symptoms have been reported.

LAMOTRIGINE

Lamotrigine was originally synthesized as a folate antagonist, although it has very weak activity in that regard. It is a member of the phenyltriazine class and is believed to work by blockade of voltage-sensitive sodium currents, slow binding of inactivated sodium channels, blockade of voltage-activated calcium currents, inhibition of presynaptic N-type calcium channels, and inhibition of glutamate and aspartate release.³⁴ It inhibits the sodium channel in a manner that is different from other sodium channel inhibiting drugs such as phenytoin and carbamazepine.

Lamotrigine is approved as adjunctive therapy for patients 2 yr or older with partial seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. It is also indicated as monotherapy in patients 16 yr or older being converted from carbamazepine, phenytoin, phenobarbital, primidone,

TABLE 10-3. PHARMACOKINETIC AND DOSING SUMMARY FOR GABAPENTIN

Bioavailability (F)	Decreases with increases in dose (F = 0.6 at low doses, 0.35 at high doses)	
t _{max}	2–4 hr	
t _{1/2}	5–7 hr	
V	0.65–1.4 L/kg	
Clearance	9 L/hr	
Protein binding	<10%	
Elimination	Almost 100% renal	
Therapeutic range	12–20 mg/L ^{7,11}	
Usual dose	Adults: Initiate at 900 mg/day and increase up to 3,600 mg/day. Doses of 5–10 g have been well tolerated. Pediatrics: 10–15 mg/kg/day	
Dosing in renal dysfunction ^a	CrCl (mL/min)	Dose (mg)
	>60	400 three times a day
	30–60	300 twice a day
	15–30	300 every day
	<15	300 every other day
Anephric ^b	200–300 mg after each 4-hr hemodialysis	
Pregnancy	Unknown	

^aThese guidelines were established before there was significant experience with large doses of gabapentin (i.e., 5–10 g). The ultimate guide to dosing is a patient's response, so the dose may be increased in patients with renal dysfunction if clinical benefit based on the guidelines was limited and no side effects are noted.

^bIf the patient is anephric and on dialysis, give 200 to 300 mg after each 4-hr hemodialysis session.

or valproate monotherapy and is effective in a wide range of seizures, including partial, primary generalized tonic-clonic, myoclonic, and absence. Lamotrigine is indicated for the treatment of bipolar disorder as well.

The pharmacokinetics of lamotrigine appear to be linear. **Table 10-4** provides a summary of the pharmacokinetics and general dosing guidelines. Bioavailability is believed to be complete. Administration with food may reduce the maximum peak concentration but does not alter the total amount of drug absorbed. Although the amount absorbed from the dispersible tablet given rectally is not the same as the amount following oral administration, there is adequate absorption to make this an alternative route of administration.^{35,36} Absorption also occurs when the compressed tablet is given rectally. Lamotrigine is metabolized predominately by glucuronidation catalyzed by UDPGT in the liver to inactive metabolites that are excreted renally.^{37,38} A 25% decrease in elimination half-life at steady state has been reported, suggesting that lamotrigine induces its own metabolism.³⁹ Half-life is significantly affected by enzyme inducers and inhibitors.^{39,40} The impact of genetic variants on varying lamotrigine pharmacokinetics has been implicated, but most findings have been inconsistent. However, higher plasma blood levels have been observed in patients with a ABCG2 protein polymorphism that was previously linked to higher plasma blood levels of rosuvastatin.⁴¹ In patients with the ABCG2 rs2231142 A allele, lower lamotrigine maintenance doses are likely to be needed.

Clearance is unaffected by age, gender, or dose, although some studies have shown an increase in children and decrease in the elderly.^{39,40,42-44} Clearance is influenced by body weight and concurrent therapy with other antiepileptic drugs, and has been reported to be 25% lower in non-Caucasians.⁴⁰ Metabolic clearance is reduced in patients with hepatic impairment, and patients with renal disease should also be monitored closely and may require a decrease in dose.⁴⁵ During hemodialysis, ~20% of lamotrigine is removed. Patients with Gilbert's syndrome may show reduced clearance.⁴⁶ Clearance during monotherapy increases markedly during pregnancy; >300% from pre-pregnancy baseline.⁴⁶ This

increase begins in the first trimester and continues through the third.⁴⁷⁻⁴⁹ After delivery, concentrations increase rapidly to pre-pregnancy levels, occurring as early as 1–2 weeks postpartum.⁴⁷ The half-life in patients taking enzyme inducers (e.g., carbamazepine, phenytoin, phenobarbital, primidone, and rifampin) is 12–14 hr and the half-life in patients taking enzyme inhibitors (e.g., valproic acid) can exceed 59 hr. The interaction between lamotrigine and valproate is believed to result from competition during glucuronidation.³⁸ Acetaminophen, in doses of 900 mg in healthy volunteers, increased the total body clearance of lamotrigine by 15%.⁵⁰

Lamotrigine does not typically affect the metabolism of other drugs and does not affect the concentration of carbamazepine or its active 10, 11-di-epoxide metabolite.^{40,51,52} Side effects may be increased in patients taking carbamazepine when lamotrigine is added, suggesting a potential pharmacodynamic interaction.⁵³ Lamotrigine may slightly decrease concentrations of ethinyl estradiol; thus, caution should be advised in patients taking concomitant oral contraceptives. Conversely, concurrent use of oral contraceptives in patients on lamotrigine has resulted in a decrease in lamotrigine concentrations and breakthrough seizures.^{54,55} There have been reports of lamotrigine side effects occurring during the oral contraceptive placebo week in some patients. Possible solutions to this issue include decreasing the lamotrigine dose during the placebo week or switching the patient to an oral contraceptive without a placebo week.

The most common side effects of lamotrigine are headache, nausea, vomiting, ataxia, somnolence, dizziness, sedation, blurred vision, diplopia, and other visual disturbances. The incidence of CNS effects is increased in patients taking carbamazepine concurrently. A generalized, morbilliform skin rash has been reported in up to 10% of patients taking lamotrigine; however, this is considered to be benign and resolves without treatment. Rarely, serious rashes may develop including Stevens-Johnson syndrome and toxic epidermal necrolysis, which have systemic involvement and can be life-threatening.⁵⁶ It occurs more frequently in children than in adults and high starting doses, rapid dosage titration, and concurrent valproic acid therapy (due to increased lamotrigine half-life) increase the incidence of rash. Therefore, the dose of lamotrigine should be started low and gradually titrated to the patient's response (commonly over several months). Doses up to 700 mg/day have been well tolerated in patients not taking enzyme inhibitors concurrently.⁵⁷ Drug Reaction with Eosinophilia and Systemic Syndrome has also been reported with lamotrigine.

TABLE 10-4. PHARMACOKINETIC AND DOSING SUMMARY FOR LAMOTRIGINE	
Bioavailability (F)	100% (F = 1)
t _{max}	1.4–4.8 hr
t _{1/2}	22 hr 15 hr (with enzyme-inducing antiepileptics) >59 hr (with valproic acid)
V	0.9–1.3 L/kg ⁵⁸
Clearance	0.076 L/hr/kg ⁵⁸
Protein binding	55%
Elimination	Hepatic via glucuronidation
Therapeutic range	2.5–15 mg/L ^{7,11}
Usual dose	Maintenance dose: 300–500 mg/day in patients taking enzyme-inducing antiepileptics; doses up to 700 mg/day have been well tolerated. 100–200 mg/day in patients taking valproic acid
Pregnancy	Marked decrease in serum concentrations beginning in first trimester and further decreasing until late pregnancy. After delivery, serum concentrations rapidly increase to pre-pregnancy levels within a few weeks.

TIAGABINE

Tiagabine was specifically designed to block the reuptake of GABA into presynaptic terminals. It selectively inhibits the neuronal and glial reuptake of GABA and enhances GABA-mediated inhibition at both GABA A and GABA B receptors.⁵⁸ It is approved as adjunctive therapy for patients 12 yr or older with partial seizures.

The pharmacokinetics and general dosing guidelines for tiagabine are shown in **Table 10-5**. Tiagabine exhibits linear absorption and the dose-adjusted t_{max} , C_{max} , and area under the plasma concentration-time curve (AUC) are independent of the administered dose, indicating linear pharmacokinetics.^{60,61} A one-compartment model with first-order absorption and elimination adequately describe the tiagabine concentration-time profile.⁶² Food delays absorption, but does not alter the extent. Tiagabine is highly protein bound, and valproic acid can dramatically increase the percentage unbound. Tiagabine is extensively metabolized by CYP3A4 and by glucuronidation, with only 2% excreted as the parent drug.⁶³ Half-life is short and is reduced in patients taking enzyme-inducing drugs such as phenytoin and carbamazepine and prolonged in patients taking enzyme-inhibiting drugs such as valproic acid.^{64,65} However, tiagabine does not interact with drug-metabolizing enzymes to any clinically significant extent, and also appears to lack any significant pharmacogenomic interactions.⁶⁶⁻⁶⁹ The pharmacokinetics are not affected by increasing age, smoking, race, or renal impairment.⁷⁰⁻⁷² Impaired liver function has been shown to decrease tiagabine elimination.⁷³ The effects of pregnancy on the pharmacokinetics of tiagabine are unknown at this time.

The primary side effects of tiagabine are CNS related. Adverse reactions reported include nausea, irritability, abdominal pain, asthenia, amblyopia, incoordination, tremors, speech disorders, nervousness, paresthesia, abnormal thinking, somnolence, and dizziness.⁷⁴ The incidence of CNS side effects may be reduced by slow dosage titration and may decrease over time.^{75,76} Tiagabine has not been associated with weight gain or visual field defects.^{77,78}

TABLE 10-5. PHARMACOKINETIC AND DOSING SUMMARY FOR TIAGABINE

Bioavailability (F)	90% (F = 0.9)
t_{max}	45 min fasting, 2.5 hr nonfasting
$t_{1/2}$	5–13 hr
	3.2 hr (enzyme-inducing antiepileptics)
	5.7 hr (valproic acid)
V	1.1–1.3 L/kg
Clearance	6.5 L/hr
Protein binding	96% (valproic acid decreases the bound percentage to 60%)
Elimination	Extensively hepatic (CYP 3A4 and glucuronidation)
Therapeutic range	20–100 mcg/L ^{7,11}
Usual dose	Initiate at 4 mg/day and titrate at weekly intervals up to 56 mg/day, if needed. Give in 2–4 divided doses
Pregnancy	Unknown

TOPIRAMATE

Topiramate blocks voltage-dependent sodium channels and inhibits the d-amino-3-hydroxy-5-methyl isoxazole-4-propionic acid (AMPA) subtype of the glutamate receptor and the release of glutamate. It also potentiates GABA-mediated inhibitory neurotransmission (at GABA A receptors) and modulates voltage-gated calcium ion channels.⁷⁹ It is a weak inhibitor of carbonic anhydrase.⁸⁰ Topiramate is approved as monotherapy for patients 10 yr or older with partial onset or primary generalized tonic-clonic seizures. It is also approved as adjunctive therapy in patients with partial onset seizures or

primary generalized tonic-clonic seizures and in the treatment of Lennox-Gastaut syndrome in patients 2 yr or older. Further, it is indicated for the prophylaxis of migraine headaches in adults and may be useful in pediatric patients with a variety of seizure types, including myoclonic seizures and possibly infantile spasms.⁸¹

Table 10-6 provides the pharmacokinetics and general dosing guidelines for topiramate. Dose proportionality studies of the drug show that the $C_{\max}$ increases linearly but clearance is not dose proportional.⁸² It is fairly rapidly absorbed, and administration with food delays the rate but not the extent of absorption.^{83,84} The volume of distribution may change depending on dose. It was reported to be 58 L after a 100-mg dose and 38.5 L after a 1.2-g dose.⁸⁵ This change may reflect saturation of low-capacity binding sites on erythrocytes. A small amount of topiramate is excreted in the milk of nursing mothers.⁸⁶ There does not seem to be a saturable carrier mechanism restricting transport across the blood-brain barrier and the concentration in the cerebral spinal fluid (CSF) is equal to the unbound proportion of topiramate in plasma, implying that the delivery to the brain occurs via transfer from the unbound plasma pool.⁸⁷ Plasma protein binding is low and variable and a high-affinity, low-capacity binding of topiramate to erythrocytes has been reported.

About 70% of an administered dose of topiramate is excreted unchanged in the urine, and the remainder may be metabolized by hydroxylation, hydrolysis, or glucuronidation. There is no change in half-life after multiple dosing. Clearance appears to change with dose and was reported to be 36 mL/min following a 100-mg dose and 22.5 mL/min following a 1.2-g dose.⁸⁷ Weight-adjusted clearance appears to be higher in children than adults. For the same mg/kg dose, the resulting concentrations are 33% lower in children. No age effect per se has been reported in older patients. If older patients have decreased renal function as a function of age, they will have decreased clearance. Clearance is decreased by 42% in patients with moderate renal impairment (CrCl 30–69 mL/min) and by 54% in patients with severe impairment (CrCl < 30 mL/min). It is recommended that half of the usual dose be used to initiate titrating therapy and that the time between dosage adjustments be increased in patients with reduced renal function. For patients with moderate-to-severe renal impairment, a dosage reduction of 50% is recommended. Hemodialysis increases the clearance of topiramate four- to six-fold. After dialysis, a supplemental dose may be required, taking into account the duration of dialysis, the clearance rate of the dialysis system, and the patient's effective renal clearance. In general, a supplemental dose equivalent to half of the daily dose of topiramate may be given. About half of this should be given before dialysis and the other half after dialysis. Clearance may also be decreased in patients with hepatic impairment.^{88,89}

Metabolism of topiramate is increased by enzyme-inducing drugs. For example, phenytoin and carbamazepine induce topiramate metabolism and decrease concentrations by 48% and 40%, respectively, while valproic acid causes a 14% decrease in clearance, leading to increased concentrations.^{90–92} Topiramate is a moderate enzyme inhibitor and has been reported to cause a 0% to 25% increase in phenytoin concentrations.⁹³ Two patients taking carbamazepine were reported to develop toxicity after topiramate was added to their regimen.⁹⁴ Topiramate may increase concentrations of the 4-ene valproic acid metabolite, which has been shown to be hepatotoxic. The interactions that impact topiramate clearance are especially important if concurrent antiepileptic drugs are withdrawn or started after dosage stabilization with topiramate, as the concentrations will increase or decrease depending on the interaction.^{95,96} At doses of approximately 200 mg/day and higher, topiramate is a moderate enzyme inducer. It may increase the clearance of oral contraceptives in a dose-dependent manner (e.g., doses >100 mg/day), and patients should report changes in menstrual patterns.⁹⁷ Women on oral contraceptives should be cautioned about breakthrough bleeding and the potential need for supplementary contraception. A 12% decrease in digoxin concentration has been reported when given concomitantly with topiramate. Because topiramate depresses CNS function, it may have an additive effect with other CNS depressants. There is a 1.5% increase in incidence of kidney stones in patients taking topiramate; the incidence is higher in men. Both kidney stones and paresthesia have been reported with other carbonic anhydrase inhibitors (e.g., zonisamide) as well.⁸¹ Patients taking topiramate should be encouraged to maintain adequate fluid intake to reduce the incidence of kidney stones.

The most common side effects seen with topiramate are CNS related.⁹⁸ These side effects include dizziness, psychomotor slowing, difficulty concentrating, speech and language problems, somnolence, paresthesia, cognitive slowing, and fatigue. Cognitive complaints are the most common reason for discontinuing the drug. Word-finding difficulties associated with topiramate were found to be independent of the dosage titration schedule. They were related to a subgroup of patients with epilepsy primarily involving the left temporal areas, mainly the posterior temporal, along with the presence of simple partial seizures who were the most likely to develop word finding difficulties.⁹⁹ Anorexia, nausea, and weight loss have been reported. Glaucoma, metabolic acidosis, and oligohydrosis (decreased sweating) have also been reported.^{100–103}

The incidence of CNS side effects with topiramate increases with high initial doses and high maintenance doses. Therefore, the dose should be low initially and escalated to the patient's response.⁸⁵ The package insert suggests an initial starting dose of 50 mg/day in divided doses with dosage increments of 50 mg/day each week in adults to improve tolerability.¹⁰⁴ Some clinicians start at an even lower dose and escalate more slowly (i.e., 12.5 to 25 mg per week).

TABLE 10-6. PHARMACOKINETIC AND DOSING SUMMARY FOR TOPIRAMATE

Bioavailability (F)	80% (F = 0.8)
t _{max}	2 hr
t _{1/2}	18–23 hr
V	0.6–0.8 L/kg
Clearance	1.2–1.8 L/hr
Protein binding	13% to 41%
Elimination	Renal, unchanged (70%)
Therapeutic range	5–20 mg/L ^{7,11}
Usual dose	Initiate at 12.5–50 mg/day and increase at weekly intervals up to 400 mg/day (two divided doses)
Dosing in renal dysfunction	Use half the usual dose and increase the time between dosing adjustments.
Pregnancy	Unknown

LEVETIRACETAM

Levetiracetam is the S-enantiomer of the ethyl analog of piracetam. It is ineffective in the classic screening models for acute seizures and does not appear to interact with any known inhibitory or excitatory neurotransmitters. It inhibits burst firing without affecting normal excitatory neurotransmitters or normal neuronal excitability. Therefore, levetiracetam inhibits seizures by a unique mechanism of action that may involve a reduction in high-voltage activated calcium currents and delayed-rectifier potassium currents as well as a unique action on GABA currents.¹⁰⁵ It is hypothesized that levetiracetam may bind to the synaptic vesicle glycoprotein 2A (SV2A) region in the CNS, which appears to be important in neurotransmitter release. Levetiracetam is approved for use in patients 4 yr or older as adjunctive therapy for the treatment of partial onset seizures, in patients 12 yr or older for the treatment of myoclonic seizures, and in patients 6 yr or older with primary generalized tonic-clonic seizures.

The pharmacokinetics and general dosing approaches for levetiracetam are shown in **Table 10-7**. Levetiracetam is rapidly and completely absorbed following oral administration with peak concentrations occurring in about 1 hr.^{106,107} Bioavailability of all dosage forms is complete and absorption is linear and independent of dose. Food decreases the rate but not the extent of absorption. Protein binding is low. In animal models, levetiracetam concentrations in the brain increase linearly with dose increases.

About 66% of a dose is excreted unchanged in the urine, and the remaining portion is metabolized by hydrolysis of the acetamide group to three inactive metabolites. Neither the CYP nor the UGT isoenzyme systems are involved in the metabolism. The clearance is decreased and half-life prolonged in patients with renal dysfunction, necessitating a dose reduction.^{108,109} The pharmacokinetics of levetiracetam are not affected by mild-to-moderate liver dysfunction. Clearance in children is relative to body weight and about 130% to 140% that of an adult, reflecting better renal elimination.¹¹⁰ Preliminary data indicate that concentrations of levetiracetam decline by as much as 50% during pregnancy.⁴⁷

Pharmacokinetic drug interactions with levetiracetam are unlikely because metabolism is neither induced nor inhibited, and there is negligible protein binding.¹¹¹ It does not affect the metabolism of other drugs.^{112,113} A pharmacodynamic interaction has been reported between levetiracetam and carbamazepine. When added to patients taking carbamazepine, there is an increased incidence of CNS side effects that is not related to a change in the concentrations of carbamazepine or its active metabolite.¹¹⁴

Levetiracetam has generally been well tolerated with the most common side effects involving the CNS such as somnolence, asthenia, dizziness, vertigo, and headaches.¹¹⁵ Psychiatric events and behavioral symptoms such as depression, nervousness, emotional lability, and hostility have been reported. A significantly higher incidence of upper respiratory tract infections has been reported in children and adults. These infections were not associated with any signs of immune impairment and did not disrupt therapy.^{116,117}

TABLE 10-7. PHARMACOKINETIC AND DOSING SUMMARY FOR LEVETIRACETAM

Bioavailability (F)	100% (F = 1) (all dosage forms)		
t _{max}	1 hr		
t _{1/2}	6–8 hr Increased in patients with renal dysfunction		
V	0.5–0.7 L/kg		
Clearance	0.06 L/hr/kg		
Protein binding	<10%		
Elimination	66% renal with the remaining drug being metabolized by hydrolysis that is independent of CYP450		
Therapeutic range	8–26 mg/L ^{7,11}		
Usual dose	Adults: Initiate at 1,000 mg daily (in two divided doses) then increase by 1,000 mg/day every 2 weeks to maximum of 3,000 mg daily Pediatrics: Initiate therapy at 20 mg/kg/day (in two divided doses) then increase by 20 mg/kg/day every 2 weeks to a maximum of 60 mg/kg/day		
Dosing in renal impairment	CrCl (mL/min)	Dosage (mg)	Frequency
	>80	500–1500	every 12 hr
	50–80	500–1000	every 12 hr
	30–50	250–750	every 12 hr
	<30	250–500	every 12 hr
ESRD patients using dialysis	—	500–1000	every 24 hr; 250–500 mg recommended post-dialysis
Pregnancy	Increased clearance		

OXCARBAZEPINE

Oxcarbazepine is the 10-keto analogue of carbamazepine. Functionally, oxcarbazepine is a prodrug because it undergoes presystemic reduction in the liver to 10, 11-dihydro-10-hydroxy-carbamazepine.¹¹⁸

This monohydroxylated derivative (MHD) is the active form of oxcarbazepine and exists as a racemic mixture. The two enantiomers of MHD showed similar median effective dose values in animal models of antiepileptic drug activity. The mechanism of action of oxcarbazepine is similar to carbamazepine in that it (as the MHD) blocks voltage-sensitive sodium channels, modulates the voltage-activated calcium currents, and increases potassium conductance. The spectrum of antiseizure activity is similar for the two drugs.¹¹⁹ Oxcarbazepine is indicated as monotherapy in patients 4 yr or older for the treatment of partial seizures and as adjunctive therapy for patients 2 yr or older with partial seizures.

Table 10-8 provides the pharmacokinetics and general dosing guidelines for oxcarbazepine. It is rapidly and almost completely absorbed following oral administration with peak concentrations occurring within 1–3 hr and peak concentrations of MHD occurring within 4–6 hr.¹²⁰ Administration with a high-fat or high-protein meal increases the area under the concentration curve of MHD by 16% and 23%, respectively. The accumulation of MHD following chronic dosing of oxcarbazepine is reported to be more than would be expected based on linear pharmacokinetics. Oxcarbazepine and MHD pass rapidly through biologic membranes including the blood–brain barrier and both cross the placenta and are excreted into breast milk, although breast feeding is not discouraged because of this (the infant should be monitored for clinical changes). Oxcarbazepine is rapidly and extensively metabolized to MHD by a stereoselective biotransformation mediated by a cytosolic, nonmicrosomal, and noninducible arylketone reductase. MHD is excreted unchanged in the urine or undergoes further metabolism by glucuronide conjugation.¹²¹ CYP450 isoenzymes are only minimally involved in the metabolism of oxcarbazepine and MHD. The clearance of MHD is decreased in patients with impaired renal function but is not affected by liver disease. Limited data indicate that pregnancy increases MHD clearance.⁴⁷ The clearance in children is 2–5 times faster than in adults relative to body weight.¹²²

Drug interactions may occur with both oxcarbazepine and MHD.¹²³ Oxcarbazepine reduces the bioavailability of ethinylestradiol and levonorgestrel by 48% and 32%, respectively, and breakthrough bleeding has been reported.¹²⁴ When given in doses of approximately 1,200 mg/day or higher, oxcarbazepine has been reported to increase the concentrations of phenytoin by ~40% and phenobarbital by ~15%, consistent with inhibition of CYP2C19. At doses of approximately 1,200 mg/day or higher, it decreases the concentrations of carbamazepine, lamotrigine, and felodipine via induction of CYP3A4.^{125,126} Oxcarbazepine may induce UGT. Unlike carbamazepine, oxcarbazepine does not induce its own metabolism. The clearance of MHD is increased in patients taking enzyme-inducing drugs. Neither cimetidine nor erythromycin, both potent inhibitors of CYP isoenzymes, affect the pharmacokinetics of MHD.¹²³ Verapamil may decrease the plasma concentration of MHD by 20%.¹²⁷

The side effect profile of oxcarbazepine is similar to carbamazepine with the most frequently reported side effects being somnolence or sedation, headache, dizziness, vertigo, ataxia, nausea, vomiting, fatigue, abdominal pain, tremor, dyspepsia, abnormal gait, abnormal vision, and diplopia.^{128,129} The reported incidence of hyponatremia, defined as a serum sodium < 125 mmol/L, is higher than with carbamazepine and has been reported in up to 25% of patients. The incidence may be higher in older patients and in patients taking sodium-depleting diuretics.^{130–132} There is a cross reactivity of 25% to 31% for rash between carbamazepine and oxcarbazepine.¹³³ Although oxcarbazepine has been reported to be better tolerated than carbamazepine, this has been studied only in patients taking immediate-release carbamazepine. The tolerability of oxcarbazepine has not been compared to extended-release carbamazepine formulations (i.e., Carbatrol, Tegretol-XR), which have been reported to be better tolerated than immediate-release carbamazepine, as these formulations lead to lower peaks.

ZONISAMIDE

Zonisamide is a sulfonamide derivative that was initially approved for use in Japan and Korea, where it was used for 10 yr prior to approval in the United States. It inhibits seizures by multiple mechanisms of action, including blocking voltage-dependent sodium channels, T-type calcium channels, and actively inhibiting the release of excitatory neurotransmitters such as glutamate.¹³⁵ Zonisamide is a weak

TABLE 10-8. PHARMACOKINETIC AND DOSING SUMMARY FOR OXCARBAZEPINE

Bioavailability (F)	90% (F = 0.9)
t _{max}	1–3 hr oxcarbazepine, 4–6 hr MHD
t _{1/2}	2 hr (oxcarbazepine) 9 hr (MHD)
V	12.5 ± 12.9 L/kg (oxcarbazepine) 11.7 L (R-isomer of MHD) 13.8 L (S-isomer of MHD)
Clearance	0.1 L/kg/hr ¹³⁴
Protein binding	60% (oxcarbazepine) 40% (MHD)
Elimination	Oxcarbazepine is extensively metabolized to MHD by non-inducible cytosolic keto-reductases, which is then eliminated unchanged in the urine and as glucuronides of MHD
Therapeutic range	13–35 mg/L (MHD) ^{7,11}
Usual dose	Adult: Initiate at 600 mg/day (in divided doses). Increase by 600 mg/day at weekly intervals to a recommended maintenance dose of 1,200 mg/day. Doses above 1,200 mg have been used effectively but side effects are dose limiting If carbamazepine is replaced by oxcarbazepine, the dose of oxcarbazepine is 1.5 times the dose of carbamazepine Pediatrics: Initiate at 16–20 mg/kg/day (in two divided doses). Maximum dose is 600 mg/day
Pregnancy	Significant increase in drug clearance of the active MHD metabolite

inhibitor of carbonic anhydrase activity and also affects dopamine and serotonin release. It has been approved for use in the United States as adjunctive therapy in adults with partial seizures. However, based on its use in Japan and Korea, it appears to be effective in a variety of seizure types including generalized tonic-clonic seizures, absence seizures, and myoclonic seizures.¹³⁶

Table 10-9 provides the pharmacokinetics and general dosing guidelines for zonisamide, which is completely absorbed.¹³⁷ Absorption is independent of dose, and the AUC is dose proportional. Administration with food reduces the rate but not the extent of absorption. Following administration, zonisamide is distributed throughout the body. The drug rapidly crosses the blood–brain barrier, and in animals the concentration in the CSF is comparable to the concentration in the plasma. Zonisamide crosses the placenta and enters into breast milk. It is about 40% bound to albumin, and erythrocytes have a higher binding affinity than plasma proteins. The binding to erythrocytes is saturable at low doses, but does not affect the pharmacokinetics. Zonisamide has mixed hepatic (70%) and renal (30%) elimination and CYP3A4 is the main isoenzyme involved in its metabolism, but CYP2D6, CYP2C19, and CYP3A5 are also involved.¹³⁸ Larger doses relative to body weight are needed in children to achieve concentrations comparable to adults, suggesting a faster clearance.¹³⁹ Pharmacokinetic parameters in the elderly are reported to be comparable to younger adults. The effects of pregnancy on the pharmacokinetics of zonisamide have not been well studied, but one case report suggests that clearance may increase at the end of the second trimester.¹⁴⁰

Zonisamide does not induce or inhibit the metabolism of other drugs and is reported to not interact with other drugs, including oral contraceptives.¹⁴¹ However, enzyme-inducing drugs such as phenytoin and carbamazepine will increase the clearance and decrease the half-life of zonisamide. Enzyme-inhibiting drugs like valproic acid decrease the clearance and increase the half-life of zonisamide.¹⁴²

The most commonly reported side effects of zonisamide are headache, nausea, agitation, irritability, fatigue, dizziness, somnolence, anorexia, psychomotor slowing, ataxia, abdominal pain, and confusion.¹⁴³ These are increased with rapid dose escalation and reduced with a slower rate of titration. Zonisamide has been associated with a slight increase in incidence of renal calculi (3.3% with zonisamide and 2.4% with placebo).¹⁴⁴ It is a sulfonamide and should be used very cautiously in a person with a history of allergy to sulfas. However, the incidence of rash has been very low. It has also been associated with oligohydrosis and hyperthermia in pediatric patients, resulting in heat stroke and hospitalization.¹⁴⁵

TABLE 10-9. PHARMACOKINETIC AND DOSING SUMMARY FOR ZONISAMIDE

Bioavailability (F)	Presumed complete (F = 1)
t _{max}	2–6 hr
t _{1/2}	63 hr (105 hr in red blood cells)
V	1.45 L/kg
Clearance	0.02 L/hr/kg (no concurrent enzyme-inducing AEDs) 0.03 L/hr/kg (concurrent enzyme-inducing AEDs)
Protein binding	40% to albumin
Elimination	Hepatic (70%) and renal (30%)
Therapeutic range	10–38 mg/L ¹¹
Usual dose ^a	Initiate at 100 mg/day and increase by 100 mg/day every 2 weeks up to 400–600 mg/day in adults. Doses may be given once a day. ^b
Pregnancy	Unknown, but clearance may be increased beginning at the end of the second trimester. ¹⁴⁰

^aThe contents of the capsule may be opened and mixed with water, apple juice, apple sauce, or pudding for patients who have trouble taking an oral solid. The mixture is stable for 48 hr.
^bThere is approximately a 28% variability around the mean concentration with once-daily dosing and 14% variability with twice-daily dosing. If the drug is given once a day, it should be given at night.

PREGABALIN

Pregabalin is a GABA analogue. It is the pharmacologically active S-enantiomer of gabapentin and is similar in structure and action. Pregabalin binds with high affinity to an auxiliary subunit of the voltage-gated calcium channels in CNS tissues. It may decrease the release of several neurotransmitters through modulation of calcium channel function and may increase the density of GABA transporter protein and the rate of functional GABA transport.

Pregabalin is indicated as adjunctive therapy for adult patients with partial onset seizures. It is also indicated for the treatment of diabetic peripheral neuropathy, post-herpetic neuralgia, and fibromyalgia. The typical starting dose is 150 mg/day in two to three divided doses. This can be increased at weekly intervals up to a maximum of 600 mg/day. Pregabalin is approximately 2.5 times more potent than gabapentin.

Pharmacokinetic and dosing summaries are provided for pregabalin in **Table 10-10**. The oral bioavailability is high and not dose-dependent.¹⁴⁶ The rate of absorption is decreased if administered with food, which decreases C_{max} by 25% to 30% and increases t_{max} from 1.5 to 3 hr. However, the administration of pregabalin with food has no clinically relevant effect on total absorption and, unlike gabapentin, its absorption from the gut is not saturable.¹⁴⁶

Protein binding is negligible, and the drug undergoes little metabolism (< 2%) with most of a dose excreted unchanged in urine.¹⁴⁶ The half-life is approximately 6 hr. Because pregabalin does not undergo liver metabolism, it has not been shown to induce or inhibit hepatic enzymes. Clearance is proportional to creatinine clearance and age- or disease-related reduction in renal function decreases its clearance, necessitating lower doses in patients with renal impairment. Pregabalin is removed by

hemodialysis, and giving a supplementary dose after each 4-hr dialysis session has been suggested.¹⁴⁶ No differences in pharmacokinetics due to race or gender have been observed, and the effects of pregnancy on pharmacokinetics are unknown at this time.¹⁴⁶ Adequate pharmacokinetic studies in pediatrics have not been performed.

Pregabalin does not undergo liver metabolism and is poorly protein bound, so it is not associated with significant drug interactions.^{146,147} It may impair cognition and motor function, and these effects may be additive with other agents such as oxycodone, ethanol, or lorazepam.¹⁴⁶

Pregabalin has a similar side effect profile to gabapentin. It is generally well tolerated with CNS effects such as somnolence, dizziness, ataxia, and diplopia noted at the onset of therapy. As tolerance develops, the CNS side effects seem to plateau.¹⁴⁶ Other side effects include weight gain, edema, and behavioral abnormalities.

TABLE 10-10. PHARMACOKINETIC AND DOSING SUMMARY FOR PREGABALIN

Bioavailability (F)	90% (F = 0.9)	
t _{max}	1–1.5 hr	
t _{1/2}	5–6.5 hr	
V	0.5 L/kg	
Clearance	4–4.9 L/hr (proportional to creatinine clearance)	
Protein binding	None	
Elimination	90% to 99% renal	
Therapeutic range	2.8–8.2 mg/L ¹⁴⁶	
Usual dose	Initiate at 150 mg/day (in two to three divided doses) then increase by 150 mg/day at weekly intervals	
	Maximum 600 mg/day	
Dosing in renal dysfunction ^a	CrCl (mL/min)	Dose (mg)
	>60	150–600/day
	30–60	75–300/day
	15–30	25–150/day
	<15	25–75/day
Anephric ^b	Dose (mg)	Supplemental dose (mg)
	25	25 or 50
	25–50	50 or 75
	50–75	75 or 100
	75	100 or 150
Pregnancy	Unknown	

^aTotal daily dose (mg/day) should be divided into two to three doses for CrCl >30 mL/min, one to two doses for CrCl 15–30 mL/min, and as a single daily dose for CrCl <15 mL/min.
^bSupplementary dose is a single additional dose given immediately after each 4-hr hemodialysis session and is based on the normal daily dose for patient.

LACOSAMIDE

Lacosamide is a functionalized amino acid that is an optical antipode of L-serine.¹⁴⁸ Unlike traditional sodium channel blocking AEDs, which primarily target the fast inactivation of these channels, lacosamide works by a novel mechanism to enhance slow inactivation without affecting fast inactivation.¹⁴⁹ Lacosamide is indicated for adjunct treatment of partial-onset seizures in patients 17 yr or older. Dosing is initiated at 50 mg twice daily and increased by 100 mg/day at weekly intervals to a maintenance dose of 200–400 mg/day.

The pharmacokinetics and general dosing guidelines of lacosamide are summarized in **Table 10-11**. After oral administration, lacosamide is rapidly and completely absorbed from the gastrointestinal (GI) tract and has linear, dose-proportional pharmacokinetics.^{148,150} Lacosamide has complete oral bioavailability, and food does not affect the rate or extent of absorption.¹⁵¹ Peak serum concentrations occur 1-4 hr after oral administration.¹⁴⁹ When infused over 30 or 60 min, intravenous (IV) administration produces concentrations similar to oral administration and C_{max} is reached at the end of infusion.¹⁵² Lacosamide has limited protein binding.¹⁵¹ Elimination of lacosamide is primarily renal with approximately 40% of the dose excreted unchanged in the urine.¹⁵¹ Up to 30% of an administered dose is converted to the inactive O-desmethyl metabolite by CYP2C19, although this is considered of minor relevance.¹⁵¹ No dose adjustments are necessary in patients with mild-to-moderate renal dysfunction, though a maximum dose of 300 mg/day is recommended for patients with severe renal dysfunction (creatinine clearance < 30 mL/min).¹⁵⁰ Lacosamide is removed by hemodialysis so a supplemental dose of up to 50% of the patient's normal maintenance dose is recommended following hemodialysis.¹⁵¹ In patients with mild-to-moderate hepatic impairment, cautious titration and a maximum dose of 300 mg/day are recommended.¹⁵⁰ Lacosamide has not been studied in patients with severe hepatic impairment, and its use is not recommended in this population.¹⁵¹ The effects of pregnancy on the pharmacokinetics of lacosamide are unknown at this time.

Due to its low protein binding, minimal interaction with the CYP450 enzyme system, and primarily renal elimination, lacosamide has a low propensity for clinically significant drug interactions.¹⁵⁰ Clinical trials have shown it to have no effect on other AEDs, metformin, digoxin, or oral contraceptives.¹⁴⁸ However, carbamazepine, phenytoin, and phenobarbital have been shown to decrease concentrations of lacosamide by 15% to 25%.¹⁵¹ At therapeutic concentrations, lacosamide was shown to not induce or inhibit any CYP450 enzymes,¹⁵¹ although at supratherapeutic concentrations, it can inhibit CYP2C19.¹⁴⁸

Lacosamide is generally well tolerated with a majority of adverse events affecting the CNS and GI tract.¹⁴⁹ Dizziness is the most commonly reported adverse event and appears to be dose-related.¹⁵⁰ Other dose-related adverse effects include nausea, vomiting, diplopia, headache, and blurred vision.¹⁴⁹⁻¹⁵¹ In some patients, liver function tests were slightly elevated and returned to baseline levels once lacosamide was discontinued.¹⁵¹⁻¹⁵⁴ A small prolongation of the PR interval has been noted, but not deemed to be of clinical significance; however, caution should be exercised when administering lacosamide to patients with known cardiac conduction problems or in combination with other drugs known to increase the PR interval.^{149,151,154} When using lacosamide in combination with traditional sodium channel blocking agents (e.g., phenytoin, carbamazepine, oxcarbazepine, lamotrigine), a small increase in some typical adverse events, including dizziness, nausea, vomiting, diplopia, blurred vision, fatigue, coordination abnormalities, tremor, nystagmus, and somnolence, has been reported.¹⁵⁵ These effects may be attenuated by decreasing the dose of the traditional sodium channel blocking agent.

TABLE 10-11. PHARMACOKINETIC AND DOSING SUMMARY FOR LACOSAMIDE

Bioavailability	100% (F = 1)
t_{max}	1–4 hr
$t_{1/2}$	13 hr
V	0.6 L/kg
Clearance	2.1 L/hr ¹⁵⁶
Protein binding	<15%
Elimination	Partially metabolized by CYP2C19, eliminated renally
Therapeutic range	10–20 mg/L, ¹⁵³ though some clinical trials have reported mean serum concentrations less than 10 mg/L when the maximum recommended dose of 400 mg/day is used. ¹⁴⁹
Usual dose	Initiate therapy at 100 mg/day (in two divided doses) and increase by 100 mg/day weekly up to 200–400 mg/day
Pregnancy	Unknown

RUFINAMIDE

Rufinamide is a triazole derivative that acts to prolong the inactive state of neuronal sodium channels.¹⁵⁷ At high concentrations, rufinamide has also been shown to inhibit the mGluR5 glutamate receptor.¹⁵⁷ Rufinamide is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in adults and children 4 yr or older. In adults, dosing is initiated at 400–800 mg/day (in two divided doses) and increased by 400–800 mg/day every 2 days up to a target and maximum dose of 3,200 mg/day. In children and adolescents, dosing is weight-based and initiated at 10 mg/kg/day (in two divided doses) and increased by ~10 mg/kg/day every 2 days up to a target and maximum dose of 45 mg/kg/day or 3,200 mg/day (whichever is lower).

The pharmacokinetic parameters and general dosing guidelines of rufinamide are summarized in **Table 10-12**. After oral administration, rufinamide is slowly absorbed.¹⁵⁸ This is due to the fact that it does not dissolve in water, and it poorly dissolves in the fluids of the GI tract.¹⁵⁹ Peak concentrations are achieved 4–6 hr after administration.¹⁵⁷ The oral bioavailability of rufinamide is considered to be 85% ($F = 0.85$); however, this is based on a study consisting of a single 600-mg dose given to healthy volunteers. It has been established that as the dose increases, the bioavailability of rufinamide decreases. Therapeutic doses are typically higher than 600 mg, so bioavailability is expected to be less than 85% in most patients.¹⁵⁸ It is recommended that rufinamide be given with food, as extent of absorption increases and time to peak concentration decreases in the fed state.¹⁵⁷ Rufinamide exhibits low protein binding.¹⁵⁹ Its volume of distribution is dependent on the dose and body surface area (BSA) of the patient, but at the recommended maintenance dose and average adult BSA, the volume of distribution is approximately 50 L.¹⁵⁷

The major pathway for rufinamide metabolism is hydrolysis of its carboxamide group to inactive metabolites via hepatic carboxylesterases, which is a non-CYP450 system.¹⁵⁸ Despite this non-CYP450 metabolic pathway, rufinamide is a weak inducer of CYP3A4 and a weak inhibitor of CYP2E1.¹⁵⁷ Elimination of rufinamide and its metabolites is primarily renal. Renal impairment does not significantly affect the pharmacokinetics of rufinamide, so no dose adjustments are necessary in this population.^{157,158} No data have been published regarding the use of rufinamide in patients with hepatic impairment.^{155,158} The effects of pregnancy on the pharmacokinetics of rufinamide are unknown at this time.

Despite not being metabolized by the CYP450 system, drug interactions are a concern with rufinamide, especially in children. In adults, valproate causes a small increase in rufinamide

TABLE 10-12. PHARMACOKINETIC AND DOSING SUMMARY FOR RUFINAMIDE	
Bioavailability	85% ($F = 0.85$) (decreases with higher doses)
t_{max}	4–6 hr
$t_{1/2}$	6–10 hr
V	~50 L
Clearance	3.4–5.1 L/hr ^{158,161}
Protein binding	34%
Elimination	Hepatic metabolism (hydrolysis of carboxamide group via carboxylesterases—not P450 dependent); primarily renal elimination
Therapeutic range	Not established ¹⁵⁸
Usual dose	Adult: Initiate therapy at 400–800 mg/day (in two divided doses) and increase by 400–800 mg/day every 2 days up to 3,200 mg/day Pediatrics: Initiate therapy at 10 mg/kg/day (in two divided doses) and increase by ~10 mg/kg/day every 2 days up to 45 mg/kg/day or 3,200 mg/day (whichever is lower)
Pregnancy	Unknown

concentrations, but in children this increase can be as much as 70%, necessitating a decrease in rufinamide dose of approximately 50%.^{148,157,158} Lamotrigine has been shown to increase concentrations of rufinamide as well.¹⁴⁶ Drugs that have been shown to decrease rufinamide concentrations include phenytoin, phenobarbital, primidone, carbamazepine, and vigabatrin.^{148,158,159} Rufinamide has been shown to increase concentrations of phenytoin and phenobarbital and to decrease concentrations of carbamazepine, lamotrigine, triazolam, and oral contraceptives.^{148,157-159}

Rufinamide is generally well tolerated. The most common side effects include headache, dizziness, diplopia, fatigue, somnolence, nausea, and vomiting.¹⁵⁷⁻¹⁶⁰ It can shorten the QT interval and is consequently contraindicated in patients with familial short QT syndrome.^{157,159} It should also be used with caution in patients taking other medications that can decrease the QT interval.

VIGABATRIN

Vigabatrin is a GABA analog that acts as an irreversible inhibitor of GABA transaminase, the enzyme responsible for the breakdown of GABA.^{162,163} Vigabatrin is indicated for the treatment of infantile spasms in children 1 month to 2 yr of age and for the treatment of refractory complex partial seizures in adults. In adults, dosing is initiated at 1,000 mg/day (in two divided doses) and increased by 500 mg/day weekly to a target dose of 3,000 mg/day. Pediatric dosing is weight-based and should be initiated at 50 mg/kg/day (in two divided doses). The dose should then be escalated by 25–50 mg/kg/day every 3 days up to a maximum of 150 mg/kg/day.

The pharmacokinetics and general dosing guidelines of vigabatrin are summarized in **Table 10-13**. After oral administration, vigabatrin is rapidly absorbed.^{162,163} Its oral bioavailability is somewhat low, and food does not appear to significantly affect absorption.^{162,163} Vigabatrin is not expected to have any interactions with drugs that are highly protein bound, as it does not bind to plasma proteins.¹⁶²⁻¹⁶⁴ Vigabatrin is widely distributed throughout the body.¹⁶⁵ It is possible to measure vigabatrin concentrations, which may provide some clinical benefit. As vigabatrin acts to irreversibly inhibit GABA transaminase, its activity persists for far longer than it is detectable in the serum.^{162,163} For the effects of vigabatrin to diminish, the body must synthesize new GABA transaminase, which takes approximately 5–7 days.¹⁶²

TABLE 10-13. PHARMACOKINETIC AND DOSING SUMMARY FOR VIGABATRIN

Bioavailability (F)	60% to 70% (F = 0.6–0.7)	
t _{max}	1–2 hr	
t _{1/2}	5–8 hr	
V	1.1 L/kg	
Clearance	7 L/hr in adults 5.8 L/hr in pediatrics (10–16 yr old) 2.4 L/hr in infants (5–24 months old) ¹⁷¹	
Protein binding	Negligible	
Elimination	Primarily eliminated unchanged in urine	
Usual dose	Adults: Initiate therapy at 1,000 mg per day (in two divided doses) and increase by 500 mg/day weekly to a target dose of 3,000 mg/day Pediatrics: Initiate therapy at 50 mg/kg/day (in two divided doses) and increase by 25–50 mg/kg/day every 3 days to a maximum of 150 mg/kg/day	
Dosage in renal dysfunction	CrCl (mL/min)	Dose adjustment
	51–80	Decrease dose by 25%
	31–50	Decrease dose by 50%
	10–30	Decrease dose by 75%
Pregnancy	Unknown	

Hepatic metabolism of vigabatrin is negligible with nearly 100% of the dose being excreted unchanged in the urine.^{162,163} Clearance is higher in children than in adults, which necessitates higher doses on a mg/kg basis in the younger population.^{163,166} Furthermore, in children less than 22 months old, clearance is up to 40% higher than in older children.¹⁶⁶ The elimination half-life of vigabatrin is short, but the actions of the drug are apparent long after drug concentrations become undetectable.^{163,164,166} Lower doses are necessary in patients with renal dysfunction ($\text{CrCl} < 80 \text{ mL/min}$). Hepatic dysfunction has no impact on vigabatrin dosing.¹⁶³ The effects of pregnancy on the pharmacokinetics of vigabatrin are unknown at this time.

Vigabatrin has a very low potential for interactions with other drugs because of its renal elimination and lack of metabolism. However, there is a clinically significant interaction between vigabatrin and phenytoin. Specifically, when vigabatrin therapy is initiated in a patient taking phenytoin, phenytoin concentrations may decrease by up to 40%.¹⁶² No other clinically significant interactions appear to occur.^{162,163} The package insert for vigabatrin states that it is an inducer of CYP2C9, but this has not been described in primary literature.

Vigabatrin is generally well tolerated, but reports of irreversible visual field defects have significantly limited its use. Visual field defects appear in approximately one-third of all patients treated with vigabatrin, and these defects are often not recognized early on by patients.¹⁷⁰ To prevent significant visual field defects from developing, adults should have a visual field test at baseline and every 6 months while on vigabatrin therapy. Infants should have the test performed at baseline, every three months for the first 18 months of therapy, and every 6 months thereafter.¹⁷⁰ Other common adverse effects of vigabatrin include fatigue, dizziness, somnolence, and weight gain.^{162,170} Depression has been reported to occur in approximately 12% of patients, so caution should be exercised when using vigabatrin in patients with a history of psychiatric disorders.^{162,170}

EZOGBABINE

Ezogabine has a unique mechanism of action through enhancing the activity of Kv7.2–7.5 voltage-gated potassium channels.^{1172–175} Kv7 channels play a pivotal role in stabilizing membrane potential in the subthreshold range of an action potential and are involved in fine-tuning of neuronal firing. Ezogabine is indicated for adjunctive treatment for partial-onset seizures in patients ≥ 18 yr who have responded inadequately to several alternative treatments. Owing to the boxed warning for potential risks of vision loss due to retinal pigment changes and of skin discoloration, consideration should be given to determine if the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity.^{176–178} The initial dose is 100 mg three times daily, with weekly increments of less than 150 mg per day to a maintenance dose of 200 to 400 mg three times daily based on tolerability (maximum: 400 mg 3 times daily, 1,200 mg per day). In clinical trials, no additional benefit and an increase in adverse effects were observed with doses more than 900 mg per day.

The pharmacokinetics and general dosing guidelines of ezogabine are summarized in **Table 10-14**. Following a single oral dose, absorption is rapid and C_{max} is typically attained after 30–120 min.^{172, 179} The absolute bioavailability of orally administered ezogabine is approximately 60%.¹⁷² When taken with a high-fat meal, C_{max} is increased by about 38%, while the AUC is unchanged.¹⁷² Ezogabine is not metabolized by CYP450 but undergoes extensive N-glucuronidation, giving rise to two major N-glucuronides.^{172,175,177} There is also a smaller extent of N-acetylation, resulting in a metabolite with weak pharmacologic effects and inconsistent antiseizure activity in preclinical models. In vitro assays identified UGT1A1, 1A9, 1A4, and 1A3 as the principal enzymes catalyzing ezogabine glucuronidation.¹⁷² In individuals with reduced UGT1A1 activity such as Gilbert's syndrome, ezogabine pharmacokinetics is unaffected, likely due to compensatory mechanism through N-acetylation and other UGT1A isoforms.¹⁸⁰ Genetic polymorphism in the N-acetyltransferase 2 (NAT2) gene results in slow acetylation phenotype.¹⁷² However, safety and tolerability of ezogabine are not affected in individuals with Gilbert's syndrome or slow acetylation polymorphisms.

Ezogabine is rapidly eliminated following first-order kinetics.¹⁷² It has a terminal half-life of approximately 7.5 hr and clearance of 0.58–0.76 L/hr/kg.¹⁷² The volume of distribution is reported to be 2–3 L/kg following IV administration and 5–7 L/kg after multiple oral dosing. Incomplete bioavailability likely contributes to the difference. Plasma protein binding is about 80%. Within the daily dosing range of 100 to 700 mg, ezogabine follows linear dose proportional pharmacokinetics.

Data from in vitro studies indicate that there is no significant inhibition of various CYP isoenzymes (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A 4/5) or significant induction of CYP1A2 and CYP3A4/5.¹⁷² These results were consistent with clinical studies indicating that ezogabine does not have any clinically significant effect on plasma concentrations of most of the AEDs, except lamotrigine where concentrations were reduced by about 20% in healthy subjects. Ezogabine does not affect the metabolism of oral contraceptives and is not known to compromise contraceptive control. The most frequently reported adverse effects were dizziness, somnolence, fatigue, and confused states. These tended to occur during the titration phase and were dose-dependent.

TABLE 10-14. PHARMACOKINETIC AND DOSING SUMMARY FOR EZOGABINE

Bioavailability (F)	60% (F = 0.6)	
t _{max}	0.5–2 hr	
t _{1/2}	7–11 hr	
V	2–3 L/kg (IV administration); 5–7 L/kg (multiple oral dosing)	
Clearance	0.57 L/hr/kg ¹⁸¹	
Protein binding	80%	
Elimination	Extensively metabolized via glucuronidation and acetylation; 20% to 30% eliminated unchanged in urine	
Usual dose	Adults: Initiate therapy at 100 mg per day (in two divided doses) and increase by 500 mg/day weekly to a target dose of 3,000 mg/day	
Dosage in renal dysfunction	CrCl (mL/min)	Dose adjustment
	>50	No adjustment needed
	<50	Initiate at 50 mg three times daily, titrate at not more than 150 mg/day weekly to maximum 600 mg/day
Dosage in hepatic dysfunction	Child Pugh score	Dose adjustment
	<7	No adjustment needed
	7–9	Initiate at 50 mg three times daily, titrate at not more than 150 mg/day weekly to maximum 750 mg/day
	>9	Initiate at 50 mg three times daily, titrate at not more than 150 mg/day weekly to maximum 600 mg/day
Pregnancy	Unknown	

CLOBAZAM

Clobazam is the only benzodiazepine that contains nitrogen atoms in the 1 and 5 positions, unlike the other classic benzodiazepines. It was originally used as an agent to treat anxiety in Australia in 1970, and subsequently for epilepsy in France in 1974. Clobazam is approved in many countries as an adjunctive therapy to treat epilepsy and anxiety since the 1970s but was only approved by the FDA in 2011 for adjunctive treatment for Lennox-Gastaut Syndrome in patients older than 2 yr. Clobazam, like other benzodiazepines, exerts its pharmacologic effect in the treatment of epilepsy through GABA A binding, which enhances GABAergic neurotransmission resulting in neuronal hyperpolarization.^{182,183}

The pharmacokinetics and general dosing guidelines of clobazam are summarized in **Table 10-15**. Clobazam exhibits first-order pharmacokinetics. It is a highly lipophilic compound with a volume of distribution of approximately 100 L. Bioavailability is approximately 87% ($F = 0.87$), with peak concentrations achieved in 1–4 hr.¹⁸² Food does not affect the extent of absorption. Clobazam and its active metabolite are both highly protein-bound (85% and 70% respectively); therefore, hepatic disease and other highly protein-bound drugs have the ability to affect the free (unbound) concentrations.

Clobazam is extensively metabolized in the liver via N-demethylation by CPY3A4, yielding an active metabolite, N-desmethyclobazam, but is also metabolized to a lesser extent by CYP2C19 and CYP2B6.^{182,183} N-desmethyclobazam is subsequently metabolized by CYP2C19.^{182,183} Both clobazam and N-desmethyclobazam are active compounds that potentiate GABAergic neurotransmission, but animal and in vitro data suggest that N-desmethyclobazam potency ranges from equal to one-fifth that of clobazam.^{183,184} Due to the rapid metabolism, plasma concentrations of N-desmethyclobazam are 3–5 times higher than those of clobazam. N-desmethyclobazam also has a longer half-life compared to the parent compound. Clobazam has a half-life of 36 to 42 hr, whereas N-desmethyclobazam’s half-life is 71 to 82 hr.¹⁸² Elimination of metabolites is 82% renal and 11% fecal; therefore, kidney function has the ability to delay clearance in the elderly or those with renal impairment.^{182,183,185} Moreover, clearance is significantly increased in young children (age 2–9 yr) resulting in a 36% decreased concentration/dose-ratio compared to adults (age 18–64 yr) and an estimated half-life of 16 hr.^{182,184,186}

TABLE 10-15. PHARMACOKINETIC AND DOSING SUMMARY FOR CLOBAZAM		
Bioavailability (F)	87% ($F = 0.87$)	
t _{max}	1–4 hr	
t _{1/2}	36–42 hr (clobazam); 71–82 hr (N-desmethyclobazam)	
V	1.3 L/kg	
Clearance	2.6 L/hr ¹⁸⁸	
Protein binding	80% to 90% (clobazam); 70% (N-desmethyclobazam)	
Elimination	Metabolized in the liver primarily via N-demethylation by CYP3A4 to the active metabolite N-desmethyclobazam. About 82% is excreted in the urine, with approximately 2% as unchanged drug. Approximately 94% of drug-related components in the urine consist of N-desmethyclobazam and its metabolites	
Usual dose	Adults and Pediatrics (>2 yr): ≤30 kg: Initiate at 5 mg once daily for at least 1 wk, then increase to 5 mg twice daily for ≥1 wk, then increase to 10 mg twice daily thereafter >30 kg: Initiate at 5 mg twice daily for at least 1 wk, then increase to 10 mg twice daily for 1 wk, then increase to 20 mg twice daily thereafter	
Dosage in renal dysfunction	CrCl (mL/min)	Dose adjustment
	≥30	No dosage adjustment necessary.
	<30	No recommendation, use with caution
Dosage in hepatic dysfunction	Mild-to-moderate	≤30 kg: initiate at 5 mg once daily for at least 2 wk, then increase to 5 mg twice daily; after at least 1 wk, increase to 10 mg twice daily based on patient tolerability and response >30 kg: initiate at 5 mg once daily for at least 1 wk, then increase to 5 mg twice daily for at least 1 wk, then increase to 10 mg twice daily; after 1 wk may increase to 20 mg twice daily based on patient tolerability and response
	Severe	No recommendations provided. Use with caution.
Pregnancy	Unknown	

Due to the extensive hepatic metabolism of clobazam and N-desmethyclobazam, drug–drug interactions via the CYP450 system should be evaluated. Both compounds in *in vitro* and *in vivo* studies demonstrated the ability to induce CYP3A4 activity, and *in vivo* studies demonstrated inhibitory activity of CYP2D6.¹⁸³ Drugs that rely primarily on CYP2D6 metabolism may require dose adjustments when given concurrently with clobazam. Dose adjustments to clobazam may also be appropriate when given with CYP2C19 inhibitors or when given to individuals with CYP2C19 polymorphisms resulting in altered rates of metabolism.¹⁸³ Individuals known to possess the CYP2C19 polymorphism that results in poor metabolism will have higher plasma concentrations of N-desmethyclobazam and are recommended to initiate clobazam therapy at lower doses and titrate slowly based on weight and clinical response.^{183,187} The most common adverse effects reported with clobazam use are constipation, drooling, ataxia, dysarthria, insomnia, lethargy, somnolence, and aggressive behavior.¹⁸⁵

PERAMPANEL

Perampanel possesses a distinct and unique mechanism of action compared to other AEDs. It is selective to the ionotropic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptor, and acts by modulating excitatory glutamatergic transmission via noncompetitive antagonism.¹⁸⁹⁻¹⁹¹ Perampanel is only approved for adjunctive therapy for patients 12 yr of age or older with partial-onset seizures with or without secondary generalized seizures or those with primary generalized tonic-clonic seizures. It has a linear dose–plasma concentration relationship with higher plasma concentrations demonstrating increased efficacy.¹⁹²

The pharmacokinetics and general dosing guidelines of perampanel are summarized in **Table 10-16**. Upon oral administration, perampanel is completely absorbed with peak concentrations reached between 0.5 to 2.5 hr when fasting. When taken with food, time to peak concentration is delayed by 2–3 hr and the C_{max} is 28% to 40% decreased, which can translate to decreased clinical efficacy.^{190,192,193} It has a large volume of distribution, and *in vitro* studies report it is up to 95% protein-bound in concentrations ranging between 20 and 2,000 ng/mL.^{190,193} Perampanel readily crosses the blood–brain barrier and, fortunately, doesn't seem to be affected by blood–brain multidrug efflux transporters.¹⁹¹

Metabolism of perampanel to various inactive metabolites is carried out via primary oxidation and sequential glucuronidation by CYP3A4/5 primarily, and CYP1A2 and CYP2B6 to a lesser extent.¹⁹⁰ Hepatic dysfunction does increase drug exposure and prolongs the drug half-life, so dosing adjustments are required depending on degree of impairment. Consideration should also be given when administering perampanel with other medications that are metabolized via the CYP450 system, enzyme inducers or inhibitors of the CYP450 system, or those that are also highly protein-bound. Clinical studies that examined perampanel administration with other AEDs have shown perampanel AUC decreases of 64% with carbamazepine, 48% with oxcarbazepine, 43% with phenytoin, and 19% with topiramate.¹⁹⁰ Eslicarbazepine also may have the ability to decrease perampanel concentrations due to its structural similarity to oxcarbazepine.

Clearance of perampanel in healthy individuals is approximately 48% fecal and 22% renal, and consists of a mixture of the oxidative and conjugated metabolites.¹⁹⁰ Decreased hepatic or renal function significantly impacts this clearance. It can also be variable based on patient sex. In an analysis of pooled phase III studies evaluating differences in efficacy and tolerability of perampanel based on sex, the clearance of perampanel was 17% lower in women compared to males; however, women did experience statistically significantly greater seizure frequency reduction at the 8-mg dose.¹⁹⁴ This analysis further supported the existing evidence that perampanel efficacy has a linear dose–plasma concentration relationship. The most common adverse effects associated with perampanel are abnormal gait, ataxia, dizziness, headache, loss of equilibrium, somnolence, irritability, and fatigue.¹⁸⁵

TABLE 10-16. PHARMACOKINETIC AND DOSING SUMMARY FOR PERAMPANEL

Bioavailability (F)	100%	
t _{max}	0.5–2.5 hr	
t _{1/2}	Variable, average ~105 hr	
V	1.1 L/kg	
Clearance	0.7 L/hr ¹⁹⁰	
Protein binding	95% (albumin, alpha 1-acid glycoprotein)	
Elimination	48% fecal	
	22% renal	
Usual dose	8–12 mg once daily	
	Dosing Consideration	Dose adjustment
Dosage in renal dysfunction	Mild	No adjustment necessary
	Moderate	Close monitoring, slower dose titration may be necessary
	Severe	Not recommended, use with caution, avoid in patients undergoing hemodialysis
Dosage in hepatic dysfunction	Mild-to-moderate	Starting dose is 2 mg daily, increase dosage by 2 mg daily no more frequently than every 2 wk. Max daily dose 6 mg for mild impairment, and 4 mg for moderate impairment.
	Severe	Not recommended, use with caution
Pregnancy	Unknown	

ESLICARBAZEPINE

Eslicarbazepine acetate, a derivative of carbamazepine and oxcarbazepine, was designed with the intent to improve safety and efficacy by circumventing the formation of toxic epoxide metabolites.¹⁹⁵ The mechanism of action of its anticonvulsant effect is through voltage-gated sodium channel blockade. Eslicarbazepine acetate is indicated for adjunctive treatment¹⁹⁶⁻¹⁹⁹ or monotherapy^{200,201} of partial onset seizures in adults at daily dosages of 400 mg to 1,600 mg/day.

The pharmacokinetics and general dosing guidelines of eslicarbazepine are summarized in **Table 10-17**. Following oral administration, the bioavailability of eslicarbazepine acetate is high at 90% (F= 0.9) and is demonstrated to be unaffected by food.^{195,202,203} It undergoes rapid and extensive biotransformation via hepatic hydrolytic first-pass metabolism to the main active metabolite eslicarbazepine. A small part of eslicarbazepine (5%) undergoes chiral inversion to R-eslicarb through metabolic oxidation to oxcarbazepine. Peak eslicarbazepine concentrations follow 1–4 hr after oral administration. Protein-binding is less than 40% and independent of concentration. The volume of distribution is reported to be 61 L for body weight of 70 kg based on population pharmacokinetics analysis. Eslicarbazepine and the other minor active metabolites undergo conjugation via the uridine diphosphate-5-glucuronosyltransferases (UGT). Renal excretion is the predominant route of elimination, with more than 90% of the oral dose in the urine—one-third is glucuronized while the other two-thirds is unconjugated. The terminal half-life of the active eslicarbazepine ranges between 13 to 20 hr. Within the dosing range of 400 mg to 1,600 mg, eslicarbazepine follows first-order pharmacokinetics.

Eslicarbazepine is a moderate inhibitor of CYP2C19 and a moderate CYP3A4 inducer.²⁰³ Concurrent administration with potent enzyme inducing antiepileptic drugs can increase the oral clearance of eslicarbazepine.²⁰⁴ Women of child-bearing potential should use additional contraceptive methods as eslicarbazepine increases the metabolism of the progestin and estrogen components in a dose-dependent fashion.²⁰⁵ The most common adverse effects include dizziness, somnolence, nausea, diplopia, headache, vomiting, abnormal coordination, blurred vision, vertigo and fatigue.¹⁹⁵⁻²⁰¹

TABLE 10-17. PHARMACOKINETIC AND DOSING SUMMARY FOR ESLICARBAZEPINE

Bioavailability (F)	90% (F = 0.9)	
t _{max}	1–4 hr	
t _{1/2}	13–20 hr	
V	0.87 L/kg (61 L for body weight of 70 kg)	
Clearance	1.2 L/hr ²⁰⁶	
Protein binding	<40%	
Elimination	Predominantly renal excretion (90%)	
Usual dose	Adults: Initiate therapy at 400 mg per day and increase by 400 mg weekly to a maximum dose of 1,600 mg/day	
Dosage in renal dysfunction	CrCl (mL/min)	Dose adjustment
	30–60	Decrease dose by 50%
	<30	No recommendation
Pregnancy	Unknown	

USE OF THE NEWER ANTIEPILEPTIC DRUGS

The availability of newer drugs with different mechanisms of action has increased the options for treating patients with epilepsy. No patient with epilepsy should be considered refractory until several different single agents or combinations of antiepileptic drugs have been tried; however, therapy should begin with the antiepileptic drug considered the most effective for the patient’s seizure type. Doses of the drug of first choice should be increased gradually until the patient becomes seizure free or to the maximum dose tolerated. A second drug with a different mechanism of action that is appropriate for the seizure type should then be added. This approach is referred to as *rational polytherapy*. In selecting the second drug, consideration should also be given to avoiding potential drug interactions and to overlapping drug side effects, if possible. It is not always possible to avoid drug interactions, and drug interactions do not necessarily contraindicate the use of interacting drugs, although they mandate closer patient monitoring. It should be mentioned that although sophisticated technologies exist, not all mechanisms of action may have been identified for many AEDs. This may explain the efficacy of a different drug of the same class when a patient has failed therapy with a drug in that class.

When combination therapy is employed, the two drugs should be given in adequate doses and for an adequate period of time to assess the frequency of seizures. One estimate is that the trial period at full dosage should encompass the period normally encompassing five seizures. Thus, the less frequent the seizures, the more difficult it is to determine if the therapy is effective. If the patient has a positive response to the second drug or becomes seizure free, consideration should be given to withdrawing the first drug. The ultimate goal of antiepileptic drug therapy is to make the patient seizure free with minimal or no side effects.

The Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society reviewed the newer AEDs for the treatment of new-onset and refractory epilepsy.^{207,208} These reports identify seizure types and syndromes where the use of the newer AEDs are appropriate either as initial monotherapy or as off-label use for situations that the FDA has not approved. These guidelines use an evidence-based approach to ensure the concept that the selection of an AED should be based on the seizure type or syndrome, the patient’s age, concomitant medications, AED tolerability, safety, and efficacy and not just on the package insert and FDA-approved indications.

GENERIC SUBSTITUTION OF AEDS

In recent years, there has been much controversy regarding the safety and efficacy of generic formulations of AEDs. Many patients and practitioners have noted increased side effects or loss of seizure control in some individuals switched from brand-name drug to a generic equivalent. This effect has, perhaps, been more pronounced in patients switching between multiple generic formulations (i.e., generic to generic substitution). It has been postulated that pharmacokinetic differences between formulations or batch to batch variations may be the culprit in these cases. Several studies have been published showing increased incidence of epilepsy-related emergency department utilization following an A-rated switch in AED.²⁰⁹⁻²¹¹ One study showed increased incidence of medical utilization and increased risk of epilepsy-related medical events when a generic AED was used compared to use of brand-name formulations.²¹²

Contrary to the previously mentioned studies, a group from the FDA published a paper showing, on average, a difference in C_{max} between generic and innovator products of 4.35% and a difference in AUC of 3.56%.²¹³ These data covered a variety of drug classes and encompassed generics approved between 1996 and 2007. The major limitation of this study, however, was the stipulation that, when submitting a new formulation for FDA approval, generic drug manufacturers were not required to submit data from all bioequivalence studies conducted, but rather can choose to submit only favorable data. This loophole was not closed until mid-2009. As the data set is limited and no consensus has been reached in the medical community, this continues to be a topic of much contention.

The EQUIGEN study, which evaluated generic to generic lamotigine switches in people with epilepsy to confirm the FDA's bioequivalent standards was published in 2016.²¹³ This was a randomized, double-blind, cross-over study that enrolled adults in six centers across the USA who were receiving immediate-release lamotigine. The study confirmed that the FDA's bioequivalent standards were appropriate for generic to generic substitution of lamotigine.

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ANTIREJECTION AGENTS

Tony K.L. Kiang and Mary H.H. Ensom

Cyclosporine is a large lipophilic polypeptide that has been a cornerstone of immunosuppression. It inhibits T-lymphocytes and also inhibits production and release of lymphokines, including interleukin-2. Cyclosporine is indicated for the prevention of rejection in solid organ and marrow transplantation as well as for a variety of other disorders such as rheumatoid arthritis and Crohn disease.¹⁻³ Cyclosporine can be administered intravenously or orally. The oral cyclosporine formulations, which are not interchangeable, are the original formulation (Sandimmune) and the modified formulation (Neoral, Gengraf, and various generics). Sandimmune has variable and incomplete gastrointestinal absorption and displays significant intra- and interpatient variability in bioavailability.¹ Neoral becomes a microemulsion in aqueous environment and demonstrates greater bioavailability than Sandimmune.¹⁻³

Tacrolimus (Prograf) is a macrolide immunosuppressant that works via potent inhibition of T-lymphocytes.^{4,5} It is indicated for the prevention of rejection following solid organ transplantation (kidney, liver, and heart) and in Crohn disease.^{4,5} Tacrolimus can be administered intravenously or orally, and various immediate-release (e.g., Prograf, and multiple generics) and extended-release (Astagraf XL, Envarsus XR)⁴ oral dosage forms are available. The interchangeability of these oral dosage forms remains to be determined, and food (e.g., a fatty meal) is the primary factor affecting tacrolimus absorption.⁵

Sirolimus (Rapamune) is a macrocyclic lactone with potent immunosuppressive activity that results from inhibition of T-lymphocyte proliferation and antibody production.⁶ It is indicated for the prevention of rejection in kidney transplant recipients older than 13 yr of age and for the treatment of lymphangioleiomyomatosis.⁶ Sirolimus is available only as oral formulations (Rapamune and generics) that are not interchangeable (between tablet and solution) due to different bioavailability.^{6,7}

Mycophenolate (CellCept and generics) is administered as a pro-drug (mycophenolate mofetil), which rapidly undergoes hydrolysis in the formation of the active moiety, mycophenolic acid.^{8,9} Mycophenolic acid is also formulated in an enteric-coated oral formulation (Myfortic) that does not require initial activation. Mycophenolate exerts its immunosuppression effects by blocking nucleotide production through inhibition of inosine monophosphate dehydrogenase, thereby affecting both B and T lymphocytes.^{8,9} It is indicated in solid organ transplantation (kidney, liver, heart, lung), autoimmune hepatitis, and various other conditions (e.g., lupus, psoriasis).^{8,9} Mycophenolate can be administered intravenously or orally. The oral formulations (CellCept and Myfortic) are not interchangeable due to documented differences in absorption and bioavailability.^{8,9}

Azathioprine (Imuran) exerts its immunosuppressant effects primarily through metabolic activation to 6-mercaptopurine and subsequently to 6-thioguanine-nucleotide, which stops DNA replication.^{10,11} It is indicated in kidney transplant, rheumatoid arthritis, and has various off-label uses (e.g., Crohn disease, lupus, ulcerative colitis).^{10,11} Azathioprine can be administered intravenously or orally (Azasan, Imuran, and generic tablets), and the interchangeability between the oral formulations remains to be determined. A key genetic factor affecting azathioprine toxicity is the individual's thiopurine methyltransferase (TPMT) activity, which will be discussed further below in the section on Drug-Gene Interactions.

Note: The important work of Christine M. Formea and Janet L. Karlix on the previous version of this chapter is acknowledged.



Corticosteroids are often used concurrently with other immunosuppressants for the prevention of graft rejection, although steroid-free regimens also exist. For the purpose of this chapter, prednisone will be discussed as the representative, although various other corticosteroids (e.g., methylprednisolone, hydrocortisone, prednisolone) are used in current practice. Prednisone’s immunosuppressive effects are primarily mediated by regulating interleukin and interferon-gamma production,^{12,13} but the drug has a myriad of pharmacological effects that can lead to undesired side effects.^{14,15} Corticosteroids can be administered intravenously or orally.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

The following dosing recommendations (pertaining only to solid organ transplant) for the antirejection agents are based on average pharmacokinetic parameters (see **Tables 11-1 to 11-5**). The dose of corticosteroids (e.g., prednisone) is usually transplant-center specific and often involves a tapering regimen (thus not presented in the table). Initial and maintenance doses of all antirejection agents may differ between transplant centers, transplantation type, and patient population. Doses are generally adjusted to achieve center-defined blood trough concentrations. Long-term administration is required to prevent rejection. All of these products should be taken on a consistent schedule relative to meals and time of day. Due to wide inter- and inpatient pharmacokinetic variability, individual monitoring is necessary.

DOSAGE FORM AVAILABILITY

Various dosage forms are available for these immunosuppressant agents (see **Table 11-6**). Cyclosporine, tacrolimus, mycophenolate, and azathioprine have intravenous (IV) dosage forms that should be used only when patients are unable to take medications orally. Potential additional side effects may occur with the IV forms.

TABLE 11-1. DOSING RECOMMENDATIONS FOR CYCLOSPORINE^{1-3,16}

Dosage Form	Initial Dosage ^{a-c}	Maintenance Dosage ^{a-c}
IV	5–6 mg/kg as a single IV dose given 4–12 hr before transplant	5–6 mg/kg once daily IV dose
Oral capsules and solutions	10–14 mg/kg single dose given 4–12 hr before transplant	5–10 mg/kg/day given in two divided doses

^aCyclosporine is most commonly administered orally every 12 hr. However, pediatric patients may require every 8-hr dosing. Pediatric patients may require and tolerate higher mg/kg doses.

^bDue to anaphylactic risk, IV cyclosporine should only be used until patients are able to take oral cyclosporine products. The IV dosage of cyclosporine is one-third the recommended oral dosage.

^cPatients with renal or hepatic impairment should receive doses at the lowest value of the recommended IV and oral dosing ranges.

TABLE 11-2. DOSING RECOMMENDATIONS FOR TACROLIMUS^{4,5}

Dosage Form	Initial Dosage ^{a-e}
IV	For heart (adult): 0.01 mg/kg/day continuous infusion For kidney/liver (adult): 0.03–0.05 mg/kg/day continuous infusion For liver (child): 0.03–0.05 mg/kg/day continuous infusion
Oral capsule	For liver (child): 0.15–0.2 mg/kg/day (divided every 12 hr) For heart (adult): 0.075 mg/kg/day (divided every 12 hr) For kidney (adult): Immediate release: 0.2 mg/kg/day (divided every 12 hr); Extended release (Astagraf XL): 0.15 mg/kg daily (with basiliximab induction), 0.1 mg/kg for 1 dose preoperatively followed by 0.2 mg/kg once daily postop (without basiliximab induction) For liver (adult): Immediate release: 0.1–0.15 mg/kg/day (divided every 12 hr); Extended release (Advagraf): 0.1–0.2 mg/kg daily

^aIn general, children require and tolerate higher mg/kg tacrolimus doses than adults.

^bInitiation with oral therapy is recommended. If IV therapy is necessary, conversion to capsules is recommended as soon as oral therapy is tolerated. The first oral dose of tacrolimus should be administered 8–12 hr after discontinuation of the continuous IV infusion.

^cPatients with renal or hepatic impairment should receive doses at the lowest value of the recommended IV and oral dosing ranges.

^dTacrolimus and cyclosporine should not be used simultaneously. Tacrolimus or cyclosporine should be discontinued for at least 24 hr before initiating the other agent.

^eBegin daily tacrolimus continuous infusions no sooner than 6 hr after transplant.

TABLE 11-3. DOSING RECOMMENDATIONS FOR SIROLIMUS^{6,7,17}

Dosage Form	Loading Dose ^{a-d}	Maintenance Dose ^{b-f}
Oral (tablet and solution)	<40 kg: 3 mg/m ² for 1 dose	<40 kg: 1 mg/m ² once daily
Low-to-moderate immunologic risk:	≥40 kg: 6 mg for 1 dose	≥40 kg: 2 mg once daily
High immunologic risk ^g :	15 mg once for 1 dose	5 mg once daily

^aThe sirolimus loading dose should be given as soon as possible after transplantation.

^bNo sirolimus dosage adjustment is needed for renal impairment.

^cIn mild-to-moderate hepatic impairment, the sirolimus maintenance dose should be reduced by one-third. In severe hepatic impairment, the maintenance dose should be reduced by one-half. The loading dose does not need to be modified.

^dSirolimus should be administered 4 hr after cyclosporine solution or capsule dosage.

^eDue to the long half-life of sirolimus, avoid frequent dose adjustments based on non-steady state sirolimus blood concentrations. Interpretation of non-steady state sirolimus concentrations may result in sirolimus underdosing or overdosing.

^fHigh immunologic risk includes African Americans, recipients of another transplant after a failure and/or high panel reactive antibodies (PRA) >80%.

TABLE 11-4. DOSING RECOMMENDATIONS FOR MYCOPHENOLATE^{8,9}

Dosage Form	Maintenance Dose ^{a-d}
Oral or IV	Mycophenolate mofetil (oral) or mycophenolate mofetil hydrochloride (IV): 1 g twice daily (kidney); 1 g oral or IV twice daily (kidney); 1.5 g oral or IV twice daily (cardiac); 1.5 g oral or 1 g IV twice daily (hepatic) Mycophenolate sodium (oral): 720 mg twice daily (kidney)

^aPatients should be converted to oral dosage forms as soon as possible. The maximum recommended duration of IV administration is 14 days.

^bChildren up to 18 yr old are dosed at 600 mg/m² twice daily mycophenolate mofetil (maximum dose 2 g/day) and 400 mg/m² twice daily mycophenolic sodium (maximum dose 1,440 mg/day).

^cNo dose adjustment is required in kidney recipients with hepatic parenchymal dysfunction or delayed graft function. Dose should be limited to maximum 2 g/day in patients with severe kidney impairment (glomerular filtration rate less than 25 mL/1.73 m²).

^dSubjects developing neutropenia (absolute neutrophil count less than 1,300/mm³) should have their mycophenolate regimen assessed. Dose reduction or temporary withdrawal may be needed.

TABLE 11-5. DOSING RECOMMENDATIONS FOR AZATHIOPRINE^{10,11}

Dosage Form	Loading Dose ^{a-d}	Maintenance Dose ^{b-f}
Oral or IV	For kidney: 3–5 mg/kg/day	1–3 mg/kg/day

^aPatients should be switched from IV to oral dosing as soon as possible. Azathioprine is usually administered as a single daily dose.

^bThe manufacturer does not provide dosage adjustment guidelines for hepatic and renal impairment.

^cNo pediatric dosing guidance available.

^dPatients concurrently administered allopurinol should have azathioprine dose reduced (up to ¼) to minimize toxicity. The evidence for routine testing of thiopurine S-methyltransferase activity requires further review, but dose reduction or consideration for the use of alternative agents is needed in patients with low or no activity.

TABLE 11-6. CYCLOSPORINE,^{1,2,3,18} TACROLIMUS,^{4,5} SIROLIMUS,^{6,7} MYCOPHENOLATE,^{8,9} AZATHIOPRINE,^{10,11} AND PREDNISONE^{14,15} DOSAGE FORMS

Drug	Dosage Form	Product
Cyclosporine	IV solution 50 mg/mL (5-mL ampule)	Sandimmune injection; multisource availability
	Oral liquid-filled capsule 25, 50, and 100 mg	Sandimmune; Neoral; Gengraf; multisource availability
	Oral solution 100 mg/mL	Sandimmune; Neoral; multisource availability
Tacrolimus	IV solution 5 mg/mL (1-mL ampule)	Prograf
	Oral capsules 0.5, 1, and 5 mg	Prograf; multisource availability
	Extended-release capsules 0.5, 1, and 5 mg	Astagraf XL
Sirolimus	Oral tablets 0.5, 1, and 2 mg	Rapamune
	Oral solution 1 mg/mL	Rapamune

Mycophenolate	Oral capsules/tablets	CellCept; Myfortic; multisource availability
	250 mg (cap)	
	500 mg (tab)	
	180, 360 mg (Myfortic)	
	Oral suspension	CellCept, multisource availability
	200 mg/mL (160 mL)	
	IV	CellCept
	500-mg vial	
Azathioprine	Oral tablets	Azasan, Imuran, multisource availability
	50, 75, and 100 mg	
Prednisone	Oral solution	Multisource availability
	5 mg/mL	
	Oral tablets	Multisource
	1, 2.5, 5, 10, 20, and 50 mg	

GENERAL PHARMACOKINETIC INFORMATION

Absorption¹⁹

Drug-food, drug-herb, or drug-drug interactions may impact the absorption of antirejection agents. The activity of P-glycoprotein and cytochrome P4503A enzymes, respectively, affect the transport and metabolism of the antirejection agents cyclosporine, tacrolimus, and sirolimus. Mycophenolate's transport and metabolism are affected by activity of multidrug-resistant transporter 2 proteins (ABCC2/MRP2) and uridine diphosphate glucuronosyltransferase (UGT) enzymes, respectively, and azathioprine's metabolism is mediated by TPMT. Genetic and environmental factors may impact all of these transporters and enzymes. Absorption of oral antirejection agents is variable, making therapeutic drug monitoring essential and particularly critical in the first 2 weeks post transplantation. All of the antirejection agents discussed in this chapter should be taken consistently with regard to time and food intake to reduce variability in drug exposure.

Cyclosporine has widely variable pharmacokinetics depending on the formulation (Sandimmune versus Neoral).²⁰⁻²⁴ Oral Sandimmune formulations demonstrate lower bioavailability than oral Neoral formulations and more erratic absorption. This results in Sandimmune's larger intra- and interpatient variability than other forms of cyclosporine. Conversely, absorption of Neoral is more consistent over time, with less inpatient variability. In addition to type of cyclosporine formulation, absorption may be impacted by first-pass metabolism, gastric motility, mode of administration, drug-drug, drug-herb, and drug-food interactions. Time to peak concentration is different with Neoral (1–2 hr) compared to Sandimmune (2–3 hr).

The oral absorption of tacrolimus is variable and incomplete.^{4,5,19} Oral bioavailability ranges from 9% to 43%. Intestinal CYP3A4 metabolism, gastric motility, and P-glycoprotein activity all affect its absorption. Although the manufacturer makes no recommendation for tacrolimus to be taken on an empty stomach, food alters tacrolimus absorption in terms of delayed rate and reduced extent. Unlike cyclosporine, the presence of bile salts does not affect the bioavailability of tacrolimus.

Because high-fat food increases absorption of sirolimus, patients should take the tablets and oral solution in a consistent manner, with or without food.^{6,7,19} Oral bioavailability is approximately 14% for sirolimus oral solution; however, the mean bioavailability of sirolimus tablets increases to approximately 18% for the oral solution in healthy persons; thus, sirolimus oral solution and oral tablets are not bioequivalent, although the 2-mg dose of the two formulations has been shown to result in clinically equivalent outcomes.

Different absorption characteristics and bioavailability of mycophenolate are evident between mycophenolate mofetil (CellCept) and mycophenolate sodium extended release tablets (Myfortic); thus, they are considered non-interchangeable.^{8,9} Mycophenolate mofetil has a shorter time-to-maximum concentration (1–1.5 hr) compared to the extended release Myfortic (2–3 hr). On average, the majority (i.e., > 90%) of orally administered mycophenolate mofetil is absorbed, which then undergoes hydrolysis to form the active moiety. Because lower exposure values of mycophenolate are commonly observed immediately post-transplant, frequent dose adjustments are needed within the first few months post transplant to maintain adequate drug concentrations. Only ~70% of mycophenolic acid from Myfortic is available after absorption. Food is the major determinant of absorption rate. The maximum concentration is reduced (up to 40% is observed when taken with food compared to an empty stomach), but not total exposure to mycophenolic acid.²⁵

Azathioprine^{10,11,26} and prednisone^{14,15} are both well-absorbed with reported bioavailabilities ~50% to 90%. Relatively low azathioprine plasma concentrations (<1 mg/L) are typically obtained with usual doses in humans. Depending on the formulation, the time-to-maximum concentration is obtained between 1–2 hr and 2–6 hr for azathioprine and prednisone, respectively. Unlike the other immunosuppressants discussed above, the effects of food on the absorption of azathioprine and prednisone are not well characterized, although both drugs can be taken with food to lessen gastrointestinal side effects.

Table 11-7 provides the bioavailability of the various dosage forms of the immunosuppressants discussed in this chapter.

Distribution

Cyclosporine—distributes widely into body fluids and tissues. In solid organ transplant recipients, the cyclosporine volume of distribution at steady state after IV dosing is 3–5 L/kg.¹⁻³ Cyclosporine distributes in a concentration-dependent manner in blood: 41% to 58% in erythrocytes, 4% to 9% in lymphocytes, 5% to 12% in granulocytes, and 33% to 47% in plasma. Cyclosporine crosses the placenta and is detected in breast milk.

Tacrolimus—partitioning of tacrolimus between plasma and whole blood is dependent on hematocrit, tacrolimus concentration, plasma protein concentration, and temperature of the sample.⁴⁻⁵ Tacrolimus crosses the placenta and is detected in breast milk.

TABLE 11-7. THE BIOAVAILABILITY OF DOSAGE FORMS OF CYCLOSPORINE, TACROLIMUS, SIROLIMUS, MYCOPHENOLATE, AZATHIOPRINE, AND PREDNISONE ^{1-11,14, 15-17, 26-28, 29-30}

Dosage Form	Bioavailability Comments
Cyclosporine oral capsules and solution	Variable (mean 30%, range = 10% to 89%) ^a
Tacrolimus oral capsules	Variable (mean 25%, range = 9% to 43%)
Sirolimus oral solution and tablets	14% to 18% ^b
Mycophenolate oral capsules and tablets	70% to 90% (dependent on time post-transplant and formulation) ^c
Azathioprine oral tablets	27% to 83% (6-mercaptopurine)
Prednisone oral tablets or solutions	50% to 90%

^aSandimmune is not bioequivalent to Neoral and cannot be used interchangeably without close supervision.
^bConcomitant administration of cyclosporine promotes sirolimus absorption and increases sirolimus bioavailability.
^cMycophenolate mofetil (CellCept or generics) and enteric-coated mycophenolate sodium (Myfortic) formulations are not interchangeable.

Sirolimus—has a large volume of distribution.^{6, 7,30–31} In human whole blood, sirolimus is extensively distributed into cellular components: red blood cells (95%), plasma (3%), lymphocytes (1%), and granulocytes (1%). Women are advised to use effective contraception before sirolimus initiation, during sirolimus treatment, and for 12 weeks after conclusion of sirolimus treatment because of the risk of teratogenicity. Although trace amounts of sirolimus can be detected in the milk of rats, it is unknown whether sirolimus distributes into human breast milk.

Mycophenolate—distributes predominantly within the plasma, and this characteristic is reflected in its relatively modest volume of distribution.³² Human studies are lacking demonstrating the distribution (or lack thereof) of mycophenolate into breast milk; thus, the use of mycophenolate in breast feeding is not recommended for risk of causing immunosuppression in the baby.

Azathioprine—little information is available on the distribution characteristics in humans because the drug is rapidly bioactivated to 6-mercaptopurine once present in plasma. 6-mercaptopurine is distributed into total body water. Low concentrations of 6-mercaptopurine are found in human breast milk, which has not been associated with signs of immunosuppression in babies.³³ However, the lack of extensive literature on safety and evidence of drug excretion into breast milk suggest that breast feeding is not recommended while on azathioprine therapy.

Prednisone—is bioactivated to form prednisolone. The distribution of prednisolone is dependent on dose due to non-linear plasma protein binding characteristics.^{34–36} Larger doses of prednisone (hence, prednisolone) are associated with increased free fraction and a larger volume of distribution.³⁵ Both prednisone and prednisolone are excreted into breast milk, albeit in low concentrations with little side effects to babies.³⁷ The timing of breast feeding prior to drug administration may minimize exposure of babies.

Table 11-8 provides the volume of distribution information for the immunosuppressants discussed.

TABLE 11-8. VOLUME OF DISTRIBUTION (V)

Drug ^{1–11,14,15,32,34}	V (range or mean ± SD; L/kg unless otherwise specified)
Cyclosporine ^a	3–5
Tacrolimus ^a	0.85–1.94
Sirolimus	12 ± 8
Mycophenolate	3.6–4 (mofetil), 54–112 L (enteric-coated sodium)
Azathioprine	Not documented in humans; total body water volume for 6-mercaptopurine
Prednisone	Dependent on dose; 0.2–0.7 for prednisolone

^aWhole blood.

Protein binding

- Cyclosporine is 90% bound to proteins (primarily lipoproteins), and approximately 50% of the drug in the blood is bound to erythrocytes.^{1–3,16, 27–28,47}
- Tacrolimus is highly bound in the plasma (99%) to albumin and alpha-1-acid glycoprotein.^{4–5}
- Sirolimus is approximately 92% bound to human plasma proteins.^{6–7} Its binding has been shown to be associated primarily with serum albumin.
- Mycophenolate is extensively bound (97% to 99%) to albumin in plasma.^{8–9}
- Azathioprine and its active metabolite, 6-mercaptopurine are not extensively bound (~ 30%) to plasma proteins.^{10–11}
- Prednisone and its active metabolite, prednisolone, are bound to plasma proteins in a concentration-dependent (inverse association) manner (65% to 91%).^{14–15}

Elimination

Metabolism and excretion

Cyclosporine, tacrolimus, and sirolimus are extensively metabolized by the hepatic and gut cytochrome P-4503A enzyme systems (CYP3A) and counter-transported by P-glycoprotein. Patients receiving potent CYP3A and P-glycoprotein inhibitors may require a decreased dose or increased dosing interval. Patients receiving potent CYP3A and P-glycoprotein inducers may require an increased dosage and a reduced dosing interval. Careful monitoring of blood concentrations is warranted with concomitant administration of antirejection agents and CYP3A inhibitors or inducers. Dosing adjustments may be needed in hepatic failure for cyclosporine, tacrolimus, and sirolimus.

Cyclosporine is highly metabolized by hepatic biotransformation into more than 25 metabolites.^{1-3,27-28} Cyclosporine and its metabolites are eliminated principally through the bile, whereas 0.1% is excreted unchanged in the urine. Tacrolimus is extensively metabolized via CYP3A. Hydroxylation and demethylation are primary biotransformation pathways.⁴⁻⁵ Tacrolimus is primarily eliminated in feces, with less than 1% of an IV dose excreted unchanged in the urine. Sirolimus is metabolized by hydroxylation and/or O-demethylation into seven major metabolites.⁶⁻⁷ Its excretion is primarily fecal with 2% excreted in the urine.

Mycophenolate mofetil, azathioprine, and prednisone are all considered inert prodrugs and require bioactivation to produce the pharmacologically active moieties. Mycophenolate mofetil undergoes extensive hydrolysis to mycophenolic acid,³² which is metabolized in the hepatocytes, primarily by the UGT2B7 enzyme to form the inactive glucuronide. Mycophenolate can also be further bioactivated by UGT1A9 to form the minor, but active acyl-glucuronide, which is postulated to cause side effects. The glucuronides are subjected to enterohepatic recirculation, mediated by ABCC2/MRP2.³² In theory, known inhibitors and inducers of these enzymes and transporters can affect the disposition of mycophenolate. The majority of the glucuronides (60% to 87%, depending on the formulation) is excreted in the urine unchanged.

Azathioprine, a prodrug, also undergoes extensive hepatic metabolism, mediated by glutathione S-transferase enzymes, to form 6-mercaptopurine; 6-mercaptopurine is inactivated by xanthine oxidase and TPMT but requires further activation by hypoxanthine guanine phosphoribosyltransferase to form 6-thioguanine-nucleotides, the latter known to mediate azathioprine's pharmacological effects.^{10,11,38} Xanthine oxidase inhibitors such as allopurinol can significantly increase 6-mercaptopurine concentrations, and dosage reduction is indicated when these drugs are administered together. However, unlike the cytochrome P450 and UGT-mediated interactions, little additional data are available supporting clinically relevant, metabolism-associated drug interactions for azathioprine based on these enzyme systems. On the other hand, genetic polymorphisms of these enzymes can theoretically affect the inactivation or bioactivation of azathioprine, and emerging data are supporting pharmacogenomic-type drug-gene interactions.^{38,39} The metabolites are primarily excreted in the urine.

Prednisone is bioactivated by 11 β -hydroxysteroid dehydrogenase to produce the active prednisolone.⁴⁰ Prednisolone is inactivated by hydroxylation (CYP3A4) and glucuronidation to form a myriad of metabolites.⁴¹ A mixture of prednisone, prednisolone, and various unconjugated or conjugated metabolites are excreted primarily in the urine.

Table 11-9 summarizes the clearance values (for subjects without additional intrinsic or extrinsic factors affecting clearance) for the immunosuppressants discussed in this chapter.

TABLE 11-9. CLEARANCE VALUES FOR IMMUNOSUPPRESSANTS

Drug ^{1,42-45}	Clearance
Cyclosporine	0.3–0.4 L/hr/kg in adult kidney or liver transplant patients (higher in pediatric patients)
Tacrolimus	0.04–0.08 L/hr/kg (varies between healthy subjects and transplant type)
Sirolimus	0.18–0.22 L/hr/kg (dependent on dose)
Mycophenolate	10.4–11.6 L/hr
Azathioprine	6-mercaptopurine: 290 ± 154 L/hr/m ²
Prednisone	Prednisolone: 6.7–11.7 L/hr/m ² (dependent on dose)

Half-life and time to steady state

The half-life of cyclosporine varies between products (see **Table 11-10**). Sandimmune's half-life ranges from 10 to 27 hr with an average of approximately 19 hr. Neoral's half-life ranges from 5 to 18 hr with an average of 8.4 hr. The wide variation in half-life may be due to enterohepatic recycling of the drug, drug interactions, and age. Pediatric patients have a shorter half-life, often requiring every 8-hour dosing rather than the usual 12-hour interval.

The elimination half-life of tacrolimus is variable with a mean of 12 hr (range of 4–41 hr).⁴⁶ Due to a long half-life with extensive distribution, dosage changes may take several days to reach steady state.

The observed elimination half-life of sirolimus in stable renal transplant patients on a 14-day regimen including sirolimus, cyclosporine, and prednisone was 62 ± 12 hr.³⁰ Administration of an appropriate loading dose will provide near target steady-state drug concentrations within one day in most patients. Hepatic impairment will increase half-life.

The elimination half-life of mycophenolic acid varies between 8 and 18 hr and can exhibit large interpatient variability, potentially due to its propensity to undergo enterohepatic recirculation.^{8,9,32}

The elimination half-life of 6-mercaptopurine, the active moiety of azathioprine, is approximately 1.5 ± 0.5 hr, but the half-lives of the active metabolites are longer, though less well characterized.¹⁰⁻¹¹

Both prednisone and its active metabolite, prednisolone, have relatively short half-lives (2–4 hr), which are dependent on various extrinsic (e.g., circadian cycle, concurrent interacting drugs) and intrinsic (e.g., pathophysiological states, age, gender) factors.^{14,15,45}

TABLE 11-10. TERMINAL ELIMINATION HALF-LIFE (T_{1/2}) ON ORAL PRODUCTS¹⁻³

Drug	t _{1/2} (mean ± SD or range; hr)
Cyclosporine	19 (10–27)
Tacrolimus ^a	11.3 (3.5–40.5)
Sirolimus ^b	62 ± 16
Mycophenolate	8–18
Azathioprine	1.5 ± 0.5 (6-mercaptopurine)
Prednisone	2–4 (prednisolone)

^aHealthy volunteers.

^bRenal transplant patients.

THERAPEUTIC RANGE

Due to the difficulty of correlating antirejection agent concentrations with the immediate clinical outcome of immunosuppression, many transplant centers have established their own specific guidelines for immunosuppressive regimens.⁴⁷ **Table 11-11** gives approximate therapeutic ranges for cyclosporine, tacrolimus, and sirolimus.

The utility of therapeutic drug monitoring for mycophenolate remains controversial.³² Although a relationship between drug exposure (i.e., area-under-the plasma concentration time curve greater than 30 mg × hr/L) and reduced kidney rejection exists, further studies are required to establish the concentration-effect relationships for adverse events and to further define the therapeutic range in specific transplant populations. As such, despite proponents⁴⁸⁻⁴⁹ and opponents⁵⁰ for conducting therapeutic drug monitoring for mycophenolate, the science remains to be proven (in contrast to the more established evidence for cyclosporine and tacrolimus). On the other hand, therapeutic drug monitoring for azathioprine and prednisone/prednisolone is not usually conducted in current practice, primarily due to their wider therapeutic range.⁵¹

Generally, the approximate desired values for cyclosporine trough concentrations on every 12-hour intervals is 100–400 mcg/L². In solid organ transplantation, patients are maintained at the higher end of the therapeutic range initially, and then the desired concentration is often lowered over time to minimize nephrotoxicity and over-immunosuppression. Patients at high risk for rejection may have better outcomes with higher trough blood concentrations.

TABLE 11-11. SUGGESTED THERAPEUTIC RANGES FOR BLOOD TROUGH MEASUREMENTS

Drug	Range (mcg/L)
Cyclosporine	100–400
Tacrolimus	5–20
Sirolimus	5–15

Several different assays for measuring drug concentrations including high performance liquid chromatography coupled with mass spectrometry, fluorescence polarization immunoassay, and monoclonal radioimmunoassays are available.^{52,53} The immunoassays are less specific for the parent drug and, therefore, their therapeutic ranges are higher.

The therapeutic range for a tacrolimus trough concentration is 5–20 mcg/L as measured in whole blood.^{29,54,56} Most transplant centers strive to maintain concentrations at the higher end of this range during the initial period after transplantation (<3 months). After that time, most patients have successful outcomes and avoid toxicity with trough concentrations at the lower end of this range.⁵⁵

Tacrolimus concentrations can be measured in plasma (processed at 37°C) or whole blood. Whole blood concentrations are generally 10–30 times higher than the corresponding plasma concentrations.⁵⁶ A consensus conference recommended whole blood as the preferred method of tacrolimus monitoring because it requires less laboratory time and a less sensitive assay due to higher concentrations.⁵⁴

When used with cyclosporine and corticosteroids, a sirolimus whole blood trough concentration range of 5–15 mcg/L has been associated with prevention of acute rejection and adverse effects;³⁰ however, various transplant centers may have developed their own specific guidelines.

THERAPEUTIC MONITORING

Suggested sampling times

Therapeutic efficacy and toxicity have been associated with cyclosporine, tacrolimus, and sirolimus trough concentrations. More frequent monitoring should be performed in patients who are likely to demonstrate altered pharmacokinetic parameters. These patients include those who are hepatically impaired, children, African Americans, or those with concomitant use of potent CYP3A inducers or inhibitors. Therapeutic drug monitoring should be performed more frequently in the early post-transplantation period and less frequently in stable transplant recipients.

Therapeutic efficacy for cyclosporine has been established according to trough concentrations.^{1-3,27,28,57,58} Sampling times should be consistent and are usually obtained at hour 12 after a dose (trough). To document acceptable steady state values, cyclosporine blood concentrations should be assessed 3–5 days after initiation of therapy, a dosage adjustment, or initiation or discontinuation of known CYP3A inducers or inhibitors. Some centers monitor the 2-hour post cyclosporine dose concentration (C2) for kidney transplant patients or area under the curve with limited sampling strategies calculated from two or more time points past the dose (for various transplant types) to establish therapeutic efficacy and toxicity.

Therapeutic efficacy and toxicity for tacrolimus have been established according to trough concentrations.⁴⁶ Sampling should be obtained at hour 12 after a dose (trough). Tacrolimus trough concentrations should be assessed 3–5 days after initiation of therapy, after a dosage adjustment, or after initiation or discontinuation of known CYP3A inducers or inhibitors.

Therapeutic efficacy has been established for sirolimus according to trough concentrations.^{6,7} Sampling times should be consistent and obtained just before the daily dose (trough). The first sirolimus trough concentration should be checked at least 3–4 days after the loading dose. Sirolimus dose adjustments based on concentrations measured before reaching steady state may result in underdosing or overdosing due to the drug's long half-life. After maintenance dose adjustment, patients should remain on the new maintenance dose for 7–14 days before adjusting the dose based on trough concentrations.

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

The establishment of concentration-efficacy (rejection) relationships for cyclosporine,⁵⁹⁻⁶² tacrolimus,^{55,63,64} sirolimus,^{6,7,30} mycophenolate,³² azathioprine, and prednisone⁵¹ is difficult for many reasons. There is a lack of direct evidence of a correlation between specific trough concentrations and efficacy; however, higher blood concentrations result in greater immunosuppression and increased side effects. Long-term therapeutic goals include prevention of graft rejection, graft survival, and patient survival. Many transplant centers use retrospective analyses to determine appropriate concentration-related efficacy parameters at their centers.

Concentration-related toxicity

Cyclosporine—demonstrates many concentration-related toxicities.^{28,62} The most common are hypertension, nephrotoxicity and neurotoxicity, and these usually respond to dosage reductions. Other toxicities include dermatologic, hepatic, gastrointestinal, and hematological effects. Most of these effects resolve with dose reduction or discontinuation.

Tacrolimus—most toxicities are dose- and concentration-dependent and include nephrotoxicity and neurotoxicity.^{4,5}

Sirolimus—demonstrates dose and concentration-related toxicities including nephrotoxicity, elevations in triglycerides and cholesterol, and decreases in platelets and hemoglobin.^{6,7}

Mycophenolate—exhibits dose-dependent toxicity, with the most common being gastrointestinal (pain, nausea, diarrhea), hepatic (elevated liver function tests), and renal (elevated serum creatinine). Some individuals intolerant to gastrointestinal side effects of mycophenolate mofetil may find relief with the enteric-coated mycophenolate sodium formulation (Myfortic).^{8,9}

Azathioprine—has been associated with dose-dependent liver abnormalities (both cholestatic and hepatocellular), most likely within the first 6 months post-transplant, and gastrointestinal side effects (nausea, vomiting, diarrhea). Dividing doses or administering azathioprine with food can alleviate the latter.^{10,11}

Prednisone (and corticosteroids in general)—have myriad adverse effects, the majority of which are dose-dependent. Common side effects include emotional changes, hypertension, various endocrine abnormalities (diabetes, pituitary suppression, fluid retention), gastrointestinal side effects (gastric ulcer), and electrolyte abnormalities. Prolonged usage at high doses is not recommended and most centers have tapering and stress dosing schedules to minimize steroid exposure.^{14,15}

Table 11-12 lists the common toxicities for the immunosuppressants discussed in this chapter.

Non-concentration-related toxicity

Cyclosporine, tacrolimus, sirolimus, mycophenolate, and azathioprine are associated with development of malignancies, post-transplant lymphoproliferative disorders, and latent virus reactivation.

Cyclosporine—the IV formulation is associated with sensitivity reactions due to the solubilizing agent Cremophor EL. IV cyclosporine should be used only when oral therapy is not possible.

IV tacrolimus—there is an increased risk of anaphylaxis as well as cardiac arrhythmias due to castor oil derivatives in the formulation.^{4,5,29} IV tacrolimus should be used only when oral therapy is not possible. Patients should be closely monitored for the first 30 min and frequently thereafter during the tacrolimus IV infusion. Epinephrine and oxygen should be at the bedside in case anaphylaxis occurs. Additional toxicities include myocardial hypertrophy and post-transplant diabetes mellitus.

Sirolimus—hypersensitivity reactions may occur including anaphylaxis, exfoliative dermatitis, angioedema, and hypersensitivity vasculitis.^{6,7} Additional toxicities include interstitial lung disease, peripheral edema, abdominal pain, and arthralgia.

Mycophenolate—administration can be associated with neutropenia (incidence < 4% in various transplant types), which commonly occurs within the first 1.5 yr post transplant.^{8,9} Absolute neutrophil counts and complete blood counts are needed regularly during the first post-transplant year after mycophenolate is initiated. Further research is needed to elucidate the mechanisms of mycophenolate-associated neutropenia.

Azathioprine—use can be associated with bone marrow suppression, an effect that may be correlated with the activity of TPMT or in individuals receiving xanthine oxidase inhibitors (e.g., allopurinol). Dose reduction is needed in patients with reduced TPMT activity, while drug discontinuation is recommended in those with no activity.^{10,11}

Prednisone—use may be associated with rare, idiosyncratic corticosteroid allergy that may be manifested by anaphylaxis, dermatitis, and asthmatic reactions.^{14,15}

TABLE 11-12. COMMON TOXICITIES AND MONITORING APPROACHES FOR CYCLOSPORINE (C), TACROLIMUS (T), SIROLIMUS (S), MYCOPHENOLATE (M), AZATHIOPRINE (A), AND PREDNISONE (P)

Adverse Effect	Monitoring Parameter
Bone marrow suppression (C/T/S/M/A/P)	Red and white blood cells, platelets
Delayed wound healing (S/A/P)	Impaired healing and dehiscence
Dermatologic (C/T/M/P)	Pruritus, rash, acne, dry skin, alopecia
Electrolyte abnormalities (C/T/P)	Potassium, magnesium, phosphate, uric acid, bicarbonate concentrations
Gastrointestinal (C/T/M/A/P)	Diarrhea, nausea, vomiting, constipation, anorexia
Gingival hyperplasia (C)	Routine checks of gums routinely
Hepatotoxicity (C/T/S/M/A/P)	Bilirubin and liver function tests
Hirsutism (C)	Evaluate for hair growth
Hyperlipidemia (C/T/S/P)	Serum cholesterol and triglycerides
Hypertension (C/T/P)	Blood pressure
Infections (C/T/S/M/A/P)	White blood cell count, temperature
Malignancy/lymphoma (C/T/S/M/A)	Routine checks for development of malignancy
Nephrotoxicity (C/S/T/M)	Serum creatinine, blood urea nitrogen, urine output, biopsy, proteinuria, cyclosporine or tacrolimus trough concentrations, concomitant nephrotoxic drugs
Neurotoxicity (C/T/M)	Tremors, seizures, headache, altered mental status and motor function, psychiatric changes, encephalopathy, parasthesia, insomnia
Post-transplant diabetes mellitus (C/T/P)	Blood glucose, frequent urination, frequent hunger or thirst

DRUG-DRUG INTERACTIONS

Due to their CYP3A hepatic/intestinal metabolism and/or P-glycoprotein gastrointestinal transport characteristics, other agents may alter disposition of cyclosporine, tacrolimus, sirolimus, and prednisolone. P-glycoprotein, a membrane-bound protein that acts as an active transport drug efflux pump, is found in many tissues including those of the intestinal lumen. Drugs, herbal supplements, and foods that affect CYP3A and P-glycoprotein have the potential to significantly interact with these drugs resulting in subtherapeutic immunosuppressant concentrations leading to graft failure or supratherapeutic concentrations leading to concentration-dependent toxicities.⁶⁵ Cyclosporine and tacrolimus are both inhibitors and substrates of CYP3A and P-glycoprotein. Sirolimus is a substrate for both CYP3A and P-glycoprotein. Prednisolone (the active metabolite of prednisone) is a substrate of CYP3A4.

Mycophenolate, on the other hand, is primarily metabolized by UGT enzymes; thus, molecular drug interactions mediated by concurrent drugs that modulate the UGT pathway are theoretically possible, although few have been documented in the literature. Food (high-fat diet) is known to significantly decrease the maximum concentration (but not exposure) of mycophenolate; thus, it is recommended that the timing of administration with respect to food intake is consistent.⁸⁻⁹ For azathioprine, few metabolism-mediated drug-drug interactions have been documented in the literature; however, the effects of xanthine oxidase inhibitors (e.g., allopurinol) on the elevation of 6-mercaptopurine concentrations and the subsequent hematologic toxicity is well known.^{10,11} It is recommended that the dose of azathioprine is reduced (by up to ¼ of typical dosing) when allopurinol is co-administered, and patients are monitored closely for any signs of myelosuppression.

In general, any co-administered immunosuppressant can potentiate the immunosuppression effects of other antirejection agents. Patients taking cyclosporine and tacrolimus concomitantly with HMG-CoA reductase inhibitors (statins) including lovastatin, atorvastatin, simvastatin, pravastatin, and fluvastatin should be monitored closely for signs of myopathy or rhabdomyolysis. If signs and symptoms of myopathy occur, statin therapy should be temporarily withheld or discontinued.^{1,3} Like many drugs, immunosuppressant drug absorption is reduced when co-administered with aluminum- or magnesium-hydroxide containing antacids; therefore, separating aluminum/magnesium hydroxide antacid doses is recommended.⁴⁶ There is the possibility of reduced immune response after vaccination. Attenuated live vaccines (e.g., measles/mumps/rubella, oral polio, Bacillus Calmette–Guérin [BCG], yellow fever, typhoid) should be avoided during treatment with antirejection agents.^{1,11} Severe hyperkalemia may result from concomitant use of cyclosporine or tacrolimus with potassium-sparing diuretics or potassium supplements.^{1,3}

Cyclosporine blood concentrations decrease when it is administered concomitantly with orlistat due to reduced absorption.^{1,3} Cyclosporine may decrease clearance of colchicine, digoxin, statins, and prednisolone resulting in toxicity of those drugs.^{1,3} Cyclosporine increases sirolimus blood concentrations; therefore, if used together, sirolimus should be administered 4 hr after cyclosporine.^{1,3}

Tacrolimus and mycophenolate mofetil co-administration results in higher mycophenolic acid exposure than cyclosporine and mycophenolate mofetil co-administration.^{4,5}

Sirolimus can be coadministered with acyclovir, atorvastatin, digoxin, glyburide, nifedipine, norgestrel/ethinyl estradiol, prednisolone, and sulfamethoxazole/trimethoprim without dosage adjustments.^{6,7}

Mycophenolate's pharmacological effects may be enhanced by acyclovir or probenecid, and reduced by antacids/cholestyramine resin (due to decreased absorption), cyclosporine, proton pump inhibitors, metronidazole, penicillin, quinolone antibiotics (by disrupting enterohepatic recirculation), and rifampin (secondary to UGT enzyme induction). Mycophenolate can decrease the effectiveness of oral contraceptives (both estrogen and progestin) and increase the concentration of ganciclovir.^{8,9}

Due to prednisone's adverse effects on the endocrine system (e.g., diabetes), it can diminish the effects of antidiabetic drugs. Prednisone's effects on fluid and electrolyte imbalance can also potentiate potassium/sodium wasting from diuretics.^{14,15} The various potential metabolic interactions mediated by corticosteroids should be considered while initiating or withdrawing prednisone from therapy.⁶⁶

Table 11-13 lists the common drug interactions for the immunosuppression drugs discussed in this chapter.

DRUG–GENE INTERACTIONS

The science on the pharmacogenomics of antirejection drugs is still evolving. Several target genes have been identified in the literature (**Table 11-14**), which may have clinically relevant impacts on the pharmacokinetics or pharmacodynamics of antirejection drugs. The clinical impact of some of these polymorphisms in the genes, however, still requires further validation to support routine genetic testing in transplant patients. Polymorphisms that decrease the activity of genes listed in Table 11-14 have been associated with adverse outcomes.

TABLE 11-13. DRUG INTERACTIONS WITH CYCLOSPORINE (C), TACROLIMUS (T), SIROLIMUS (S), MYCOPHENOLATE (M), AZATHIOPRINE (A), AND PREDNISONE (P)^a

Potentiate Renal Dysfunction	Decrease CL ^b	Increase CL ^c
ACE ^d inhibitors (C/T)	Allopurinol (A/C)	Anticonvulsants ^f (C/T/S/P)
Aminoglycosides (C/T)	Aluminum/Mag Hydroxide (T)	Caspofungin (T)
Amphotericin B (lipid also) (C/T)	Amiodarone (C/P)	Nafcillin (C)
Cimetidine (C)	Antibiotics ^g (C/T/S)	Octreotide (C)
Ciprofloxacin (C)	5-aminosalicylic acid (A)	Rifabutin (T/S)
Cisplatin (T)	Antifungals ^g (C/T/S)	Rifampin (C/T/S/M/P)
Cotrimoxazole (SMX–TMP) (C)	Aprepitant (P)	Rifapentine (S)
Cyclosporine (T)	Boceprevir (P)	Sirolimus (T)
Fibric acid derivatives (C)	Bromocriptine (C/T/S)	St. John's Wort (C/T/S/P)
Ganciclovir (C/T)	Ca channel blockers ^h (C/T/S)	Terbinafine (C)
Ketoconazole (C)	Chloramphenicol (T)	
Melphalan (C)	Cimetidine (T/S)	
Non-steroidal anti-inflammatory drugs (NSAIDs) (C/T)	Colchicine (C)	
Tacrolimus (C)	Cyclosporine ⁱ (T/S/P)	
Vancomycin (C)	Danazol (C/T/S)	
	Febuxostat (A)	
	Grapefruit juice (C/T/S/P)	
	Imatinib (C)	
	Oral contraceptives (C/T)	
	Methylprednisolone (C/T)	
	Metoclopramide (C/T/S)	
	Nefazadone (T)	
	Protease inhibitors ⁱ (T/S)	
	Proton pump inhibitors (T)	
	Quinupristin/dalfopristin (C)	
	Ritonavir (P)	

C = reported for cyclosporine, T = reported for tacrolimus, S = reported for sirolimus, M = reported for mycophenolate, A = azathioprine, P = prednisone.

^aAlthough not all interactions are reported for each agent, there is a possibility that some occur in the other agents as well. Some interactions are well documented, while others “may” occur.

^bEnzyme inhibitors that decrease antirejection drug metabolism in liver and/or gut.

^cHepatic and/or gut enzyme inducers that increase antirejection drug metabolism in liver and/or gut.

^dAngiotensin converting enzyme inhibitors.

^eAntibiotics: clarithromycin, erythromycin, telithromycin, and troleandomycin.

^fAnticonvulsants: carbamazepine, phenobarbital, phenytoin.

^gAntifungals: fluconazole, voriconazole, itraconazole, clotrimazole, and ketoconazole.

^hCalcium channel blockers: diltiazem, nifedipine, nifedipine, and verapamil.

ⁱProtease inhibitors: indinavir, nelfinavir, ritonavir, and saquinavir.

^jConcomitant administration of cyclosporine and sirolimus results in elevated sirolimus blood concentrations; therefore, it is recommended that the daily sirolimus dose be taken 4 hr after administration of cyclosporine.

TABLE 11-14. GENES PROPOSED TO AFFECT THE PHARMACOKINETICS AND PHARMACODYNAMICS OF DRUGS⁶⁷⁻⁷³

Drug	Affected Genes	Proposed Effects
Cyclosporine	P-glycoprotein	Increased toxicity
Tacrolimus	CYP3A4*22 and CYP3A5*3	Increased concentration
Sirolimus	CYP3A5*3	Increased concentration
Mycophenolate	UGT1A9*3	Increased concentration
	UGT2B7*2	Increased concentration
Azathioprine	TPMT (various polymorphisms)	Myelosuppression

MOLECULAR WEIGHTS FOR UNIT CONVERSIONS

To facilitate the conversions between the international units of measure, molecular weights for the immunosuppressants discussed in this chapter are presented in **Table 11-15** for quick reference. To convert from weights (e.g., mg) to molecular units (e.g., moles), divide the chemical weight by the molecular weights listed below.⁷⁴

TABLE 11-15. MOLECULAR WEIGHTS

Drug	Molecular Weight (g/mole)
Cyclosporine	1,202
Tacrolimus	804
Sirolimus	914
Mycophenolate	321
Azathioprine	277
Prednisone	358

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CARBAMAZEPINE

Jacquelyn L. Bainbridge, Pei Shieen Wong, and Felecia M. Hart

The Food and Drug Administration (FDA) approved carbamazepine for the treatment of partial seizures with complex symptomology, generalized tonic-clonic seizures, and mixed seizure patterns in adults and children. It is also approved for the treatment of trigeminal and glossopharyngeal neuralgia in adults and may be useful in the treatment of other types of neuropathy. The extended-release formulation is approved for the treatment of bipolar I disorder in adults. Originally, carbamazepine was marketed for the treatment of trigeminal neuralgia and was later found to be effective for the treatment of seizures.¹ It is ineffective in absence or myoclonic seizures and can worsen or precipitate absence seizures.² Target concentrations (4–12 mg/L) have been evaluated only for the treatment of seizures, although this range has also been suggested for other conditions.

USUAL DOSAGE RANGE IN THE ABSENCE OF CLEARANCE-ALTERING FACTORS

Carbamazepine is unique in that it induces its own metabolism (autoinduction), which complicates dosing. Autoinduction takes approximately 3–5 weeks on a fixed dosing regimen.

Generally, doses are started at one-fourth to one-third of the expected maintenance dose and gradually increased to allow for development of tolerance to side effects, especially central nervous system (CNS)-related side effects. For adults (age ≥ 15 yr), dosing may be initiated with 400 mg/day in divided doses and increased by 200 mg daily at weekly intervals, up to 1,600 mg/day. For children age 12–15 yr, the initial dosing is the same as for adults, although the maximum recommended dose is 1,000 mg/day. For patients 6–12 yr of age, the initial starting dose is 200 mg/day (100 mg twice daily), which can then be increased by 100 mg daily at weekly intervals up to 1,000 mg/day. For patients less than 6 yr of age, the initial dose is 10–20 mg/kg/day, given in three to four divided doses, and may be increased at weekly intervals up to 35 mg/kg/day. Children less than 12 yr old may be converted to extended-release preparations if they receive 400 mg/day or more. The same total daily dose is used and given in two equally divided doses. Older adult patients may be started at 100–200 mg daily and increased in weekly intervals by 100 mg daily up to 1,000 mg/day.³ **Table 12-1** summarizes the initial and maximum daily dosing recommendations for carbamazepine.

The dose is titrated based on the patient's clinical response and tolerability of side effects,⁴ especially CNS side effects.⁵ Methods for rapid loading in critically ill patients using carbamazepine suspension and tablets have been described.^{6–8} One rapid switch-over technique using the pharmacokinetics derived from a single 10 mg/kg dose has been used to convert patients from other antiepileptic drugs (AEDs) to carbamazepine.⁸ Using this approach, the conversion to carbamazepine with the removal of other AEDs was achieved in 6 days, with no adverse effects.

Because the metabolism of carbamazepine is subject to enzyme induction and inhibition, the maintenance dosage will depend in part on the presence or absence of other drugs that may induce or inhibit hepatic enzymes (see Drug–Drug Interactions section).

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TABLE 12-1. INITIAL AND MAXIMUM MAINTENANCE DOSING AND DOSAGE FORMS

Dosage Form and Age Groups	Initial Dose	Maximum Maintenance Doses
Intravenous (IV) ^a		
Oral (tablets or suspension)—slow titration indicated		
Children <6 yr	10–20 mg/kg/day	35 mg/kg/day
Children 6–12 yr	100 mg twice daily	1,000 mg/day
Children 12–15 yr	200 mg twice daily	1,000 mg/day
Adults >15 yr	200 mg twice daily	1,600 mg/day
Older adult	100 mg once or twice daily	1,000 mg/day
Rapid loading for critically ill patients ^b		
Children (≤12 yr)	10 mg/kg	
Children (>12 yr) and adults	8 mg/kg	

^aRecently approved for use when oral therapy not an option. The total daily dose should be 70% of the total daily oral dose, divided equally into four separate 30-min infusions given every 6 hr.

^bThis rapid loading procedure should result in peak concentrations of ~10 mg/L. A maintenance dose should be started 6–8 hr after the loading dose.

There is significant intersubject variability in the pharmacokinetics of carbamazepine, which can impact the frequency of daily dosing. Some patients may be dosed twice a day, while others may require dosing as often as four times a day with immediate-release tablets. The dosage form can also affect the frequency of daily dosing. Controlled- and sustained-release dosage forms are designed for every 12-hr dosing, while the suspension is usually administered four times daily. Because bioavailability is fairly uniform, no matter which formulation is used, the total daily dose is the same. **Table 12-2** summarizes the available dosage forms of carbamazepine products.

There has been much discussion regarding whether generic versions of carbamazepine are truly equivalent to the brand name products. Although there are numerous case reports of patients experiencing break-through seizures or side effects after a switch from one formulation to another, controlled trials have demonstrated bioequivalency of the generic formulations compared to the brand formulation. The argument against generic products is that there is a potential that clinically important variations might occur with frequent switches of immediate-release dosage forms. Also, individual patients may have a narrow therapeutic range for seizure control and incidence of side effects. Therefore, it is prudent to initiate patients on one formulation (brand or generic) and maintain them on that formulation unless they are converted to a sustained- or controlled-release dosage form.

TABLE 12-2. DOSAGE FORM AVAILABILITY

Dosage Form	Product
IV	Carnexiv (approved by FDA October 2016)
Oral immediate-release tablets:	
100 mg chewable	Tegretol, carbamazepine (multiple sources)
200 mg	Tegretol, Eptol, carbamazepine (multiple sources)
Oral suspension: 100 mg/5 mL	Tegretol, carbamazepine (multiple sources)
Extended-release tablets:	
100, 200, and 400 mg	Tegretol-XR
Extended-release capsules ^a	
100, 200, and 300 mg	Carbatrol, Equetro, carbamazepine (multiple sources)
Rectal enema	Use suspension diluted 1:1 with water

^aMay be used as a sprinkle.

GENERAL PHARMACOKINETIC INFORMATION

Absorption

The oral bioavailability of all formulations is considered equivalent; however, the rate of absorption can vary between formulations. The manufacturer of the recently approved IV formulation of carbamazepine has compared oral bioavailability to the IV formulation and has determined the absolute bioavailability cannot be determined. However, the manufacturer of the IV formulation that is currently in development has compared oral bioavailability to the IV formulation and has determined that when administered intravenously, 70% of the oral total daily dose is required to maintain a similar plasma concentration as the oral formulations if the IV formulation is given four times daily.⁹ The gastrointestinal (GI) absorption of immediate-release carbamazepine is slow, erratic, and unpredictable, due to carbamazepine's slow rate of dissolution and/or anticholinergic properties.¹⁰ Secondary peaks in drug concentration may occur due to a slow but constant rate of absorption and absorption occurring in the upper and lower intestine.^{10,11} There is no first-pass metabolism. There is significant inter- and intraindividual variability in the absorption rate for immediate-release tablets and circadian variation in the rate of absorption may be observed, with the evening dose absorbed more slowly than a morning dose.¹² **Table 12-3** summarizes the bioavailability of the different formulations of carbamazepine.

Concurrent administration with food affects the rate but not the extent of absorption. Immediate-release tablets, extended-release tablets, and the suspension should be administered with a meal, while the extended-release capsules (Carbatrol) can be taken without regard to food.¹³ Food may increase the rate of carbamazepine absorption from the extended-release tablets. In one report the administration of a single dose of immediate-release carbamazepine with an acidic beverage (cola) resulted in an enhanced rate and extent of carbamazepine absorption.¹⁴

A linear relationship between dose and concentration has been shown at doses between 600 and 1,400 mg/day; however, at higher doses the increases in the steady-state concentration tend to be less than proportional. Carbamazepine may exhibit saturable absorption; doses higher than 20 mg/kg may have reduced bioavailability. Carbamazepine undergoes simultaneous first-order and zero-order absorption with about 35% of the available dose being absorbed at a zero-order rate.¹⁵

Carbatrol is the extended-release capsule formulation that contains immediate-release, intermediate-release, and extended-release beads of carbamazepine. Tegretol-XR, the extended-release tablet, utilizes the osmotic controlled-release oral delivery (OROS) system, which is a matrix system with a semipermeable membrane for drug delivery. These formulations can be given twice a day, preferably at 12-hr intervals. When equivalent daily doses of immediate-release carbamazepine administered every 6 hr were compared with either extended-release carbamazepine capsules or tablets given every 12 hr, they were bioequivalent.^{16,17}

TABLE 12-3. BIOAVAILABILITY OF DOSAGE FORMS

Dosage Form	Bioavailability/Comments
IV	100% ⁹
Immediate-release tablets ^a	85% to 90% ($F = 0.85-0.9$) ^{8,9}
Chewable tablets ^a	85% to 90% ($F = 0.85-0.9$) ^{10,11}
Oral suspension ^a	85% to 90%, ($F = 0.85-0.9$) but at a faster rate compared to immediate-release tablets. ¹⁶
Extended-release capsules and tablets ^a	85% to 90%, ($F = 0.85-0.9$) capsules may provide less variation in the concentration-time curve than extended-release tablets. ^{17,18}
Rectal enema (extemporaneous compounding required)	80% to 100% as compared to immediate-release tablets ($F = 0.7-0.9$) in total amount absorbed but with longer time to peak. ²¹

^aA recent comparison of the IV product in development suggests F may be 0.7 for oral products.⁹

Results from a 5-day study of normal volunteers indicate that Carbatrol is bioequivalent to Tegretol-XR, but there was less variability in the rate of absorption with Carbatrol.¹⁸ Variability in GI transit time may affect the absorption of Tegretol-XR.¹¹

The FDA reported that moisture might decrease the potency of carbamazepine immediate-release tablets by up to one-third or more; therefore, these tablets must be stored in a cool, dry place.^{19,20} Tablets that are continuously exposed to 97% relative humidity at room temperature for 2 weeks become hardened and dissolve poorly.¹⁶

Distribution

Animal studies indicate that carbamazepine distributes rapidly and uniformly to various organs and tissues, achieving higher concentrations in organs of high blood flow (e.g., liver, kidney, and brain).¹⁰ The drug has been detected in the cerebral spinal fluid (CSF), brain, duodenal fluids, bile, and saliva.²¹ The active metabolite, 10,11-epoxide, has also been detected in the CSF. Carbamazepine rapidly crosses the placenta, and accumulates in fetal tissue with higher concentrations in the liver and kidney than the brain and lungs.²¹ The placenta does not participate in the metabolism of carbamazepine.²²

The carbamazepine concentration in breast milk is about 25% to 60% of the concentration in the mother’s plasma.¹⁰ Strong and highly significant correlations between saliva and plasma concentrations have been found over a wide range of carbamazepine concentrations following citric acid stimulation of saliva.²³ The utility of salivary sampling is limited, however, and should be restricted to those occasions when a blood sample cannot be obtained.

The volume of distribution of carbamazepine varies by age.³ Carbamazepine binds to albumin and to alpha-1-acid glycoprotein (AAG).⁵ The concentration of AAG and the free (unbound) fraction of carbamazepine may vary with the presence of inflammation, trauma, concurrent AED therapy, and age (**Table 12-4**).²⁴ Binding is slightly less in neonates than in other age groups,¹⁰ although it has recently been reported that carbamazepine binds to nonglycated albumin, which decreases with age.²⁵ There was a higher free fraction in older adult patients that was attributed to the decrease in nonglycated albumin. The study suggested that this might explain the increased sensitivity to carbamazepine that has been reported in the older adult.

Monitoring of the unbound concentration may be indicated when the patient’s clinical presentation does not coincide with the plasma concentration (e.g., presence of side effects or lack of response).²⁶ However, there is no defined target concentration range for unbound carbamazepine, and unbound concentrations are not routinely measured. Poorly controlled diabetic patients may have an increased unbound fraction of carbamazepine due to a decrease in nonglycosylated albumin concentrations, which may make measurement of unbound concentrations useful in some diabetic patients.²⁷

Elimination

Although carbamazepine does not appear to undergo first-pass metabolism, it is about 99% metabolized by oxidation, hydroxylation, direct conjugation with glucuronic acid, and sulfur conjugation pathways. Oxidation and hydroxylation pathways account for about 65% of its metabolism.²⁸ The most important carbamazepine metabolite is 10, 11-epoxide, which appears to be active and may contribute to the efficacy and toxicity of carbamazepine.^{29,30} The isoenzymes responsible for catalyzing 10, 11-oxidation of carbamazepine in the human liver are CYP3A4, CYP2C8, and CYP1A1. CYP3A4 is the most

TABLE 12-4. VOLUME OF DISTRIBUTION AND PERCENT BOUND TO PROTEIN²⁴

Age Category	Volume (L/kg) ^a	Protein Binding (%)
Neonates	1.5	65–70
Children	1.9	75
Adults (>15 yr)	0.6–2	75

^aBased on actual body weight.

important of the three.³¹ While there is some polymorphic distribution of CYP2C8, it does not seem to have a major effect on the pharmacokinetics of carbamazepine. CYP1A2 and uridine diphosphoglucuronosyltransferase (UGT) are involved in forming the inactive metabolites of carbamazepine.^{32,33}

The 10, 11-epoxide metabolite is further metabolized to a diol by a xenobiotic epoxide hydrolase.³³ Clearance of the 10, 11-epoxide metabolite is higher than that of the parent drug.³⁴ The metabolites and a small percentage of unchanged drug are excreted in the urine (72%) and feces (28%), (with 1% to 3% excreted unchanged).³ Drug interactions may alter the metabolism of the 10, 11-epoxide metabolite without altering the carbamazepine concentration.³⁵

The metabolism of carbamazepine may be altered by other drugs and by itself (autoinduction), with clearance increasing on continued dosing.³⁶ Autoinduction begins 3–5 days after the initiation of therapy and takes 3–5 weeks to complete.^{36,37} The 10, 11-epoxide diol pathway is the pathway primarily affected. Autoinduction occurs with each dosage increase in children and adults.^{37,38} Because of autoinduction, concentrations achieved initially can be expected to fall over time on a fixed dose. This should be considered early in therapy and during dosage titration because a drop in carbamazepine concentration on a fixed dose may reflect autoinduction rather than patient nonadherence. The potential for other drugs to enhance or inhibit the metabolism of carbamazepine makes drug–drug interactions likely and potentially significant.¹

Because the IV form of carbamazepine was only recently approved by the FDA (October 2016), studies that determined clearance for these tables did not use the IV dosage form. Thus, all reported clearance values are relative to bioavailability (CL/F), which was assumed to be nearly complete. **Table 12-5** shows clearance values relative to patient age. Carbamazepine clearance increases with continued dosing and can be altered by enzyme-inducing or inhibiting drugs.³⁹ It decreases with increasing age and as weight increases in children 2–16 yr old.⁴⁰ In children 1–14 yr old, clearance has been shown to increase linearly with total body weight and nonlinearly with age; thus, older children have a lower clearance with respect to total body weight than do younger children.³⁸ One study showed no effect for older patients (age range 66–84), although others have shown that age alters carbamazepine pharmacokinetics.^{41–43} Carbamazepine is metabolized by oxidative metabolism, which decreases with age.⁴⁴ One population pharmacokinetic analysis demonstrated an age-related decrease in CL/F.⁴⁵

Clearance relative to mass has been shown to decrease with increasing body mass. It has also been shown to increase with surface area and dose,⁴⁶ although the relationship of clearance to dose remains controversial.⁴⁷ Carbamazepine concentrations were significantly higher in lean subjects (BMI < 20) than those with a normal body mass index (BMI 20–25); the degree of obesity may affect carbamazepine concentrations.⁴⁸ Weight reduction in one patient did not affect carbamazepine clearance.⁴⁹

A study done in patients aged 6–17 yr to test for the associations of carbamazepine clearance with physical measurements, age, and plasma hormonal levels found urinary clearance of carbamazepine

TABLE 12-5. CLEARANCE BASED ON AGE

Age (yr)	Clearance (L/hr/kg) ^a
Children: initial dosing	
0–3 yr	0.32
4–9 yr	0.19
10–15 yr	0.12
Children (≤15 yr): chronic dosing	0.05–0.4 ^b
Adults (>15 yr)	
Initial dosing	0.01–0.03
Chronic dosing	0.05–0.1

^aClearance relative to bioavailability (CL/F).

^bThough the clearance range includes a lower value than what are reported as the means for initial dosing, it should be assumed that all patients will undergo autoinduction to some degree, with initial clearance lower than the clearance observed after autoinduction is complete.

and its metabolites was proportional to the size of the liver, which was, relative to total body weight, larger compared to adults.⁵⁰

Metabolic changes can occur during pregnancy ultimately affecting the level of drug clearance. In a study evaluating drug concentrations and seizure frequency during pregnancy, there was no significant change in drug clearance, but an increase in free carbamazepine fraction over time was observed from 23% at baseline to 32% in the third trimester. This observed increase did not translate to a change in seizure frequency, indicating the metabolic changes during pregnancy did not affect the overall clearance of carbamazepine.⁵¹

Half-life and time to steady state

The half-life ($t_{1/2}$) of carbamazepine changes with continued dosing and is affected by other drugs. The time to steady state depends on the completion of autoinduction.³⁹ A true half-life is difficult to ascertain from measured concentrations because of the variability of absorption, as it may continue throughout the dosing interval. **Table 12-6** summarizes the half-life and time to steady state. The 10, 11-epoxide metabolite of carbamazepine has a half-life of 25–43 hr with single doses and 6.1 hr with chronic fixed dosing.^{3,52}

DOSING STRATEGIES

The variability in the pharmacokinetics of carbamazepine makes dosage prediction difficult. Statistical models and population methods are generally not clinically useful,^{53,54} although a Bayesian nonlinear method that used three to four data points was shown to be clinically acceptable.⁵⁵ In a study of 829 adult patients with 1,834 concentration measurements, clearance relative to CL/F predictors were developed using NONMEM analysis and the following regression equations resulted for carbamazepine used alone or in combination with several other antiepileptic agents⁴⁵:

- 1. CL/F (L/hr) = [(0.0134 × ABW) + 3.58], where ABW = actual body weight
- 2. If the patient is also receiving phenytoin, the CL/F determined in (1) is multiplied by 1.42.
- 3. If the patient is receiving phenobarbital or felbamate in addition to carbamazepine, the CL/F determined in (1) is multiplied by 1.17.
- 4. If the patient is receiving phenytoin and phenobarbital or felbamate, the CL/F determined in (1) is multiplied by 1.62.
- 5. If the patient is ≥70 yr of age, the CL/F determined in (1 to 4) is multiplied by 0.749.

The predicted clearance values can be used to estimate the post-induction dose of carbamazepine. An additional 50 patients were used to test the predictors developed in the study and the mean prediction error was 0.6 mg/L and the median absolute error 2.4 mg/L.⁴⁵

Tegretol XR should not be crushed or chewed. Patients taking this product should be warned that the casing will be excreted in the feces and will increase in size. Carbatrol capsules may be opened and the contents used as a sprinkle. Both formulations have reduced peak to trough fluctuation and may be associated with fewer of the side effects related to higher peak concentrations. The twice a day dosing of both formulations may also improve patient adherence.

TABLE 12-6. HALF-LIFE AND TIME TO STEADY STATE^{2,3}

Dosing	Half-Life (hr)	Time to Steady State
Single dose	25–65	N/A ^a
Chronic dose	12–17	N/A ^a
Concurrent AED	5–14	N/A ^a

^aTime to steady state is not applicable (N/A) to single doses and, due to autoinduction, is based more realistically not on the half-life but on the time for full autoinduction to occur when dosing chronically (3–5 weeks).

The sustained-release carbamazepine capsules (Carbatrol) may be opened and mixed with a diluent and quickly administered through a feeding tube if the tube is larger than 12 French. In an *ex vivo* study, the contents of the 200- and 300-mg capsules were mixed with 30 mL of either sterile water, D5W, normal saline, or apple juice. The suspension was aspirated into a 60-mL syringe and administered down a 12-French pediatric tube, a 16-French Levine tube, and a 20-French gastrostomy tube. The tubes were flushed with two additional washings of diluent. All fluid coming through the tubes was collected and assayed. Sporadic clogging was noted with the pediatric and Levine tubing when sterile water or D5W was used, but a reproducible recovery was found for all three types of tubing when the fluid was normal saline or apple juice.⁵⁶ The ability to administer the contents of Carbatrol via feeding tubes was evaluated in six children. The contents of one capsule was added to 15 mL of liquid and flushed with 10 mL of water. Four children had 152 of 154 doses administered without difficulty. Two patients had tube occlusions, but these children had a history of frequent tube occlusions.⁵⁷ If this technique is used, the dose should be administered immediately after the suspension is made.

THERAPEUTIC RANGE

The reported therapeutic range of carbamazepine is 4–12 mg/L for the treatment of seizures, and the range for psychiatric disorders and trigeminal neuralgia is assumed to be the same.⁴ The therapeutic range for a given patient must be individually determined with the goal of therapy as cessation of seizures while minimizing side effects.

The 10, 11-epoxide metabolite of carbamazepine is active and may contribute to efficacy as well as toxicity. Drug interactions may increase the concentration of the metabolite without changing the carbamazepine concentration. Ideally both the parent drug and metabolite concentrations should be measured, but an assay for 10, 11-epoxide is not commercially available. Nevertheless, the contribution of this metabolite should be considered when the response to carbamazepine is evaluated.

Patients in the therapeutic range may still show limited response. One study compared the pharmacokinetics of carbamazepine in 16 controlled and 15 uncontrolled adult patients with epilepsy. The uncontrolled patients were taking higher doses of carbamazepine and had higher serum concentrations. There were no pharmacokinetic differences between the two groups. The lack of efficacy in the uncontrolled group was felt to be pharmacodynamic resistance and not related to any pharmacokinetic factor.⁵⁸

THERAPEUTIC MONITORING

Suggested sampling times and effect on therapeutic range

Patients should have baseline measurements that include a complete blood count with platelet count, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, blood urea nitrogen, thyroid function tests, serum sodium and ophthalmic exams. Follow-up measurements, including carbamazepine concentration determinations, can be done at the clinician's judgment, but should be considered when there is a change in therapy, change in seizure status, or when unacceptable side effects occur.

The sampling time for carbamazepine depends on the duration of treatment and whether the clinician is evaluating efficacy or side effects. A blood sample is not needed for carbamazepine concentration determination after the first dose unless a rapid loading dose was given in an emergency situation and the clinician needs to ensure the concentration is appropriate. While concentrations should be determined during dosage titration to evaluate end-points, they may be expected to fall due to autoinduction. Autoinduction must also be considered when doses are changed during chronic therapy. A trough concentration measurement is most appropriate for the evaluation of efficacy and steady state concentrations.

The dose of carbamazepine should be started low and titrated to patient response. The rate of titration will determine the sample collection. If the dose is being increased weekly or every 2 weeks, autoinduction will occur for some time and the concentration will change, even with good adherence. Samples may be obtained during this period to correlate dose with side effects or with seizure control, but sampling will be more meaningful after autoinduction is complete.

Many side effects associated with carbamazepine are concentration related, and each patient has a threshold for the occurrence of side effects.⁵⁹ Therefore, for some patients, the sample may be appropriately obtained when side effects are occurring. Given the variability of absorption from immediate- and controlled-release products, it is difficult to predict when the peak carbamazepine concentration will occur.

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

The effectiveness of carbamazepine as an AED is associated with concentrations of 4–12 mg/L.⁴ This range is intended as a guide—not as an absolute—because of the variable amount of free drug, the contribution of the 10, 11-epoxide metabolite, and the intersubject variability in response. The patient response and occurrence of side effects should determine the target concentration for a patient. A concentration should be obtained and documented along with the dose and concomitant drugs when the patient is doing well in terms of seizure management and side effects. This provides patients and providers with additional information when evaluating concentrations in the future..

Concentration-related toxicity

A concentration >15 mg/L is associated with a higher frequency of adverse effects. Symptoms of toxicity include dizziness, ataxia, drowsiness, nausea, vomiting, tremor, agitation, nystagmus, urinary retention, headache, blurred vision, diplopia, dysrhythmias, coma, seizures, twitches, respiratory disorders, and neuromuscular disturbances.^{2,3,19} Patients on monotherapy have fewer side effects and tolerate higher concentrations of carbamazepine than do patients on polytherapy.⁶⁰ The occurrence of side effects can be reduced or minimized by slow titration, decreasing the dose, giving smaller doses more frequently, or switching to a sustained- or controlled-release product. Slow dosage titration allows a patient time to develop tolerance to certain side effects associated with carbamazepine. The use of sustained-release or controlled-release dosage forms reduces the peak to trough fluctuations and may reduce associated side effects. A dose reduction may decrease side effects in some patients without loss of seizure control.

Other possible concentration-related side effects include hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and osteomalacia.⁵ An exact dose and concentration effect for these side effects has not been established, but they occur more frequently at higher doses or after prolonged exposure. Carbamazepine has been associated with atrioventricular block, especially in older women, and it is suggested that electrocardiograms and drug concentrations be carefully monitored in older adult patients.^{61,62} Carbamazepine is associated with skin rash and rarely with a Stevens-Johnson syndrome (SJS) reaction. The mechanism may involve reactive metabolites in the epidermis⁶³ or could be due to genetic variation in the human leucocyte antigen (HLA) complex.⁶⁴ One case of skin rash was associated with an increased concentration of nicotinamide and vitamin B6.⁶⁵ Other case reports of adverse reactions include hearing loss, alopecia, hypogammaglobulinemia, tubulointerstitial nephritis, an auditory disturbance (flat A tone), abnormal pitch perception, and pemphigus.^{66–72}

Idiosyncratic reactions also include bone marrow suppression, aplastic anemia, and agranulocytosis, which are all very rare. Carbamazepine can cause a leukopenia that is not considered dangerous or a harbinger of agranulocytosis or aplastic anemia, so a decrease in the white blood cell (WBC) count is not an automatic requirement for stopping carbamazepine. Many patients taking carbamazepine routinely have low WBCs without being immunosuppressed. Carbamazepine appears to affect the

distribution of neutrophils without affecting their ability to mobilize at the time of infection. Routine monitoring of complete blood counts is not felt to be useful for preventing bone marrow suppression in patients taking carbamazepine.

Carbamazepine overdoses should be managed like overdoses of tricyclic antidepressants (TCAs) that involve general supportive care.⁷³ Hemodialysis should also be considered in cases of severe overdose^{73, 74} with intermittent hemodialysis as the preferred method.⁷⁴

DRUG-DRUG INTERACTIONS

Carbamazepine is an enzyme inducer and enhances the metabolism of many drugs that are metabolized by the cytochrome P450 (CYP) system, including itself. Carbamazepine induces and is metabolized extensively by the isoenzyme CYP3A4, and to a lesser extent CYP1A2, CYP2B6, CYP2E1, CYP2C8, CYP2C9, and UGT 1A4.⁴¹ Therefore, drugs that induce or inhibit these liver microsomal enzymes may affect the metabolism of carbamazepine.⁷⁵⁻⁷⁷ Carbamazepine also undergoes phase 2 metabolism through UGT2B7 substrate to form an *N*-glucuronide metabolite.⁴¹

Drugs that are inhibitors of the CYP3A4 isoenzyme will decrease the clearance of carbamazepine due to decreased metabolism. Carbamazepine is reported to be an inhibitor of CYP2C19 as it can increase concentrations of phenytoin, selegiline, and clomipramine.⁴¹ Valproate is an inhibitor of UGT2B7 and may account for the reduction in transformation of the carbamazepine epoxide metabolite to the *trans*-dihydrodiol metabolite.⁴¹ This results in increases of the epoxide concentration when carbamazepine is administered with valproate. Carbamazepine is a substrate and inhibitor of P-glycoprotein, but significant interactions are not likely to occur at concentrations used clinically.⁴¹

Drugs that are inducers of the CYP450 system, specifically 3A4, will increase the clearance of carbamazepine due to enhanced metabolism. **Tables 12-7** and **12-8** summarize common drug interactions between carbamazepine and other drugs and the expected result.^{16,75-117}

Other types of interactions have been described. When chlorpromazine oral solution is administered with carbamazepine suspension, a rubbery, orange precipitate results.³ The effect on bioavailability of either drug is unknown. Therefore, these drugs should not be administered together in this form. When lithium and carbamazepine are used together, there is an increased risk for neurological effects.^{2,3} Possible serotonin syndrome may result if carbamazepine is administered concurrently with a monoamine oxidase inhibitor (MAOI) inhibitor; therefore, combined therapy is contraindicated.^{2,3} When used with phenytoin, the concentration of phenytoin may increase or decrease. There is a complex interaction with valproic acid, and the results are unpredictable.⁷⁸ Carbamazepine and theophylline induce each other's metabolism resulting in changes in the half-life and plasma concentrations of both drugs.⁷⁹ Concurrent use with alcohol may increase the risk of additive CNS effects such as sedation.

Significant amounts of carbamazepine are lost through adsorption if undiluted suspension is administered through polyvinyl chloride nasogastric feeding tubes. Dilution with an equal volume of diluent and flushing after administration minimizes the carbamazepine loss and maximizes the drug delivery.¹¹⁸ Enteral feedings do not appear to alter the absorption of carbamazepine suspension significantly.¹¹⁹

Pharmacodynamic interactions have been reported between carbamazepine and lamotrigine and between carbamazepine and levetiracetam.¹²⁰⁻¹²² When either lamotrigine or levetiracetam is added to a regimen including carbamazepine, there is an increase in the incidence of CNS side effects. These effects are not associated with an increase in the concentrations of the carbamazepine or the 10, 11-epoxide active metabolite. A dosage reduction of carbamazepine may be necessary when these drugs are added. The composite of lacosamide and a traditional sodium channel blocking drug, such as carbamazepine, may increase the incidence of CNS and GI side effects. If this does occur the dose of the sodium channel blocking drug should be decreased.¹²³

TABLE 12-7. COMMON CARBAMAZEPINE DRUG INTERACTIONS THAT IMPACT CONCENTRATIONS OF THE COADMINISTERED DRUG^{16,75-117}

CBZ Increases Concentration	CBZ Decreases Concentration
Clomipramine	Acetaminophen
Selegiline	Anticoagulants (warfarin, dicumarol)
	Antidepressants (sertraline, citalopram, escitalopram, duloxetine, bupropion, mirtazapine, trazodone, imipramine, amitriptyline, nortriptyline)
	Antiepileptics (ethosuximide, lamotrigine, tiagabine, topiramate, valproate, zonisamide)
	Antifungal agents (fluconazole, itraconazole, ketoconazole)
	Antipsychotics (aripiprazole, clozapine, fluphenazine, haloperidol, olanzapine, risperidone, ziprasidone)
	Benzodiazepines (alprazolam, clonazepam, midazolam)
	β-blockers (e.g., propranolol)
	Corticosteroids (dexamethasone, prednisolone)
	Dihydropyridine calcium-channel blocking agents (felodipine)
	Digoxin
	Doxycycline
	Fentanyl
	Hormonal contraceptives
	Immunosuppressants (cyclosporine, tacrolimus)
	Levothyroxine
	Methadone
	Pancuronium bromide, vecuronium
	Phenytoin
	Primidone
	Protease inhibitors (Indinavir)
	Statins (atorvastatin, lovastatin, simvastatin)
	Tramadol

CBZ = carbamazepine.

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

Children with mixed seizure disorders may have an exacerbation of certain seizure types if carbamazepine therapy is used. Carbamazepine is structurally related to tricyclic compounds so it has mild anticholinergic properties and should be used in caution in patients are sensitive to anticholinergic effects, such as the older adult or those who have increased intraocular pressure. Reports of cardiovascular effects including congestive heart failure, edema, coronary artery disease, arrhythmias, and AV block have been reported.² The older adult may also be at an increased risk for SIADH.

Carbamazepine is extensively metabolized in the liver and, therefore, should be used with caution in patients with liver disease. Because carbamazepine (to a very small degree) and its active metabolite are excreted renally, it should be used with some caution in patients with renal disease. Hemodialysis does not affect the clearance of carbamazepine.¹²⁴

Congestive heart failure that causes gut edema may contribute to variable absorption of the drug. Carbamazepine may cause sodium and water retention, aggravating congestive heart failure. Fever (increased metabolism) and pulmonary disease (decreased metabolism) have been associated with alterations of AED clearance. Changes in protein binding and altered metabolism were believed to be responsible for carbamazepine toxicity in patients following cardiothoracic surgery and myocardial infarction.¹²⁵

TABLE 12-8. COMMON DRUG INTERACTIONS THAT RESULT IN CHANGES IN CARBAMAZEPINE CONCENTRATIONS^{16,75-117}

Drug Increases CBZ Concentration	Drug Decreases CBZ Concentration
Acetazolamide	Antineoplastic agents (cisplatin, doxorubicin)
Antifungal agents (fluconazole, itraconazole, ketoconazole)	Felbamate
Cimetidine	Phenobarbital
Danazol	Rifampin
Felbamate (CBZ-E)	Phenytoin
Fluoxetine (CBZ and CBZ-E)	Primidone
Fluvoxamine	
Grapefruit juice	
Isoniazid	
Macrolide antibiotics (clarithromycin and erythromycin but not azithromycin)	
Nefazodone	
Niacinamide	
Non-dihydropyridine calcium channel blockers (diltiazem, verapamil)	
Omeprazole	
Pomegranate juice	
Propoxyphene, dextropropoxyphene (removed from U.S. market)	
Protease inhibitors (ritonavir, saquinavir)	
Quetiapine	
Valproic acid (CBZ-E)	
CBZ-E = 10,11-epoxide.	

The clearance of AEDs increases during pregnancy, therefore, the carbamazepine concentration should be more closely monitored.¹²⁶ The need for a dose increase should be anticipated. Following delivery, the clearance returns to normal and the dose may be reduced.¹²⁷ Carbamazepine may interfere with some pregnancy tests and, in terms of previously utilized pregnancy categories, is an FDA pregnancy category D medication. However, the benefit of being seizure free may outweigh the risk of fetal abnormalities.

Absorption may be decreased in malnourished patients.¹²⁸ Any alterations in the GI system could potentially affect the absorption of carbamazepine. Serum thyroid levels may be reduced by carbamazepine although the clinical significance of this is unclear.²

Genetic variation in the HLA complex is involved in a wide variety of hypersensitivity reactions to carbamazepine including SJS, toxic epidermal necrosis (TEN), maculopapular eruptions (MPEs), and hypersensitivity syndrome. Patients positive for the HLA-B*15:02 allele have a more than 100-fold increased risk of developing carbamazepine-induced SJS.^{64,129} The patient populations most likely to possess the HLA-B*15:02 allele correlating with the increased risk of SJS/TEN are those from parts of China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan, where a prevalence of 10% to 15% is seen.¹³⁰ Caucasian and Japanese patients positive for the HLA-A*31:01 allele are at greater risk for all hypersensitivity reactions, including SJS, TEN, MPEs, and hypersensitivity syndrome, but patients throughout all ethnic groups positive for the allele have been shown only to be at an increased risk for hypersensitivity syndrome.^{64,129} Currently, the FDA has only made a recommendation suggesting practitioners consider genetic testing for the HLA-B*15:02 allele in at risk populations prior to initiating carbamazepine therapy.¹³⁰ In patients who have already initiated therapy, carbamazepine-induced SJS/TEN risk is highest within the first 3 months of therapy and, in the absence of any sort of hypersensitivity reaction, becomes low risk thereafter.^{129,130}

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DIGOXIN

Robert DiDomenico and Robert L. Page II

In 1785, Sir William Withering published the first accounts of digitalis (dried leaves of the purple foxglove) in cardiovascular medicine.¹ Since that time, digoxin has become well established for use in systolic heart failure (HF) and controlling ventricular response in atrial fibrillation and flutter.^{2,3}

Digoxin's mechanism of action is multifaceted. Historically, digoxin's positive inotropic effects were thought to result primarily from inhibition of the sodium-potassium ATPase pump. This inhibition reduces the transmembrane sodium gradient, which indirectly inhibits the sodium-calcium exchanger and thereby allows calcium to accumulate in myocytes. As intracellular calcium increases, so does the heart's contractile force. Over the past decade, digoxin has also been noted to alter neurohormonal systems, particularly through the autonomic nervous system. These autonomic effects include a vagomimetic action that is responsible for digoxin's sinoatrial and atrioventricular (AV) nodal effects and an increase in baroreceptor sensitization, which enhances afferent inhibitory activity and diminishes sympathetic nervous system and renin-angiotensin system activities.⁴

Unfortunately, digoxin has a fairly narrow therapeutic range and warrants reasonably cautious dosage determination. It should generally be avoided in patients with sinus node disease, second- or third-degree AV block, accessory AV pathways (Wolff-Parkinson-White syndrome), cardiac amyloidosis, and hypertrophic cardiomyopathy.⁵

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

The loading and maintenance dosage ranges shown in **Table 13-1** are based on lean or ideal body weight in patients with normal renal function for their age and on administration of the tablet or elixir form of digoxin.^{6,7}

TABLE 13-1. LOADING AND MAINTENANCE DOSES^{6,7,11}

Dosage Form	Loading Dose ^a	Maintenance Dose ^a
IV		
Premature neonates (<4 wk)	15–25 mcg/kg	5–10 mcg/kg/day ^b
Full-term neonates	20–30 mcg/kg	8–10 mcg/kg/day ^b
Oral (elixir) ^c		
Infants (<2 yr)	38–63 mcg/kg	13–15 mcg/kg/day ^b
Children (2–10 yr)	25–44 mcg/kg	10–13 mcg/kg/day ^b
Children (>10 yr)	10–15 mcg/kg	4–13 mcg/kg/day ^d
Oral (tablets)		
Adults	10–15 mcg/kg ^e	62.5–250 mcg/day ^d

IV = intravenous.

^aBased on ideal body weight (IBW) or lean body weight (LBW).

^bDivided into two doses given every 12 hr for children <10 yr.

^cDoses adjusted according to dosage form bioavailability.

^dAdministered once daily except 62.5 mcg/day dose, which may be given as 125 mcg every other day.

^eThree divided doses.



For adults with normal renal function, the usual approach is administration of a total loading dose of approximately 10 mcg/kg based on ideal body weight, generally 0.75–1.5 mg for most patients.^{8,9} Approximately 50% of the total load is given as the first dose (e.g., 0.5 mg) followed by 25% (e.g., 0.25 mg) administered at 6- to 8-hr intervals orally or IV after the first dose is given. Whether given IV or orally, the digoxin load is usually carried out over 24 hr with three to four divided doses. This approach is based on the onset of digoxin’s effect (and primarily onset of negative side effects that can be averted by holding the remainder of the load if necessary), which is determined by the rate of distribution to the site of action. For an IV dose, 1–4 hr is required to achieve the full effect from the dose while 2–6 hr is required for an oral dose.⁷ Larger loading doses and more aggressive dosing regimens may be required to control the ventricular rate in atrial fibrillation and flutter.^{2,10} In patients with HF, digoxin loading is not recommended.³ Once completed, the load is followed by a daily maintenance dose, typically 0.125–0.25 mg/day.^{6,7,11}

For patients with impaired renal function (creatinine clearance [CrCl] ≤ 20 mL/min), a smaller loading dose (e.g., 0.5 mg), given either IV or orally (two 0.25-mg doses 6 hr apart), may be considered followed by 0.0625–0.125 mg/day.^{6,7,11}

Maintenance doses should be based on the condition being treated, renal function, patient response, and digoxin concentrations. When used for the management of systolic dysfunction in patients with normal sinus rhythm, digoxin is typically not loaded, but rather initiated at a daily maintenance dose of 0.125 mg or 0.25 mg, depending on renal function. This approach decreases the risk of overshooting digoxin concentrations. **Table 13-2** lists proposed maintenance dosages and interval adjustments based on CrCl.

Digoxin is available in a number of different dosage forms, making it convenient to switch forms when necessitated by changing patient condition. Dosage forms are shown in **Table 13-3**.

It is important to note that the bioavailability of digoxin differs among the dosage forms (**Table 13-4**), and when patients are changed from one route of administration or dosage form to another, differences in bioavailability should be considered.

TABLE 13-2. CRCL-BASED MAINTENANCE DOSAGES AND INTERVAL ADJUSTMENTS¹²

CrCl	Percent of Normal Recommended Maintenance Dose	Interval
>50 mL/min	100%	24 hr
10–50 mL/min	25% to 75%	24–36 hr ^a
<10 mL/min	10% to 25%	48 hr

^aThe 36-hr interval is not recommended, because of complicated dosing schedules.

TABLE 13-3. DOSAGE FORM AVAILABILITY⁷

Dosage Form	Product
IV	
0.25 mg/mL	Digoxin injection, Lanoxin injection
0.1 mg/mL	Digoxin pediatric injection, Lanoxin injection pediatric
Oral capsules (liquid filled)	
0.05, 0.1, and 0.2 mg	Lanoxicaps
Oral tablets	
0.125 mg	Digitek
0.0625, 0.125, 0.1875, and 0.25 mg	Lanoxin
Oral elixir	
0.05 mg/mL	Digoxin elixir; Lanoxin elixir pediatric

TABLE 13-4. BIOAVAILABILITY (F) OF DOSAGE FORMS¹³

Dosage Form	Bioavailability
IV	100% (1)
Intramuscular	Not recommended ~80% (0.8)
Oral capsules ^{a,b}	95 ± 13% (0.95)
Oral tablets ^a	75 ± 14% (0.75)
Oral elixir ^a	80 ± 16% (0.8)

^aSeveral agents may decrease absorption and erythromycin and tetracycline can increase it (see Table 13-11). Food may reduce the peak concentration achieved without affecting total absorption.

^bThe dose of oral capsules is 80% of that of tablets, allowing for almost equivalent bioavailable dose between the capsules and tablets.

General pharmacokinetic information

The various pharmacokinetic parameters for digoxin along with comments relative to the parameter are shown in **Tables 13-5 to 13-8**.

In adults with CrCl < 10 mL/min, the V is 4.8 ± 1 L/kg.¹⁵ See the dosing strategies section for estimating the volume of distribution (V) in patients with reduced renal function.

TABLE 13-5. PHARMACOKINETIC PARAMETERS^{7,13}

Parameter	Outcome	Comments
Distribution	Highly distributed to lean organ tissues (e.g., heart, muscle, kidneys, and liver)	Serum to cardiac tissue concentrations approximately 1:70; distribution decreased by co-administration of quinidine and in patients with renal impairment
Excretion (renal unchanged)	50% to 70%	Primarily glomerular filtration with some tubular secretion
Elimination (nonrenal)	30% to 50%	Primarily through biliary and intestinal tracts with some gut flora elimination; small amount through metabolism; digoxin is a substrate for p-glycoprotein (P-gp) and concentrations are impacted by polymorphisms and drugs that alter P-gp (see Table 13-11)
Protein binding	20% to 30%	Reduced during hypoalbuminemia but not clinically significant

TABLE 13-6. CLEARANCE¹⁴

Age	Clearance
Neonates ^a	1.5 ± 0.5 L/hr/m ²
Infants ^a	11.2 ± 0.9 L/hr/m ²
Children ^a (1–12 yr)	8 ± 2.7 L/hr/m ²
Adults	See Dosing Strategies

^aIn patients with normal renal function for age.

TABLE 13-7. VOLUME OF DISTRIBUTION^{14,15,a,b}

Age	Volume ^a (Mean ± SD)
Neonates	10 ± 1 L/kg
Infants	16.3 ± 2.1 L/kg
Children (1–12 yr)	16.1 ± 0.8 L/kg
Adults	6.7 ± 1.4 L/kg ^c

^aWhen patient weight is used in V calculations, IBW is used for patients whose actual weight > IBW.

^bV is decreased in patients with renal impairment (see Dosing Strategies), so a reduced total loading dose should be used.

TABLE 13-8. HALF-LIFE AND TIME TO STEADY STATE^{7,8,14-17,a}

Age	Half-Life (Mean ± SD)	Time to Steady State ^b
Premature neonates (<4 wk)	61 ± 16 hr	225–385 hr
Full-term neonates (<4 wk)	44 ± 13 hr	157–283 hr
Infants (4 wk–1 yr)	18 ± 9 hr	45–135 hr
Children		
>1–<1.5 yr	Not available	Not available
1.5–2.5 yr	36 ± 11 hr	124–232 hr
2.5–<7 yr	37 ± 16 hr	104–267 hr
7–12 yr	Not available ^c	Not available ^c
Adults ^d	36 ± 8 hr	140–220 hr

^aIn patients with normal renal function for age.

^bFive half-lives using ± 1 standard deviation of mean $t_{1/2}$.

^cAlthough not verified, the half-life ($t_{1/2}$) and time to steady state for children 7–12 yr old are probably similar to the values found in adults.

^dIn patients with normal renal function. Half-life is >4 days in anuric patients.

DOSING STRATEGIES

Estimating digoxin clearance in adults

For adults (and children >12 yr of age), several methods based on population pharmacokinetic parameters have been proposed.

Method 1^{18,a,b}

HF ABSENT

$$CL_{\text{dig}} = (1.303 \times CrCl) + 41 \text{ mL/min}$$

HF PRESENT

$$CL_{\text{dig}} = (1.303 \times CrCl) + 20 \text{ mL/min}$$

^aF was assumed to be 0.6 by study authors when calculating clearance.

^b CL_{dig} and CrCl are expressed in units of mL/min.

Method 2^{19,a,b}

HF ABSENT

$$CL_{\text{dig}} = 1.94 \text{ L/hr/m}^2 + (CrCl \times 1.02)$$

HF PRESENT

$$CL_{\text{dig}} = 0.78 \text{ L/hr/m}^2 + (CrCl \times 0.88)$$

^aF was assumed to be 0.6 by study authors when calculating clearance.

^b CL_{dig} and CrCl are expressed in units of L/hr/m². CrCl is converted from mL/min to L/hr/m² by multiplying the CrCl value in mL/min by 0.06 and then dividing by 1.73.

Method 3^{20,21,a,b}

$$CL_{\text{dig}} = 3.1 \text{ L/hr} + (0.0516 \times CrCl)$$

(if concomitant quinidine, multiply by 0.57)

^aF was assumed to be 0.82 by study authors when calculating clearance.

^b CL_{dig} is expressed in units of L/hr, whereas CrCl is in units of mL/min. No conversion of CrCl units is necessary.

Method 1 was developed prior to the identification of the digoxin-quinidine interaction. Because some of the study patients may have been receiving quinidine (and would appear to have lower digoxin clearance), use of these predictors might lead to estimation of lower doses for patients not on quinidine. Method 2 may be a better predictor of digoxin concentrations across all populations.^{19,21}

Method 4^{22,a,b,c}

A predictive performance model based on creatinine clearance values for patients with HF

$$D = C_{ss_{avdesired}} \times [2.22 \times (CrCl + 25.7)]$$

^aD = dose in mcg/day

^bC_{ss} in mcg/L

^cCrCl in mL/min

Method 5^{10,a,b,c}

A predictive performance model based on creatinine clearance values and ideal body weight for patients with HF. The target digoxin concentration for the nomogram is 0.7 mcg/L.

$$D = -2.247 + (0.0244 \times CrCl) + (0.0383 \times IBW)$$

^aDigoxin doses are determined based on D as follows:

If $D \leq 1$, digoxin dose = 0.0625 mg daily;

If $D > 1$ but ≤ 2.5 , digoxin dose = 0.125 mg daily;

If $D > 2.5$, digoxin dose = 0.25 mg daily

^bCrCl in mL/min

^cIBW (ideal body weight) in kg

Alternatively, digoxin dose can be plotted as a function of CrCl and either IBW or gender/height (see **Figure 13-1**).

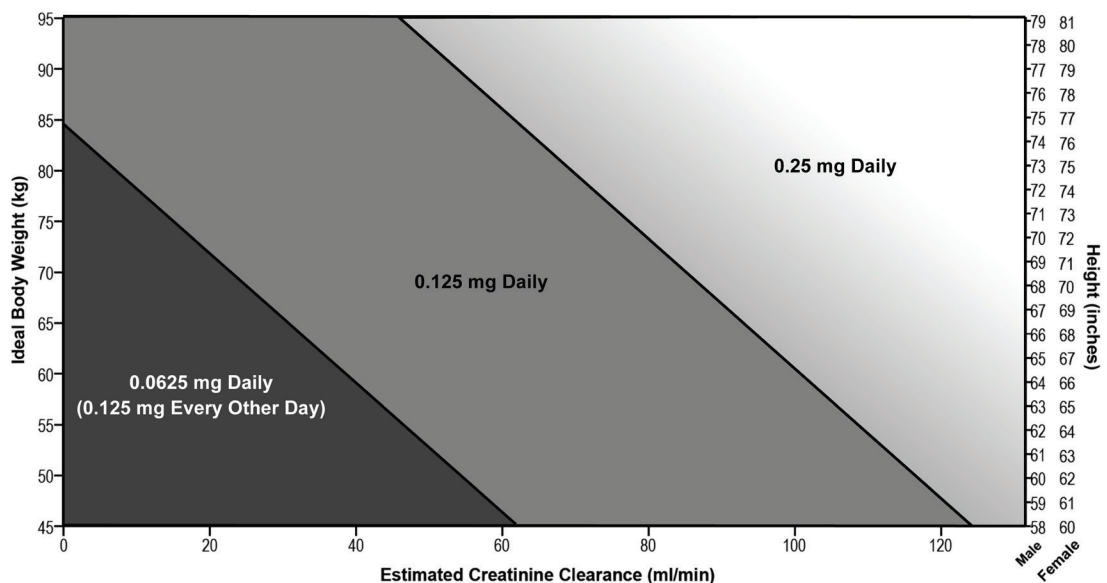


Figure 13-1. Dosing nomogram for digoxin in patients with heart failure.¹¹ To select an appropriate digoxin maintenance dose, plot a patient's CrCl (x-axis) (to convert creatinine clearance to milliliter per second, multiply by 0.01667) and his or her IBW (y-axis). The point at which these lines intersect is the recommended digoxin dose. If ideal body weight has not or cannot be calculated, an appropriate digoxin maintenance dose can be determined by plotting a patient's creatinine clearance (x-axis) and his or her height (z-axis), depending on patient sex. In the 0.25-mg daily area of the nomogram, one may also consider a digoxin maintenance dose of 0.125 mg alternating with 0.25 mg every other day (average daily dose of 0.1875 mg/day), as represented by the gradual shading of this area.

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Estimating V in patients with reduced renal function

The following equations adjust volume of distribution estimates based on renal function.

Method 1²³

$$V(L/1.73\text{ m}^2) = V_{\min} + V_n(CrCl)/(K_d + CrCl)$$

where

$$V_{\min} = 226\text{ L}/1.73\text{ m}^2$$
$$V_n = 298\text{ L}/1.73\text{ m}^2$$
$$K_d = 29.1\text{ mL}/\text{min}/1.73\text{ m}^2$$
$$CrCl\text{ in mL}/\text{min}/1.73\text{ m}^2$$

Method 2²⁰

$$V_{(L)} = [5.05 + (0.0882 \times CrCl)] \times IBW$$

where CrCl is in units of mL/min and IBW is ideal body weight in kg. No unit cancellation is required.

THERAPEUTIC MONITORING

Therapeutic range

The therapeutic range of digoxin (see **Table 13-9**) varies by what is being treated, although the value of serum concentrations as a guide to therapeutic benefit in HF is questionable.^{3,24-27}

Suggested sampling times

Because of digoxin’s long half-life and large volume of distribution, concentrations vary only slightly over a few hours, except during the first 4–6 hr after a dose when initial distribution is slow. Concentrations shortly after an IV dose can be greater than 10 mcg/L and do not reflect pharmacologic response. Therefore, to ensure that drug distribution is complete and to avoid misinterpretation of the reported concentration, no sampling should occur during the first 8–12 hr after a dose.^{28,29} These higher pre-distribution concentrations of digoxin occur with both IV and oral administration (although not as pronounced with oral).

The variation from concentrations just after distribution to the trough concentration before the next dose is usually 30% or less. However, therapeutic monitoring and evaluation of a patient’s digoxin clearance will be improved if all concentrations are taken at approximately the same time after doses. A variation in the collection time of only 2–3 hr will generally be inconsequential, making exact timing prior to a dose unnecessary.

TABLE 13-9. THERAPEUTIC RANGE

Therapeutic Range	Comment
0.5–0.9 mcg/L	Most optimal in patients with heart failure (ejection fraction <40%). Concentrations exceeding 1.2 mcg/L are associated with increased mortality. ³
0.5–2 mcg/L	Patients may require concentrations as high as 3.1 mcg/L to control ventricular response; overlap may occur between therapeutic and toxic ranges. Neonates and infants can tolerate higher concentrations than adults, although this may be due in part to endogenous digoxin-like substance assay interference. ²⁴⁻²⁷

For outpatients on a stable dose of digoxin who do not have an obvious change in clearance due to disease state or drug interaction, an annual digoxin concentration measurement is often sufficient.³⁰ Appointments should be scheduled to ensure that the daily dose has not been taken in the few hours before sampling; if necessary, outpatients can hold the dose for a few hours until sampling is conducted. For hospitalized patients, trough concentrations can usually be scheduled 1–4 hr before the usual morning daily dose.

Assay issues

Digoxin concentrations are predominately measured using commercially available immunoassay methods, which include radioimmunoassay, fluorescence polarization immunoassay (FPIA), microparticle enzyme immunoassay, and chemiluminescent immunosorbent assay.^{31,32} Due to its ease of use and low expense, the FPIA assay is the more commonly used method for clinical measurement of digoxin concentrations. The digoxin antibodies used in these immunoassays can cross-react with digoxin metabolites, endogenous digoxin-like substances (EDLS), drugs, diagnostic compounds, and certain Chinese medicines or plant products, thereby falsely elevating or decreasing digoxin concentrations. This interference varies among different immunoassay methods and antibody lots.³³ **Table 13-10** summarizes agents that may interfere with digoxin immunoassays.^{28,32,34–41} EDLS may occur in patients with renal or liver impairment, pregnant women, and neonates.^{28,42–44} Various techniques have been developed to eliminate this interference, which include extending serum incubation periods, use of ultrafiltration, and combined use of high and low pressure liquid chromatography.⁴⁵

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

Patients with HF should be monitored for heart and lung sounds, heart rate, changes in urine output, edema, and neck vein distention. Patients with atrial fibrillation should be monitored for decreased ventricular rate and electrocardiogram (ECG) changes.^{2,3} All patients receiving digoxin should have serum creatinine, potassium, magnesium, digoxin concentrations, and general fluid and electrolyte status monitored periodically to avoid toxicity. Changes in status can indicate a need to increase or reduce doses or to monitor digoxin concentrations.^{2,3}

Concentration-related toxicity

Toxicity in all patients taking digoxin can be noted as a decrease in heart rate, other ECG changes, and arrhythmias; anorexia, nausea, vomiting, and diarrhea; and visual disturbances.⁴⁶ A study of adverse drug events (ADEs) leading to emergency department (ED) visits found that digoxin, along with insulin and warfarin, were implicated in one in every three estimated ADEs treated in EDs among patients ≥ 65 yr old.⁴⁷ These results demonstrate the importance of monitoring for toxicity with digoxin, particularly in elderly patients. Digoxin toxicity can occur within the normal therapeutic range, especially in patients with metabolic derangement (e.g., hypokalemia) or severe underlying disease.⁴⁶ Because the volume of distribution is decreased and response to a given concentration is increased in hypothyroidism, patients should be monitored to avoid increased digoxin concentrations and toxicity. Digoxin immune Fab (ovine) is administered to treat life-threatening digoxin toxicity due to iatrogenic or purposeful overdosing. The presence of Fab fragments may interfere with digoxin serum concentration determination. In this situation, ultrafiltration may be used to remove digoxin-bound Fab fragments allowing for a more reliable measurement of the unbound digoxin concentration.^{7,46}

Although there has been no prospective, randomized evaluation of the relative efficacy or safety of different plasma concentrations of digoxin in patients with HF with reduced ejection fraction, retrospective analysis of the Digitalis Investigation Group trial found that digoxin concentrations exceeding 1.2 ng/mL were associated with an increase in all-cause mortality.^{48,49}

TABLE 13-10. POTENTIAL DIGOXIN ASSAY INTERACTIONS^{28,32,34-41}

Drug	Effect on Digoxin Concentrations	Comment
Canrenoate	False increase or decrease	May be dose related
Capromab pendetide	False increase	
Ch'an Su	False increase	Interference can be eliminated by measuring unbound digoxin concentrations
Danshen	False increase	Interference can be eliminated by measuring unbound digoxin concentrations
Digoxin immune Fab (ovine)	False increase	Interference can be eliminated by measuring unbound digoxin concentrations
EDLS	False increase	Seen in patients with renal and/or hepatic failure, neonates, and pregnant women in the third trimester
Fluorescein	Invalid results	
Ginseng	False reading	Seen with American, Asian, Indian, and Siberian ginseng
Kyushin	False increase	
Lu-Shen-Wan	False increase	Interference can be eliminated by measuring unbound digoxin concentrations
Oleander	False increase	
Steroid hormones: cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, progesterone	False increase	
Spironolactone	False increase	May be dose related
Veratrum viride (false hellebore)	False increase	

EDLS = endogenous digitalis-like substance.

Digoxin concentration measurements taken during the distribution phase after digoxin dosing can be quite high and may not be indicative of pharmacologic impact or toxicity.⁵⁰ Concentration elevations due to drawing during the distribution phase must not be incorrectly diagnosed and treated with digoxin immune Fab. Signs and symptoms of digoxin toxicity should be present before such treatment.^{28,46}

Non-concentration-related toxicity

A number of retrospective and observational studies as well as a meta-analysis of patients with atrial fibrillation have questioned the safety and efficacy of digoxin therapy.⁵¹⁻⁵⁵ In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), digoxin was associated with a 1.14-fold increase in all-cause mortality in patients with atrial fibrillation after correcting for clinical characteristics and comorbidities, regardless of gender or of the presence or absence of heart failure.⁵² Prospective studies are needed to truly elucidate the effect of digoxin on mortality in patients with atrial fibrillation.

DRUG–DRUG INTERACTIONS

There are a variety of important drug–drug interactions with digoxin. Some are relatively easily avoided, while others are not. Research has shown that ADEs occur with important frequency with digoxin, and interactions that increase the potential for digoxin related toxicity should be carefully monitored or avoided when possible. Potentially important pharmacokinetic and pharmacodynamic digoxin–drug interactions are listed in **Table 13-11**.

TABLE 13-11. DIGOXIN DRUG–DRUG INTERACTIONS⁷

Drug	Effect on Digoxin	Comments
ACE inhibitors	Increased digoxin concentrations	Decreased renal CL.
Amiodarone	Increased digoxin concentrations	Interaction is dose dependent; digoxin concentrations may increase >70%; digoxin dose should be decreased by 25% to 50%; reduced renal and nonrenal CL (inhibition of P-gp).
Antacids (magnesium/aluminum liquids)	Decreased digoxin concentrations	Absorption reduced by 25%. Doses should be separated by ≥2 hr.
SA/AV nodal blocking agents: amiodarone; disopyramide, beta-blockers, flecainide, nondihydropyridine calcium channel blockers, ivabradine, sotalol	Increased risk for bradycardia and heart block	Reduced sinoatrial or AV node conduction (pharmacodynamic interaction).
Carvedilol	Increased digoxin concentrations	Reduced renal and nonrenal CL; increased bioavailability by 9% to 20%. May be due to competition for intestinal P-gp; in children, digoxin dose may need to be reduced by 25%.
Canagliflozin	Increased digoxin concentrations	Increased digoxin AUC and C_{max} by 20% and 36%, respectively. Monitor digoxin concentrations.
Colchicine	Increased risk for rhabdomyolysis and myopathy	Possible competition for intestinal and renal P-gp. Avoid combination if alternative gout therapies are appropriate.
Cholestyramine	Decreased digoxin concentrations	Absorption reduced (most when given concomitantly). Reduction may be minimized by twice-daily dosing of cholestyramine 8 hr before and after digoxin.
Dasabuvir	Increased digoxin concentrations	Due to inhibition of intestinal and renal P-gp; monitor digoxin concentrations.
Diltiazem	Increased digoxin concentrations	Reduced renal and nonrenal CL (inhibition of P-gp); interaction is dose dependent.
Dronedarone	Increased digoxin concentrations	Digoxin concentrations may increase 2.5-fold; reduced nonrenal CL (inhibition of P-gp); digoxin dose should be decreased by 50%.
Erythromycin and clarithromycin	Increased digoxin concentrations	Due to inhibition of intestinal and renal P-gp; monitor digoxin concentrations.
Kaolin-pectin	Decreased digoxin concentrations	Time-dependent decrease in absorption (62% when given concomitantly; 20% when given 2 hr apart). Doses should be separated by ≥2 hr.
Itraconazole	Increased digoxin concentrations	Reduced renal and nonrenal CL; reduced V. May be due to inhibition of intestinal and renal P-gp; monitor digoxin concentrations.
Ledipasvir	Increased digoxin concentrations	Due to inhibition of intestinal and renal P-gp; monitor digoxin concentrations
Non-potassium sparing diuretics: thiazide and loop	Increased risk for arrhythmias	May be due to reductions in potassium and magnesium.

TABLE 13–11. DIGOXIN DRUG-DRUG INTERACTIONS⁷(cont'd)

Drug	Effect on Digoxin	Comments
NSAIDs	Increased digoxin concentrations	Decreased renal CL.
Posaconazole	Increased digoxin concentrations	Due to inhibition of intestinal and renal P-gp; monitor digoxin concentrations.
Propafenone	Increased digoxin concentrations of 80% or more	Reduced renal and nonrenal CL; decreased V. Interaction is dose dependent; digoxin dose may be reduced by 50%; obtain digoxin concentrations within 48–96 hr of adding or removing propafenone.
Quinidine	Increased digoxin concentrations	Reduced renal CL and tissue binding. Digoxin concentrations should be monitored carefully; digoxin dose may need to be decreased by 50%.
Ranolazine	Increased digoxin concentrations	Reduced nonrenal CL (inhibition of P-gp); digoxin concentrations may increase 1.5-fold.
Rifampin	Decreased digoxin concentrations	Increased nonrenal CL (induction of P-gp and hepatic metabolism)
Ritonavir	Increased digoxin concentrations	Reduced renal and nonrenal CL; increased bioavailability. May be due to inhibition of P-gp; monitor digoxin concentrations.
St. John’s wort	Decreased digoxin concentrations	Reduced absorption. May be mediated by inducing P-gp; monitor clinical response and digoxin concentrations in patients titrated to effective digoxin dose who start or discontinue St. John’s wort.
Spironolactone	Increased digoxin concentrations	Reduced renal CL, V, and tissue binding. Monitor digoxin concentrations.
Tetracycline	Increased digoxin concentrations	Increased absorption; reduced intestinal metabolism. Eradication of gut flora (e.g., <i>Eggerthella lenta</i>).
Thyroid hormones	Reduced digoxin concentrations	Increased renal and nonrenal CL. May be due to increased expression of P-gp by thyroid hormones.
Verapamil	Increased digoxin concentrations	Reduced renal and extrarenal CL. Interaction is dose dependent; digoxin concentrations may increase 60% to 90%; digoxin concentrations may decline over a period of weeks with concomitant therapy; may be due to inhibition of P-gp resulting in decreased digoxin renal tubular elimination.

ACE = angiotensin converting enzyme, AUC = area under the curve, C_{max} = maximum serum concentration, NSAID = nonsteroidal anti-inflammatory drug, P-gp = P-glycoprotein.

DRUG–DISEASE/CONDITION INTERACTIONS

Digoxin concentrations may decrease during pregnancy due to increased renal clearance and possible upregulation of p-glycoprotein.⁵⁶ Reductions in renal function below the average for age and size lead to lengthening of the half-life and reduction of clearance. Research has shown that there are no significant sex-based differences in digoxin pharmacokinetics when actual or ideal body weight is used to control for dose differences due to weight on concentration outcomes. When adjusted for BMI however, differences were detected.⁵⁷

Patients with hyperthyroidism may have reduced myocardial responsiveness to digoxin therapy. Digoxin response may be improved by treating the hyperthyroidism. The opposite applies when treating hypothyroidism.^{2,3}

Finally, patients carrying polymorphism for the multi-drug-resistance 1 (MDR1) gene that codes for p-glycoprotein may experience a significant increase in the bioavailability of digoxin, leading to higher digoxin concentrations.^{58–60}

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ETHOSUXIMIDE

Jacquelyn L. Bainbridge, Pei Shieen Wong, and Felecia M. Hart

The Food and Drug Administration (FDA) approved ethosuximide for marketing in 1960. It is indicated only for the treatment of absence seizures alone or in combination with other antiepileptic drugs (AEDs) in patients 3 yr of age and older.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

A loading dose is not needed for the treatment of absence seizures with ethosuximide. The starting dose (see **Table 14-1**) should be low, so that the patient can accommodate to the initial central nervous system (CNS) depression seen with ethosuximide and most AEDs. The dose should be titrated to the individual patient's response.^{1,2}

A once-daily dosage regimen can be used successfully due to the long half-life of ethosuximide. However, gastrointestinal (GI) side effects increase as the dose increases in some patients. Therefore, ethosuximide may need to be given twice a day.^{3,4} **Table 14-2** shows the availability of the dosage forms.

GENERAL PHARMACOKINETIC INFORMATION

The pharmacokinetics of ethosuximide are poorly understood, even though it is an old AED and a sensitive and specific assay exists. Ethosuximide disposition has been described as following a one-compartment model with first-order elimination.^{2,5}

Absorption

In humans, ethosuximide is well absorbed and peak concentrations are achieved in about 4 hr for adults and in 3–7 hr for children.^{2,6} The time-to-peak concentration is somewhat faster with a single dose than after repeated dosing. Absorption from the syrup is faster than from the capsule, but the extent of absorption is the same (see **Table 14-3**).

TABLE 14-1. INITIAL MAINTENANCE DOSAGES^{2,2}

Dosage Form	Initial Maintenance Dosage ^a
Intravenous (IV)	Not available
Oral	
Adults and children (>6 yr)	20–40 mg/kg/day
Children (3–6 yr)	15–40 mg/kg/day
Children (2.5–13 yr)	10–60 mg/kg/day or 200 mg/day, whichever is lower

^aSee Dosing Strategies section.

Note: We would like to thank William R. Garnett for his groundwork on this chapter. We would also like to thank Michael D. Egeberg and Sarah L. Johnson for their past contributions.



TABLE 14-2. DOSAGE FORM AVAILABILITY

Dosage Form	Product
IV	Not available
Oral capsules: 250 mg	Zarontin; generics
Oral syrup: 250 mg/5 mL	Zarontin syrup; ethosuximide syrup

TABLE 14-3. BIOAVAILABILITY (F) OF DOSAGE FORMS⁵

Dosage Form	Bioavailability Comments
IV	Not available
Oral capsules and solution	Assumed complete (100%, F = 1)

Distribution

Ethosuximide does not bind to plasma proteins. A cerebrospinal fluid to plasma to saliva ratio of 1 indicates that most of the drug in the plasma is in the unbound form. Ethosuximide is uniformly distributed throughout the body, with the exception of body fat, into which it does not distribute appreciably.

The apparent volume of distribution (V) of ethosuximide is approximately 70% of ideal body weight, which is equivalent to total body water. The apparent V is 0.69 L/kg in children younger than 10 yr of age and 0.72 L/kg in adults older than 18 yr of age (see **Table 14-4**).^{2,7}

Ethosuximide crosses the placenta and passes into breast milk, achieving a concentration similar to that in the mother’s plasma.⁵ Spinal fluid, saliva, and tears have concentrations similar to that in plasma.

TABLE 14-4. VOLUME OF DISTRIBUTION (V)

Age	Volume ^a
Children (<10 yr)	0.69 L/kg
Adults (>18 yr)	0.72 ± 0.15 L/kg

^aIdeal body weight.

Protein binding

Protein binding of ethosuximide is negligible (0%) in both children and adults.

Elimination

Ethosuximide is 80% metabolized by the liver, and the remaining 20% is excreted unchanged by the kidneys. However, it does not undergo first-pass metabolism because it is poorly extracted by the liver. The apparent clearance of ethosuximide in normal adults has been estimated at 0.01 ± 0.004 L/hr/kg, which is less than hepatic blood flow and demonstrates that the elimination is not flow dependent (see **Table 14-5**). Ethosuximide is first hydroxylated and then conjugated to inactive metabolites before being excreted into the urine.⁸ CYP3A and CYP2E are primarily involved in ethosuximide metabolism with CYP2B and CYP2C playing a minor role.⁸

Two studies suggested that ethosuximide might display nonlinear clearance at the upper end of the therapeutic range. Smith et al.⁹ reported that, in individual patients, successive dose increments of equal size produced disproportionately greater increases in steady-state concentrations. Bauer et al.⁷ found that 7 of 10 patients demonstrated evidence of nonlinearity. Therefore, the dose and steady-state concentration relationship of ethosuximide may vary, especially at the upper end of the therapeutic range.

TABLE 14-5. CLEARANCE (CL)

Age	Clearance ^a
Children (<10 yr)	0.013–0.016 L/hr/kg
Adults (>18 yr)	0.01 ± 0.004 L/hr/kg

^aAs there is no IV form of ethosuximide, clearance calculations are relative to bioavailability of the oral product used (CL/F).

Half-life and time to steady state

The half-life in children has been reported to be ~30 hr versus ~60 hr in adults (see **Table 14-6**). Although not FDA approved for this patient group, data for neonates derived from case reports indicate that the half-life is between 32 and 41 hr. The half-life of ethosuximide was reported to be unaffected by dose size and to be constant with repeated dosing. However, a 15% decrease in total body clearance has been described between the first dose and steady state and was attributed to a decrease in the nonrenal clearance.²

TABLE 14-6. HALF-LIFE AND TIME TO STEADY STATE

Age	Half-Life	Time to Steady State ^a
Children (<10 yr)	~30 hr	6 days
Adults (>18 yr)	~60 hr	12 days

^aBased on approximately five half-lives.

DOSING STRATEGIES

Attempts to predict concentrations of ethosuximide associated with doses in epileptic patients have not been very successful. The actual dose of ethosuximide used may depend on the dosage form available. A rough guideline is to initiate therapy with 15 mg/kg/day (maximum of 250 mg/day) in children 3–6 yr old and with 500 mg/day in patients older than 6 yr. The dose may be increased by 250 mg/day every 4–7 days until seizure control is achieved, the maximum dose of 1.5 g/day has been reached, or side effects become intolerable. The 1.5 g/day dose may be exceeded to achieve concentrations necessary for seizure control if the patient does not have side effects. If side effects occur, the dose of ethosuximide should be reduced.

The exact ethosuximide concentration at which a given patient will respond is not predictable, so the dose must be titrated to individual response. Although ethosuximide may be assumed to generally follow a first-order pharmacokinetic model, dosage adjustments should be made gradually to allow for patient tolerance. Once steady state has been achieved, the patient's response (both efficacy and toxicity) should be assessed. After the patient has been free of absence seizures for 2–4 yr, discontinuation of ethosuximide may be attempted; however, dose reduction should occur gradually.

THERAPEUTIC RANGE

The therapeutic range of ethosuximide is 40–100 mg/L for the treatment of absence seizures.^{1,2} Within this range, 80% of patients will achieve partial control and 60% will become seizure free. However, concentrations up to 150 mg/L or higher may be needed for complete seizure control in some patients. These concentrations have been used without signs of toxicity in some patients, but those with high concentrations should be monitored closely. Factors that predict therapeutic success are: (1) absence seizures as the only seizure type, (2) normal electroencephalogram (EEG) background activity, and (3) normal intelligence.^{1,2}

THERAPEUTIC MONITORING

Suggested sampling times and effect on therapeutic range²

The indications for monitoring ethosuximide concentrations include:

- A poor response to therapy
- Questionable adherence to therapy
- Low doses and good response (to evaluate if there are pharmacokinetic issues, drug accumulation)
- Initial and chronic maintenance of optimal concentrations

Ethosuximide has a long half-life. This half-life should be considered in determining when to collect blood samples after therapy is initiated or the dosage is changed. The initial sample or the sample after a dosage change should not be drawn for at least 6 days in children or 12 days in adults so that the patient can reach steady state. Samples may be drawn earlier if the patient experiences unexpected side effects.

The long half-life of ethosuximide would generally suggest minimal changes in the peak to trough ratio. However, trough concentrations are recommended for monitoring, particularly if the patient is on a once-a-day regimen, as there is reduced variation in trough concentrations compared to concentrations drawn earlier or at different times in the regimen.

There is no indication that serum ethosuximide concentrations differ from plasma concentrations. Because of the negligible protein binding, there is no indication for determining unbound ethosuximide. The concentration in saliva or tears equals its serum concentration and may be used in some patients if blood sampling is not possible.

The asymmetric center in ethosuximide is quaternary, making racemization unlikely,¹⁰ and metabolism does not appear to be stereo-selective. Therefore, the measurement of total ethosuximide is adequate for therapeutic monitoring.

Once the desired therapeutic response has been achieved, concentrations may be periodically monitored for use as a historical control for an individual patient. A change in response or the onset of unusual side effects indicates a need to monitor concentrations.

PHARMACODYNAMIC MONITORING

Concentration-related efficacy^{1,2}

The desired therapeutic endpoint for ethosuximide is the abolition of absence seizures. In refractory patients, the combination of ethosuximide and valproate may be more effective than either drug alone, however, valproate is contraindicated in pregnancy and should not be used in women of child bearing potential. Ethosuximide is indicated only for the treatment of absence seizures and may exacerbate other seizure types.

Concentration-related toxicity¹¹

Patients should be monitored for ethosuximide side effects. The most frequent side effects, nausea and vomiting, may be related to the dosage. Other side effects that may be dose- or concentration-related are abdominal discomfort, anorexia, drowsiness, fatigue, lethargy, dizziness, hiccups, and headache. Headaches may persist after a dosage reduction.

Behavioral and cognitive side effects of ethosuximide have been reported in some patients, however, these side effects are not well documented. Rare side effects include skin rashes, systemic lupus erythematosus, blood dyscrasias, and changes in liver function tests.

DRUG–DRUG INTERACTIONS

Ethanol, haloperidol, loxapine, phenothiazines, and tricyclic antidepressants can decrease the effectiveness of ethosuximide by lowering the seizure threshold and, therefore, should not be used concurrently.⁶ Animal studies indicate that its metabolism may be induced or inhibited, although clinical reports of drug interactions with ethosuximide are rare and often poorly documented. In one report, the ratio of ethosuximide concentrations to dose was significantly higher when it was given alone than when it was administered with carbamazepine, primidone, or valproic acid, indicating these drugs likely induce ethosuximide metabolism.¹² Barbiturates and phenytoin may also induce metabolism resulting in lower serum concentrations and shorter half-life.⁶ Other studies found increased concentrations when ethosuximide was given with valproic acid. Ethosuximide may also result in a lower serum concentration of valproic acid when given concurrently.^{8,13} The interaction with valproic acid may be complex and may require the presence of other concurrent AEDs or high concentrations of valproic acid.^{13–15} Isoniazid increased ethosuximide concentrations and ethosuximide increased phenytoin concentrations in single-case studies.^{16,17}

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

Hemodialysis

Based on results from a small study evaluating ethosuximide in the setting of hemodialysis, it appears to be dialyzable.¹⁸ Four patients with chronic renal failure dependent on intermittent hemodialysis were given a single test dose of 500 mg. Blood and dialysate samples were collected within the first 4 hr of the 6-hr hemodialysis. Dialysate contained 38.8% to 52.4% of the administered ethosuximide dose. The elimination half-life was decreased to an average of 3.5 hr. Based on these results, patients on hemodialysis may require increased monitoring during and after dialysis, as well as supplemental dosing.

Pregnancy

Pregnancy has been reported to increase the clearance of some AEDs, such as lamotrigine, levetiracetam, and oxcarbazepine.¹⁹ Based on two case reports, this effect appears to be true for ethosuximide.^{20,21}

Renal and hepatic dysfunction

Ethosuximide is 80% metabolized by the liver and 20% excreted unchanged. Therefore, although unconfirmed by clinical studies, patients with impaired liver or renal function may require altered dosing.²

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UNFRACTIONATED HEPARIN, LOW MOLECULAR WEIGHT HEPARIN, AND FONDAPARINUX

A. Joshua Roberts and William E. Dager

Heparin (unfractionated and low molecular weight) is used primarily as an anticoagulant to (1) treat active thrombosis, (2) to prevent clot formation in patients at increased risk (e.g., due to surgery, prolonged bed rest, or pregnancy) or during extracorporeal circulation (e.g., hemodialysis, cardiopulmonary bypass, and extracorporeal life support [ECLS] in neonates), and (3) in the setting of acute coronary syndromes (ACS). Additionally, unfractionated heparin may help prolong the patency of arterial and venous catheters.

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) has been a mainstay of anticoagulant therapy for over 60 yr. In many situations, close monitoring and careful dose adjustment is required. It is most commonly administered by intravenous (IV) infusions or by intermittent subcutaneous (sub-Q) injections. Prior to 2009, the methods used to calibrate heparin units varied between the United States Pharmacopeia (USP) drug monograph and other industrialized nations. After the noted failure in 2009 of the standard testing to detect the introduction into circulation of tainted lots of heparin, the USP monograph was updated to align with the heparin unit calibration approach of the World Health Organization (WHO) international standardized unit. This new assay has led the Food and Drug Administration (FDA) to note the potential for a 10% reduction in heparin USP unit potency when compared to the previous assay and reference standards. The clinical significance of this change is debatable with current consensus suggesting minimal impact.¹

UFH: USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

When UFH therapy is used for active venous thrombosis formation, a loading dose of 70–100 units/kg is typically administered to render an immediate effect in suppressing further expansion of the thrombus. The Ninth American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines recommends a loading dose of 80 units/kg for treatment of venous embolic disease.^{2,3} Lower loading doses such as 50–70 units/kg have been recommended in the setting of ACS, especially in situations where Glycoprotein IIb/IIIa inhibitor drug therapy or thrombolytic drug therapy may be co-administered.^{3–5} In selected settings such as high bleeding risk (i.e., stroke) or no emergent need for rapid onset of anticoagulation, a bolus loading dose may not be warranted.

The use of UFH and the dose used should be individualized for each patient, because target end-points differ for its various therapeutic uses and assays. The patient's actual body weight (ABW) is most commonly used in weight-based dosing approaches although current ACCP guidelines do not address the issue of dosing weight in obese patients (i.e., whether ideal body weight [IBW] or ABW should be used).^{2,3} Use of an adjusted dosing weight has been suggested to account for obesity (e.g., 30% to 40% of the difference between the ABW and IBW is added to the IBW to result in the dosing



weight) or modified to their body mass index.^{6,7} The use of ABW, and thus a higher dose, is supported by a randomized controlled trial demonstrating that reaching target goals earlier in the treatment course was associated with a reduction in recurrent thromboembolic events.⁸ For safety concerns, maximum bolus and maintenance dosing limits should be considered to avoid unintended excessive dosing. Depending on the setting of use, loading doses up to 80 units/kg or 5,000 units for acute venous thromboembolism (VTE) have been suggested.³ Such high doses will saturate most sites of action, yield elevated activated partial thromboplastin time (aPTT) levels for several hours, and prolong the time to be removed and ability to assess an aPTT that reflects the infusion rate.⁹

Initial continuous infusion UFH maintenance doses can vary depending on the therapeutic indication. Typical starting doses range between 12 and 18 units/kg/hr with titration to the desired aPTT or anti-factor Xa activity goal.^{3,5} Previous studies have shown that using weight-adjusted initial maintenance doses, as compared to fixed doses, has decreased recurrence of thromboembolic events.⁸ Although not addressed specifically in the ACCP guidelines, some authors have suggested an initial infusion rate cap in obese patients for safety.¹⁰

UFH: DOSAGE FORM AVAILABILITY

UFH is available only as a solution for injection. It is usually administered by IV or sub-Q routes, but has also been given by inhalation and intrapulmonary instillation.¹¹ UFH should not be given intramuscularly (IM) because it increases the likelihood of hematoma formation and can cause pain and irritation. Heparin sodium and heparin calcium (the latter not currently available in the United States) for injection are supplied by several manufacturers in concentrations ranging from 1,000 to 20,000 units/mL. Preparations for IV infusion are usually diluted to the desired concentration in either a dextrose or saline solution. Due to the large variation in available concentrations, extreme caution should be exercised in ordering and preparing heparin solutions to avoid errors in dosing.

UFH is also marketed as a heparin sodium flush solution in concentrations of 10–100 units/mL. This flush solution, diluted to 1 unit/mL or less, can be used to maintain the patency of IV catheters. Tragic events have occurred when incorrect doses were administered for purpose of maintaining patency of IV catheters highlight the importance of creating a system for multiple checks or redundancy for determining that the correct heparin sodium flush concentration has been dispensed or sent from pharmacy.

UFH is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties. The molecular weight of UFH ranges from 3,000 to 30,000 Daltons with a mean of 15,000 Daltons (approximately 45 monosaccharide chains).²

UFH: GENERAL PHARMACOKINETIC INFORMATION

The pharmacokinetic parameters of UFH have been determined using methods that (1) measure a global coagulation test parameter such as aPTT, (2) directly measure UFH effect by anti-Factor Xa activity, or (3) directly measure neutralization of UFH by protamine titration. Since heparin is an indirect anticoagulant that works thru anti-thrombin (AT), the presence of sufficient AT is necessary for activity.

Absorption

Heparin is not absorbed from the gastrointestinal tract. Although bioavailability is 100% after IV administration, it can be reduced to roughly 30% after sub-Q administration.¹² sub-Q bioavailability may vary substantially between patient populations, site of injection, and in the presence of vasopressors. Absorption from the sub-Q route is more rapid than would be seen with IM administration (IM use is not recommended). **Table 15-1** provides the bioavailability based on the route of administration of UFH.

Distribution

The volume of distribution (V) of UFH closely approximates blood volume at approximately 0.05–0.07 L/kg.¹³ Estimation of blood volume by the formula $V = 0.07 \text{ L/kg}$ of body weight provides a reasonable estimate of heparin V when pharmacokinetic calculations are performed. When a large amount of heparin is administered during bypass graft surgery, a rebound in anticoagulant effects can occur up to 6 hr after post-surgery protamine neutralization due to redistribution of heparin from tissue back into the plasma.¹⁴

TABLE 15-1. UFH: BIOAVAILABILITY (F) OF ROUTES OF ADMINISTRATION

Dosage Form	Bioavailability
IV	100% (F = 1)
sub-Q	~20% to 30% (F = 0.3) (range 10% to 90%) ^a

^aAlthough studies have shown bioavailability of sub-Q to be low, others have found no difference in sub-Q or IV in terms of mean daily dose needed. Thus, the every 12 hr mg/kg dose for sub-Q is approximately similar to 12 × the mg/kg/hr IV rate. Some authors recommend increasing the 12-hr dose by 20% (see Dosing Approaches).

Studies employing weight-based dosing regimens (loading and maintenance) have shown reduced time to therapeutic aPTT when compared to fixed dose regimens.^{8,10} These individualized dosing schemes clearly show that as individual size varies and, by default, V and clearance (CL) changes, so should the heparin dosing. Some studies suggest additional variables such as age, sex, and height may better approximate the V.¹⁵

Protein binding

Because heparin products are mixtures of a wide range of molecular weights, pharmacokinetic parameters may vary with the particular preparation used. This variability is caused by UFH’s nonspecific binding to proteins and cells. Heparin-binding proteins are quite variable in their concentration during acute illness. These proteins are acute phase reactants and may be elevated in acutely ill patients, accounting for variability in the aPTT results,¹⁶ unpredictable anticoagulant response, and the potential for heparin resistance. These outcomes are demonstrated as a shortening of the aPTT that is seen in some patients. The impact of low molecular weight heparins (LMWHs) in addressing these problems is discussed later.

Elimination

UFH is cleared by both zero-order and first-order elimination processes. In the saturable, rapid zero-order process, it is metabolized and depolymerized by endothelial cells and macrophages. As for first-order elimination, heparin is cleared renally in a slower, nonsaturable process. The half-life of UFH varies from 0.4 to 2.5 hr, increasing as the administered dose increases from 25 to 400 units/kg.¹⁷⁻¹⁹ Patient-specific variables such as age, thromboembolic disease state, hepatic or renal impairment, and obesity, may significantly alter the CL and V of UFH. Although hepatic or renal impairment may influence these pharmacokinetic parameters, no significant dosage modification is typically required.

Table 15-2 illustrates the pharmacokinetic parameters for UFH.¹¹ Differences in parameters may exist depending on whether direct (anti-Factor Xa assay)^{11,13,20-22} or indirect (activated clotting time [ACT] or aPTT)^{11,20-27} measurement of the heparin concentration is performed. These differences may account in part for the inter- and intra-patient variability seen in dose responsiveness for patients receiving UFH.

TABLE 15-2. UFH PHARMACOKINETIC PARAMETERS ASSUMING A LINEAR ONE-COMPARTMENT MODEL

Parameter	Mean Value and/or Range
CL	0.015–0.12 L/hr/kg
V	0.07 L/kg (range 0.04–0.14 L/kg)
Half-life ($t_{1/2}$)	1.6 hr (range 0.4–2.5 hr)

DOSING STRATEGIES

Treating venous thromboembolic disease

For treatment of a VTE, initial anticoagulation with UFH for 5–7 days before changing to dabigatran or edoxaban (without an overlap), or concomitant UFH and warfarin therapy may be used except during pregnancy or when contraindicated. Patients with suspected or confirmed VTE should receive UFH and an oral anticoagulant (see warfarin chapter and other appropriate references for specific guidance on dosing oral anticoagulants) as follows.⁷

Suspected VTE⁷

- Obtain baseline aPTT, prothrombin time/international normalized ratio (PT/INR), complete blood count (CBC), and basic metabolic panel.
- Check for contraindications to heparin therapy.
- Initiate parenteral anticoagulant with UFH (bolus plus infusion or sub-Q), LMWH, or fondaparinux at doses typically used for initial management of an acute VTE. Warfarin, dabigatran, or edoxaban should not be started until the VTE is confirmed. If the VTE is ruled out, the parenteral agent can be stopped.
- Order imaging study.

Confirmed VTE⁷

- Bolus with 80 units/kg IV of UFH and start maintenance infusion at 18 units/kg/hr if another parenteral anticoagulant has not yet been started and heparin is the chosen agent.
- Check aPTT at 4–8 hr and adjust dose as needed to maintain a range corresponding to a therapeutic heparin concentration. If no bolus is administered, an earlier (e.g., 4 hr) aPTT can be measured. A large bolus can affect the aPTT up to 8 hr after administration, suggesting a greater response of the infusion than is actually occurring (see **Figure 15-1**). Check platelet count prior to starting therapy, and then on a routine basis (e.g., every 2–3 days for 2 weeks). Carefully monitor patients with a recent exposure to heparin products for potential heparin induced thrombocytopenia (HIT). If recent exposure to heparin has occurred, a platelet count should be checked immediately.
- If there is a desire to switch to a LMWH, the LMWH can generally be given at the time the UFH infusion is stopped. An acute thrombus or bleeding are unlikely to occur if there is a slight difference in the time (i.e., 1–2 hr) between stopping the UFH and starting the LMWH. To initiate a UFH infusion in a patient on a LMWH, consider starting the infusion when the next LMWH dose would be administered. A bolus would not typically be required.
- Either initiate a vitamin K antagonist (VKA) such as warfarin together with UFH on the first treatment day once a rise in the aPTT has been observed, or switch UFH to dabigatran or edoxaban after at least 5–7 days of parenteral therapy without overlapping agents.
- When using warfarin, discontinue UFH after a minimum of 4–5 days and when the international normalized ratio (INR) is stable and above 2.
- Anticoagulate with warfarin or a direct acting oral anticoagulant (DOAC) for 3 or more months (patient/disease-state specific). See the warfarin chapter for more extensive discussion of warfarin dosing and monitoring

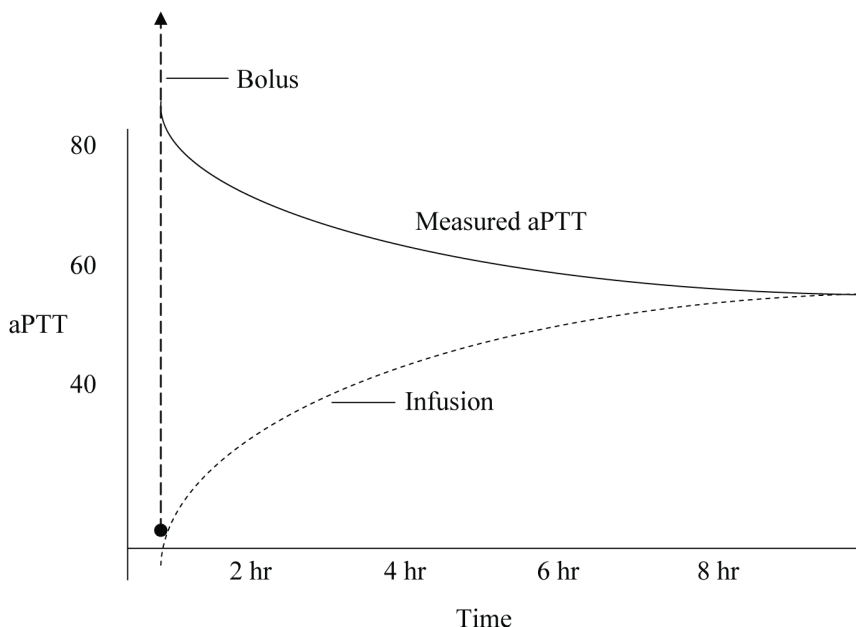


Figure 15-1. Timing of aPTT values when a bolus is given with the initiation or increase in an infusion rate. Depending on the amount of a bolus (dashed line) administered, the aPTT may rise to a point higher than achieved by the continuous infusion (dotted line). The measured aPTT (solid line) in this situation will then drop over time to a value reflective of the infusion rate. Checking aPTT values earlier than 6 hr after initiating the UFH infusion may be requested in order to determine if an inadequate infusion rate is present (aPTT value close to baseline). When interpreting this “early” aPTT value, it has to be noted that the bolus dose may artificially increase this reading. UFH bolus doses of > 5,000 units can also have an effect on aPTT values drawn up to 8 hr later.²⁸

Source: Used with permission from Dager W, Gulseth M, Nutescu E, eds. *Anticoagulation Therapy: A Point-Of-Care Guide*. Bethesda, MD: American Society of Health-System Pharmacists; 2011.

Pharmacokinetic dosing approaches

UFH dosing can be adjusted either empirically or by pharmacokinetic calculations using one of several approaches:

1. For practical dosing, the onset of heparin’s therapeutic effect can be expedited by a loading dose. This IV bolus dose may be empirically selected (e.g., 2,500–5,000 units) or loading doses may be individualized using the patient’s weight, for example 70–100 units/kg. In some instances, the weight-based approach to loading patients is based on the indication for use; in many situations 80 units/kg should suffice to provide a therapeutic aPTT.

A variety of approaches to continuous dosing have been employed. Empiric dosing of 1,000–1,300 units/hr may be used.²⁹ Due to variability in clearance among individuals, use of the lower dose can lead to aPTTs below the therapeutic range, but they may also sometimes be above the targeted range. Other approaches to continuous dosing with UFH include use of weight-based dosing nomograms, for which initiation may vary between 15 and 25 units/kg/hr (ACCP recommends 18 units/kg/hr).³ In the setting of a PE, doses of 25 units/kg/hr may be necessary due to increased heparin clearance.²⁵

After the patient has been started on UFH, dosing adjustment nomograms can be used to assist in revising the initial weight-based dosing efforts. However, such nomograms should be adapted for a specific aPTT reagent. Examples of dosing adjustment nomograms are depicted in **Tables 15-3**³⁰ and **15-4**.⁸

TABLE 15-3. UFH DOSAGE ADJUSTMENT PROTOCOL^{a,30}

Patient's aPTT ^b	Repeat Bolus Dose	Hold Infusion (min)	Infusion Rate Change (units/hr)	Timing of Next aPTT
<50	5,000 units ^c	0	+120	6 hr
50–59	0	0	+120	6 hr
60–85	0	0	0	Next morning
86–95	0	0	–80	Next morning
96–120	0	30	–80	6 hr
>120	0	60	–160	6 hr

^aStarting dose of 5,000 units IV bolus followed by 1,300 units/hr (32,000 units/24 hr) as a continuous infusion. An aPTT is performed 6–8 hr after the bolus injection; dosage adjustments are made according to protocol, and the aPTT is repeated as indicated in the right-hand column.

^bNormal range for aPTT with the example reagent where a therapeutic range of 60–85 sec is equivalent to a heparin concentration of 0.2–0.4 units/mL by whole blood protamine titration or 0.3–0.7 units/mL as a plasma anti-Factor Xa concentration. The therapeutic range varies with the responsiveness (sensitivity) of the particular aPTT reagent to heparin.

^cWhen the aPTT is measured at 6–8 hr or longer, steady state can be assumed. An 8-hr aPTT may need to be considered if a larger bolus (e.g., 5,000 units) is given to allow the effects of the bolus to wash out, allowing the aPTT to reflect the infusion rate (see Figure 15-1).

TABLE 15-4. aPTT AND WEIGHT-BASED DOSING ADJUSTMENT SCHEME FOR UFH^{a,8,31}

aPTT (sec)	Infusion Change (units/kg/hr)	Next Action	Repeat aPTT
<35 (<1.2 times normal)	+4	Rebolus with 80 units/kg	6 hr
35–45 (1.2–1.5 times normal)	+2	Rebolus with 40 units/kg	6 hr
46–70 (1.5–2.3 times normal)	0	0	6 hr ^b
71–90 (2.3–3 times normal)	–2	0	6 hr
>90 (>3 times normal)	–3	Hold infusion 1 hr	6 hr

^aInitial dosing: loading dose is 80 units/kg; maintenance infusion is 18 units/kg/hr (aPTT in 6 hr).

^bDuring the first 24 hr, repeat aPTT every 6 hr. Thereafter, monitor aPTT once every morning unless it is outside of the therapeutic range.

Table 15-5 shows outcomes that might be expected if the dosing approaches used in Table 15-4 are employed.

TABLE 15-5. OUTCOMES NOTED USING TABLE 15-4 DOSING APPROACHES (N = 115, VTE = 80)

Time	Standard UFH ^a	Weight-Based UFH ^b	P value
24 hr aPTT			
Therapeutic	35%	57%	<0.001
Subtherapeutic	58%	15%	<0.001
Supratherapeutic	7%	27%	<0.001
48 hr aPTT			
Therapeutic	44%	65%	<0.001
Subtherapeutic	49%	18%	<0.001
Supratherapeutic	8%	18%	<0.001
Minor/major bleeding	2%/1%	2%/0%	
Recurrent VTE (3 mo)	3.8%/1.9% (standard)	3.2%/0% (weight-based)	

^aBolus 5,000 units then continuous infusion started at 1,000 units/hr.

^b80 units/kg load then 18 units/kg/hr (actual body weight).

- For a pharmacokinetic modeling and dosing approach, a new infusion rate (R_2) for a target activated clotting time (ACT) [ACT_2] can be estimated from a steady state ACT (ACT_1) on the UFH dosing rate (R_1) that produced the ACT_1 and the patient's baseline pre-treatment ACT (ACT_0) using the formula^{11,17}:

$$R_2 = R_1 \times \frac{(\log ACT_2) - (\log ACT_0)}{(\log ACT_1) - (\log ACT_0)}$$

- If aPTT monitoring of heparin's effect is used, doses must be adjusted with the understanding that aPTT rises disproportionately with heparin dose and concentration increases in a nonlinear manner. Further, the changes noted in the aPTT with adjustments in UFH doses are relatively unpredictable. Thus, such guidelines are only rough estimates and clinicians may have to frequently deviate from them. Cruickshank et al.³¹ described a dosing protocol where 66% and 81% of the patients were above the lower limit of the therapeutic range by 24 and 48 hr, respectively. Of 350 aPTT measurements following the initial dosing adjustments using the protocol, however, only 59.4% were within the therapeutic range, whereas 25.2% were below and 15.4% above the therapeutic range.
- If anti-Factor Xa heparin activity can be measured concomitantly with coagulation studies, a combined pharmacokinetic-pharmacodynamic model can be used. The target anti-Factor Xa heparin concentration (sometimes referred to as a heparin level) is determined from the relationship of anti-Factor Xa heparin concentrations and coagulation studies drawn 1 and 4 hr after initiation of UFH.³² Subsequent UFH infusion rates to achieve the targeted anti-Factor Xa heparin concentrations are then calculated using the pharmacokinetic infusion model developed by Chiou et al.²⁹

$$CL = \left(\frac{2R}{C_1 + C_2} \right) + \left(\frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 + t_1)} \right)$$

where

CL = apparent heparin clearance in units/hr

R = UFH infusion rate in units/hr

V = volume of distribution, equal to patient's estimated blood volume in milliliters (0.07 L/kg)

C_1 = first anti-Factor Xa heparin concentration, drawn at time 1 (t_1), 1 hr after initiation of UFH (in units/mL)

C_2 = second anti-Factor Xa heparin concentration, drawn at t_2 , 4 hr after initiation of UFH (in units/mL).

The clearance may then be used to determine a dose to produce anti-Factor Xa heparin concentrations in the therapeutic range. This particular model lends itself well to issues regarding disease-state dependent clearance, e.g., in the setting of pulmonary embolism (PE)—where clearance has been suggested to be increased.¹¹ The validity of this dosing approach has been confirmed using plasma heparin concentrations determined by anti-Factor Xa assay, which is more readily adapted to routine clinical applications.³³

- UFH dosing also may be estimated using blood volume calculations to estimate V and population half-life estimates (see Table 15-2) to calculate k. Correction factors for pharmacokinetic parameter changes caused by diseases and conditions are shown in **Table 15-6**. These can also be used to alter parameters for dosing estimations.

Target anti-Factor Xa heparin concentrations are usually 0.3 to 0.7 units/mL, and UFH doses can be calculated with these formulas^{26,34}:

$$\text{Loading dose (in units)} = (V) \times (\text{target heparin concentration} \times 1,000 \text{ mL/L}) = (0.07 \text{ L/kg} \times \text{patient's actual body weight}) \times (0.6 \text{ units/mL} \times 1,000 \text{ mL/L})$$

$$\text{Maintenance dose (in units/hr)} = (\text{target heparin concentration} \times 1,000 \text{ mL/L}) (V)(k).$$

This dosing approach may be particularly useful for morbidly obese patients because obesity has been identified as a factor associated with increased heparin dosage requirements. This has been attributed to the potential for decreased concentrations of antithrombin (AT) associated with morbid obesity that causes under-dosing to be a problem as UFH is dependent on AT as a cofactor to exert its anticoagulant response.^{34,35}

6. Determining a sub-Q dose from a currently administered IV infusion:

$$\text{Dose sub-Q administered every 12 hr} = (\text{Last IV infusion rate/hr} \times 12) \times (1.2)$$

(1.2) = reflects the approximately 20% loss of bioavailability with the sub-Q route.

The common 250 units/kg sub-Q every 12 hr dose for VTE treatment is based on this concept; 20% over the common 18 units/kg/hr IV infusion rate used in VTE (i.e., 18 units/kg/hr $\times$ 1.2 $\times$ 12 hr = 259 units/kg).

TABLE 15-6. ADJUSTMENT FACTORS FOR DRUG–DISEASE STATE OR CONDITION INTERACTIONS WITH COMPARISONS MADE TO AVERAGE DVT PATIENTS^a

Disease State or Condition	Assay	Clearance	Volume of Distribution ^b	Half-Life
PE	Xa	1.5	1	0.75
	ACT	1	1	1
Liver disease	Xa	1.5	1	0.75
Renal disease	Xa	1	1	1
Hemodialysis	Xa	1	1	1
	ACT	NA ^c	NA ^c	1
NEONATES				
>32 weeks	Xa	2.5	1	0.33
≤32 weeks	Xa	2.6	1.3	0.33
	Clotting time	1.6	1.2	0.85
Neonates on ECMO	ACT	5.5	NA ^c	NA ^c
ADULTS				
Male	ACT	1.1	1	0.85
Female	ACT	0.8	1	1.1
Smoker	ACT	1.2	1	0.67
Nonsmoker	ACT	1	1	1

DVT = deep vein thrombosis.
^aStandard values for adjustments are CL = 0.03 L/hr/kg, V = 0.07 L/kg, and t_{1/2} = 1.6 hr. To correct pharmacokinetic parameters for underlying condition, these values are multiplied by the adjustment factors.
^bThe V of heparin correlates to the patient's blood volume.
^cNA = data not available.

UFH: THERAPEUTIC RANGE

Historically, the targeted pharmacologic effect for heparin had been prolongation of the selected clotting test to 1.5–2.5 times the patient's normal baseline value.^{7,11,20} It is now observed that use of a standard aPTT therapeutic range of 1.5–2.5 for all reagents and methods of clot detection leads to the

systematic administration of subtherapeutic doses of heparin. This is due to limitations of the aPTT test, including wide variation in responsiveness to the anticoagulant in different laboratories that is caused by differences in thromboplastin reagents and coagulometer instruments. Prolongation of the aPTT that is seen with lupus anticoagulant antibodies, certain congenital factor deficiencies, or the presence of oral anticoagulation with warfarin, limits the approach of using a standard aPTT therapeutic range of 1.5–2.5 for dosing decisions. In all circumstances, the therapeutic range should be adapted to the responsiveness of the specific reagent and lot used (see monitoring section).³⁶

The targeted outcome varies with the specific indication for its use (see **Table 15-7**).^{4,23,37-43} Current recommendations of the ACCP and the College of American Pathologists indicate that patients should be treated with continuous IV UFH (CIUFH) to prolong the aPTT to a range that corresponds to a whole-blood heparin concentration of 0.2–0.4 units/mL by protamine titration or 0.3–0.7 units/mL by anti-Factor Xa heparin assay. This approach of targeting a heparin concentration works to overcome the limitations of the global aPTT test previously described. These recommendations are based on well-controlled, randomized trials in patients with both PE and DVT.^{2,46}

TABLE 15-7. UFH: THERAPEUTIC ENDPOINTS FOR SPECIFIC TREATMENT INDICATIONS

Disease or Condition	Therapeutic Range	Comments
Prevention of catheter clotting	Nonspecific low doses	No studies on survival of catheters related to degree of anticoagulation.
ECLS in neonates	ACT 180–240 sec ^{2,23} ; anti-factor Xa heparin level 0.1–1 units/mL ²	Range apparently based on anecdotal experience and can vary considerably. Fibrinogen, AT levels can decline over time. ⁴⁴ Any benefits of replacing AT or alterations in the heparin response with AT supplementation are unclear. ACT low-range cards may provide more accurate values than high-range counterpart; suggest periodic anti-Factor Xa activity.
Cardiopulmonary bypass in adults or pediatrics	ACT 400–600 sec ^{38,39}	Range based on animal studies and anecdotal experience.
Hemodialysis	ACT 180–240 sec	
Treatment of DVT and PE	Prolong the aPTT to a range that corresponds to a whole blood heparin concentration of 0.2–0.4 units/mL by protamine titration or plasma anti-Factor Xa activity of 0.3–0.7 units/mL by amidolytic assay	Recommendation based on studies in patients with DVT and PE and on the relationship between the aPTT and effectiveness. ⁷
Treatment of myocardial infarction	CIUFH sufficient to prolong the aPTT 1.5–2 times control	With or without thrombolytic therapy having been administered. ⁴⁵

Several coagulation tests are used for monitoring heparin’s effect, and each has different limitations (see **Table 15-8**).^{11,42,47-51} Heparin concentration measurements may be used to reach a target therapeutic range (e.g., 0.3–0.7 units/mL), especially in unusual coagulation situations such as pregnancy where the reliability of clotting studies is questionable.⁴³ For DVT or PE, it may be preferable to correlate anti-Factor Xa activity concentrations with a target aPTT.^{11,52-54} Pharmacokinetic information derived from anti-Factor Xa activity concentrations may help to achieve therapeutic values more rapidly.³²

UFH: THERAPEUTIC MONITORING

Monitoring

The anticoagulant effects of heparin are most frequently monitored by the aPTT or anti-factor Xa concentration, although it is important to be familiar with each global test’s shortcomings and their potential impact on reliable interpretation of the results. When UFH is administered in fixed doses, the anticoagulant response varies among patients and within the same patient (inter- and intra-patient variability). This variability is caused by differences in heparin concentrations, neutralizing proteins, and rates of heparin clearance. Traditionally, for many aPTT reagents, therapeutic effect was thought to have been achieved with an aPTT ratio of 1.5–2.5 (measured by dividing the patient’s observed aPTT by the mean of the normal laboratory control aPTT). With newer, more sensitive aPTT reagents and differing laboratory instrumentation, the therapeutic range today could be higher, or even change in either direction with a new lot of reagents depending on its sensitivity to heparin. For less sensitive reagents the reported aPTT is lower.

Because aPTT reagents may vary in their sensitivity, the same aPTT ratio (1.5–2.5) for all reagents should be avoided. The therapeutic range for each aPTT reagent should be calibrated to be equivalent to an anti-Factor Xa heparin concentration of 0.2–0.4 units/mL by whole blood (protamine titration) or to an anti-Factor Xa heparin concentration of about 0.3–0.7 units/mL by amidolytic assay.⁵⁶

TABLE 15-8. COAGULATION TESTS USED TO REGULATE HEPARIN DOSING^{2,11,47-51}

Test	Range	Advantages	Disadvantages
aPTT	28–42 sec ^a Patient’s baseline should be used ^b	DVT and PE studies done using this test; recognized standards available; laboratory control equipment and quality control better; extensive clinical experience.	Lacks reproducibility with different instruments, reagents, and laboratories; nonlinear relationship to increasing heparin concentration; loss of accuracy of value above 150 sec.
ACT	80–130 sec ^a Patient’s baseline should be used ^b	Rapid bedside test; linear increase with heparin concentration in usual therapeutic range; extensive experience in hemodialysis, cardiopulmonary bypass, and ECLS patients.	Lacks reproducibility with ACT of >600 sec and with different reagents and instruments; limited clinical trials in DVT or PE patients. Affected by platelets, hemodilution, and hypothermia. The sensitivity and range of heparin intensity can vary between tests. Low-range and high-range kits are available and give different results. ⁵⁵
Whole blood heparin anti-Factor Xa concentrations	0.2–0.4 units/mL ^c	Overcomes inadequacies of aPTTs. Useful in heparin resistance and pregnancy.	Relative expense; not available in all institutions.
Plasma heparin anti-Factor Xa concentrations	0.3–0.7 units/mL	Overcomes some inadequacies of aPTTs. Useful in heparin resistance not attributed to low antithrombin, pregnancy, with lupus antibodies, and Antiphospholipid Antibody Syndrome. Less labor intensive than whole blood test.	Relative expense; not available in all institutions. May miss AT deficiency (if AT incorporated into the assay) and suggest adequate level of anticoagulation that may not be present. Variability in results can occur between clinical laboratories.

^aNormal range; varies by manufacturer and instrumentation.
^bIf unavailable or elevated, laboratory control values may be used.
^cTherapeutic range.

Anti-Factor Xa heparin concentrations, used by themselves with no reporting of an aPTT value, are another method of monitoring the anticoagulant effects of UFH. This method can be very useful in situations of potential heparin resistance, with the exception of AT deficiency. Elevated concentrations of fibrinogen or factor VIII, which can suppress aPTT values despite therapeutic heparinization, may not affect the ACT as much. In many cases, existing on-site laboratory instruments may be used to perform these tests and with increased utilization the per-test costs may be reduced.

Although there is evidence relating a higher UFH dose to the likelihood of a bleeding complication, there is also strong evidence supporting the contributions of patient-related factors such as recent surgery, generalized hemostatic abnormalities, peptic ulcers, neoplastic lesions, and use of concomitant antithrombotic medications (e.g., glycoprotein IIb/IIIa inhibitors, thrombolytic agents, anticoagulants, and antiplatelet agents) to an increase in the likelihood of bleeding complications.⁵⁷ Given these observations, most published guidelines, especially in cardiology settings, advocate a lower dose of UFH when administering antithrombotic agents together. Specific guidelines should be considered when treating the corresponding patient population.^{5,45}

Suggested sampling times

Specific sampling times for patients receiving UFH therapy vary according to the treatment indication. The times suggested for PE, DVT, extracorporeal circulation, and prophylaxis against venous thrombosis are listed in **Table 15-9**.^{2,58}

TABLE 15-9. SUGGESTED SAMPLING TIMES FOR PATIENTS RECEIVING UFH FOR VARIOUS INDICATIONS	
Indication	Sampling Time
PE or DVT	Continuous infusion UFH: coagulation test obtained 4–8 hr after start of infusion or after change in infusion rate (4 hr if without bolus and 6–8 hr if bolus given) ^{a,b}
	Intermittent sub-Q heparin: coagulation test obtained 6 hr after any dose
Prophylaxis of venous thrombosis	Coagulation test obtained 6 hr after sub-Q heparin dose
Extracorporeal circulation	Neonatal ECLS or cardiopulmonary bypass: ACT obtained every 30–60 min during dialysis treatment
	Hemodialysis: ACT obtained at least every 60 min during dialysis
	Neonatal ECLS using ACT, aPTT or Anti-Factor Xa heparin activity concentration: per institutional protocol

^aIf heparin is dosed using a combined pharmacokinetic and pharmacodynamic approach (see pharmacokinetic dosing approaches section), samples for heparin concentrations and clotting studies should be obtained 1, 4, and 12 hr after initiation of a continuous infusion. Doses should be adjusted after 1- and 4-hr samples, and precision should be checked with 12-hr samples.^{32,33}

^bRefer to dosing method 2.

Assay issues

Several technical variables may impact the responsiveness of the aPTT to UFH’s effect including the type of clot detection system used within the instrumentation and the contact activator and phospholipid composition of the reagent used. The response of the aPTT to UFH can be reduced in the presence of acute phase reactants such as elevated concentrations of fibrinogen or factor VIII. AT deficiency may cause a spurious “shortening” of aPTT that might lead to unnecessary increases in UFH dosing or inappropriately suggest heparin resistance.² Clot burden or size, duration of therapy, and concomitant disease states may also affect aPTT responsiveness. In general, the anti-Factor Xa assay may be a better test in the presence of high factor VIII or fibrinogen. However, anti-Factor Xa assays that have AT added to the test may miss resistance caused by low AT levels in the patient, or provide a higher result than anti-Factor Xa measurements using a test that does not add AT.

UFH: PHARMACODYNAMIC MONITORING—
CONCENTRATION-RELATED EFFICACY

Thrombus formation, extension, or embolization can be markers of inadequate heparin dosing or the development of heparin-associated thrombocytopenia. Factors that affect heparin concentrations and the anticoagulant effect relationship include AT, platelet factor 4 (PF4), and the elevated concentrations of factor VIII that can occur in a number of clinical states, including pregnancy, malignancy, acute thrombosis, and major surgery.^{51,52} These and other factors are discussed in **Table 15-10**.^{35,59-66}

TABLE 15-10. FACTORS TO CONSIDER WHEN INTERPRETING UFH
PHARMACODYNAMICS

Factor	Comments
AT (obtained with baseline coagulation studies and on day 3) ^{35,59-62}	If AT concentrations are notably below normal values for a given age group, heparin may not exert its full anticoagulant effect at usual doses and concentrations (i.e., heparin resistance). ³⁵ Decreased AT predisposes the patient to thrombus formation ³⁵ and PE during heparin therapy for DVT. ⁵⁹ AT concentrations may fall due to heparin therapy, ⁵⁹ but AT is easily replaced with administration of blood, plasma, or AT concentrates. Normal AT values are lower in neonates and infants compared to adults.
PF4 (not routinely measured) ^{61,62}	PF4 neutralizes heparin effect and promotes thrombus formation. When PF4 is increased (e.g., during disseminated IV coagulation or immune thrombocytopenia), patients may be relatively heparin resistant. ^{63,64} Elevated PF4 in plasma also may inactivate heparin in vitro, giving falsely low heparin activity assessments.
Heparin cofactor II (not routinely measured) ⁶⁵	This factor plays a minor role when AT concentrations are adequate but can be important if AT deficiency occurs.
Coagulation tests	Correlation of heparin concentrations with coagulation tests shows at least a five-fold variation in clotting tests at the same concentration. ¹¹
Pregnancy	During the third trimester, pregnant patients display relative heparin resistance and require higher doses. ⁴³
Circadian effect	Effects of heparin on coagulation tests (both the aPTT and anti-Factor Xa activity) may be greater (up to 50% to 60%) at night or during sleeping periods than during the daytime. ⁶⁶ This suggests the variability is a pharmacokinetic effect instead of an assay issue.

UFH: PHARMACODYNAMIC MONITORING—
CONCENTRATION-RELATED TOXICITY

Heparin use can lead to a variety of toxic outcomes related or not related to its pharmacological effect. **Table 15-11** outlines the various heparin-related toxicities.

TABLE 15-11. HEPARIN-RELATED TOXICITIES

Toxicity	Monitoring and Detection	Prevention and Management
Major bleeding ⁶⁷ (leading to blood transfusion, heparin discontinuation, prolonged hospital stay, or death)	Clinical signs depend on site of bleeding. Increased risk correlated with increased dose, but studies of relationship to coagulation tests are limited. Risk factors include female >60 yr old, dose of >25 units/kg/hr, concomitant aspirin, recent invasive procedure or traumatized sites, heavy alcohol use, increased length of use, and intermittent IV bolus dosing.	Coagulation tests kept below upper limit of targeted therapeutic endpoint. A lower bolus dose strategy can also be considered. Length of use limited by early initiation of warfarin. Heparin effects reversed with protamine sulfate (see reversing heparin's effect section).

Minor bleeding ⁶⁷	Relationship to heparin dose and coagulation studies was noted in some reports. Guaiac-positive stool and bleeding from nose, gums, puncture sites, urine, sputum, etc., occur.	Intramuscular route avoided for medications. Coagulation tests kept below upper limit of targeted therapeutic endpoint.
Thrombocytopenia ^{70,71}	Direct platelet effect is not dose related, with onset 1–20 (usual 5–9) days after start of heparin. Effect may be transient. Suspect HIT if there is a 50% decline in baseline platelet count after commencing UFH. Platelet counts should be monitored at least every other day while patient receives heparin. ⁷⁰	Use pork intestine heparin instead of beef lung (no longer available in many countries) heparin when possible. Heparin stopped if platelets are <100,000, there is a 50% decline from baseline platelet count, or if bleeding occurs. ^{69,70} May need to replace with an alternative anticoagulant.
Thrombosis due to immune thrombocytopenia ⁶⁸⁻⁷⁰	Triad of decreased platelets, high heparin dose requirements, and formation of arterial thrombi may be present. If platelet count decreases, a functional or activation assay designed to detect HIT-related antibodies should be done if possible. Do not await results of confirmatory tests before discontinuing heparin.	Initiate warfarin cautiously and at low dose. Avoid heparin in patients with prior history. If thrombosis is suspected, stop heparin immediately, including flushes and arterial catheters. Initiate parenteral direct thrombin inhibitor or fondaparinux given as treatment until warfarin effect is adequate. ^{69,70} Warfarin should not be used alone initially. ⁷⁰
Osteoporosis ^{2,71}	Problem only occurs with long-term use (>6 months) of doses over 20,000 units/day. Bone films in otherwise at-risk patients may be appropriate.	Risk reduced by assuring adequate calcium intake. May consider use of LMWH.
Hyperkalemia	Monitor K ⁺ at least every 3–4 days during therapy.	Fluids and electrolytes adjusted.
Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	Monitoring of laboratory values probably is not routinely necessary.	Initiate warfarin and stop heparin as soon as possible. Probably not due to liver disease.
Transient alopecia	No special monitoring necessary.	No special treatment performed.
Other side effects: Skin lesions Skin necrosis Hypersensitivity Priapism	Observation.	Suspect heparin-induced thrombocytopenia with thrombotic complication with skin lesions/skin necrosis. Remove all forms of heparin therapy and initiate alternative therapy.

REVERSING HEPARIN'S EFFECT

Protamine sulfate is used to neutralize heparin following severe UFH overdosing or severe, unexpected bleeding. Each milligram of protamine sulfate neutralizes approximately 90 units of beef lung heparin sodium, 115 units of heparin sodium derived from porcine intestinal mucosa, or 100 units of heparin calcium. Overdosing with protamine must be avoided as it, too, can independently promote bleeding. Its administration can also cause severe hypotension and anaphylactoid or anaphylactic reactions. Protamine should be administered slowly over at least 10 minutes to reduce the possibility of anaphylaxis. Outside of reversing heparin after going off cardiopulmonary bypass (CPB), a total single dose of 50 mg should not be exceeded. In CPB, a repeat dose of protamine sulfate may be necessary to

neutralize large amounts of heparin given during a procedure or operation and that may redistribute from the tissues back into the plasma. Prothrombin complex concentrate (PCC) and/or recombinant activated factor VII (rFVIIa) have been used to assist in establishing hemostasis, but these products have no activity to directly neutralize heparin and should not be used as a substitute for protamine sulfate. **Table 15-12** provides dosing guidelines for protamine sulfate based on time after UFH dosing. There are antidotes currently under development to neutralize anti-factor Xa anticoagulants that will neutralize the effects of heparin while in the system.

Because the half-life of IV heparin is relatively short at 60–90 min; only heparin given during the preceding several hours needs to be considered when calculating the dose of protamine sulfate. For example, a patient receiving UFH at 1,250 units/hr requires approximately 30 mg of protamine sulfate. Neutralization of sub-Q UFH may require a prolonged infusion or repeat doses of protamine sulfate due to continued absorption from the site of administration. The aPTT can be used to assess the effectiveness of protamine sulfate neutralization in reversing the anticoagulant effects of heparin.² Currently under development are parenteral agents (e.g., Andexanet alfa and Ciraparantag) that directly reverse the effects of both oral and parenteral anti-factor Xa agents.⁷² Thus, these agents can also reverse the effects of UFH or prevent the effects of heparin occurring when used in emergent procedures such as placing the patient on a cardiac bypass circuit. Clinicians may need to wait for the effects of these agents, which have fairly short half-lives, to diminish prior to initiating heparin.

TABLE 15-12. PROTAMINE SULFATE DOSING TO REVERSE UFH EFFECT

Time after Heparin Dose	Protamine Sulfate Dose ^a
<30 min	1–1.5 mg for each 100 units of heparin in last dose
30–120 min	0.5–0.75 mg for each 100 units of heparin in last dose
>120 min	0.25–0.375 mg for each 100 units of heparin in last dose
Heparin IV infusion	25–50 mg after infusion is stopped

^aIn the event of major bleeding, some clinicians recommend using the lower end of these ranges to avoid potential bleeding caused by excess protamine sulfate. Prescribing directions for protamine sulfate should be carefully followed due to the risks associated with its use. Doses of 50 mg should not be exceeded outside of the operating room. The risk of severe adverse reactions, such as hypotension and bradycardia, can be minimized by administering protamine slowly (i.e., over approximately 10 min).

UFH: DRUG-DRUG INTERACTIONS

Heparin does not have definitively identified pharmacokinetic or pharmacodynamic drug interactions, although platelet-inhibiting drugs or drugs irritating to the gastrointestinal tract could in theory lead to complications. Use of the drugs listed in **Table 15-13** in patients receiving UFH may warrant adjustments in dosing or sampling procedures.

UFH: DRUG–DISEASE STATE OR CONDITION INTERACTIONS

UFH’s pharmacokinetic parameters may be influenced by a patient’s condition or underlying disease state. Table 15-6 provides adjustment factors for several such conditions and disease states.

LOW MOLECULAR WEIGHT HEPARINS

LMWHs are now widely used for the prevention and treatment of venous and arterial embolic disease. They are obtained by fractionating or depolymerizing UFH, which is a heterogeneous mixture of heparin chains with molecular weights of 5,000–30,000 Daltons. The mean molecular weight of LMWHs is approximately 4,000–5,000 Daltons.

TABLE 15-13. HEPARIN-DRUG INTERACTIONS

Drug	Interaction	Prevention and Management
Nitroglycerin (IV) ^{73,74}	Resistance to anticoagulant effect of heparin.	Infuse drugs at different sites. Adjust doses for therapeutic aPTT.
Platelet function inhibitors ⁷⁵ (e.g., aspirin and nonsteroidal anti-inflammatory agents)	Increased risk of bleeding.	Avoid if possible. Salsalate, an alternative anti-inflammatory agent, does not inhibit platelet aggregation.
Decreased in vitro binding of basic and acidic drugs ⁷⁶ (e.g., propranolol and quinidine; in vivo effect not shown)	Increased lipoprotein lipase activity by heparin increases free fatty acid (FFA) formation, leading to displacement by FFAs.	Heparinized samples should be processed rapidly when analyzing for free (unbound) drug. Interpret results cautiously.
Warfarin ⁷⁷	aPTT is prolonged.	Heparin dose reduced, if necessary, to prevent excessive aPTT. May consider role of anti-Factor Xa heparin monitoring.
Thrombolytics GPIIb/IIIa antagonists	Risk of bleeding increases.	Heparin dose reduced.

FDA-approved indications for the LMWHs vary by drug. Each has proven to be reasonably safe and effective for the prevention and treatment of VTE. LMWHs are used for prevention of DVT after hip replacement, knee replacement, abdominal surgery, and for trauma, oncology, medical, and spinal cord injury patients. In addition, LMWHs are used in the treatment of unstable angina, non-ST elevation myocardial infarction (NSTEMI), DVT, and PE.

The LMWHs are often viewed as a homogeneous group, but their derivation from UFH using different methods of enzymatic or hydrolytic cleavage results in different molecular weight profiles for each product. These variations may result in clinically relevant differences in pharmacokinetic and pharmacodynamic effects. Compared with UFH, which has a ratio of anti-Factor Xa to anti-Factor IIa activity of approximately 1:1, the various commercially available LMWHs have anti-Factor Xa to anti-factor IIa ratios varying between approximately 2:1 and 4:1 depending on their molecular size distribution (see **Table 15-14**).⁷⁹ A generic form of enoxaparin was approved for distribution in the United States. Although no comparative phase III clinical trials have been undertaken, the measured activity profile appears to be similar to that of the original brand.^{80,81}

The pharmacokinetics of UFH and LMWHs differ. LMWHs are less protein bound than UFH. Because of their longer elimination half-lives, some LMWHs may be administered as single daily doses, which can provide certain advantages over UFH.² Routine monitoring of coagulation tests (e.g., aPTT) or anti-Factor Xa heparin concentrations during LMWH therapy is generally considered unnecessary and is not routinely recommended.^{2,82} Sub-Q injection of the LMWHs produces only minimal effects on the aPTT. Thus, aPTT values cannot be reliably used to monitor or document efficacy and safety of LMWHs. Anti-Factor Xa assay by either whole blood or plasma determinations can be used, although routine monitoring with this assay is not necessary. The Ninth ACCP Conference on Antithrombotic and Thrombolytic Therapy recommends against routine monitoring with anti-Factor Xa when LMWHs are used for initial treatment of DVT in most settings.² Anti-Factor Xa heparin activity measurements may be considered in selected populations including pregnancy and pediatrics. Monitoring anti-Factor Xa has been proposed in patients with renal impairment (CrCl < 30 mL/min) because LMWHs are partially eliminated by the kidneys, and in the morbidly obese where response may show increased variation when fixed doses are used relative to weight-based dosing. However, correlation between measured anti-Factor Xa activity and renal function or weight is poor, limiting the utility of using these measurements for dosing adjustments.⁸⁶ Data validating the use of anti-Factor Xa activity for dosing adjustments overall are not currently available, limiting any validity with this approach to management.

If anti-Factor Xa results are used for monitoring, the therapeutic range by chromogenic/amidolytic assay for venous embolic disease treated twice-daily is 0.6–1 units/mL.² This should be measured

at the time of peak effect post injection (i.e., 4 hr after sub-Q administration) for LMWHs. Current data supporting the use of anti-Factor Xa are limited in the setting of ACSs. In the setting of elective percutaneous coronary intervention (PCI), anti-Factor Xa concentrations greater than 0.9 units/mL were correlated with increased non-coronary artery bypass grafting major and minor bleeding, but not major bleeding alone.⁸⁷ In the setting of NSTEMI, anti-Factor Xa less than 0.5 units/mL was an independent predictor of increased mortality within 30 days.⁸⁸

TABLE 15-14. LMWH PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS⁸²⁻⁸⁵

LMWH	Brand Name	Average Molecular Weight (Daltons)	Percent Bioavailability (F)	Half-Life (hr)	Xa:IIa Binding Affinity Ratio
Dalteparin	Fragmin	5000	87 (0.87)	3	2.7:1
Enoxaparin	Lovenox	4500	92 (0.92)	4.5	3.8:1
Tinzaparin	Innohep	6500	87 (0.87)	3.5	1.9:1

LMWH: USUAL DOSAGE RANGE IN THE ABSENCE OF CLEARANCE-ALTERING FACTORS

LMWHs have a longer half-life and more predictable anticoagulant response to weight-adjusted doses than UFH. These characteristics allow some LMWHs to be administered once daily. The ABW should be used for dosing, and it has been suggested to avoid capping the dose at a certain weight, although some clinicians may choose to do so.⁸⁹ Dosing of LMWHs is disease state- and product-specific, with different doses being administered based on the specific indication and product. **Table 15-15** shows suggested dosing for product by specific indications.

TABLE 15-15. LMWH PRODUCT SUB-Q DOSING BY DISEASE-STATE INDICATION^{82-85,92}

LMWH	General Surgery Prophylaxis against DVT	Orthopedic Surgery Prophylaxis against DVT	DVT Treatment
Dalteparin	5,000 units sub-Q daily	2,500 units sub-Q daily or 5,000 units sub-Q daily	Cancer related DVT; 200 units/kg for the first month followed by 150 units/kg daily for up to 6 months. Therapy beyond 6 months has not been established. ^{90,91}
Enoxaparin	40 mg sub-Q daily ^a	30 mg sub-Q every 12 hr ^a or 40 mg once daily if initiated pre-operative	1 mg/kg sub-Q every 12 hr ^a or 1.5 mg/kg sub-Q daily. ^a
Tinzaparin	Not indicated	Not indicated	175 units/kg sub-Q daily.

^aDosing guidelines for enoxaparin in patients with severe renal impairment (CrCl <30 mL/min) are as follows: For approved prophylaxis indications (hip and knee replacement, general abdominal surgery and medical prophylaxis) the dose is 30 mg sub-Q daily. For approved treatment indications (acute coronary syndromes and DVT with or without PE) the dose is 1 mg/kg sub-Q daily.^{83,89}

For the dosing of enoxaparin in renal failure, analysis was primarily done from patients with SCr values below 2.5. Dosing of enoxaparin when the CrCl is less than 20 mL/min remains unclear beyond regimens explored to maintain the dialysis circuit.^{89,93} The use of enoxaparin 0.6–0.7 mg/kg once daily has been reported to be safely used in patients requiring hemodialysis while transitioning to warfarin.⁹⁴ For tinzaparin or dalteparin, no dosing adjustment is necessary above 20 mL/min.⁸⁹

LMWH: DOSAGE FORM AVAILABILITY

LMWHs are available only as solutions for injection. Currently FDA approved for sub-Q use, some clinical trials have investigated the IV route of administration for procedural use, emergent situations where immediate effect is needed prior to peak onset of sub-Q route (e.g., ACS), or instances of questionable sub-Q absorption. Manufacturers supply LMWHs for injection in a variety of different concentrations

in various delivery devices. Enoxaparin and dalteparin may be diluted and stored in syringes for use in low-weight infants.^{95,96}

LMWH: GENERAL PHARMACOKINETIC INFORMATION

Sub-Q doses of LMWHs are 87% to 92% bioavailable ($F = 0.87\text{--}0.92$), which is considerably greater than that of sub-Q doses of UFH (30%; $F = 0.3$). This may make dose changes unnecessary when converting from sub-Q to IV if IV dosing is approved in the future.^{97,98} In selected situations, such as in the setting of ACS, LMWHs may be administered IV for a more rapid onset of anticoagulation. LMWHs have been shown to achieve heparin activity concentrations (by anti-Factor Xa assay) in the detectable range of 0.5–1 units/mL as soon as 30 min after sub-Q injection⁹⁹ and 3–10 min after IV administration of appropriate doses.

This high degree of bioavailability does not appear to hold true in all patient populations. Those medically critically ill and critically ill trauma and surgical patients may have altered pharmacokinetics or pharmacodynamics leading to an impaired response to standard dosing as measured by anti-Factor Xa, possibly leading to greater incidence of VTE.^{100–103} Site of administration may also be important. In one analysis, the measured anti-Factor Xa activity of enoxaparin was significantly lower in obese patients when administered in the thigh compared to the abdomen.¹⁰⁴

The plasma recoveries and pharmacokinetics of LMWHs differ from UFH due to differences in the binding properties of the two sulfated polysaccharides to plasma proteins and endothelial cells. LMWHs bind much less avidly to heparin-binding proteins than UFH, a property that contributes both to the superior bioavailability of LMWHs at low doses and their more predictable anticoagulation response in noncritically ill patients. LMWHs also do not bind to endothelial cells (in culture), a property that could account for their longer half-life and dose independent clearance.⁷⁹ Active and inactive fragments of LMWHs are partially cleared by the kidney and their half-life is increased in patients with renal failure.^{104–106} Pharmacokinetic and pharmacodynamic differences among the LMWHs are shown in Table 15-14.

LMWH: DOSING STRATEGIES

The following are guidelines for treating and monitoring VTE with LMWHs.

Suspected VTE^{2,3,7,108}

- Obtain baseline aPTT, PT/INR, platelet count, and CBC.
- Check for contraindication to heparin therapy.
- For patients with a high clinical suspicion of DVT, ACCP Guidelines recommend initiating treatment with immediate-acting parenteral anticoagulant while awaiting the outcome of diagnostic tests. See treatment guidelines for confirmed VTE in UFH and LMWH sections.
- Order imaging study.

Confirmed VTE^{3,108–110}

- In patients with acute VTE, current ACCP recommendations cite initial treatment with LMWH once or twice daily over UFH as an outpatient if possible and as an inpatient if necessary.³ LMWH is preferred for treatment in patients with cancer.¹¹⁰
- Start VKA (e.g., warfarin) therapy on day 1 if no opposing reasons to initiate; adjust subsequent daily dosing according to INR. See Chapter 23, Warfarin, for detailed discussion of warfarin initiation.¹⁰⁸ Another option is to start dabigatran or edoxaban at least 5–7 days after receiving therapeutic LMWH treatment (no need to overlap agents).
- For patients who first received UFH and are now on LMWH, ACCP recommendations suggest platelet count monitoring every 2–3 days from day 4 to day 14, with less frequent monitoring (i.e., once weekly) taking place outside this time period until LMWH is stopped.¹⁰⁹

- For patients who have received only LMWH and would be considered to have low risk (<1%) for HIT, ACCP guidelines recommend that clinicians not use routine platelet count monitoring.¹⁰⁹ However, FDA-approved package labeling for the respective LMWHs still suggests continued vigilance against the potential of thrombocytopenia by periodic platelet count determinations.
- With warfarin, stop LMWH after at least 5–7 days of combined therapy and once the INR is >2 and stable. With dabigatran or edoxaban, stop LMWH after at least 5 days of treatment and begin DOAC therapy.
- For recurrent VTE while on therapeutic oral anticoagulant therapy, ACCP guidelines recommend temporarily changing to a LMWH for 1 month.¹¹⁰
- For recurrent VTE on LMWH in a compliant patient, increase the LMWH dose by 1/4 to 1/3.¹¹⁰

LMWH: THERAPEUTIC RANGE

LMWHs have been monitored by use of anti-Factor Xa heparin concentrations.^{2,111} Desired anti-Factor Xa heparin concentrations for twice-daily dosing in venous embolic disease are 0.6–1 units/mL.² For patients receiving once-daily dosing, a target range of 1–2 units/mL has been suggested, but no recommendations are currently available due to lack of supporting data.⁵⁹ If used, measurements for anti-Factor Xa should be taken 4 hr after a sub-Q dose.^{2,59}

LMWH: THERAPEUTIC MONITORING

LMWHs are not monitored by aPTT determinations. Neither the manufacturers nor the Ninth ACCP Conference on Antithrombotic and Thrombolytic Therapy recommend routine Anti-Factor Xa monitoring of treatment with these agents.²

LMWH: ASSAY ISSUES

Different assays and instrumentation along with correct measuring of anti-Factor Xa can result in notable differences in reported values. Practitioners should be aware of their institution's methods and how these values compare to other observations or established standards.

LMWH: PHARMACODYNAMIC MONITORING— CONCENTRATION-RELATED EFFICACY

It is generally accepted that some minimum concentration of LMWH must be maintained to achieve an effective antithrombotic state and that inadequate anticoagulant therapy results in higher rates of thromboembolic disease recurrence. Animal experiments support the concept that a plasma concentration of heparin between 0.2 and 0.4 units/mL (measured by protamine sulfate titration) is necessary to interrupt an ongoing thrombotic process.¹¹² Studies examining the efficacy of LMWHs for treatment of thromboembolic disease have often used symptomatic recurrent disease as the end-point. No differences in outcomes for recurrence of thromboembolic disease have been noted for LMWHs when compared to titrated UFH.^{113,114} For prophylaxis against thromboembolic disease, development of a VTE, or bleeding have been end-points for determining lack of efficacy and toxicity.

Much of the literature focused on the utility of anti-Factor Xa measurements for monitoring patients receiving LMWHs gives conflicting information on decisions that should be made with the results. In general, the therapeutic range with this class of agents is wide enough that monitoring is not perceived to be necessary. However, some special dosing populations have been suggested as potentially benefiting from such monitoring. Recommendations of the Ninth ACCP Conference on Antithrombotic and Thrombolytic Therapy are to avoid monitoring concentrations for LMWH therapies except in pregnant women, neonates, and children receiving therapeutic doses.² The recommendations to avoid monitoring are due in large part to the absence of data correlating anti-Factor Xa values with clinical outcomes.

Caution should be exercised when interpreting measured anti-Factor Xa values. Data suggest a high degree of variability in the measured anti-Factor Xa activity at standard dosing in both obese⁸⁶ and normal weight patients. For the anti-factor Xa assay, UFH and LMWH calibrators are available, and depending on which one is used, results will vary. Wide variability also occurs between laboratories. Due to the limited information on dosing in the obese population, common sense would suggest the need for monitoring anti-Factor Xa and adjusting the dose if necessary. However, a current review of the data does not support the routine monitoring due to obesity alone.¹¹⁵ Unfortunately, therapeutic outcomes associated with this approach are unknown, and given the variability in assay methods, the potential exists for this approach to lead to either over- or under-dosing the patient.

LMWH: PHARMACODYNAMIC MONITORING—
CONCENTRATION-RELATED TOXICITY

The antithrombotic and hemorrhagic effects of LMWHs have been compared with UFH in various experimental animal models. When compared on a gravimetric basis, LMWHs exhibit decreased potential for hemorrhagic episodes in animal models.

Contemporary studies evaluating alternative regimens of CIUFH versus LMWHs reveal rates of major bleeding ranging from 0 to 7% for CIUFH and rates of fatal bleeding ranging from 0% to 2%. For LMWHs, the rates of major bleeding range from 0% to 3% and fatal bleeding from 0% to 0.8%. These data suggest that LMWHs do not result in increased risk of major bleeding compared to UFH.¹¹³ Differences in the relative antithrombotic to hemorrhagic ratios among these polysaccharides might be explained by the observations that LMWHs have less inhibitory effects on platelet function and vascular permeability.⁷⁹

The potential for neuraxial hematoma exists if epidural, spinal anesthesia, or other spinal punctures are performed while patients are anticoagulated for prevention of thromboembolic complications with any of the LMWHs or heparinoids.

LMWHs have a lessened incidence of thrombocytopenia compared to UFH,⁷⁹ but patients with antibodies to UFH may have similar reactions to LMWHs, leading to HIT.⁷¹ Because of the high incidence of cross-reactivity with heparin antibodies, LMWH should be avoided in patients with HIT.

LMWH: REVERSING THE EFFECT OF LMWHs

The effect of LMWHs may be partially reversed by protamine sulfate, but care should be taken to avoid overdosing as it may also cause bleeding. Higher sulfated compounds (tinzaparin > dalteparin > enoxaparin) may be neutralized to a greater extent by protamine, but the clinical significance of this is unclear.¹¹⁶ Administration of protamine can also cause severe hypotension and anaphylactic reactions. Manufacturers recommend slow IV injection of 1 mg of protamine for every 100 anti-Factor Xa International Units of dalteparin or 1 mg of enoxaparin for reversal if less than 8 hr has elapsed since the dose of LMWH. Based on time of dose of the LMWH relative to the hemorrhagic complication, protamine sulfate may not be necessary. **Table 15-16** gives guidelines for reversal of LMWHs with respect to time since the last LMWH dose. There are antidotes currently under development to neutralize the effect of anti-Factor Xa anticoagulants.⁷²

TABLE 15-16. PROTAMINE DOSES FOR REVERSAL OF LMWHs ^a			
LMWH	<8 hr	8–12 hr	>12 hr
Dalteparin	1 mg/100 anti-Factor Xa units	0.5 mg/100 anti-Factor Xa units	Not necessary
Enoxaparin	1 mg/1mg	0.5 mg/1mg	Not necessary
Tinzaparin	1 mg/100 anti-Factor Xa units	0.5 mg/100 anti-Factor Xa units	Not necessary

^aPrescribing directions for protamine sulfate should be carefully followed because of the risks associated with its use. Doses of 50 mg of protamine should not be exceeded. The risk of severe adverse reactions, such as hypotension and bradycardia, can be minimized by administering protamine slowly (i.e., over ~10 min).

LMWH: DRUG–DRUG INTERACTIONS

Similar to UFH, LMWHs do not have definitively identified drug interactions, although platelet-inhibiting drugs or drugs irritating to the gastrointestinal tract could theoretically lead to complications. See Table 15-13 for heparin drug interactions.

LMWH: DRUG–DISEASE STATE OR CONDITION INTERACTION

LMWHs bind less avidly than UFH to the acute phase reactant plasma proteins that are often increased during illness. Endogenous plasma proteins, platelet factor 4 (released from activated platelets), and von Willebrand's factor are circulating substances released during illness and clotting respectively. Thromboembolic disease and comorbid conditions account for changes in these plasma proteins that, in turn, causes variable anticoagulant responsiveness with UFH. Such variability is seen less often with LMWHs because of their decreased binding to these acute phase reactant substances and their improved bioavailability.

Smaller doses of LMWHs are used for prophylaxis than for documented thromboembolic disease. As might be expected, low-weight patients treated with fixed prophylaxis doses (non-weight adjusted) of enoxaparin show an increase in exposure (AUC). These patients, and perhaps low-weight patients treated with other LMWHs, should be observed carefully for signs and symptoms of bleeding. The safety and optimal use of prophylactic doses of LMWHs in elderly patients with impaired renal function was evaluated in 125 elderly patients (mean $\pm$ SD age 87.5 ± 6.3 yr, body weight 56.4 ± 11.9 kg, and CrCl 39.8 ± 16.1 mL/min) who received 40-mg daily doses of enoxaparin for up to 10 days.¹¹⁷ The authors reported that the mean anti-Factor Xa concentration was 0.64 ± 0.23 units/mL (range 0.24–1.5) and concluded that CrCl < 30 mL/min and bodyweight < 50 kg were associated with significantly higher maximal anti-Factor Xa activity. Larger clinical trials assessing the safety of LMWH in elderly patients are needed to determine the clinical relevance of these findings.

Anti-Factor Xa concentrations are not significantly increased when LMWHs are administered to obese patients in doses based on ABW. This observation has been made for enoxaparin in patients with ABW up to 144 kg (body mass index [BMI] = 48); dalteparin in patients with ABW up to 190 kg (BMI = 58); and tinzaparin in patients with ABW up to 165 kg (BMI = 61).^{2,89}

Although current product labeling for LMWHs makes no specific recommendations for prophylaxis dosing in obese patients (BMI > 30), recommendations of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy state that “in the absence of clear data, it seems prudent to consider a 25% increase in the fixed thromboprophylactic dose of LMWHs in very obese patients.”³⁰ The Eighth ACCP conference suggested that for general surgical patients at higher risk, “higher than standard doses of LMWH” should be used.¹¹⁸ Currently, the Ninth ACCP Antithrombotic Therapy and Prevention of Thrombosis Guidelines make no specific suggestions or recommendations as to prophylaxis dosing in the obese patients.² For VTE treatment, use of the LMWH enoxaparin once daily is associated with a higher incidence of recurrent thrombosis in obesity and cancer.^{119,120}

There are conflicting data on the use of LMWHs and monitoring anti-Factor Xa activity in renally impaired patients. These include questions on the appropriate cutoff value that defines renal impairment that correlates with an increased risk of bleeding. The manufacturer's recommendation and FDA-approved labeling for enoxaparin suggest a dosage reduction and interval increase (e.g., 30 mg administered sub-Q once daily for any approved prophylaxis indication; 1 mg/kg administered once daily for any approved treatment indication) for patients with CrCl ≤ 30 mL/min (excluding hemodialysis patients).⁸³ The challenge with this recommendation is that patients with a CrCl below 20 mL/min or on hemodialysis were excluded in clinical trials. The Ninth ACCP Conference observed that in the setting of diminished renal function most well-designed studies demonstrated increased

anti-Factor Xa activity with diminished renal function and that the pharmacokinetic effect may differ among LMWHs.² One retrospective study of chronic dialysis patients demonstrated long-term use of enoxaparin 30 mg sub-Q daily for VTE prophylaxis was not associated with an increased incidence of bleeding or thrombosis compared to UFH.¹²¹ Another analysis showed that once-daily administration of a full dose (1.5 mg/kg) of enoxaparin did not result in accumulation among nonhemodialysis patients with a CrCl $\leq$ 30 mL/min.⁸⁶ However, it has been suggested that individuals with CrCl between 30 and 60 mL/min receive a 25% reduction in the dose.⁹³ When dose adjusted, LMWHs (enoxaparin 0.7 mg/kg; dalteparin 39 units/kg) appear to provide predictable anti-Factor Xa measurements in hemodialysis patients.¹²² Insights for the use of LMWH at treatment doses in the setting renal failure requiring hemodialysis is very limited. In one single center retrospective analysis reported the successful and safe use of enoxaparin 0.6 to 0.7 mg/kg once daily without measuring any anti-Factor Xa activity while transitioning to warfarin.⁹⁴

FONDAPARINUX

Fondaparinux is the 5-sugar moiety analogue of the pentasaccharide binding sequence that allows heparin to exact activity through AT, and it has highly selective anti-factor Xa activity. It does not appreciably inhibit factor IIa and is made artificially and is an option in patients with a porcine allergy. Unlike UFH or the LMWHs, it is a synthetic compound. Fondaparinux can rapidly bind to AT causing an irreversible conformational change. It is subsequently released, allowing binding to other AT molecules. The absence of the additional chains may diminish its triggering of immune-mediated HIT.

FONDAPARINUX: DOSAGE RANGE

Fondaparinux has been studied in several dose response phase II trials. In the management of proximal DVT, no differences were observed between 5-, 7.5-, and 10-mg dosing regimens for recurrent VT or bleeding events.¹²³ In the setting of ACSs, no differences between 2.5 mg, 4 mg, 8 mg, and 12 mg were seen for the primary end-points of death, myocardial infarction, recurrent ischemia, or bleeding. Overall, it appears that there are no differences in response based on doses from 2.5 mg to 10 mg.^{123,124} Fondaparinux has been studied in phase III clinical trials using 2.5 mg for VTE prophylaxis in elective knee and hip replacements, hip fracture, ACSs, high-risk abdominal surgery, and for medical prophylaxis.¹²⁵⁻¹³⁰ It has also been studied in doses of 5 mg (weight < 50 kg), 7.5 mg (weight 50–99 kg), and 10 mg (>100 kg) in the treatment of VTE. In general, fondaparinux was found have similar efficacy to CIUFH and enoxaparin with a slight advantage in reducing recurrent thrombotic events, which was balanced by a slight increase in reported bleeding.¹³¹

Due to its prolonged half-life and renal elimination profile, use in individuals with a CrCl below 30 mL/min is discouraged. In patients with severe renal insufficiency or on hemodialysis, limited information exists on the safe use of fondaparinux. In limited case reports and small case series, a dose of 1.5 mg daily or 2.5 mg every other day has been explored when the CrCl is between 20 and 50 mL/min.⁹³ In patients on hemodialysis, 0.05 mg/kg prior to hemodialysis has provided adequate anticoagulation, but with a potential for accumulation over time.¹²¹ Additional studies are needed to determine the safest approach to using fondaparinux in severe renal insufficiency. Generally, UFH or LMWH may be preferred agents.

Fondaparinux should not be initiated until 6 to 8 hr after joint replacement procedures. In one analysis, no differences in major or minor bleeding or symptomatic VTE were observed between initiating therapy 8 $\pm$ 2 hr after surgery compared to the morning after.¹³³ This provides some option in the initiation of therapy postoperatively. In a meta-analysis of 4 randomized phase III clinical trial for major orthopedic surgery, a 55% reduction (13.7% versus 6.8%) in thrombus by venography was observed with fondaparinux compared to enoxaparin.¹²⁵

Dosage form availability

Fondaparinux is supplied only as a solution for injection. Although FDA-approved for sub-Q administration, fondaparinux has been administered IV for procedural use in clinical trials.

General pharmacokinetic information

Fondaparinux is rapidly and completely absorbed after sub-Q injection ($F = 1$) and distributes primarily into the blood ($V = 7\text{--}11\text{ L}$). It is primarily eliminated renally, with 77% excreted unchanged in the urine. It has a relatively long half-life (17–21 hr) that is longer than UFH or LMWH and can be administered once daily.¹³⁴ Total clearance is approximately 25% lower in patients with a CrCl of 50–80 mL/min, 40% lower when 30 to 50 mL/hr, and 55% lower when less than 30 mL/min. As such, effects can last more than one day, especially in renal insufficiency. Peak effect is reached approximately 2 hr after sub-Q injection and 10 minutes after IV administration.¹³⁵ PT, INR, and aPTT are not typically altered during its use. A linear relationship between the AUC and dose has been observed.¹³⁶

Therapeutic monitoring

Because fondaparinux exerts its anticoagulant effects thru the inhibition of activated Factor Xa, it would theoretically be useful to measure anti-Factor Xa activity to assess the degree of effect. A linear correlation with the concentration of fondaparinux and anti-Factor Xa activity has been demonstrated,¹³⁷ suggesting that activity could be measured using the anti-Factor Xa activity as a surrogate marker. However, the lack of a dose-dependent response or other observed pharmacodynamic measures diminish the potential value of its use.

Reversing the effect of fondaparinux

Because of the small molecular size of fondaparinux and the lack of sulfide bonds, protamine is not considered effective in reversing this drug's effects. The use of rFVIIa has been explored, with some ability to re-establish hemostasis observed for a short period of time.^{138–140} In one ex-vivo analysis, low-dose prothrombin complex concentrate containing activated clotting factors (FEIBA® 20 units/kg) showed enhanced reversal of anticoagulation over rFVIIa in thrombin production.¹⁴¹ The suggested explanation is the presence of multiple clotting factors including prothrombin that are already bound to free Factor Xa encourages thrombin generation, and that the anti-Factor Xa activity from fondaparinux might inhibit free Factor Xa and diminish the impact of rFVIIa.

Drug–condition interactions

Early observations suggested that fondaparinux might be an option for the treatment or prophylaxis of DVT/PE in patients with HIT.^{70,71} This may be attributed to the limited ability for the small molecule to trigger platelet factor 4 and the immune-mediated response leading to HIT.¹⁴² Single center analysis and case series have also suggested that the lack of an immune response and limited cross-reactivity with HIT antibodies make fondaparinux a viable anticoagulation option during HIT management.^{143,142} However, cases of fondaparinux-induced HIT have been reported.¹⁴⁵ The ability to administer an agent once daily and avoid more continuous infusion direct thrombin inhibitors has made fondaparinux an attractive option, especially after platelet count recovery and clinical stability has occurred. Given the lack of clinical trials for this use, the role of fondaparinux is unclear in HIT management.

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LIDOCAINE

Toby C. Trujillo

Lidocaine is a class IB antiarrhythmic that is also used as a local anesthetic, analgesic, and anticonvulsant.¹ In usual serum concentrations, lidocaine's cardiac electrophysiological effects are largely limited to the His-Purkinje system and ventricular myocardium. It has minimal effects on the autonomic nervous system. Lidocaine is most often used as an alternative to other antiarrhythmic drugs in the treatment of symptomatic or life-threatening ventricular arrhythmias. Lidocaine is generally not indicated for the treatment of supraventricular arrhythmias.

Historically lidocaine was recommended as initial treatment of isolated ventricular premature beats, couplets, or nonsustained ventricular tachycardia or as prophylaxis against ventricular arrhythmias in the setting of acute coronary syndrome/acute myocardial infarction (ACS/AMI), but it no longer carries that recommendation.² The rationale for this change in practice is that overall mortality may not be altered or may increase.²⁻⁶ Furthermore, the frequency of adverse effects attributed to prophylactic lidocaine are significantly greater than placebo.^{2,7}

With respect to other arrhythmias, recently updated guidelines for advanced cardiac life support (ACLS) recommend that lidocaine can be used in the management of defibrillation-resistant ventricular tachycardia/fibrillation (VT/VF) that fails to respond to amiodarone.⁸ In the setting of ACS/MI, lidocaine may be useful in terminating unstable sustained monomorphic VT with normal or low left ventricular ejection fractions as well as polymorphic VT with or without prolonged baseline QT interval.⁹ However, it appears relatively ineffective in terminating hemodynamically stable, sustained monomorphic VT that is unrelated to ACS/MI.¹⁰⁻¹² Additional antiarrhythmic uses for lidocaine include acute termination of Wolff-Parkinson-White syndrome with atrial fibrillation,¹³ lidocaine-sensitive atrial tachycardia,¹⁴ verapamil-sensitive idiopathic left VT,¹⁵ and prevention of reperfusion ventricular fibrillation following release of aortic cross-clamping in patients undergoing coronary artery bypass graft surgery.¹⁶

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

The dosage ranges in **Table 16-1** are suggested for the treatment of ventricular arrhythmias; dosages should be adjusted according to individual requirements.¹ Lidocaine also can be administered via an endotracheal tube or intraosseously during cardiac arrest.^{1,8,17}

DOSAGE FORM AVAILABILITY

All listed preparations are intended for cardiac use (**Table 16-2**). Lidocaine preparations containing epinephrine (intended for anesthesia) should never be used for cardiac or anticonvulsant purposes. All lidocaine parenteral preparations are available as the hydrochloride salt and provide 86% lidocaine base (**S = 0.86**).

Note: The contributions of Paul E. Nolan, deceased, to the previous versions of this chapter are sincerely appreciated.



TABLE 16-1. SUGGESTED DOSAGE RANGES FOR THE TREATMENT OF VENTRICULAR ARRHYTHMIAS¹

Dosage Form	Initial Dosage (Lidocaine Hydrochloride)
IV (bolus)	
Children (<18 yr) ^a	For ACLS: 1 mg/kg, up to a maximum of 100 mg; a second dose of 0.5–1 mg/kg should be given if there is greater than a 15-min delay from the time of the initial bolus to the start of the continuous infusion (see below). Alternatively, 0.5–1 mg/kg dose via slow IV push at 25–50 mg/min; dose may be repeated every 3–5 min if needed; total loading dose should not exceed 3–5 mg/kg.
Adults (>18 yr)	For cardiac arrest secondary to either ventricular fibrillation or pulseless ventricular tachycardia: 1–1.5 mg/kg; then 0.5–0.75 mg/kg repeated every 5–10 min up to a total of three doses or up to 3 mg/kg. For initial treatment of (other) ventricular arrhythmias: 50–100 mg (0.7–1.4 mg/kg) or alternatively 1–1.5 mg/kg either at a rate of 25–50 mg/min; supplemental doses of 25–50 mg or 0.5–0.75 mg/kg every 5–10 min up to a maximum total loading dose of 3 mg/kg may be administered if the desired clinical response is not achieved; total dose should not exceed 300 mg in a 1-hr period.
Intraosseous dosing	Refer to IV bolus dosing guidelines.
IV (maintenance)	
Children (<18 yr)	Infusion of 10–50 µg/kg/min; with an additional 0.5–1 mg/kg bolus if clinically indicated.
Adults (>18 yr)	Infusion of 20–50 µg/kg/min (~1–4 mg/min in 70-kg adult) depending on patient's clinical condition; if the arrhythmia recurs, a small bolus of 0.5 mg/kg followed by an increase in the infusion rate may be warranted.
Intramuscular ^b	
Children (<18 yr)	Not FDA-approved.
Adults (>18 yr)	300 mg (4.3 mg/kg in a 70-kg adult) injected into deltoid muscle (or lateral thigh if autoinjector device is used), with dose repeated in 60–90 min if clinically indicated.
Endotracheal ^c	
Children (< 18 yr)	2–3 mg/kg flushed with 5 mL of 0.9% sodium chloride followed by 5 assisted manual ventilations.
Adults (>18 yr)	2–2.5 times the recommended IV dose and diluted in 5–10 mL of 0.9% sodium chloride or sterile water.
Oral	Not applicable.

^aControlled clinical studies to establish dosing schedules for lidocaine in pediatric patients have not been conducted.

^bIntramuscular form not available in the U.S.

^cOptimal endotracheal doses of lidocaine for either adult or pediatric patients have not been established.

Table 16-3 gives the absorption of various dosage forms and administration methods. Because the intramuscular method of drug administration avoids the first-pass metabolism of the liver, bioavailability should be similar to that for intravenous (IV) lidocaine. The deltoid muscle is preferred for intramuscular administration, resulting in a superior rate and extent of absorption compared to the gluteus and vastus lateralis muscles.^{18,19}

Although the oral bioavailability of lidocaine averages 39% in patients without hepatic impairment, a large intersubject variability exists due to first-pass hepatic metabolism.²⁰ Therapeutic lidocaine concentrations may not be rapidly and predictably attained in many patients, thus preventing its use as an oral agent.

TABLE 16-2. DOSAGE FORM AVAILABILITY BY PRODUCT¹

Dosage Form	Product
IV (bolus): 10 and 20 mg/mL	Various manufacturers
IV (for infusion preparation) 100 mg/mL (1 g) and 200 mg/mL (1 or 2 g)	Various manufacturers
IV (premixed infusion solution)	
4 mg/mL (1 or 2 g) in dextrose 5%	Various manufacturers
8 mg/mL (2 or 4 g) in dextrose 5%	Various manufacturers
Oral	Not available

TABLE 16-3. BIOAVAILABILITY (F) OF DOSAGE FORMS

Dosage Form	Bioavailability Comments
IV ²⁰	100% (F = 1)
Intramuscular	Absolute bioavailability not determined
Oral ²⁰	91% ± 6% for hepatically impaired patients (F = 0.91) 39% ± 5% for patients with normal hepatic function (F = 0.39)

GENERAL PHARMACOKINETIC INFORMATION

Distribution

Following IV administration, the disposition of lidocaine is usually described by an open, two-compartment model.²¹ However, some studies best describe lidocaine disposition by a three-compartment model.^{21,22} For this chapter, a two-compartment model is assumed.

Volume of distribution^{17,23,30}

Lidocaine is widely distributed into body tissue following distribution from the central compartment (i.e., heart, lungs, and kidneys). **Table 16-4** presents the volume of distribution (V) after administration of a single lidocaine dose to different patient populations.

TABLE 16-4. VOLUME OF DISTRIBUTION OF LIDOCAINE

Population	Volume (Mean ± SD)
Adults ²³	$V_c = 0.5 \pm 0.21 \text{ L/kg}$ $V_B = 1.66 \text{ L/kg}^a$ $V_{ss} = 1.32 \pm 0.27 \text{ L/kg}$
Adults (endotracheal tube) ¹⁷	$V_B = 1.06 \pm 0.54 \text{ L/kg}$
Children ^{24,25}	$V_c = 0.31 \pm 0.07 \text{ L/kg}$ $V_B = 1.1 \pm 0.11 \text{ L/kg}$ $V_{ss} = 1.18 \pm 0.36 \text{ L/kg}$
Neonates ²⁶	$V_B = 2.75 \pm 1.61 \text{ L/kg}$
Elderly males ²⁷	$V_B = 2.91 \pm 0.88 \text{ L/kg}$
Elderly females ²⁷	$V_B = 3.45 \pm 0.79 \text{ L/kg}$
Morbidly obese adult males ²⁸	$V_B = 2.67 \pm 0.82 \text{ L/kg}^b$
Morbidly obese adult females ²⁸	$V_B = 2.88 \pm 1.03 \text{ L/kg}^b$
Chronic CHF ²⁹	$V_c = 0.3 \text{ L/kg}^c$

TABLE 16-4. VOLUME OF DISTRIBUTION OF LIDOCAINE (cont'd)

Population	Volume (Mean ± SD)
	$V_{ss} = 0.88 \text{ L/kg}^c$
Chronic hepatic dysfunction ²⁹	$V_c = 0.61 \text{ L/kg}^c$
	$V_{ss} = 2.31 \text{ L/kg}^c$
Chronic renal failure ²⁹	$V_c = 0.55 \text{ L/kg}^c$
(receiving hemodialysis)	$V_{ss} = 1.2 \text{ L/kg}^c$
Severe trauma ³⁰	$V_c = 0.26 \pm 0.15 \text{ L/kg}^d$
	$V_{ss} = 0.72 \pm 0.28 \text{ L/kg}^d$

CHF = congestive heart failure, SD = standard deviation.

^aCalculated using $V_B = (CL_{total})/k$.

^bBased on actual body weight (ABW).

^cOnly mean data reported.

^dPatients had no prior history of significant cardiac, pulmonary, hepatic, or renal disease.

V_B = volume of distribution; V_c = volume of central compartment; V_{ss} = volume at steady state.

Elimination

Determination of the total body or systemic clearance (CL_{total} or $CL_{systemic}$) of lidocaine depends on the method of administration. Compared to a single IV bolus dose, the CL_{total} decreases during a prolonged (longer than 24 hr) constant-rate infusion (i.e., time-dependent pharmacokinetics).^{22,31,32} The magnitude of the reduction in CL_{total} of lidocaine with a continuous infusion may depend on its absolute duration as well as on the patient's underlying clinical condition.

The mechanism for the time-dependent decline in CL_{total} of lidocaine is a reduction in the intrinsic clearance of lidocaine mediated either by lidocaine itself³³ or by monoethylglycinexylidide (MEGX), its principal metabolite.³⁴

Lidocaine is extensively hepatically metabolized via sequential deethylation steps by several cytochrome P450 isozymes: CYP3A4, CYP3A5, and CYP1A2.^{21,35-39} CYP1A2 may be principally responsible for lidocaine biotransformation at clinically relevant lidocaine concentrations in individuals with normal hepatic function.^{38,39} The hepatic extraction ratio is high, ranging from 62% to 81% of the dose administered.²⁰ As with other highly extracted drugs, hepatic blood flow appears to be the primary determinant of clearance.^{40,41} However, changes in lidocaine clearance also can result from hepatic enzyme induction or inhibition.^{21,41} Therefore, alterations in either hepatic blood flow or intrinsic hepatic metabolic capacity can influence the elimination of lidocaine.

The hepatic metabolism of lidocaine results in the formation of two active metabolites, MEGX and glycinexylidide (GX) (see **Table 16-5**).^{34,42,47} MEGX may contribute to both the therapeutic and toxic effects, whereas GX may contribute to the toxicity.

Conditions that decrease lidocaine clearance also may potentially decrease MEGX clearance, resulting in increased adverse effects secondary to accumulation of MEGX.^{34,43} On the other hand, patients with renal impairment may be at greater risk of adverse effects secondary to accumulation of GX.^{43,44}

Protein binding

Protein binding of lidocaine depends on many variables, including drug concentration, type and concentration of plasma proteins, sample collection method, pH, and quantification method.²¹ Lidocaine exhibits concentration-dependent binding; that is, the degree of binding decreases as the total (bound plus unbound) drug concentration increases.⁴⁸ Although lidocaine binds to albumin (~25%), alpha-1-acid glycoprotein (AAG), an acute phase reactant, serves as the primary binding protein (~50%).

Disease, stress, or other clinical situations may significantly alter the concentration of AAG.⁴⁹⁻⁵⁷ Decreased concentrations of AAG result in a higher unbound fraction of lidocaine (increased free drug concentration) and possibly increased pharmacologic and/or toxic effects at any given total lidocaine concentration. Conversely, increased AAG levels decrease the proportion of unbound (active) drug and may decrease the pharmacologic effect at any given total lidocaine concentration.

Displacement of lidocaine bound to AAG by another basic drug (e.g., disopyramide, quinidine, propranolol, and tricyclic antidepressants) may result in a higher free fraction of lidocaine, but without significant enhancement of the pharmacologic or toxic effect.^{50-52,58}

TABLE 16-5. FORMATION AND ACTIVITY OF LIDOCAINE METABOLITES^{34,42-47}

Compound	Percent Excreted in Urine ^a	Antiarrhythmic Activity	Pro-Convulsant Activity
Lidocaine	2%	Yes	Yes
MEGX	4%	Yes	Yes
GX	2.5%	No ^b	Yes
4-OH 2, 6-xylylidine	73%	No	No
Others	10% to 20%	No	No

^aPercentage of administered lidocaine dose.

^bGX has only 10% of the antiarrhythmic activity of lidocaine. GX's antiarrhythmic activity is not clinically significant.

CLEARANCE

Lidocaine's CL in different patient populations determined during different administration techniques is presented in **Table 16-6**. Aging as well as a variety of diseases and body conditions alter lidocaine CL.

HALF-LIFE AND TIME TO STEADY STATE

Unless otherwise specified, the half-lives and anticipated times to steady state in **Table 16-7** are based on IV bolus dosing. As previously described, CL decreases with prolonged infusions of lidocaine, thus increasing the half-life and time to steady state.^{31,32} When time-to-steady state is assessed, the method of drug administration must be considered along with patient population characteristics.^{19,31,32}

DOSING STRATEGIES

The optimal dosing strategy for lidocaine should rapidly achieve and consistently maintain therapeutic concentrations. However, the multicompartment disposition characteristics of lidocaine, the interpatient variability in its pharmacokinetics, and its relatively narrow therapeutic index make designing a dosing strategy somewhat difficult.

Loading doses of lidocaine are required to quickly attain adequate concentrations within the central compartment. Following distribution in the central compartment, lidocaine rapidly moves into the peripheral compartment, so subtherapeutic concentrations may be observed until the maintenance infusion reaches steady state. This therapeutic gap may require additional bolus doses or other dosing interventions to maintain effective concentrations and may occur during a critical timeframe when drug concentrations are inadequate to prevent or reduce arrhythmias.^{65,66} Although numerous dosing schemes have been tested for lidocaine,^{1,8,65,69} **Table 16-8** focuses on seven representative methods for clinical application.

TABLE 16-6. CLEARANCE OF LIDOCAINE^{17,23,24,26,28-30,59-62}

Population ^a	Clearance (Mean ± SD)	Mode of Administration
Adults ²³	0.72 ± 0.15 L/hr/kg	Single dose
Adults ³¹	0.51 ± 0.13 L/hr/kg	Continuous infusion
Adults (endotracheal tube) ¹⁷	0.55 ± 0.18 L/hr/kg	Single dose
Children ²⁴	0.71 ± 0.2 L/hr/kg	Single dose
Neonates ²⁶	0.61 ± 0.38 L/hr/kg	Single dose
Morbidly obese adult males ²⁸	0.69 ± 0.22 L/hr/kg ^b	Single dose
Morbidly obese adult females ²⁸	0.68 ± 0.17 L/hr/kg ^b	Single dose
Chronic CHF ²⁹	0.38 L/hr/kg ^c	Single dose
Chronic CHF ⁵⁹	0.23 ± 0.08 L/hr/kg	Continuous infusion
Mild-to-moderate chronic CHF ⁵⁹	0.35 L/hr/kg ^c	Continuous infusion
Severe chronic CHF ⁵⁹	0.12 L/hr/kg ^c	Continuous infusion
Chronic hepatic dysfunction ²⁹ (hepatic dysfunction level unspecified)	0.42 ± 0.19 L/hr/kg	Single dose
Child-Pugh Class A hepatic dysfunction ⁶⁰	0.41 L/hr/kg ^c	Single dose
Child-Pugh Class B hepatic dysfunction ⁶⁰	0.31 L/hr/kg ^c	Single dose
Child-Pugh Class C hepatic dysfunction ⁶⁰	0.25 L/hr/kg ^c	Single dose
Chronic renal failure (with dialysis) ²⁹	0.82 L/hr/kg ^c	Single dose
Chronic renal failure without dialysis ⁶¹ (CrCl < 30 mL/min/1.73 m ²)	0.36 ± 0.15 L/hr/kg	Single dose
Acute MI without heart failure ⁶²	0.54 ± 0.12 L/hr/kg ^d	Continuous infusion
Acute MI with heart failure ⁶²	0.33 ± 0.09 L/hr/kg ^d	Continuous infusion
Severe trauma ³⁰	0.4 ± 0.1 L/hr/kg	Single dose

^aMost studies had small numbers of patients.

^bBased on ABW.

^cOnly mean data reported.

^dBlood to plasma conversion applied.

The efficacy of lidocaine as an antiarrhythmic agent is directly linked to the rapid achievement and maintenance of therapeutic lidocaine concentrations.²¹ For example, avoiding the therapeutic gap may be critical during the first few hours following MI when the incidence of lethal or potentially lethal arrhythmias is greatest.⁷⁰ Salzer et al.⁶⁶ reported comparative data for the percentage of time that total lidocaine concentrations were within the therapeutic range (2–4 mg/L) in a small number of patients dosed using Methods 1–4a. They concluded that Method 4a resulted in total lidocaine concentrations within the stated therapeutic range nearly 80% of the time. Riddell et al.⁶⁷ reported that all eight of their subjects dosed using Method 5 maintained total concentrations between 1.5 and 5 mg/L 100% of the time.

TABLE 16-7. HALF-LIFE AND TIME-TO-STEADY STATE FOR LIDOCAINE

Population	Terminal Half-Life (Mean ± SD)	Time to Steady State ^a
Adults ²³	1.6 ± 0.4 hr	6–10 hr
Adults (endotracheal tube) ¹⁷	1.2 ± 0.5 hr	3.5–8.5 hr
Children ²⁴	1 ± 0.3 hr	3.5–6.5 hr
Neonates ²⁶	3.2 ± 0.1 hr	15.5–16.5 hr

Elderly males ²⁷	2.7 ± 0.5 hr	11–16 hr
Elderly females ²⁷	2.3 ± 0.6 hr	8.5–14.5 hr
Morbidly obese adult males ²⁸	2.7 ± 0.8 hr	9.5–17.5 hr
Morbidly obese adult females ²⁸	3 ± 1 hr	10–20 hr
Chronic CHF ²⁹	1.9 hr ^b	9.5 hr
Chronic hepatic dysfunction ²⁹ (degree of hepatic dysfunction unspecified)	4.9 hr ^b	24.5 hr
Child-Pugh Class A hepatic dysfunction ⁶⁰	2.2 hr ^c	11 hr
Child-Pugh Class B hepatic dysfunction ⁶⁰	5.6 hr ^c	28 hr
Child-Pugh Class C hepatic dysfunction ⁶⁰	7.8 hr ^c	39 hr
Chronic renal failure (with hemodialysis) ²⁹	1.3 hr ^b	6.5 hr
Chronic renal failure (CrCl < 30 mL/min/1.73 m ²) (without hemodialysis) ⁶¹	4.6 ± 1.7 hr	14.2–31.3 hr
Severe trauma ³⁰	1.5 ± 0.6 hr	4.5–10.5 hr
Acute MI without heart failure ⁶³	3.2 ± 0.5 hr ^d	13.5–18.5 hr
Acute MI with heart failure ⁶⁴	10.2 ± 5.3 hr ^d	24.5–77.5 hr

^aTime to steady state estimated using + and –1 SD of the mean $t_{1/2}$ and assuming steady state is achieved in five half-lives.

^bOnly mean data reported.

^cOnly mean data listed because of large SD.

^dContinuous infusion of longer than 24 hr.

These dosing regimens serve only as guidelines for lidocaine administration. To achieve optimal efficacy, maintenance infusion rates always must be adjusted according to the patient's underlying clinical condition and other clearance-altering factors.

Each of these methods has both advantages and disadvantages. Although Method 5 requires no human intervention once the drug delivery system is set up, preparation of the delivery system is somewhat complicated and time-consuming. The complexity of this method limits its utility in many hospital settings. Methods 3 and 4 require interventions to adjust infusion rates but do not require specialized delivery systems. Method 4a provides acceptable concentration-time results that are better than those achieved with Methods 1–3. Both Methods 4a and 4b are relatively simple to administer and require minimal nursing intervention. Ultimately, the choice of method should be determined by available personnel, equipment, and facilities in addition to the patient's clinical condition.^{66,67,69}

TABLE 16-8. LIDOCAINE HYDROCHLORIDE DOSING METHODS^{1,8,65,69}

Method	Bolus Dose and Timing ^a	Loading Infusion	Maintenance Infusion ^b
1. Single bolus plus infusion technique ^{65–67}	100 mg initially	NA	120 mg/hr
2. Multiple bolus plus infusion technique ^{65–67}	100 mg initially 50 mg at 20 min	NA	120 mg/hr
3. Two-step infusion technique ^{65,66}	NA	200 mg over 25 min	120 mg/hr
4a. Two-step bolus plus infusion technique ^{66,67}	1.5 mg/kg (100 mg) plus simultaneous loading infusion	0.12 mg/kg/min for 25 min (or 200 mg over 25 min)	1.8 mg/kg/hr (120 mg/hr)
4b. Two-step bolus plus infusion technique ⁶⁸	75 mg plus simultaneous loading infusion	150 mg over 20 min	120 mg/hr

TABLE 16-8. LIDOCAINE HYDROCHLORIDE DOSING METHODS (cont'd)^{1,8,65,69}

Method	Bolus Dose and Timing ^a	Loading Infusion	Maintenance Infusion ^b
5. Exponentially declining infusion technique ⁶⁷⁻⁶⁹	92 mg	8.3 mg/min exponentially declining to maintenance infusion rate	120 mg/hr
6. ACLS bolus technique for cardiac arrest due to VF or pulseless VT ⁸	1.5 mg/kg followed by additional bolus of 0.5–0.75 mg/kg if necessary for refractory VT/VF; total dose should not exceed 3 mg/kg (or >200–300 mg) during a 1-hr period	NA	120–240 mg/hr (Note: Guidelines recommend only bolus therapy in cardiac arrest; however, it is reasonable to continue with an infusion of lidocaine if the drug was associated with restoration of a stable rhythm.)
7. Endotracheal administration ^{1,8,c}	3–3.75 mg/kg (i.e., 2–2.5 times recommended IV dose)	NA	NA

NA = not applicable.
^aBolus dosing based on IBW in obese patients.
^bmg/kg dosing in obese patients based on ABW.
^cEndotracheal administration has sometimes been used during cardiac arrest in situations where peripheral venous access was not possible.

THERAPEUTIC RANGE

When a therapeutic range for lidocaine is determined, it is important to note that plasma, serum, and whole blood concentrations are not interchangeable. For conversion from blood (C_b) to serum (C_s) concentrations, a factor of 1.3 should be applied⁴⁸:

$C_s = (C_b)(1.3)$

The usual therapeutic range in serum is 1.5–6 mg/L of total drug or 0.5–2 mg/L of free or unbound drug.⁷⁰

Suggested sampling times and effect on therapeutic range

Assessment or confirmation of suspected lidocaine toxicity is the most likely clinical situation for which lidocaine concentrations may be measured. Other circumstances may include^{21,71}:

- Patient at increased risk for developing lidocaine toxicity (e.g., patient with cardiogenic shock, moderate to severe CHF, severe hepatic disease, or severe renal insufficiency and not receiving hemodialysis).
- Patient concomitantly receiving medications with potential for clinically major or moderate drug interactions. (See Drug–Drug Interactions.)
- Prolonged infusion (longer than 24 hr), especially in patients with underlying disease states or conditions that may decrease lidocaine clearance.
- Patient requiring doses that exceed the usual maximum recommended amount.
- Research investigation.

Table 16-9 provides suggestions for sample collection times.⁷¹

TABLE 16-9. SAMPLE COLLECTION TIMES

Monitoring Goal	Suggested Sampling Time
Assessment of efficacy	1–2 hr following initiation of therapy in patients who fail to respond ^a
Dosage adjustment	12–24 hr following initiation of therapy to assess steady state concentration 24–48 hr following initiation of ongoing continuous infusion to avoid drug accumulation resulting from time-dependent reduction in clearance
Confirmation of toxicity	When clinical signs and symptoms of suspected lidocaine toxicity appear

^aFailure to respond may result from the therapeutic gap, high systemic lidocaine clearance, or intrinsic resistance to lidocaine therapy.

PHARMACODYNAMIC MONITORING: CONCENTRATION-RELATED EFFICACY AND TOXICITY

Lidocaine serum concentrations associated with the control of ventricular arrhythmias have generally fallen in the range of 1.5–6 mg/L.^{70,72} Adverse effects with lidocaine principally involve the central nervous system (CNS) or cardiovascular (CV) system. CNS effects include confusion, dizziness, slurred speech, numbness of the lips and tongue, diplopia, tremor, severe nausea and vomiting, and seizures. CV adverse effects include sinus bradycardia, sinus arrest, and atrioventricular conduction disturbances. Adverse effects have been weakly correlated to bound and unbound lidocaine concentrations.^{7,21} In **Table 16-10**, possible signs of toxicity are correlated to total serum lidocaine concentrations.

DRUG–DRUG INTERACTIONS

Pharmacokinetic drug–drug interactions affecting lidocaine largely result from drug-induced alterations in hepatic clearance. Hepatic clearance depends on three factors⁴¹:

- free fraction of the drug
- hepatic blood flow
- intrinsic metabolic clearance

For lidocaine, drug-induced decreases in hepatic blood flow would be expected to produce more clinically important interactions (moderate to major), whereas drug-induced changes in lidocaine intrinsic clearance or in lidocaine free fraction appear less significant (mild to moderate). An exception would be the effects of fluvoxamine, a potent inhibitor of CYP1A2, which decreases lidocaine CL by 40% to 60%.³⁹ Drug–drug interactions with lidocaine are listed in **Table 16-11** along with the postulated mechanism and clinical significance of the interactions. Although there appear to be no clinical reports regarding the effects of lidocaine on the pharmacokinetics of other agents, lidocaine may be anticipated to diminish the clearance of drugs metabolized by CYP1A2 given the *in vitro* inhibitory effects of lidocaine on the function of this isozyme.⁷³

TABLE 16-10. LIDOCAINE CONCENTRATION–TOXICITY CORRELATION

Total Serum Lidocaine Concentration	Underlying Toxicity
<1.5 mg/L	Idiosyncratic
1.5–4 mg/L	Mild CNS and CV effects
>4 mg/L	Mild CNS toxicity ^a ; CV toxicity ^b more common with pre-existing CV disease present
>6 mg/L	Major CNS ^c and CV depressant effects
>8 mg/L	Seizures, obtundation, hypotension, respiratory depression, and decreased cardiac output

^aMild CNS toxicity includes somnolence, dizziness, numbness, slurred speech, and confusion.

^bCV toxicity includes sinus bradycardia, sinus arrest, atrioventricular conduction disturbances, hypotension, and decreased cardiac output.

^cMajor CNS toxicity includes severe confusion, severe slurred speech, tremor, diplopia, respiratory arrest, and seizure.

Maintenance infusion rates may have to be adjusted for lidocaine when it is administered concomitantly with drugs that result in interactions of moderate or major clinical significance. Table 16-11 also provides suggestions for initial dosage reductions associated with drug-drug interactions for patients with normal hepatic function. Careful monitoring for clinical signs and symptoms of lidocaine toxicity is also recommended. Furthermore, the extent of any drug interaction may increase in the presence of other clearance-altering factors, which may necessitate additional dose adjustments. However, in patients with advanced hepatic dysfunction (i.e., Child-Pugh Class C), the coadministration of fluvoxamine did not result in additional decreases in the total body clearance of lidocaine relative to the non-fluvoxamine condition.³⁹ Similar findings also have been reported for erythromycin, an inhibitor of CYP3A4.⁷⁴

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

Congestive heart failure

A significant inverse relationship exists between cardiac index and lidocaine concentrations.⁷⁸ For example, in adult patients the increasing severity of CHF results in an increased potential for drug accumulation and decreased dosing requirements.⁵⁹

For adults with mild-to-moderate CHF (i.e., presence of S₃ gallop and basilar pulmonary rales), an initial maintenance infusion of 1.4 mg/kg/hr is suggested to achieve steady state lidocaine serum concentrations of ~4 mg/L.⁵⁹ For patients with severe CHF (i.e., pulmonary edema or cardiogenic shock), the initial maintenance infusion should be 0.6 mg/kg/hr to achieve steady state concentrations of ~4 mg/L. As always, careful individual assessment of efficacy and toxicity is prudent. Loading doses may need to be reduced because of smaller central volume in patients with CHF.⁵⁹

TABLE 16-11. DRUG-DRUG INTERACTIONS WITH LIDOCAINE^{31,38,39,73–90}

Interacting Agent	Interaction	Significance and Initial Dosage Change Recommendations
Amiodarone ^{75–77}	Likely due to inhibition of CYP3A4-mediated metabolism	<i>Mild to moderate:</i> decrease lidocaine infusion rate by 20%
Beta-adrenergic blockers ^{31,78–80}	Decreases in hepatic blood flow and intrinsic metabolism of lidocaine; more likely to occur with lipophilic Beta-adrenergic blockers and those without intrinsic sympathomimetic activity	<i>Moderate to major:</i> decrease lidocaine infusion rates by 30% when coadministered with metoprolol and 40% to 50% with propranolol
Cimetidine ^{81–83}	Likely due to decreases in hepatic blood flow; V _{ss} of lidocaine also decreased; interaction only occurs with orally administered cimetidine	<i>Mild to moderate:</i> decrease lidocaine infusion rate by 15% to 25%
Erythromycin ^{74,84,85}	Concentrations of lidocaine and MEGX metabolite increased, likely due to inhibition of CYP3A4-mediated metabolism	<i>Mild to moderate:</i> decrease lidocaine infusion rate by 10% to 20%
Fluvoxamine ^{38,39,85}	Likely due to inhibition of CYP1A2-mediated metabolism	<i>Moderate to major:</i> decrease lidocaine infusion rate by 40% to 60%
Mexiletine ^{73,86}	CL _{total} of lidocaine decreased; V of lidocaine decreased; possible inhibition of CYP1A2-mediated metabolism and possible displacement from tissue binding sites	<i>Mild to moderate:</i> decrease lidocaine infusion rate by 20% to 25%
Propafenone ⁸⁷	CL _{total} decreased and may be accompanied by increased CNS adverse effects	<i>Mild:</i> decrease lidocaine infusion rate by 10%
Ciprofloxacin ⁸⁸	Probably via inhibition of CYP1A2-mediated metabolism	<i>Mild to moderate:</i> decrease lidocaine infusion rate by 20%

Acute myocardial infarction

For adult patients with AMI without CHF, a constant rate infusion of 2.6 mg/kg/hr should achieve steady state concentrations of ~4 mg/L.⁶² Patients with AMI and CHF require lower continuous infusion rates.⁶² Therefore, an initial continuous infusion rate of 1.5 mg/kg/hr is suggested for this population. Furthermore, loading doses may need to be reduced ~40% because of a decreased V_c .²⁹

AAG concentrations increase following AMI.⁵¹ The implications of altered binding were previously addressed (see General Pharmacokinetic Information). Because binding alterations are unpredictable and may not be of great clinical significance, especially in patients receiving short-term or prophylactic lidocaine, empiric dosage adjustment recommendations are not needed. However, clinical parameters should be carefully monitored, with appropriate reductions in lidocaine dosages made based on clinical response and lidocaine concentrations when available.

Hepatic disease

Chronic hepatic disease generally diminishes lidocaine clearance.^{29,39,60,74} Due to the anticipated reduction in protein binding for this patient population, a continuous infusion should be initiated at 1.3 mg/kg/hr for steady state serum concentrations of around 3 mg/L.²⁹ The degree of hepatic dysfunction as determined by Child-Pugh classification will influence the choice of the initial infusion rate.^{39,60,74}

An additional consideration for patients with hepatic dysfunction receiving lidocaine is the potential accumulation of the active metabolite MEGX. This accumulation may increase the risk for developing toxicity despite therapeutic concentrations.³⁴

Renal disease

Since lidocaine is almost exclusively hepatically eliminated in healthy humans, renal dysfunction is generally thought to have little effect on its disposition and elimination.²¹ Two studies have reported no significant effects of chronic renal dysfunction on systemic clearance.^{29,43} These studies suggest that loading and maintenance doses of lidocaine do not require adjustment in patients with chronic renal failure. However, they examined patients only with chronic renal failure undergoing long-term hemodialysis. Another study showed that clearance of lidocaine is significantly decreased in patients with severe chronic renal insufficiency (i.e., $\text{CrCl} < 30 \text{ mL/min/1.73 m}^2$) not undergoing hemodialysis.⁶¹ Therefore, reductions in lidocaine infusion rates should be anticipated in this patient population.

Morbid obesity

Ideal body weight (IBW) should be used for the calculation of bolus dosing, and ABW should be used for the calculation of continuous IV infusion rate.²⁸

Advanced age (elderly)

Compared to young adult control subjects, the elderly have an increased V and a decreased clearance of lidocaine.²⁷ There may be gender-specific effects on the distribution and clearance of lidocaine with V and CL higher in elderly females compared to elderly males, although not to a statistically significant degree.²⁷

Severe trauma

Adult patients with severe trauma (but without a history of clinically significant pre-trauma heart, lung, liver, or kidney disease) given single IV doses of lidocaine to suppress the stress response associated with endotracheal intubation or bronchoscopy show about 33% decreases in lidocaine total body clearance and ~50% decreases in volume of distribution of lidocaine.³⁰

Pregnancy and lactation

Lidocaine is currently listed as Risk Category B.⁹¹ Although lidocaine rapidly crosses the placenta to the fetus, observational clinical studies where lidocaine was administered to the mother any time during the pregnancy, found no evidence of an association between the use of lidocaine with large categories of major or minor fetal malformations or to individual birth defects.⁹¹ Although small amounts of lidocaine are excreted into breast milk with concentrations ~40% of maternal serum concentrations, it is considered to be compatible with breast feeding by The American Academy of Pediatrics.⁹¹

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LITHIUM

Stanley W. Carson and Lisa W. Goldstone

Lithium is a monovalent cation ($1 \text{ mmol/L} = 1 \text{ mEq/L}$) that is indicated in the treatment of manic episodes of bipolar disorder and for maintenance therapy to prevent or diminish the intensity of subsequent episodes in those patients with bipolar disorder with a history of mania.¹ Lithium is also used as monotherapy and combination therapy for acute bipolar depression.^{2,3}

Off-label uses include augmentation of antidepressant pharmacotherapy for depression, borderline personality disorder, traumatic brain injury, improvement of neutrophil count, prophylaxis of cluster headache, premenstrual tension, bulimia, alcoholism, syndrome of inappropriate secretion of antidiuretic hormone, tardive dyskinesia, hyperthyroidism, postpartum affective psychosis, and corticosteroid-induced psychosis.^{4,5} The anti-suicidal effects of lithium are also well-documented.⁶ Its neuroprotective properties have led to the study of lithium for applications in acute head injuries and chronic neurodegenerative disorders.⁷⁻¹³

Lithium shares properties of physiologic cations, particularly sodium (Na^+) and potassium (K^+), and all are regulated in the kidney in a similar fashion. Previous theories regarding the mechanism of action of lithium held that Li^+ was likely substituted for these cations in the body, thereby improving ion dysregulation, modifying monamine neurotransmitter signaling, or interacting with second messengers such as adenylyl cyclase, inositol phosphate, or protein kinase C systems.^{14,15} Recent advances suggest lithium may inhibit glycogen synthase kinase-3, which phosphorylates and inhibits nuclear factors that regulate cell growth and protection programs, thereby preventing apoptosis and enhancing neuroplasticity and cellular resilience.¹¹ Taken altogether these mechanisms may augment cellular homeostasis and may be neuroprotective.^{11,16}

Lithium concentrations are closely related to therapeutic response and side effects. Changes in fluid and sodium balance due to changes in the glomerular filtration rate (GFR) or renal tubular reabsorption of lithium and/or sodium are of particular importance and can affect lithium pharmacokinetics. Consideration of drug–drug interactions or drug–drug disease state or condition interactions is also important when monitoring patients receiving lithium. Because of lithium’s relatively narrow therapeutic index, periodic lithium concentration determinations are essential to achieve optimal therapeutic response with minimal side effects.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

The following dosage recommendations are guidelines for the initiation of lithium therapy. Acute and maintenance dosage regimens should be individualized for all patients and guided by lithium concentration determinations. Patients with reduced renal function, and therefore diminished renal clearance of lithium, need lower doses.

Acute therapy

Recommendations for initiation of lithium for acute therapy are given in **Table 17-1**. In adults, acute lithium therapy is initiated with 300–600 mg of lithium carbonate tablets or capsules in two to three divided doses. Sustained-release products may be initiated with 300–600 mg of lithium carbonate tablets or capsules two to three times daily.¹⁷ Loading doses are not commonly used.¹⁸⁻²⁰ Dosage regimens



should be individually titrated to desired concentrations and clinical response of the patient. For most individuals an increase of 300 mg (or 8 mEq) equates to an increase of approximately 0.3 ± 0.1 mEq/L in steady-state lithium concentration.^{19,20} However, it has been suggested that a 35% to 50% decrease in dose for patients 40 yr of age and older may result in similar concentrations to those obtained in patients younger than 40 yr of age with usual dosing regimens.²¹ Titrating initial dosage regimens over several days may minimize initial side effects.

TABLE 17-1. LITHIUM DOSING RECOMMENDATIONS FOR INITIATION OF ACUTE THERAPY¹⁷

Population	Dosage ^a (Oral Tablets, Capsules, or Syrup)
Children (<18 yr)	15–20 mg/kg daily ^{b,c}
Adults (19–59 yr)	900–1800 mg/day (~15 mg/kg)
Elderly (>59 yr)	600–900 mg/day ^d

^aDosage should be given in divided doses and titrated to achieve therapeutic serum lithium concentrations based on clinical response and patient tolerance.

^bNot FDA approved for use in children below 12 yr of age.

^cLesser of 15–20 mg/kg daily or 150 mg twice daily (ages 6–11) or 300 mg twice daily (ages 12 and older). Further dose adjustment should be made based on serum concentration and response.

^dThe elderly may have altered lithium clearance due to reduced renal function and concomitant medications.

Maintenance therapy

Currently, there are no standardized guidelines for the use of long-term lithium therapy for prophylaxis or prevention of relapse (i.e., maintenance) after an acute bipolar episode. Traditionally, the criteria for the initiation of maintenance lithium therapy have been the requirement of two or three episodes of mania or depression in a 5-year period; however, the American Psychiatric Association recommends maintenance therapy after a single manic episode.¹⁹ The decision to initiate maintenance or prophylaxis therapy should be made with the following considerations: frequency and severity of episodes, seasonality of prior episodes, prior response to other bipolar medication, and possible consequences of relapse. Lithium dosage regimens for maintenance or prophylactic therapy (900–1,200 mg daily) are usually lower than those used for acute therapy with target trough lithium concentrations of ~0.6–0.8 mEq/L (see **Table 17-2**).^{17,19,22,23} Several studies suggest that concentrations >0.7–0.8 mEq/L may be more likely to result in a positive response; however, individual patients may respond well to lower concentrations, particularly those who do not tolerate concentrations in the upper part of the therapeutic range (see Therapeutic Range for additional details).²³ Once- or twice-daily dosing schedules that simplify the maintenance regimen may enhance long-term adherence to treatment. It has been suggested to decrease maintenance doses slowly to minimize the risk of relapse in previously stable patients who require dose reduction.^{19,23,24}

TABLE 17-2. LITHIUM DOSING RECOMMENDATIONS FOR INITIATION OF MAINTENANCE THERAPY¹⁷

Population	Dosage ^a (Oral Tablets, Capsules, or Syrup)
Children (<18 yr)	150–300 mg/day ^b
Adults (19–59 yr)	900–1200 mg/day
Elderly (>59 yr)	600–900 mg/day ^c

^aDosage should be given in divided doses and titrated to achieve therapeutic serum lithium concentrations based on clinical response and patient tolerance.

^bNot approved for use in children below 12 yr of age by FDA.

^cThe elderly may have altered lithium clearance due to reduced renal function and concomitant medications.

DOSAGE FORM AVAILABILITY

Lithium salts are available in a number of dosage forms.²⁵ Lithium carbonate is the most commonly formulated salt and has the longest stability and shelf life. The use of different salts does not generally affect the pharmacokinetics of lithium. Injectable lithium preparations are not available for clinical use in the United States.²⁶ Lithium is most commonly administered by the oral route as the carbonate or citrate salt. Because lithium is a monovalent ion, lithium concentrations are reported as milliequivalents per liter (mEq/L) or millimoles per liter (mmol/L) rather than in the more familiar concentration term of milligrams per liter (mg/L). Dosages are listed as millimole (mmol) equivalents of lithium carbonate (300 mg lithium carbonate = 8.12 mmol Li⁺ = 8.12 mEq Li⁺; 5 mL lithium citrate = 8 mmol Li⁺ = 8 mEq Li⁺).¹⁷ Lithium is available in capsules, immediate- and prolonged-release tablets, and oral syrup formulations; a summary of available lithium products is given in **Table 17-3**.

GENERAL PHARMACOKINETIC INFORMATION

Absorption

Lithium is readily absorbed in the gastrointestinal tract, primarily in the jejunum and ileum with some inherent intra- and interindividual variability.^{27,28} Oral solutions of lithium are the most rapidly absorbed, with peak concentrations occurring within 15–45 minutes. Nearly complete absorption of immediate-release lithium carbonate tablets and capsules occurs within 1–6 hr after dosing, with peak lithium concentrations occurring within 0.5–3 hr. Absorption from extended-release products is typically prolonged with peak concentrations occurring within 4–12 hr after dosing.¹⁷

TABLE 17-3. LITHIUM DOSAGE FORM AVAILABILITY

Formulation/Brand	Salt Form S = 1	Dosage Unit (1 mEq = 1 mmol)	F
Oral tablets			
Generic lithium carbonate	Carbonate	300 mg/8.12 mEq	~1
Oral capsules			
Generic lithium carbonate	Carbonate	150 mg/4.06 mEq	~1
Generic lithium carbonate		300 mg/8.12 mEq	~1
Generic lithium carbonate		600 mg/16.24 mEq	~1
Extended-release tablets			
Generic lithium carbonate	Carbonate	300 mg/8.12 mEq	~1
Lithobid (slow release)		300 mg/8.12 mEq	0.8
Generic lithium carbonate		450 mg/12.18 mEq	0.97
Oral syrup			
Generic lithium citrate		5 mL/8 mEq	1

The presence of food may significantly delay the rate of lithium absorption due to slower gastric emptying into the intestinal tract, but it does not affect the extent of absorption. Administering immediate-release preparations with food may be used as a strategy to minimize potential side effects associated with rapidly increasing lithium concentrations sometimes seen with these products.^{29,30} Controlled-release products also are associated with lower and sustained plasma concentrations, and this may reduce the occurrence of these concentration-related side effects.^{28,31}

Bioavailability (F) of dosage forms

Because an intravenous preparation is not available in the United States, the oral syrup dosage form is usually used as the reference product to calculate bioavailability of other oral dosage forms and is assumed to be 100% bioavailable. The bioavailability from the immediate-release, sustained-release, and syrup lithium formulations is very high and ranges from 80% to 104%.³² Lithium carbonate capsules and tablets are 95% to 100% absorbed. Extended-release lithium carbonate tablets are 60% to 90% absorbed.¹⁷ Food does not appear to affect the bioavailability of lithium.^{27,28} A comparison of lithium citrate syrup and lithium capsules found no significant differences in lithium concentrations at steady state.³³

Distribution

Lithium is widely distributed in the body, with initial distribution into the extracellular fluid followed by gradual accumulation in tissues. Lithium more rapidly distributes into the central compartment (e.g., heart, lung, kidney) and less rapidly into peripheral compartments (e.g., brain, bone, muscle, and thyroid).¹⁷ Lithium also distributes into saliva and erythrocytes, and concentration measurements at these sites have been suggested for surrogate measures of toxicity and/or noncompliance. However, considerable variability in these concentrations limit their usefulness in routine clinical practice.^{34,35} Lithium crosses into the placenta with similar concentrations in maternal and fetal serum. Lithium concentrations in breast milk are ~33% to 50% of that in maternal serum, and high lithium concentrations have been reported in infant serum following breast-feeding. Therefore, babies of mothers receiving lithium and breast-feeding should be closely monitored.^{1,36-40} Lithium does not bind to plasma proteins.

A two-compartment, open pharmacokinetic model classically describes the disposition of lithium. In clinical practice, the early distributional phase may be obscured by prolonged absorption of lithium from tablets and capsules and sparse blood sampling and, therefore, appear as a one-compartment model (monoexponential elimination).³²

The volume of the central compartment approximates 25% to 40% of body weight, with the combined central and peripheral compartments comprising 123% of body weight.⁴¹⁻⁴³ The apparent steady state volume of distribution (V_B or V_{area}) was ~0.8 L/kg with micro-rate constants of 0.24 hr⁻¹ (k_{12}) and 0.19 hr⁻¹ (k_{21}) in normal volunteers.⁴¹ Additional studies indicate that the volume of distribution for lithium typically ranges from 0.5–1.2 L/kg.^{20,41,42,44,45} There is an age-dependent reduction in volume of distribution, probably due in part to decreased total body water and lean body mass seen with advancing age.^{46,47} In one study, the volume of distribution in elderly subjects was reportedly 20% to 40% lower compared with healthy, young volunteers.⁴⁶ **Table 17-4** provides typical estimates for volume of distribution by age. A recent population pharmacokinetic (PK) analysis on single dose lithium pharmacokinetics in children 7–17 yr of age⁴⁵ confirmed the volume of distribution range previously reported by Vitiello.⁴⁸ When fat free mass was included in the model as a covariate, it explained most of the variability in the estimates of V and CL in children, in good accordance with previous results in elderly and obese patients.⁴⁵

TABLE 17-4. LITHIUM VOLUME OF DISTRIBUTION ESTIMATES BY AGE

Population	Volume of Distribution (Mean ± SD)
Children and adolescents ⁴⁸	0.93 ± 0.25 L/kg ^a
Adults (19–59 yr) ^{41,49}	0.85 ± 0.25 L/kg ^a
Elderly (>59 yr) ⁴⁶	0.53 ± 0.12 L/kg ^a

^aBased on ideal body weight.

Elimination

Lithium is primarily eliminated in urine as the free ion and is not metabolized. Lithium clearance is largely renal, with saliva, sweat, and feces accounting for minor amounts (<5%).⁵⁰ The lithium ion is completely filtered across the glomerular membrane, similar to sodium and potassium, and is 80% reabsorbed via the proximal renal tubules. Lithium clearance is directly proportional to GFR and blood flow to the kidney and is ~20% of creatinine clearance (CrCl).⁵¹ Estimates for lithium clearance by age are given in **Table 17-5**. Lithium clearance decreases in parallel with age-related decreases in GFR, which is ~10 mL/min per decade after 30 yr of age.⁵² Based on a population pharmacokinetic study, lean body weight and CrCl are important predictors of lithium clearance.⁵³ Circadian rhythm changes in GFR, CrCl, and lithium clearance all result in higher daytime clearances and variations in elimination half-life, which may affect therapeutic concentration monitoring.³² The clearance of lithium also appears similar in children compared with adults.^{45,48} Modest decreases in glomerular filtration rate occasionally occur in patients receiving long-term lithium therapy, but a causal relationship has not been established. Lithium may also inhibit its own clearance via its effects on antidiuretic hormone and aldosterone.^{54,55}

Increases in lithium concentrations occur with sodium depletion or with a low-salt diet secondary to enhanced proximal tubular reabsorption of the lithium ion.^{56,57} Renal excretion of lithium does not appear to be enhanced by increasing water intake or acidification of urine. Drug–drug interactions or drug–disease state/conditions that result in changes in GFR or in the reabsorption of lithium and/or sodium are likely to affect lithium clearance and should be considered when designing or modifying lithium regimens.^{32,49}

TABLE 17-5. LITHIUM CLEARANCE ESTIMATES BY AGE^a

Population	Clearance (Mean) ^b
Children and adolescents ^{45,48}	0.021 L/hr/kg
Adults (19–59 yr) ^{41,49}	0.024 L/hr/kg
Elderly (>59 yr) ⁴⁷	0.015 L/hr/kg

^aIn patients with normal renal function for age.

^bBased on 70 kg weight.

Half-life and time to steady state

Lithium exhibits biphasic elimination (two-compartment model). The elimination half-life of lithium is dependent on volume of distribution and clearance rates, and possibly on duration of therapy. **Table 17-6** provides estimates for half-life and time-to-steady state concentrations by age. In patients with normal renal function, the initial ($t_{1/2\alpha}$) and terminal half-lives ($t_{1/2\beta}$) have been reported as 0.8–1.2 hr and 20–27 hr, respectively, after single-dose administration; however, the initial (distributional) phase is typically not adequately characterized in clinical practice. For clinical purposes, the disposition of lithium can be estimated by a single terminal half-life (one-compartment model).⁵⁸ In patients with normal renal function the mean terminal $t_{1/2}$ ranged from 16 to 30 hr after multiple dosing.^{41,42,44,59} Treatment duration has been associated with increases in elimination half-life. Significantly longer half-lives have been reported in patients receiving continuous lithium therapy for more than 1 year compared with those receiving therapy for less than 1 yr (2.4 versus 1.7 days).⁶⁰ Lithium-associated nephrotoxicity or changes in lithium transport across red cell membranes over time may account for these effects.^{61,62} Longer elimination half-lives of 36 hr and 40–50 hr have been reported in elderly patients and in those with impaired renal function, respectively. The elimination half-life of lithium in children (9–12 yr) was 17.9 hr after a single 300-mg oral lithium dose.⁴⁸ However, a recent population PK analysis of lithium kinetics in children after a single dose determined this shorter half-life to be an artifact of the noncompartmental analysis and a higher lower limit of quantification.⁴⁵

In this new study, it was concluded that when taking into account the concentration time profiles of all subjects simultaneously and considering concentrations below the quantification limit by population PK analysis, the allometrically-scaled clearance in children was within the range of values reported for adults. The authors concluded that the differences in lithium PK parameters between children and adults might be explained by including the effect of body weight.

TABLE 17-6. LITHIUM HALF-LIFE AND TIME TO STEADY STATE ESTIMATES BY AGE^a

Population	Half-life (Mean ± SD)	Time-to-Steady State ^b (Range)
Children and adolescents ^{45,48}	27± 11 hr	80–190 hr
Adults (19–59 yr) ^{41,49}	22 ± 7 hr	75–145 hr
Elderly (>59 yr) ⁴⁶	27 ± 8 hr	95–175 hr

^aIn patients with normal renal function for age.

^bFive half-lives were assumed for steady state, using ± 1 standard deviation of the mean half-life.

Dosing strategies

Dose prediction methods

Numerous equations and dosage prediction methods have been proposed to help clinicians identify an appropriate lithium dose for desired therapeutic concentrations. Although many methods use lithium concentrations and a specific pharmacokinetic model, some use principles of population pharmacokinetics to relate patient characteristics to changes in lithium clearance.

Comparative evaluations of some dose prediction methods are available.⁶³⁻⁷² For example, in a comparative study, three dose prediction methods (i.e., the Zetin, Pepin, and Jermain methods) described below yielded more precise estimates than an empiric method for dosing lithium. The Jermain method was more precise at predicting steady-state concentrations within 20% of actual lithium concentrations measurements from doses.⁷² However, no one method was significantly better than another.

When lithium clearance is estimated or determined from measured concentrations, the clinician can select the dose (D) and dosage interval (τ) necessary to achieve the target trough (12 hr) steady-state concentration (approximated by Css_{av}). When patients are at steady state and lithium pharmacokinetic parameters are stable, lithium dosages can be adjusted proportionately to reach the desired concentration.

Dosage prediction using the traditional pharmacokinetic method

Lithium exhibits linear pharmacokinetics that can be adequately described with a one-compartment model following oral dosing. The following equation may be used to estimate the dose required to produce a 12-hr trough concentration at steady state when an individual's lithium clearance is known or can be estimated.

$$D = \frac{CL \times \tau \times Css_{av}}{S \times F}$$

where D = dose (mEq), CL = clearance of lithium (L/hr), τ = dosing interval (hr), Css_{av} = average steady-state concentration (mEq/L), F = fraction absorbed (~90% for most patients), and S = salt form (1).⁶¹ The dose is then converted from mEq to mg.

Though rarely done, a patient's individual elimination half-life can be determined directly from two or more lithium concentrations obtained in the post-absorptive, post-distributive phase following an oral dose.⁷³ The multiple-point prediction method of Perry and colleagues employs a 1,200-mg test dose, 12-, 24-, and 36-hr post dose concentration determinations, and direct estimation of the patient's individual elimination half-life.⁷⁴

Dosage prediction by a priori demographics

The most common characteristics used for prediction methods include estimations of renal function, age, and body weight as represented by the method of Zetin et al.⁷⁵

$$\begin{aligned} \text{Dose (mg/day)} = & 486.9 + (746.83 \times \text{desired concentration}) \\ & - (10.08 \times \text{age}) + (5.95 \times \text{weight}) + (92.01 \times \text{status}) \\ & + (147.8 \times \text{sex}) - (74.73 \times \text{TCA}) \end{aligned}$$

where desired concentration is in mEq/L, age in years, actual body weight in kg; status is 1 for inpatient, 0 for outpatient; sex is 1 for male and 0 for female; and tricyclic antidepressant administration (TCA) is 1 for concomitant TCA or otherwise 0 for none.

Terao et al.⁷⁶ proposed an a priori demographic method based on stepwise multiple linear regression and blood urea nitrogen (BUN) as a measurement of renal function:

$$\begin{aligned} \text{Dose (mg/day)} = & 100.5 + (752.7 \times \text{desired concentration}) - (3.6 \times \text{age}) \\ & + (7.2 \times \text{actual body weight}) - (13.7 \times \text{BUN}) \end{aligned}$$

where desired concentration is in mEq/L, age in years, weight in kg, and blood urea nitrogen (BUN) in mg/dL.

Dosage prediction by lithium renal clearance estimation

Pepin et al.⁷⁷ devised a prediction method based on their population pharmacokinetic findings that lithium clearance CL_{Li} is related to estimated creatinine clearance (CrCl); however, this method is not consistently precise or accurate.^{63,78}

$$CL_{Li} = 0.235 \times CrCl$$

Units for CL_{Li} are the same as those used for CrCl. If CrCl in mL/min is used, multiplying by 0.06 will convert the CL_{Li} units to L/hr.

Jermain et al.⁵³ devised a method that predicts lithium clearance based on population pharmacokinetics. It was developed using nonlinear fixed-effects models:

$$CL_{Li} = [0.0093 \text{ (L/hr/kg)} \times LBW] + (0.0885 \times CrCl)$$

where LBW is the lean body weight in kg (see Chapter 4, Table 4-1, for lean body weight equation) and CrCl is the estimated creatinine clearance *in liters per hour*. This method suggests that LBW and CrCl are the most important predictors of lithium clearance. Age is not directly represented in this method, but decreases in CrCl and changes in total body water and muscle mass, as reflected in the lean body weight, likely account for the changes in lithium clearance usually attributed to age. This method yielded a coefficient of variation for predicted lithium clearance of about 24% and gave fairly accurate predictions of steady-state lithium concentrations (coefficient of variation, 16%).

Dosage prediction by population pharmacokinetics and measured concentration(s)

The classic dosing chart of Cooper et al.⁷⁹ is based on population clearance values for lithium and uses a 600-mg standard release lithium carbonate test dose and a single 24-hr lithium concentration. This method does not predict a specific lithium concentration but provides a dose that is likely to result in a lithium concentration within the appropriate therapeutic range as indicated by a nomogram. The clinical utility and limitations of this method have been reviewed elsewhere.^{80,81}

Perry and colleagues reported on both single-point and multiple-point prediction methods based on their findings of a significant correlation between observed lithium concentrations and predicted steady-state concentrations.^{74,82} Their single point method uses a 1200-mg test dose and a 24-hr post dose concentration determination, with use of a nomogram to predict steady-state lithium concentrations.

THERAPEUTIC RANGE

Some controversy exists regarding a standard therapeutic range for lithium; this is due, in part, to the search for the lowest possible range effective in maintenance and prophylaxis therapies.¹⁹ The therapeutic ranges shown in **Table 17-7** are generally accepted. In patients with acute mania, more than 90% of patients respond at lithium concentrations <1.2 mEq/L. Higher concentrations (1.2–1.5 mEq/L) may be required in select patients. No definitive study is available to show a relationship between lithium concentrations and clinical response in children. However, several studies that evaluated lithium in children/adolescents showed that although mean lithium concentrations in the adult range were achieved; concentrations were not different between responders and nonresponders. Until more information is available, lithium concentration recommendations for children/adolescents are similar to that of adults.⁸³⁻⁸⁵ Lower target concentrations (0.5–0.8 mEq/L) are often recommended in elderly patients, especially in the presence of other comorbidities such as renal disease or diabetes, primarily in an effort to minimize side effects.^{86,87} Lithium concentrations ≤ 0.8 mEq/L may also be safer in terms of negative short-term effects on GFR in patients 65 yr of age and older who do not have pre-existing chronic renal failure.⁸⁸ A target range of 0.4–0.6 mEq/L may be indicated for patients who have had a good therapeutic response to lithium but are unable to tolerate dose-related side effects.^{88,89}

According to the most recent guidelines for the treatment of bipolar disorder, the therapeutic range traditionally targeted for lithium is 0.6–0.8 mEq/L for maintenance and prophylaxis therapies for patients with bipolar illness.¹⁹ Several studies evaluating lower target concentrations (<0.7 mEq/L) indicate that the risk of relapse was substantially higher, and patients maintained in the lower portion of the therapeutic range had fewer satisfactory responses.⁹⁰⁻⁹⁴ Maintaining higher lithium concentrations (0.8–1 mEq/L) may increase the likelihood of successful prophylactic treatment, but some patients do respond at lower concentrations.^{95,96} Similarly, small changes in concentrations (0.2–0.3 mEq/L) may be clinically significant and substantially affect relapse rates.^{19,23,91,95} Although dosing of lithium should be based on symptom response and tolerability, appropriate therapeutic drug monitoring and use of sound pharmacokinetic principles to more precisely target desired lithium concentrations may be beneficial.¹³

TABLE 17-7. PROPOSED THERAPEUTIC RANGE FOR LITHIUM^{13,19}

Disease or Condition	Therapeutic Range
Acute mania	0.5–1.2 mEq/L
Prophylaxis of mania	0.6–1 mEq/L
Prophylaxis of depression	0.4–0.8 mEq/L

THERAPEUTIC MONITORING

Suggested sampling times and effect on therapeutic range

Considerable efforts have been made to standardize the sampling time for steady-state lithium concentration determinations.²⁰ Several factors including daily lithium schedule, timing of sampling, patient compliance, diurnal variation, lithium preparation, and changes in salt intake, renal function, hydration status, and concomitant medication all may affect measured lithium concentrations.²³ Based on divided daily dosing schedules (two or three times daily), the conventional lithium concentration determination is a 12-hr (±30 min) post dose trough concentration, collected after the evening dose but before the morning dose (hold the morning dose if necessary). This 12-hr time point is arbitrary but usually occurs in the post absorption and post distribution phase, thus minimizing the intra- and interindividual variability in lithium measurements over time. If an 8-hr post dose trough concentration time point is used, then lithium concentrations would be higher than the standard 12-hr concentration and, therefore, would affect interpretation.

In the case of once-daily dosing, there are much greater peak-to-trough fluctuations around the average steady-state lithium concentration compared with the same daily dosage given in divided doses. Therefore, the 12-hr lithium concentration measurement may be higher and a 24-hr trough lithium concentration may be lower than the standard 12-hr concentration measurements obtained after a divided daily dosing schedule. A 10% to 26% increase in the standard 12-hr lithium concentrations may be expected with a change to a once-daily dosing schedule using the same total daily dose.⁹⁷ As shown in **Figure 17-1**, simulated steady-state lithium concentration-time profiles using the same lithium dosage divided into different daily schedules illustrate the variability of the 12-hr lithium concentration determination due to differences in dosing interval. The 12-hr lithium concentration measurements were 1.37 versus 1.07, 1, and 0.96 mEq/L when the same daily dose was given once daily versus divided into two, three, or four doses, respectively.³² Current therapeutic ranges assume multiple daily dosage regimens, and no therapeutic range has been established for once-daily regimens.

Concentration measurement frequency

Because lithium concentrations are closely related to therapeutic response and side effects, the use of lithium concentration monitoring is an important clinical tool to manage patients receiving lithium. Therapeutic drug monitoring can be used to monitor efficacy, toxicity, compliance, and accuracy of prediction models. In general, a lithium concentration should be determined 3–7 days after therapy has been commenced.⁹⁸ In acute mania, initial 12-hr lithium trough concentrations should be performed once or twice weekly until the desired therapeutic concentration is achieved, with continued follow-up monitoring at least every 3–6 months, or as necessary during periods of therapeutic nonresponse or appearance of side effects in acutely manic patients.¹⁹ A conventional monitoring method for the once-daily dosage patient is to identify the 12-hr lithium concentration that is therapeutic for that individual and to carefully screen for side effects, toxicity, or relapse of manic symptoms.

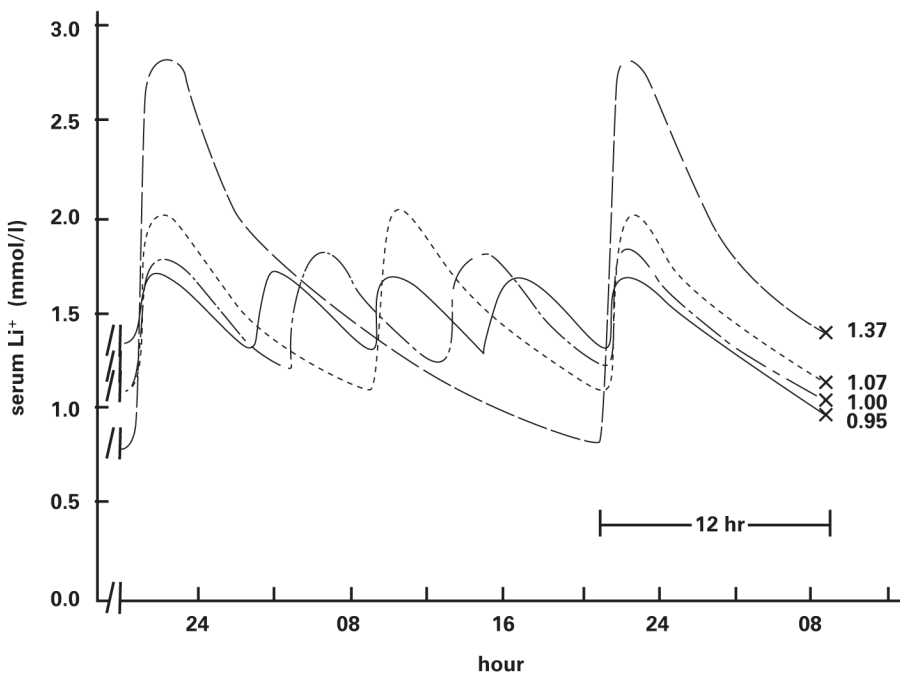


Figure 17-1. Simulated steady state serum lithium (S_{Li}) concentration–time profiles of identical lithium doses divided into one, two, three, or four doses illustrate the variability of 12-hr S_{Li} concentrations due solely to differences in dosage interval.

Source: Reprinted with permission from Carson S. Lithium. In: Evans WE, Schentag JJ, Jusko WJ, eds., *Applied Pharmacokinetics—Principles of Therapeutic Drug Monitoring*. 3rd ed. 34–11; ©1992, Wolters Kluwer/LWW.

Current practice guidelines for the treatment of patients with bipolar disorder also recommend that lithium concentrations be obtained at least every 3–6 months during maintenance therapy in stable patients.^{19,99} More frequent monitoring may be required with changes in fluid and electrolyte balance, unstable renal function, or if toxicity is a concern. Other laboratory monitoring parameters and information for patient and family counseling can be found elsewhere.^{18,100}

A treatment initiation and monitoring scheme for patients receiving lithium is shown in **Figure 17-2**.

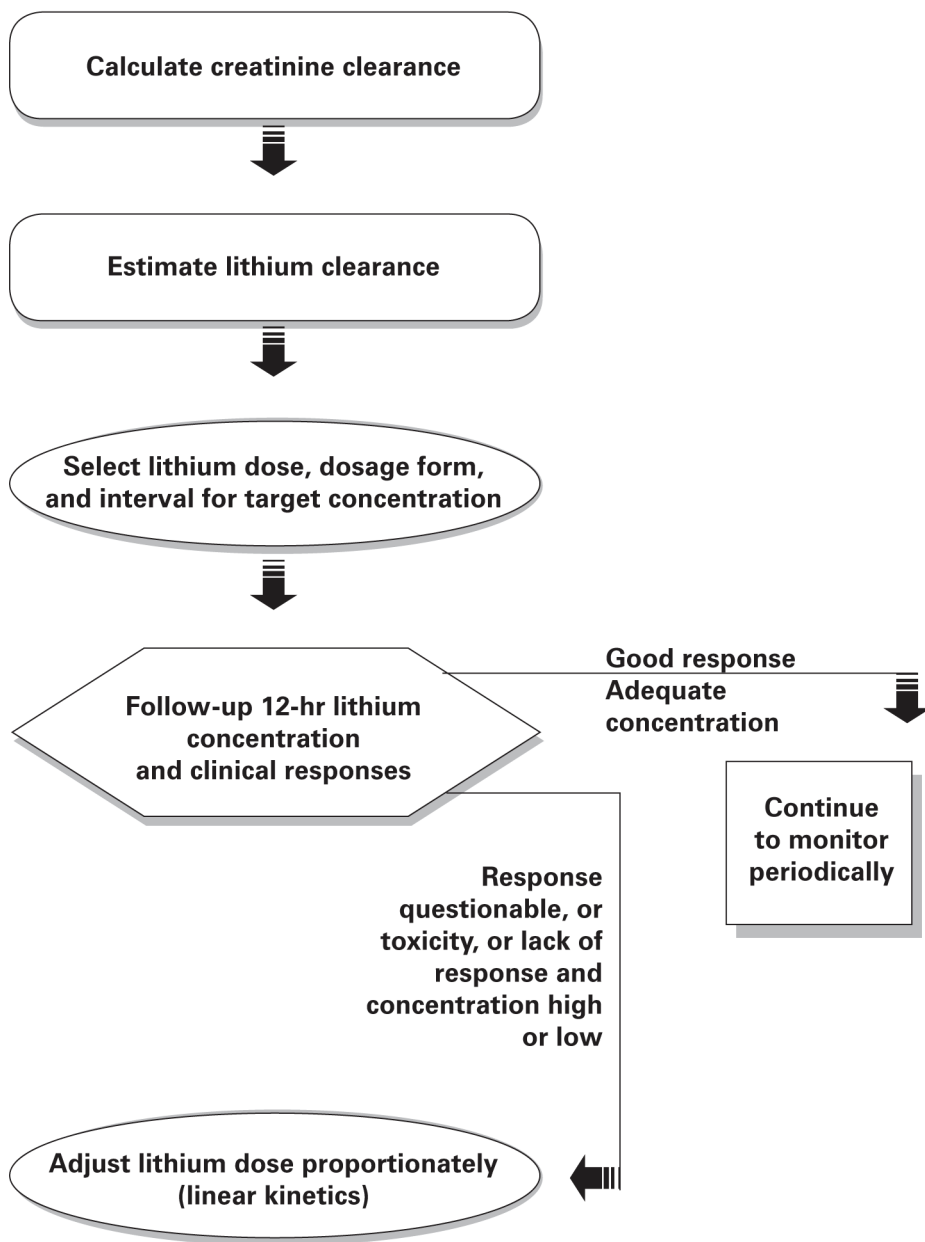


Figure 17-2. General scheme for therapeutic drug monitoring of lithium therapy in patients with bipolar disorder.

Assay issues

Plasma or serum may be used to determine lithium concentrations; both provide similar results. Bioassay methods for lithium include flame photometry and atomic absorption. Both are commonly used in the determination of lithium concentrations in biofluids and provide comparable results.^{66,101}

A third methodology used to determine lithium concentrations is the ion-specific or ion-selective electrode analyzer.¹⁰²⁻¹⁰⁴ Recently, several spectrophotometric and colorimetric methods have also been evaluated to monitor lithium serum concentrations; the advantage of these methodologies is that they are fast and easy to perform and often require only small volumes of sample; however, hemoglobin can interfere with the determinations and these methods are applied only to serum samples.¹⁰⁵⁻¹⁰⁸ A methodology based on capillary zone electrophoresis with indirect detection has been described in the literature.¹⁰⁹ This method is more time consuming than ion-selective electrodes or flame photometry; however, the sophisticated separation mechanism prior to detection excludes potential interferences from endogenous and exogenous compounds present in the sample. Therefore, it is proposed to be used as a confirmatory tool in controversial analysis or nonstandard samples such as forensic specimens. Finally a methodology based on a microchip capillary electrophoresis method has been developed to analyze minute amounts of blood with the final goal to allow for self-monitoring at home from simple capillary blood obtained by finger stick.¹¹⁰ To avoid interferences, sample tubes containing lithium-heparin should not be used to collect biofluid samples for lithium determinations.¹¹¹

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

The application of pharmacokinetic principles to monitor pharmacodynamic responses in clinical practice assumes that the response is objective, reversible, and relatively rapid. In psychiatric diseases, some evaluated responses may fail to meet all of these assumptions. Response measurements evaluated in patients with psychiatric illness typically are affected by subjective rating scales, delayed responses (days or weeks), and significant placebo effects. Thus, percent of response or relative risk of relapse at a particular drug concentration may be used to account for these discrepancies. In patients receiving lithium, target symptom response is most often used to gauge the effectiveness of lithium therapy. Improvements in manic or depressive symptoms, such as sleep patterns, agitation, and anxiety, are good indicators of lithium efficacy (Table 17-8).

TABLE 17-8. THERAPEUTIC RESPONSE SEQUENCE FOLLOWING INITIATION OF LITHIUM THERAPY ¹²⁹	
Manic Symptoms	
1–3 weeks	Decrease in pressured speech Decreases in hostile or assaultive behaviors
2–3 weeks	Improved thought pattern disturbances
2–4 weeks	Increased attention to appearance or hygiene
1–2 months	Less grandiosity Less irritability
Depressive Symptoms	
2–4 weeks	Improved motor and mental activities Improved sleep pattern Decrease in any psychotic features
1–2 months	Improved mood

Due to the heterogeneity of response in the bipolar patient population, the optimal lithium concentration for individual patients may vary depending on the indicated use. Different target concentrations have been suggested to manage acute mania, maintain remission, or provide prophylaxis against future episodes (see Therapeutic Range). The paradigm of using the lowest effective dose to limit the appearance of side effects is widely held when managing patients on lithium. Several studies have shown that as lithium concentrations increase from 0.3 to 1.4 mEq/L, the risk of relapse decreases and the incidence of side effects increases.^{90,91,112} The risk of relapse was 2.6 times higher when median lithium concentrations (12-hr post dose) were targeted in the range of 0.4–0.6 mEq/L compared with a higher target range of 0.8–1 mEq/L.⁹² This finding suggests considerable variation in clinical response within the typical concentration range of 0.5–1.2 mEq/L.

Concentration-related toxicity

Lithium toxicities appear to increase with increasing lithium concentrations (**Table 17-9**). Toxicity most often occurs with 12-hr trough concentrations greater than 1.5 mEq/L, but side effects may occur in some patients at therapeutic concentrations. Mild and transient effects such as fine tremor, nausea, diarrhea, muscle weakness, polyuria, and polydipsia can be seen at concentrations of less than or equal to 1.5 mEq/L. Moderate toxicity usually occurs at concentrations of 1.5 to 2.5 mEq/L, with more severe toxicities observed at trough concentrations greater than 2.5 mEq/L. Concentrations above 3–3.5 mEq/L are usually considered life threatening; hemodialysis, the most effective extrarenal clearance mechanism, should be considered.^{61,113}

DRUG-DRUG INTERACTIONS

A number of lithium drug–drug interactions are associated with effects on fluid and/or sodium balance, thus, GFR and sodium excretion are of particular importance. An extensive review of lithium drug interactions is reported elsewhere.¹¹⁴ Drugs causing a decrease in GFR or a compensatory increase in sodium reabsorption result in reduced lithium clearance and elevated lithium concentrations. Examples of this type of lithium–drug interaction include the non-thiazide, thiazide, and loop diuretics; nonsteroidal anti-inflammatory agents; angiotensin-converting enzyme inhibitors; platinum-containing chemotherapeutics; and iodides (see **Table 17-10**). The concurrent use of these medications should be avoided when possible to avoid possible toxicity. When there is a compelling indication warranting the use of an interacting medication with lithium, adjustment factors can be used to estimate changes in pharmacokinetic parameters and the impact of these drug–drug interactions. For example, angiotensin converting enzyme inhibitors may decrease lithium clearance by 30% in patients ≥ 50 yr of age, while caffeine or theophylline may increase lithium clearance by 20% to 25%. Because there is considerable interindividual variation in drug–drug interactions with lithium, these adjustment factors should be used with caution.

Other drugs that have been reported to interact with lithium include antipsychotics, anticonvulsants, selective-serotonin receptor antagonists, calcium-channel blockers, antibiotics, and neuromuscular-blocking agents.^{115–118} Several case reports or series also have suggested potential lithium interactions with tetracycline, metronidazole, diazepam, opiates, beta-adrenergic antagonists, topiramate, levofloxacin, doxycycline, methyldopa, digoxin, mefenamic acid, angiotensin receptor blockers, and possibly minocycline.^{17,116,119–128}

DRUG–DISEASE STATE INTERACTIONS AND SPECIAL POPULATIONS

Disease state or condition interactions with lithium are often related to an individual's renal function and usually to GFR and/or sodium excretion. Disease states or conditions that increase GFR, such as pregnancy or excess fluid administration, are likely to increase lithium clearance, resulting in shorter half-lives and lower lithium concentrations.

TABLE 17-9. CONCENTRATION-RELATED TOXICITY ASSOCIATED WITH LITHIUM THERAPY¹³⁵⁻¹⁴¹

Concentration-Related Toxicity ^a	Comment
Potential side effects observed with therapeutic concentrations Agitation Cog-wheel rigidity Confusion Delirium Dysarthria Increased deep tendon reflexes Memory impairment Seizures	Measure lithium concentration; consider reduction in dose.
Mild toxicity (<1.5 mEq/L) Fatigue Fine tremors of the limbs Gastrointestinal disturbances Muscle weakness	Measure lithium concentration; interview patient regarding changes in diet, health, or concomitant medications; consider reduction in dose; hold dose until lithium concentration returns to usual range and signs/symptoms of toxicity resolve.
Moderate toxicity (1.5–2.5 mEq/L) Ataxia Coarse tremors Dysarthria Headaches Hyperthermia Impaired sensorium Increased deep tendon reflexes Lethargy Nystagmus Sedation	Measure lithium concentration; interview patient regarding changes in diet, health, or concomitant medications; consider reduction in dose; consider supportive care to correct any fluid imbalance; hold dose until lithium concentration returns to usual range and signs/symptoms of toxicity resolve.
Severe toxicity (>2.5 mEq/L) Basal ganglia dysfunction Coarse tremors Delirium Respiratory complication Seizures Death	Occurs in overdose, in patients receiving high lithium doses, and with concomitant illnesses; hold dose until lithium concentration returns to usual range and signs/symptoms of toxicity resolve; consider use of hemodialysis or peritoneal dialysis; reduce dose unless efficacy shown to be compromised at lower concentration and cause of elevation determined to be temporary.

^aToxicities that occur at lower concentrations may also occur at higher concentrations.

Children typically have increased renal function and higher excretion rates compared with adults and may require higher lithium doses per kilogram of body weight to achieve therapeutic concentrations. Compared to other treatments there are more data available for lithium than for any other medications in children for bipolar disorder. Even though only limited data are available in children receiving lithium, the clinical response has ranged from 50% to 100% in various studies.^{19,48,84,130-134} Lithium is not approved for use in children below 12 yr of age and, therefore, should be used with special caution.

Conversely, conditions such as advancing age or renal impairment are associated with a decrease in GFR. Alterations in total body water and lean muscle mass that accompany aging are associated with a reduced volume of distribution and higher lithium concentrations. Conditions that result in a compensatory increase in sodium reabsorption, such as dehydration, increase lithium reabsorption and decrease lithium clearance, leading to increased lithium concentrations. Lithium should be used cautiously in patients with restricted sodium intake. Patients with underlying cardiovascular or thyroid disease should be monitored for signs and symptoms of dysrhythmia while receiving lithium since sinus nodal arrhythmias may occur. Comorbidities such as heart failure or hyponatremia may result

TABLE 17-10. SELECTED LITHIUM–DRUG INTERACTIONS AND ADJUSTMENT FACTORS

Drug	Affected Pharmacokinetic Parameter	Adjustment Factor ^a
Angiotensin converting enzyme inhibitors ^{115,147}	Renal clearance	<50 yr, 0.87 ≥50 yr, 0.69
Caffeine ⁴⁹	Renal clearance	1.2–1.25
Celecoxib ^{148–151}	Renal clearance	0.43–0.95 ^o
Cisplatin/fluids ^{152,153}	Renal clearance	1.6
Diclofenac ^{148,151}	Renal clearance	0.53–0.80
Flurbiprofen ^{148–151,154}	Renal clearance	0.84–0.92
Ibuprofen ^{148,155}	Renal clearance	0.60–1.1
Indomethacin ^{148,156}	Renal clearance	0.62–0.83
Ketorolac ^{148,157}	Renal clearance	0.64–0.79
Mefenamic acid ¹⁴⁸	Renal clearance	0.25 ^b
Meloxicam ¹⁴⁸	Renal clearance	0.71
Naproxen ^{148,158,159}	Renal clearance	0.67–1
Nonsteroidal anti-inflammatory agents ^{148,160}	Renal clearance	0.33–1
Phenylbutazone ¹⁴⁸	Renal clearance	0.87
Piroxicam ¹⁴⁸	Renal clearance	0.26–0.79
Sodium-containing intravenous fluids ^{116,161}	Renal clearance	1.2
Sulindac ^{c,148}	Renal clearance	0.50–0.71 ^b
Theophylline ¹⁶²	Renal clearance	1.21
Thiazide diuretics ^{163–168}	Renal clearance	0.32–0.74

^aAdjustment factor is the fraction of usual dose (or clearance or half-life) of lithium that would be suggested in cases where both drugs are used concomitantly.
^bAdjustment factor based on one or more individual case reports.
^cTransient changes in lithium plasma concentrations after sulindac administration returned to baseline with continued sulindac treatment.

in increased lithium concentrations.¹²When assessing the impact of these disease state or condition interactions, adjustment factors can be used to estimate changes in pharmacokinetic parameters (see **Table 17-11**). For example, dehydration may decrease lithium clearance to 81% of normal, whereas pregnancy may increase it two-fold.

Dialysis

Lithium may be removed by either hemodialysis or peritoneal dialysis; rebound increases in lithium concentrations may occur for up to 8 hr after dialysis.^{17,142,143}

Geriatrics

Geriatric patients are more likely to experience neurotoxicity from lithium use.¹² Lithium has some anticholinergic properties that could lead to cognitive impairment or contribute to anticholinergic delirium, especially if it is combined with other anticholinergic agents.¹⁴⁴

TABLE 17-11. SELECTED LITHIUM–DISEASE STATE OR CONDITION INTERACTIONS AND ADJUSTMENT FACTORS

Population	Affected Pharmacokinetic Parameter	Adjustment Factor
Acute mania ¹⁷⁴	Renal clearance	0.6
Elderly ^{41,46,175}	Renal clearance	0.6–0.7
	Distribution volume	0.6–0.8
Dehydration ¹⁷⁵	Renal clearance	0.8 ^a
Lithium therapy for >1 yr ¹⁷⁵	Half-life	1.3–1.4 ^b
Low-salt diet ^{176,177}	Renal clearance	<1
Obesity ¹⁷⁸	Renal clearance	1.5
	Distribution volume	0.6
Pregnancy ^{41,42}	Clearance	2
Strenuous exercise ¹⁷⁹	Renal clearance	1.2 ^a

^aLithium clearance based on single concentration in case reports.

^bNot consistent in all studies.

Pregnancy

Lithium is currently classified as a Category D drug, although this is likely to change in the future as a result of the Food and Drug Administration Pregnancy and Lactation Labeling Rule. There is evidence of human fetal risk, but benefits to the pregnant woman may outweigh the risk. Untreated pregnant women are at increased risk of relapse, and the high incidence of post-partum affective disorders poses some question regarding the discontinuation of prophylactic therapy. Current recommendations suggest avoiding first-trimester exposure if possible.¹⁴⁵ The lowest effective dose should be used in women who are pregnant.¹⁴⁶

Fetal exposure to lithium in the first trimester is associated with a 1/1,000 to 1/2,000 risk of developing Ebstein's anomaly of the tricuspid valve. The risk in the general population is 1/20,000. The risk for this very rare malformation remains very low, and other recent studies concluded that the use of lithium during pregnancy did not increase the number of congenital malformations.^{40,145} Because GFR increases and creatinine clearance may double during pregnancy, lithium dosage requirements will likely increase in the third trimester. Careful monitoring of lithium concentrations during pregnancy and immediately before and after delivery is essential.¹⁴⁶ Lithium concentrations, along with thyroid and electrolyte measurements, should be monitored at least monthly throughout pregnancy and at least weekly during the last month of pregnancy in women at higher risk (i.e., unstable symptoms, other medical comorbidities).^{145,146,169} Women who are stabilized on lithium and remain euthymic may only require lithium concentration monitoring every trimester up until the time of delivery. Subsequent downward titration by 25% to 30% or discontinuation of lithium immediately prior to delivery may decrease the risks of neonatal toxicity and toxicity due to rapid postpartum shifts in plasma volume.^{146,170,171} In women for whom decreasing the dose or discontinuing lithium prior to delivery is not clinically indicated, increasing hydration around the time of delivery may be helpful in avoiding lithium toxicity.¹³

Lithium concentrations in breast milk are ~50% of the maternal concentrations, and because an infant's renal status is immature, any lithium ingested from breast milk may be cleared slowly.¹⁷¹ In a study of 10 maternal-infant pairs of carefully selected patients with bipolar disorder, breast milk concentrations averaged ~50% of maternal trough concentrations (10–14 hr post-dose) and infant concentrations averaged ~50% of breast milk concentrations. There were no reports of treatment emergent adverse events or behavioral effects in the infants.^{172,173} Nevertheless, infants should be carefully monitored for hypotonia, lethargy, cyanosis, hydration status, renal function, thyroid function, and perhaps lithium concentration if breast fed.¹⁴⁵

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PHENOBARBITAL

Kimberly B. Tallian and Douglas M. Anderson

Although the use of phenobarbital has declined in favor of newer, nonbarbiturate medications, it remains an agent of choice in a variety of central nervous system disorders. Properly administered, phenobarbital continues to afford safe and effective therapy to many patients in a reliable and convenient fashion. Approved uses include febrile seizures in children and all forms of epilepsy except absence seizures.¹ Some frequent uses, which are not Food and Drug Administration (FDA)-approved, include prevention of seizures associated with intracranial hemorrhage in preterm neonates, treatment of essential tremor in adults, and cerebral salvage related to traumatic and/or hypoxic brain injury.²

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS^{3,4}

Phenobarbital exhibits a predictable pharmacokinetic profile with a relatively wide therapeutic window. As a result, dosing protocols are often used with satisfactory results. The dosing recommendations in **Table 18-1**, based on average pharmacokinetic parameters, should produce concentrations in the therapeutic range for most patients. However, significant interpatient variation necessitates therapeutic monitoring.

Once-daily dosing at bedtime is preferred to minimize daytime sedation and increase compliance in ambulatory patients.^{5,6} If the clinical situation allows, initial sedation may be minimized by starting therapy with 25% of the desired maintenance dose and increasing it weekly by another 25% until the full maintenance dose is achieved.⁷ Because phenobarbital exhibits first-order elimination, linear relationships exist between dose adjustments and resultant drug concentrations during steady-state conditions.

For intravenous (IV) and intramuscular (IM) routes, the sodium salt of phenobarbital is used, which has a *salt fraction* (*S*) of approximately 0.9 (91% phenobarbital). Phenobarbital is used for oral dosage forms (*S* = 1). IV phenobarbital loading doses have been reported to cause hypotension, particularly in neonates (possibly an effect of the propylene glycol in the product). However, recommended loading doses should be safe if administered at less than 50 mg/min in adults.³ In neonates and children, phenobarbital should not be administered intravenously at a rate >1 mg/kg/min with a maximum of 30 mg/min.⁶ Phenobarbital's slow elimination precludes the need for continuous IV infusions or sustained-release products (see **Table 18-2** for product availability).

TABLE 18-1. LOADING AND MAINTENANCE DOSES BY AGE GROUP

Age Group	Loading Dose ^{a,b,3}	Maintenance Doses ^a
Neonates (<2 wk)	15–25 mg/kg	2–4 mg/kg/day
Infants (2 wk–<1 yr)	15–25 mg/kg	5 mg/kg/day
Children		
1–<5 yr	10–20 mg/kg	4.5 mg/kg/day
5–<10 yr	10–20 mg/kg	3.6 mg/kg/day
10–<15 yr	10–20 mg/kg	2.9 mg/kg/day
15–<19 yr	10–20 mg/kg	2.5 mg/kg/day
Adults (19–65 yr)	10–20 mg/kg	2 mg/kg/day
Geriatrics (>65 yr)	10–20 mg/kg	1.1–2 mg/kg/day

^aOral (capsules, tablets, and elixir), IV, and IM.

^bIV loading doses should be administered at <50 mg/min in adults and <1 mg/kg/min or ≤30 mg/min in children.



TABLE 18-2. DOSAGE FORM AVAILABILITY⁸

Dosage Form	Manufacturer
Phenobarbital sodium injection (IV and IM) 30, 60, 65, and 130 mg/mL	Various manufacturers
Oral elixir 15 mg/5 mL ^a and 20 mg/5 mL	Various manufacturers
Oral tablets 15, 16.2, 30, 32.4, 60, 64.8, 97.2, and 100 mg	Various manufacturers

^aAvailable outside the United States.

GENERAL PHARMACOKINETIC INFORMATION

Absorption

Phenobarbital is slowly but completely absorbed. Oral products are most often >90% bioavailable (F = 1) (**Table 18-3**). With oral dosage forms, large single doses over 750 mg may exhibit delayed or reduced absorption in adults due to the insolubility of phenobarbital crystals that form and remain for some time in the gastrointestinal (GI) tract. Drugs or diseases that affect GI motility may influence the rate of absorption. The effect on the extent of absorption is unclear. The presence of food apparently does not affect the extent of absorption.

TABLE 18-3. BIOAVAILABILITY (F) OF DOSAGE FORMS^{4,8}

Dosage Form	Bioavailability	Comments
IM	100% (F = 1)	Onset of action within 30 min; time to peak concentrations ≤3 hr
IV	100% (F = 1)	Immediate onset of action
Rectal	90% (F = 0.9)	Faster rate of absorption than oral or IM routes
Oral (capsules, tablets, elixir)	90% to 100% (F = 0.90–1)	Time to peak variable (~2 hr)

Distribution

Phenobarbital’s volume of distribution ranges from 0.5–1 L/kg (**Table 18-4**). Volumes relative to body weight are largest at birth through infancy, decline slightly in childhood, and reach the lowest L/kg population values in adults. Significant variation may exist within each age group, due in part to fluctuation of plasma proteins and a correlation with pH.⁴ A weak acid, phenobarbital has a pKa of 7.3, approximating plasma pH. Increases in plasma or urine pH may increase clearance and vice versa.

Distribution occurs in a biphasic manner, normally reaching the beta phase about 2 hours after administration.⁶ At this time point after an IV dose, central nervous system (CNS) concentrations approximate the serum unbound concentrations and range from 43% to 60% of serum values.⁴ As a result of slow distribution into the CNS, phenobarbital has not historically been used for status epilepticus. However, one study found phenobarbital’s efficacy comparable to that of benzodiazepines.⁹

Phenobarbital has been associated with reduced cognitive outcomes for children if given during pregnancy and should be avoided.¹⁰ It also readily crosses placental tissue and achieves fetal concentrations approximately equal to that of the mother^{3,11} but may exceed the mother’s concentration because of reduced fetal elimination.¹¹ Data regarding excretion into breast milk vary with 1.5% to 41% of maternal phenobarbital serum concentrations detected in breast milk.^{4,11} Only large doses are reported to produce clinically significant concentrations and resultant sedation in nursing infants and neonates.¹¹

TABLE 18-4. VOLUME OF DISTRIBUTION AND PROTEIN BINDING BY AGE GROUP

Age	Volume (Mean $\pm$ SD) ⁴	Protein Binding (Mean $\pm$ SD)
Neonates (<2 wk)	0.96 $\pm$ 0.02 L/kg ^a	37 $\pm$ 17%
Infants and children (2 wk–19 yr)	0.63 $\pm$ 0.09 L/kg	51%
Adults and geriatrics (>19 yr)	0.61 $\pm$ 0.05 L/kg	51%

^aVolume may be increased by extracorporeal membrane oxygenation (ECMO). One case reported a volume of 1.2 L/kg.¹²

Protein binding

Phenobarbital binds primarily to albumin in the plasma with the free (unbound) fraction affected by albumin concentration. This effect appears to be clinically significant only when combined with renal failure and acidosis.¹³ The degree of protein binding is affected by age (see Table 18-4). The unbound fraction increases with hypoalbuminemia and hyperbilirubinemia^{3,4} and may be as high as 90% of the total plasma concentration at birth, followed by a gradual decline to 70% after 1 wk.³

Clearance

Phenobarbital undergoes extensive non-first-pass, non-dose-dependent biotransformation by hepatic microenzymes into inactive metabolites. Phenobarbital is a potent inducer of P-glycoprotein and CYP1A2, CYP 2A6, CYP2B6, CYP2C8, CYP2C9, CYP3A4, and CYP2D6 hepatic enzymes. Approximately 1 wk is required for the effects of induction to be observed.¹⁴ Although some enterohepatic cycling occurs, fecal excretion does not significantly affect clearance.⁴

Renal excretion of unchanged drug is urine flow and pH dependent (increasing with alkaline urine) and varies from 20% to 40% of a dose in patients with normal renal function.¹⁵ Combined diuresis and alkalization can increase renal clearance up to fourfold.⁴

Although hepatic disease may decrease phenobarbital clearance, renal excretion apparently increases with impaired hepatic function, thereby averting severe reductions in clearance.⁸ Likewise, renal insufficiency, even in end-stage disease, appears to have little effect on phenobarbital concentrations because of increased hepatic metabolism.³

Phenobarbital clearance can be affected by certain drugs, disease states, and age (see sections on drug–drug interactions and drug–disease state or condition interactions). A CYP2C19 hepatic enzyme genetic polymorphism was reported to slightly reduce clearance of phenobarbital in some Japanese adults. One study demonstrated an average of 18.8% reduction in clearance in the 8% of patients expressing the phenotype.¹⁶

The clearance values presented in **Table 18-5** can be assumed in the absence of disease or drug interactions.^{3,17,18}

TABLE 18-5. CLEARANCE AND FRACTION EXCRETED UNCHANGED BY AGE GROUP

Age	Clearance (Mean $\pm$ SD)	Fraction of Parent Drug Excreted in Urine
Neonates and infants (<1 yr)	0.0047 $\pm$ 0.0002 L/hr/kg	~0.2 ^a
Children (1–<19 yr)	0.0082 $\pm$ 0.0031 L/hr/kg	0.2–0.4
Adults (19–65 yr)	0.0056 $\pm$ 0.0026 L/hr/kg	0.24–0.5
Geriatrics (>65 yr)	0.0024 L/hr/kg	Not available

^aThis value was reported to be ≥ 0.6 during the first week of life.

HALF-LIFE AND TIME TO STEADY STATE^{1,18–20}

Phenobarbital’s half-life and time to steady state are age group dependent (**Table 18-6**) and can be affected by certain drug interactions, conditions, and disease states (see sections on drug–drug interactions and drug–disease state or condition interactions).

TABLE 18-6. HALF-LIFE AND TIME TO STEADY STATE BY AGE GROUP		
Age	Half-Life (Mean ± SD)	Time to Steady State ^a
Neonates (<2 wk)	111 ± 34 hr	16–30 days
Infants (2 wk–<1 yr)	63 ± 5 hr	12–14 days
Children (1–<19 yr)	69 ± 3 hr	14–15 days
Adults and geriatrics (>19 yr)	96 ± 13 hr ^b	17–23 days ^b

^aTime to steady state estimated using + and – 1 SD of the mean $t_{1/2}$ and assuming steady state is achieved in five half-lives.
^bMay be higher for patients >65 yr old.

THERAPEUTIC RANGE

Of the patients whose seizure activity responds to phenobarbital, 84% respond at concentrations of 10–40 mg/L.⁴ These concentrations are generally considered the therapeutic range. However, patient response should be the definitive guide for dosage adjustment. Behavioral effects may occur in the absence of overt signs of clinical toxicity, especially in children. One study showed that 42% of children treated with phenobarbital developed behavioral disturbances, namely hyperactivity and somnolence.²¹ Once phenobarbital was discontinued, improvement and resolution of symptoms were observed in 73% of these patients. Although the study found no correlation between these disturbances and phenobarbital concentrations, maintaining this population at the lowest effective concentration remains desirable pending further research. **Table 18-7** provides additional condition-specific therapeutic ranges that have been reported.

DRUG MONITORING ASSAY CONSIDERATIONS

Although determinations of phenobarbital serum concentrations remain the standard for therapeutic drug monitoring, studies have shown saliva sample assay to be an acceptable alternative to venipuncture under certain conditions. This method is noninvasive, less expensive than serum determinations, and has a high correlation between saliva and plasma across a wide range of concentrations in patients ≥8 yr of age (patients studied were also receiving concurrent carbamazepine and phenytoin).²² Saliva samples can also be useful for monitoring medication compliance and in situations where repeat sampling is necessary. Several factors, however, can influence the medication concentrations in saliva, such as salivary flow rate and pH, sampling conditions, and contamination. Regardless of sample type, most phenobarbital assays are performed using fluorescence polarization immunoassay.

SUGGESTED SAMPLING TIMES AND EFFECT ON THERAPEUTIC RANGE^{3,7}

Since peak-to-trough fluctuation is minimal during normal dosing intervals, sampling time after a dose at steady state is not usually critical. However, sampling times relative to dose administration should be fairly consistent when comparing to previous values. A post-loading dose measurement at approximately 2–3 hr following administration is helpful in confirming therapeutic concentrations and can allow for determination of a patient’s volume of distribution. If the clinical situation warrants, a concentration may be repeated in 3–4 days to determine if the maintenance dose is sufficient. If the

TABLE 18-7. CONDITION-SPECIFIC THERAPEUTIC RANGES

Clinical Condition	Recommended Therapeutic Range	Comments
Febrile convulsions	16–30 mg/L ⁴	A 6-month recurrence rate of <4% was demonstrated at these concentrations vs. 21% at ≤15 mg/L or with no drug. ⁷ Prophylaxis following febrile convulsion may be necessary only when complicated by underlying neurologic disorders, prolonged febrile seizures, or family history of nonfebrile seizures. ⁴
Hypoxic ischemic seizures in neonates (perinatal asphyxia)	>30 mg/L initially	20–30 mg/L may be acceptable 24–48 hr after birth; may require lower maintenance doses due to longer than usual half-life. ²⁰
Antenatal therapy to prevent intracranial hemorrhage in preterm infants	10–15 mg/L	Conflicting studies exist with regard to efficacy. A dose of 780 mg IV given to the mother up to 1 hr prior to delivery was shown to achieve recommended neonatal concentrations in 24 of 26 neonates. ²³
Generalized tonic-clonic seizures	10–25 mg/L	10 mg/L has improved EEGs (but not necessarily controlled seizures) in 90% of patients. ⁷ Due to increased incidence of adverse effects, concentrations should generally not exceed 30 mg/L unless required for seizure control in refractory patients. ²⁴
Refractory status epilepticus	≥70 mg/L	May be employed without consideration of maximum dose or concentration (ICU required). ²⁵ This treatment has initiation advantages over high-dose benzodiazepines and phenytoin, as well as a more predictable pharmacokinetic profile.
Cerebral salvage from hypoxic or traumatic brain damage	>75 mg/L ³	These concentrations may induce barbiturate coma, particularly in nonhabituated patients. ^{7,26}

EEG = electroencephalogram, ICU = intensive care unit.

loading dose concentration was satisfactory, a decrease from the post-load value may indicate the need for a larger maintenance dose and vice versa. This second concentration may not reflect steady state conditions due to the long $t_{1/2}$ of phenobarbital.

To document acceptable steady state values, another concentration may be obtained 2–4 wk after initiation of therapy or dose adjustments. Sampling should be repeated when known enzyme inhibitors or inducers are added, adjusted, or discontinued. Concentrations should be determined if seizure control is lost or toxicity is suspected. More frequent monitoring may be required during pregnancy and for 8 wk following delivery.

PHARMACODYNAMIC MONITORING—CONCENTRATION-RELATED EFFICACY

The efficacy of therapy for seizure disorders is usually determined by seizure frequency, although the absence of seizures may not be the therapeutic endpoint for some conditions. Noncompliance must always be considered with patients receiving anticonvulsants since noncompliance rates range from 25% to 75%.²⁷ For intracranial hemorrhage or ischemic cerebral lesions in neonates, therapy should be directed primarily by serial electroencephalograms instead of seizure patterns or phenobarbital concentrations.^{28,29} One study found that CC homozygotes of the C3435T polymorphism of the ABCB1 gene of the P-glycoprotein transmembrane transporter had significantly lower cerebrospinal fluid (CSF) phenobarbital concentrations and a lower CSF/serum phenobarbital concentration ratio. Further, the patients with this polymorphism have significantly higher seizure frequency, suggesting a possible cause for pharmacoresistance in idiopathic epilepsy.³⁰

PHARMACODYNAMIC MONITORING—CONCENTRATION-RELATED TOXICITY^{3,7,31-35}

Toxicity with phenobarbital therapy can present as either neurologic or non-neurologic adverse effects. Neurologic effects may or may not be concentration related. **Table 18-8** lists several concentration-related neurologic adverse effects. Neurologic adverse effects that may occur without regard to concentration are sedation (in naive patients), neonatal feeding disorders, sexual dysfunction, and behavioral abnormalities (including lethargy, sleep disorders, hyperactivity in children, irritability, depression, and suicide-risk). See **Table 18-9** for non-neurologic adverse effects.

TABLE 18-8. PHENOBARBITAL CONCENTRATION-RELATED NEUROLOGIC ADVERSE EFFECTS³³

Adverse Effect	Phenobarbital Concentration
Sedation ^a	≥5 mg/L
Impaired cognition (with or without sedation) ^b	>19 mg/L
Decreased neonatal feeding, respirations, and muscle tone ^b	>30 mg/L
Sedation, slowness, and ataxia ^b	35–80 mg/L
Potential coma ^b	≥65 mg/L
Coma without reflexes (potentially lethal) ^b	≥80 mg/L

^aIn nonhabituated patients.
^bIn habituated or nonhabituated patients.

TABLE 18-9. NON-NEUROLOGICAL ADVERSE EFFECTS OF CHRONIC PHENOBARBITAL THERAPY^{a,32,33}

Adverse Effect	Relative Frequency	Monitoring Parameter
Folate deficiency	52%	Folate concentrations
Fetal vitamin K deficit from maternal phenobarbital therapy	<50%	Neonatal coagulation studies
Gingival hyperplasia	16%	Increased frequency of dental exams to monitor for developing caries and gingivitis
Vitamin D deficiency	10%	Calcium and alkaline phosphatase concentrations
Shoulder–hand syndrome	<6%	If bone joint or bone pain are present, therapy should be reevaluated
Hepatotoxicity	<1%	No monitoring is necessary unless overt signs of hepatotoxicity exist

^aIn general, non-neurologic adverse effects lack a clear relationship to phenobarbital concentration and most often present during chronic therapy.

DRUG–DRUG INTERACTIONS

Certain drugs may either increase or decrease phenobarbital concentrations (see **Table 18-10**). Although conflicting studies exist, phenytoin seldom affects phenobarbital concentrations in a significant manner.^{33,36} Newer anticonvulsants such as gabapentin and levetiracetam do not appear to affect, or be affected by, phenobarbital concentrations.^{37,38}

Phenobarbital has been shown to induce the metabolism of many medications through its induction effect on various cytochromes (CYP). **Table 18-11** provides a list of medications known to be metabolized by various CYPs and therefore potentially impacted by co-administration with phenobarbital. In

addition to the medications listed in the table, induction of CYP2C may lead to reduced concentrations of S-warfarin and voriconazole while induction of CYP2B6 could reduce cyclophosphamide, ifosfamide, and methadone concentrations.

TABLE 18-10. DRUGS AFFECTING PHENOBARBITAL CONCENTRATIONS

Drug	Clearance Factor ^a	Mechanism of Interaction
Bicarbonate ^{3,7,36,39}	>1	Decreased tubular reabsorption
Charcoal with sorbitol ⁴⁰	>1	Adsorption of oral phenobarbital or during enterohepatic cycling
Charcoal without sorbitol ⁴⁰	≥1.5	Adsorption of oral phenobarbital or during enterohepatic cycling
Chloramphenicol ^{36,b}	0.6	Competitive inhibition of hepatic metabolism
Methsuximide ^{36,b}	<1	Competitive inhibition of hepatic metabolism
Propoxyphene ^{36,b,c}	0.8	Competitive inhibition of hepatic metabolism
Pyridoxine ^{20,c}	1.4	Unknown
Rifampin ²⁰	>1	Hepatic induction
Thioridazine/mesoridazine ^{20,d}	1.3	Hepatic induction
Valproic acid ^{17,41,e}	0.7	Competitive inhibition of hepatic metabolism

^aWhen multiplied by normal phenobarbital clearance, this factor adjusts clearance for the particular drug interaction. Clearance factors <1 lead to increases in phenobarbital concentrations, whereas factors >1 lead to decreases.

^bNo longer available in the United States.

^cAnecdotal data, or from small study populations. Reliability of clearance factor or clinical significance of interaction is not well substantiated.

^dA similar interaction may exist with other phenothiazines.

^eOne study demonstrated dose dependence in the change in clearance. When valproic acid doses where 1,000 mg/day the phenobarbital clearance decreased by 25%. When doses were 2,000 mg/day the clearance decreased by 50%.⁴¹

TABLE 18-11. CYP ENZYMES INDUCED BY PHENOBARBITAL AND DRUGS THAT MAY HAVE REDUCED CONCENTRATIONS IN THE PRESENCE OF PHENOBARBITAL^{a,16,20,33,42,43}

CYP3A4	CYP3A4 (contd.)	CYP3A4 (contd.)	CYP2D6	CYP1A2
Abiraterone	Fentanyl	Pomalidomide	Aripiprazole	Clomipramine
Apixaban	Haloperidol	Quetiapine	Carvedilol	Clozapine
Apremilast	HMG CoA reductase Inhibitors	Quinidine	Chlorpheniramine	Fluvoxamine
Aripiprazole	Hydrocodone	Quinine	Chlorpromazine	Griseofulvin
Atazanavir	Ifosfamide	Ranolazine	Donepezil	Lidocaine
Bedaquiline	Indinavir	Rilpivirine	Fluoxetine	Olanzapine
Beta-blockers (except sotalol)	Irinotecan	Risperidone	Fluvoxamine	Propranolol
Benzodiazepines (except lorazepam & oxazepam)	Ivabradine	Ritonavir	Haloperidol	Theophylline
Boceprevir	Ivacaftor	Rivaroxaban	Lidocaine	Tizanidine
Buprenorphine	Ixabepilone	Saquinavir	Methadone	
Calcineurin inhibitors	Lidocaine	Sildenafil	Methylphenidate	
Calcium channel blockers	Linagliptin	Simeprevir	Metoclopramide	
Carbamazepine	Losartan	Tamoxifen	Propranolol	
Chlorpheniramine	Lurasidone	Tasimelteon	Risperidone	
Clozapine	Macitentan	Taxol	Tricyclic antidepressants	
Cobicistat	Macrolide antibiotics	Telaprevir		
Corticosteroids	Maraviroc	Tetracyclines		
Daclatasvir	Methadone	Tiagabine		
Digoxin	Mifepristone	Ticagrelor		
Disopyramide	Naloxegol	Tolvaptan		
Dolutegravir	Nelfinavir	Trazodone		
Donepezil	Netupitant	Triazole antifungals (except fluconazole)		

TABLE 18-11. (cont'd)

CYP3A4	CYP3A4 (contd.)	CYP3A4 (contd.)	CYP2D6	CYP1A2
Doxorubicin	Olaparib	Tyrosine kinase inhibitors		
Dronedarone	Ondansetron	Valproic acid		
Efavirenz	Oral contraceptives	Vincristine		
Elvitegravir	Palbociclib	Vilazodone		
Enzalutamide	Panobinostat	Vinflunine		
Eslicarbazepine	Paritaprevir	Vorapaxar		
Etoposide	Perampanel	Zonisamide		
Etravirine	Phenytoin			

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

A limited number of disease states and conditions have been reported to alter phenobarbital clearance. The known effects of certain disease states and clinical conditions on phenobarbital pharmacokinetics are listed in **Table 18-12**.

TABLE 18-12. CONDITIONS THAT ALTER PHENOBARBITAL PHARMACOKINETICS^a

Clinical Condition	Effect on Clearance	Effect on Half-Life
Hepatic dysfunction ⁴		
Cirrhosis ^b	Decreased	Extended
Acute viral hepatitis ^b	No change	No change
Renal failure ³		
Mild or moderate ^{b,c}	No change	No change
Severe ^{b,c}	Decreased	Increased
Hepato–renal ^b	Decreased	Increased
Continuous renal replacement therapy ^{44,45,d}	Increased (up to 7.5 fold) ⁴⁵	Not available
Hemodialysis (4 hr) ^e	~30% of drug removed	Not available
Perinatal asphyxia (Apgar <5 at 5 min) ^{15,b}	0.0048 ± 0.0018 L/hr/kg	148 ± 55 hr
Peritoneal dialysis ^f	~7.5% to 15% of drug removed ^d	Not available
Pregnancy ^{3,4,g}	Increased	Decreased
Prolonged starvation ^{4,b}	Increased	Decreased
Therapeutic hypothermia ^{46,47,48,h}	No change/increased	No change/increased

^aFew data exist regarding changes in volume of distribution (V) in these conditions. However, with perinatal asphyxia, V has been reported to increase by 13%.

^bA decrease in albumin may cause an increase in free (unbound) fraction of drug.

^cStudies to date do not suggest that dosage adjustments are necessary for moderate-to-severe renal failure.³ Few data exist regarding hepatorenal disease.

^dClearance may increase resulting in more frequent and higher doses. In a case report doses of 500 mg twice daily were necessary for therapeutic concentrations.

^eOne-third of daily phenobarbital dose should be replaced after hemodialysis.³ Clearance may be higher with more recent, high-efficiency hemodialyzers (up to 50% in one case report⁴⁹).

^fThe effect of peritoneal dialysis on phenobarbital clearance is unpredictable. Patients may require more frequent serum concentration monitoring to guide dosing.³ In phenobarbital toxicity, removal may be increased with 5% albumin dialysate.⁵⁰

^gClearance may gradually increase through gestation before returning to baseline within 4–8 wk following delivery.³

^hOne study showed no change in clearance or concentration, while another showed increases in concentration and half-life. An editorial suggested no overall need for dose adjustment in neonates receiving therapeutic hypothermia for hypoxic ischemic encephalopathy.

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PHENYTOIN AND FOSPHENYTOIN

Michael E. Winter

Phenytoin, a hydantoin-derivative anticonvulsant, is indicated for the treatment of tonic-clonic and complex partial seizures and for seizure prophylaxis following neurosurgery. Phenytoin also exhibits antiarrhythmic properties similar to those of lidocaine but is seldom if ever used as an antiarrhythmic.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

Loading dose¹⁻⁷

When a rapid therapeutic concentration is desired, a loading dose is recommended (**Table 19-1**). Because of the slow absorption characteristics of phenytoin, the loading dose is often administered by the intravenous (IV) route.

The maximum IV infusion rate of phenytoin sodium injection is 0.5 mg/kg/min for neonates, 1 mg/kg/min for children and adolescents, and for adults, the maximum infusion rate is 50 mg/min. Fosphenytoin, administered as phenytoin equivalents (PE), has a maximum administration rate of 1.5 mg PE/kg/min for neonates, 3 mg PE/kg/min for children and adolescents, and for adults the maximum infusion rate is 150 mg PE/min.

For children, adolescents, and adults, oral loading doses are usually given in 5 mg/kg increments every 2 hr until the total dose has been administered (**Table 19-1**). The usual adult dose is 1,000 mg (~15 mg/kg multiplied by 70 kg), given in three doses: 400-, 300-, and 300-mg doses, each separated by 2 hr.

TABLE 19-1. LOADING DOSES

Age	Loading Dose
Neonates and infants (<1 yr)	15–20 mg/kg
Children (1–<12 yr)	15–18 mg/kg
Adolescents (≥12 yr), adults, and geriatrics	15–18 mg/kg

Maintenance dose^{1-3,8,9}

In infants, children, and adolescents, the total daily dose (**Table 19-2**) is usually divided into equal doses and given at evenly spaced intervals of 6, 8, or 12 hr. In adults, the usual initial daily dose is 300 mg given once a day at bedtime (for the once-daily schedule, phenytoin sodium extended must be used).

TABLE 19-2. MAINTENANCE DOSES

Age	Maintenance Dosage
Neonates (<4 wk)	3–5 mg/kg/day ^a
Infants (4 wk–<1 yr)	4–8 mg/kg/day ^a
Children (1–<12 yr)	4–10 mg/kg/day ^a
Adolescents (12–<18 yr)	4–8 mg/kg/day ^a
Adults and geriatrics (≥18 yr)	4–7 mg/kg/day

^aUsually given in divided doses.



DOSAGE FORM AVAILABILITY^{1-3,10-16}

Phenytoin is available in the acid or sodium salt form and as the phosphate ester prodrug (fosphenytoin) of phenytoin. The sodium salt has a salt fraction (S) of ~92% phenytoin (**S = 0.92**) and 8% sodium. Phenytoin sodium is available both IV and as a capsule. Phenytoin as the acid form is available as a suspension or chewable tablet (**S = 1**). Fosphenytoin is available only as an injectable dosage form that can be administered either IV or intramuscularly (IM). Fosphenytoin is labeled as milligrams of phenytoin equivalents (PE) of phenytoin sodium injection; therefore, the S factor for fosphenytoin PE to calculate the milligrams of acid phenytoin is 0.92.

Phenytoin sodium injection contains propylene glycol, a cardiac depressant. The maximum recommended infusion rate is 50 mg/min for adults and 0.5 mg/kg/min for neonates and 1 mg/kg/min for older children is primarily due to this cardiac depressant. Patients receiving phenytoin sodium injection should be monitored for bradycardia, hypotension, and, if electrocardiogram is available, widened PR, QRS, or QT intervals as indications of myocardial depression. In most instances, the actual infusion rate is about ½ to ¼ of the usually recommended maximum. If phenytoin sodium injection is diluted prior to infusion, normal saline should be used as other IV diluents result in rapid precipitation. Fosphenytoin does not contain propylene glycol and, therefore, can be administered more rapidly (maximum recommended infusion rate for adults is 150 mg/min). However, bradycardia and hypotension can still occur and transient pruritus is relatively common. Therefore, cardiovascular monitoring is required and infusion rates of less than 150 mg/min should be considered. Fosphenytoin, although requiring refrigeration for storage, is more soluble than phenytoin for injection and when reconstituted can be prepared in either dextrose or saline solution. Even though fosphenytoin is probably a better parenteral product, with fewer side effects, some institutions may limit its use because it is somewhat more expensive.

Daily doses of phenytoin injectable (fosphenytoin and IV sodium phenytoin) and oral acid phenytoin (chew tabs and suspension) should be divided. Phenytoin sodium extended may be dosed once daily; but in children, even if the extended product is used, the daily doses are often divided. In addition, to minimize phenytoin concentration fluctuations and potential gastrointestinal (GI) disturbances, single daily doses of phenytoin sodium extended greater than 6 mg/kg/day also may need to be divided.

The suspension form requires complete dispersion and accurate volume delivery to ensure accurate dose administration. The suspension should be shaken vigorously prior to administration (1–2 min if the container has not been used for some time).

IM administration of phenytoin sodium injection is not recommended. Although absorption following IM administration is probably complete, it is erratic due to precipitation at the injection site. Absorption of IM fosphenytoin appears to be complete with peak phenytoin concentrations occurring ~30 minutes after injection. However, the IV route is still preferred for fosphenytoin and phenytoin sodium injection when rapid achievement of phenytoin concentration is the goal (e.g., acute seizures or status epilepticus). **Table 19-3** gives the available dosage forms.

GENERAL PHARMACOKINETIC INFORMATION

Absorption^{1,2,5,8,17-30}

Although all dosage forms of phenytoin, including generic products, are assumed to have a bioavailability of 100%, phenytoin has capacity-limited metabolism; as a result, bioavailability studies are difficult to interpret. Unless the capacity-limited metabolism is carefully considered in the bioavailability analysis, drug products with the same fraction absorbed but having different rates of absorption can appear to have different bioavailabilities. In addition, because phenytoin is a weak acid with limited water solubility, its absorption is slow and peak concentrations are delayed for several hours following oral administration.

TABLE 19-3. AVAILABLE DOSAGE FORMS

Dosage Form	Product
Phenytoin sodium injection:	
50 mg/mL	Phenytoin sodium injection
Fosphenytoin injection:	
50 mg PE/mL	Cerebyx and generic
ORAL CAPSULES	
Phenytoin sodium extended:	
30 mg	Dilantin and generic
100 mg	Dilantin and generic
200 and 300 mg	Phenytek and generic
Oral phenytoin chewable tablets:	
50 mg	Dilantin Infatab
Oral phenytoin suspension:	
125 mg/5 mL	Dilantin, 125 suspension

The time to achieve peak concentration is both product- and dose-dependent. The suspension and chewable tablets appear to be absorbed more rapidly than capsules. Fosphenytoin, when administered orally, can achieve peak concentrations in 1 hr (0.5 to 2 hr). Furthermore, the rate of absorption and time to peak concentration are dose-dependent for the oral dosage forms. Single Dilantin extended capsule doses of 400, 800, and 1,600 mg achieve peak concentrations at approximately 8, 13, and 30 hr after administration, respectively. Peak concentrations following these oral doses are on average only about half of what would be expected after administration of single IV doses. The reduced peak concentration following large oral doses is most likely the result of slow absorption rather than a reduced extent of absorption.

Data indicate that the phenytoin suspension is completely absorbed in most patients; however, two notable exceptions are neonates and patients receiving liquid nutritional support (e.g., nasogastric feedings). The reason for the low phenytoin concentrations in these two patient populations following oral administration of the suspension is unclear, and, although debated, the most likely explanation is a decreased bioavailability.

There are a number of generic brands of phenytoin. Initially there was concern that the absorption of the generic products might be different from the brand Dilantin. Although there were reports of apparent increases in seizure activity when generic products were substituted for the Dilantin brand, more recent studies suggest that the clinical outcomes are equivalent. It is difficult to understand why some have seen an increase in seizure activity when patients were switched to the generic product. It is possible that increased vigilance and more active reporting of seizures could be a contributing factor. Also, when generic products were introduced, most of the emphasis was on the extent of absorption, and it was not recognized that a slower rate of absorption is an important factor/advantage when phenytoin is administered once daily as the Dilantin brand.

Distribution

Volume of distribution^{1,3,8,31-33}

The volume of distribution (V) for phenytoin (see **Table 19-4**) is calculated in part by using plasma concentrations. Any factor that alters plasma protein binding can alter the concentration and, therefore, the apparent V. The phenytoin that is displaced from the albumin binding sites, while a large percent of the plasma concentration, is only a small percent of the total amount of phenytoin in the body. The “extra” phenytoin that is not bound to the albumin is rapidly distributed into the tissues; as a result, the bound concentration decreases but the unbound concentration, tissue concentrations,

and pharmacologic effect are relatively unchanged. The decrease in plasma-bound phenytoin with no change in the unbound phenytoin concentration results in an equally offsetting increase in the apparent V. Therefore, no change in loading dose is required in patients with altered plasma binding.

TABLE 19-4. VOLUME OF DISTRIBUTION

Age	Volume (Mean ± SD)
Neonates and infants (<1 yr)	1 ± 0.3 L/kg
Children (≥1 yr), adults, and geriatrics ^a	0.65 ± 0.2 L/kg

^aThe geriatric population is more likely to have decreased serum albumin and, therefore, a larger apparent V. The altered binding that results in a larger V will be offset by a lower observed total phenytoin concentration; therefore, no change in the usual loading dose is required.

Because phenytoin is a relatively lipid-soluble drug, obese patients have a larger volume of distribution (in liters) equal to:

$$V_{\text{obese}}(\text{L}) = \left(0.65 \frac{\text{L}}{\text{kg}} \right) \times [(\text{IBW}) + 1.33(\text{ABW} - \text{IBW})] \tag{Eq. 1}$$

where ABW is actual body weight in kg and IBW is ideal body weight in kg.

Ideal body weight can be calculated by the following:

$$\text{IBW}_{\text{males}}(\text{kg}) = 50 + [(2.3)(\text{H} - 60)] \tag{Eq. 2}$$

and

$$\text{IBW}_{\text{females}}(\text{kg}) = 45.5 + [(2.3)(\text{H} - 60)] \tag{Eq. 3}$$

where H is the patient’s height in inches.

Protein binding^{1-3,8,34-40}

Phenytoin is bound primarily to albumin in the plasma (fraction bound in plasma equals 0.9); although <5% of the total body phenytoin is bound to albumin. As a result, changes in plasma binding have little impact on the unbound plasma concentration, tissue stores, and pharmacologic response.

Most clinical assays measure the total (total = bound + unbound) phenytoin concentration. Therefore, alterations in plasma binding require adjustment for the change in the bound concentration. The two factors most commonly associated with altered phenytoin plasma protein binding are hypoalbuminemia and end-stage renal failure (i.e., patients receiving dialysis). Phenytoin concentrations reported (C_{reported}) in these patients can be adjusted to represent the phenytoin concentration anticipated under normal plasma protein binding ($C_{\text{normal binding}}$) conditions by using Equations 4 and 5 below.

For low albumin and creatinine clearance >25 mL/min:

$$C_{\text{normal binding}} = \frac{C_{\text{reported}}}{\left[(0.9) \left(\frac{\text{albumin}}{4.4} \right) \right] + 0.1} \tag{Eq. 4}$$

For normal or low albumin and patient receiving dialysis:

$$C_{\text{normal binding}} = \frac{C_{\text{reported}}}{\left[(0.9)(0.48) \left(\frac{\text{albumin}}{4.4} \right) \right] + 0.1} \quad (\text{Eq. 5})$$

where

$C_{\text{normal binding}}$ = total phenytoin concentration that would be observed if patient had normal protein binding (90% bound)

C_{reported} = patient's total phenytoin concentration reported by laboratory (represents decreased plasma protein binding)

albumin = patient's albumin concentration in grams per deciliter (g/dL).

These equations should be used only as a guide or approximation, because considerable variability has been reported. In most cases the variability suggests that Equation 4 underpredicts the unbound concentration and the associated $C_{\text{normal binding}}$. Although not as well studied, it would seem logical that if Equation 4 underpredicts that Equation 5, used in patients with end-stage renal failure, might also underpredict $C_{\text{normal binding}}$. However, regardless of the errors or the equation used, data would suggest that any attempt to adjust for low albumin and the resulting decrease in C_{reported} provides better guidance for therapy than no adjustment.

Valproate in concentrations exceeding 30–40 mg/L displaces phenytoin from plasma albumin. Equation 6 (revised slightly from the original for consistency with similar equations throughout the text) can provide an estimate of the phenytoin concentration in normal plasma binding (90% bound)³⁷:

$$C_{\text{normal binding}} = \frac{\left[0.1 + (0.001 \times C_{\text{valproic acid}}) \right]}{0.1} \times C_{\text{reported}} \quad (\text{Eq. 6})$$

where $C_{\text{valproate}}$ and C_{reported} are the measured concentrations of valproate and total phenytoin, respectively, obtained at the same time and $C_{\text{normal binding}}$ is the total phenytoin concentration that would have been measured if valproate was not present.

It is the $C_{\text{normal binding}}$ concentration that should be used when comparing the phenytoin concentration to the usual therapeutic range of 10–20 mg/L. In addition when performing pharmacokinetic calculations it is the $C_{\text{normal binding}}$ that should usually be used as most of the equations have other pharmacokinetic parameters that assume normal plasma binding (volume of distribution, K_m , etc.).

Equation 6 does have some limits. One of the most common is that the valproate and phenytoin concentrations have to be obtained at the same time. In addition, Equation 6 is not valid when there are factors other than valproate that also alter the phenytoin binding, e.g., hypoalbuminemia or end-stage renal failure.

Elimination

Clearance ^{1,3,31,43–47}

Renal elimination accounts for less than 5% of phenytoin clearance (CL) and is generally considered to be negligible. Phenytoin is cleared primarily (over 95%) by hepatic metabolism, which is capacity limited.

Clinically important implications of this clearance include:

- $C_{ss_{av}}$ is not proportional to the maintenance dose (see Equations 8 and 9).
- Time to steady state (accumulation) is not three to five half-lives. (For a more detailed discussion, refer to the half-life and time to steady state section.)

This capacity-limited clearance is illustrated by:

$$CL_{\text{phenytoin}} = \frac{V_{\text{max}}}{K_m + C_{\text{SS}_{\text{av}}}}$$

(Eq. 7)

where V_{max} is the maximum rate (or velocity) of metabolism, and K_m is the concentration at which metabolism is occurring at half the maximum rate. Note that the clearance of phenytoin is dependent on the concentration and decreases with rising concentration.

This nonlinear relationship can then be used to calculate maintenance doses and steady state concentrations:

$$\left(\frac{(S)(F)(D)}{\tau}\right) = \frac{(V_{\text{max}})(C_{\text{SS}_{\text{av}}})}{K_m + C_{\text{SS}_{\text{av}}}}$$

(Eq. 8)

$$C_{\text{SS}_{\text{av}}} = \frac{K_m \times \left(\frac{(S)(F)(D)}{\tau}\right)}{V_{\text{max}} - \left(\frac{(S)(F)(D)}{\tau}\right)}$$

(Eq. 9)

Depending on the specific values of V_{max} and K_m used in these equations, a wide range of maintenance doses and steady state concentrations can be calculated. Since reported values of V_{max} and K_m (see **Table 19-5**) vary widely, care should be taken that any calculated dose is reasonable for the patient in question. Phenytoin concentration monitoring is also appropriate to refine or adjust initial dose recommendations.

Pharmacogenomics⁴⁸⁻⁵²

Phenytoin is eliminated primarily by hepatic metabolism. Approximately 90% is by CYP 2C9 and 10% by CYP 2C19. Patients who are deficient in CYP 2C9 have a limited ability to metabolize phenytoin and are at risk for toxicity when receiving usual phenytoin maintenance doses. Unfortunately, prior knowledge of a patient’s genotype is uncommon. Patients with a limited ability to metabolize phenytoin are often

TABLE 19-5. REPORTED VALUES OF V_{MAX} AND K_M		
Age	K_m (Mean ± SD)	V_{max} (Mean ± SD) ^a
Neonates and infants (<1 yr) ^b	^b	^b
Children		
6 months–<4 yr	6.6 ± 4.2 mg/L	14 ± 4.2 mg/kg/day
4–<7 yr	6.8 ± 3.5 mg/L	10.9 ± 3 mg/kg/day
7–<10 yr	6.5 ± 3 mg/L	10.1 ± 2.6 mg/kg/day
Adolescents (10–16 yr) ^c	5.7 ± 2.7 mg/L	8.3 ± 2.8 mg/kg/day
Adults (18–≤59 yr)	4.3 ± 3.5 mg/L	7 ± 3 mg/kg/day
Geriatrics (>59 yr) ^d	5.8 ± 2.3 mg/L	7 ± 3 mg/kg/day

^aFor obese patients, the maximum velocity of drug elimination (V_{max}) for phenytoin probably should be based on ideal body weight (IBW).

^bEstimates for V_{max} and K_m in neonates and infants up to 1 year are uncertain. Some data suggest an initial slow rate of metabolism followed by a rapid increase in the ability to eliminate phenytoin over the first 3 months following birth. The limited data available suggest a K_m of 4–6 mg/L and a V_{max} of 10–13 mg/kg/day.

^cData unavailable for the 17-year-old.

^dThe limited data available suggest that K_m and V_{max} are similar to adults.

identified only after they have developed high phenytoin concentrations and demonstrated clinical side effects or toxicity. Monitoring of clinical symptoms and phenytoin concentrations coupled with knowledge of the nonlinear accumulation pattern for phenytoin should help to identify patients who are 2C9 deficient before they accumulate excessive concentrations.

Half-life and time to steady state^{1,3,53}

The relationship of half-life to a drug's accumulation or decline is applicable only to first-order drugs, i.e., those with a constant CL and V. Because the elimination of phenytoin is capacity limited and clearance decreases with increasing concentrations (see Elimination), estimating time to achieve steady state is a complex process. Under certain conditions, accumulation can be slow and may continue for a prolonged period.

Equation 10 can be used to estimate the time necessary to achieve 90% of the steady state concentration:

$$t_{90\%} = \left[\frac{(K_m)(V)}{\left[V_{\max} - \left(\frac{(S)(F)(D)}{\tau} \right) \right]^2} \right] \left[(2.3 \times V_{\max}) - (0.9) \left(\frac{(S)(F)(D)}{\tau} \right) \right] \quad (\text{Eq. 10})$$

where the following units apply:

V in L, K_m in mg/L, $V_{\max}$ in mg/day, and dose/ τ in mg/day.

The accuracy of Equation 10 and the calculated time to steady state depends on the values used for $V_{\max}$, K_m , and V. When literature estimates or uncertain patient-specific values are used, the actual steady state concentration and time to achieve 90% of steady state may be considerably different than the calculated values. The errors are especially large when the anticipated steady state concentrations are high or the time to 90% of steady state is long. In addition, compliance to the prescribed dosage regimen is an important variable. Probably the best use of Equation 10 is as a reminder that time to steady state is not anything like what is known for first-order drugs and under certain conditions (low K_m and high steady state concentrations) accumulation can be quite prolonged.

The time required for a phenytoin concentration to decline from an initial concentration (C_i) to a lower concentration (C) is described by Equation 11, which assumes that no absorption occurs in the time between C_i and C:

$$t = \frac{\left[(K_m) \left(\ln \left(\frac{C_i}{C} \right) \right) \right] + (C_i - C)}{\left(\frac{V_{\max}}{V} \right)} \quad (\text{Eq. 11})$$

where the following units apply:

K_m , C and C_i in mg/L; $V_{\max}$ in mg/day; V in L; and t in days.

As long as the phenytoin concentrations are much greater than K_m (4 to 5 times higher than K_m), the rate of phenytoin elimination approaches and is only slightly less than $V_{\max}$, the maximum rate of metabolism. Under these conditions, the time required to decline from C_{initial} to C is determined primarily by $V_{\max}$ and V. Therefore, at high concentrations the daily decline in the phenytoin concentration can be estimated by using $V_{\max}/V$. Using this approach, the expected maximum decline in phenytoin concentration for the average patient with phenytoin concentrations greater than 15 mg/L would be ~10 mg/L/day, i.e., ($V_{\max}/V = 7 \text{ mg/kg/day}$ divided by 0.65 L/kg).

THERAPEUTIC RANGE^{1,54,55}

For seizure disorders, the therapeutic range is 10–20 mg/L of total (bound + unbound) phenytoin in patients with normal binding. Approximately 50% of patients show decreased seizure frequency with phenytoin concentrations equal to or greater than 10 mg/L, and almost 90% respond with concentrations $\geq$ 15 mg/L. It should be remembered that the target concentrations of 10–20 mg/L represent unbound or free phenytoin concentrations of 1–2 mg/L. It is the unbound drug that is in equilibrium with the tissue and pharmacologic receptors.

Phenytoin also is reported to be effective in some neurological (nonseizure) disorders. However, most cases are anecdotal, with little or no reference to phenytoin concentrations.

THERAPEUTIC MONITORING^{1,3,8,35,56–61}

Suggested sampling times

The time of sampling depends on the clinical situation as well as the route and/or dosage form (**Table 19-6**). As a general rule, IV loading doses are reasonably reliable in achieving the desired phenytoin concentrations, but oral loading and oral or IV maintenance regimens are less predictable.

When fosphenytoin or phenytoin sodium injection is administered parenterally, sampling should not be performed during the hydrolysis or distribution phase (i.e., within 2 hr after the end of infusion or within 4 hr of an IM fosphenytoin injection).

After a maintenance regimen is started—the first sample should be obtained within 3–4 days (not steady state) to ensure that concentrations are not too low or high for a prolonged period. Then, sampling should be performed with decreasing frequency if concentrations are acceptable and reasonably stable or every 3–4 days if the maintenance dose must be changed or if phenytoin concentrations are declining or increasing.

At steady state—the sampling interval is debatable during stable chronic therapy. Sampling probably should be done every 7–14 days in the acute care setting and every 1–6 months in ambulatory patients.

Following a change in status—(e.g., change in route, maintenance dose, dosage form, or addition of drugs known to alter metabolism or absorption), phenytoin concentrations should be monitored in a manner similar to when a regimen is started. In addition, the appearance of side effects or breakthrough seizures would warrant obtaining a phenytoin concentration.

TABLE 19-6. SUGGESTED SAMPLE TIMES

Administered Dose	Suggested Sampling Time
Loading dose:	
IV phenytoin sodium injection (or fosphenytoin)	>2 hr after end of infusion ^a
IM (fosphenytoin)	>4 hr after injection
Oral	About 24 hr after loading dose
Maintenance dose:	
Oral single daily dose	Trough recommended ^b
IV (divided dose)	Trough
Oral divided dose	Trough recommended

^aConcentration measurements not necessarily recommended but may be useful for assessing V. If V appears to be unusually large, consider potential of decreased protein binding.

^bMorning sampling time is probably acceptable with bedtime dosing if time of sampling after dose is consistent.

Analytical Methods.^{35,56-68} While there are many assay techniques available, immunologic methods are by far the most common in clinical practice. Most are either fluorescence polarization or enzyme multiplied assay techniques. These methods are usually specific but on occasion have cross-reactivity with phenytoin metabolites or other drugs. In uremia, phenytoin metabolites can accumulate and cross-react, but, for the most part, development of more specific antibodies that recognize only the parent compound has resolved these problems. Sampling soon after administration of fosphenytoin results in inaccurate estimates of the actual phenytoin concentration. Samples that are obtained early will contain both fosphenytoin and phenytoin. With time, the fosphenytoin in the sample will be hydrolyzed to phenytoin. As a result the phenytoin concentration will increase and the fosphenytoin concentration will decrease, so the sample no longer reflects the phenytoin concentration at the original time of sampling.

The usual assay error for clinical samples in the normal therapeutic range is ~5% to as much as 10%. Although this error is acceptable for clinical monitoring, it should be kept in mind that significant errors can occur with this nonlinear drug, especially when extrapolating to higher or lower concentrations. In addition, improper collection or storage of samples can lead to invalid assay results. Caution should be used when the reported assay results are inconsistent with the clinical picture.

Monitoring unbound or free concentrations would seem to be a logical approach considering the known problems with altered plasma binding of phenytoin. However, use of unbound phenytoin concentrations is relatively uncommon in clinical practice. This may be attributed to the fact that most patients do not experience significant alterations in their plasma binding. In addition, assay procedures that measure unbound concentrations are more expensive, and there are limited data supporting the use of unbound phenytoin concentrations. When unbound concentrations are measured, it is important to adjust the assay procedure to increase assay sensitivity. Most assays have a *percent error* and a *fixed error*. In the case of phenytoin, the fixed error is usually in the range of 1 mg/L. An error of 1 mg/L is acceptable when measuring concentrations of 10–20 mg/L but would not be acceptable when measuring the unbound concentrations of 1–2 mg/L that would be associated with the usual total concentrations of 10–20 mg/L. The fixed error of ~1 mg/L is also a problem when considering dose adjustment based on concentrations of less than 5 mg/L. Nonetheless, the clinician should always consider the possibility of altered binding and how, if present, altered binding would affect the relationship between the measured total phenytoin concentration (bound + unbound) and the patient's clinical response.

PHARMACODYNAMIC MONITORING¹⁻³

Concentration-related efficacy

In the treatment of seizures, efficacy directly relates to seizure frequency and improvement of electroencephalogram findings. In patients who are being treated prophylactically or whose seizures are infrequent, assessing the adequacy of therapy based on the number or frequency of seizures is difficult.

Concentration-related toxicity

The concentrations associated with the various side effects listed below are only approximate guidelines; many patients experience significant side effects at much lower concentrations or no side effects at considerably higher concentrations. These differences may be due to individual susceptibility or sensitivity to phenytoin or, possibly, to alterations in plasma protein binding and, as a result, an underestimate of the unbound phenytoin concentration.

How often a patient should be monitored for concentration-related side effects depends on the course of treatment and the stability of the patient's clinical status and phenytoin concentrations. For example, the patient should be observed continuously and blood pressure and heart rate should be monitored very frequently when IV loading doses are administered.

Nystagmus and a simple assessment of mental status (e.g., “How do you feel?” “Are you tired or sleepy?”) are easily checked every time an outpatient is examined or daily in the acute care setting.

Nystagmus. Nystagmus is a tremor or slight twitching of the eye. This is one of the clinical signs that practitioners look for when they ask patients to hold their head still and follow their finger with their eyes as they move their finger from side to side. Nystagmus can be progressive and be present only on a far lateral gaze at phenytoin concentrations of 15 to over 20 mg/L to present when the patient is looking straight ahead at concentrations greater than 50 mg/L. Some patients have baseline nystagmus that is unrelated to phenytoin while others do not develop nystagmus until phenytoin concentrations are well above the usual therapeutic range. Although nystagmus is frequently used to document the presence of phenytoin, it is not generally considered to be a toxic symptom and by itself is not a reason to adjust the phenytoin dose.

CNS depression. This side effect can vary from mild sedation to an inability to concentrate to confusion to coma. Most patients experience relatively mild effects at concentrations of 5–15 mg/L; others tolerate phenytoin concentrations >20 mg/L. Ataxia and impaired motor function are usually observed with phenytoin concentrations >20 mg/L and become more frequent and obvious at concentrations >30 mg/L. It is unclear whether patients, with time, develop true tolerance to CNS effects or simply learn to accept them.

Nonconcentration-related side effects

Some side effects may be more associated with the duration of phenytoin therapy. They include hypertrichosis, coarsening of facial features, folate deficiency, glucose intolerance, gingival hyperplasia, vitamin D deficiency, osteomalacia, peripheral neuropathy, and, very rarely, systemic lupus erythematosus.

The presence of propylene glycol in IV phenytoin sodium injection has been reported to cause myocardial depression, hypotension, bradycardia, and widened PR, QRS, and QT intervals. Without propylene glycol, phenytoin has less effect on the myocardium, hence, the more rapid infusion rate for fosphenytoin. However, bradycardia and hypotension still occur with fosphenytoin but are usually less profound than with phenytoin sodium injection. When cardiovascular side effects occur during IV administration, the usual approach is to decrease or stop the infusion.

DRUG–DRUG INTERACTIONS

Numerous drugs are reported to interact with phenytoin, but capacity-limited metabolism makes assessment of these interactions difficult. For example, a 10% change in $V_{\max}$ may have relatively little impact on a steady state phenytoin concentration of 5 mg/L but a significant effect on a steady state concentration of 15 mg/L. Likewise, small changes in absorption have similar effects on low and high steady state phenytoin concentrations. As C_{ss} becomes much greater than K_m , the maintenance dose approaches $V_{\max}$. Under these conditions, a small change in either the maintenance dose or the $V_{\max}$ can result in disproportionate changes in the new steady state concentration.

Because of the potential for very small changes in metabolism or absorption to alter phenytoin concentrations significantly, patients should be closely monitored following any change in their regimen.

Table 19-7 is a partial list of drugs that influence phenytoin. Emphasis is given to those drugs most likely to alter phenytoin pharmacokinetics and/or to be encountered in the clinical setting. Because it is eliminated primarily by hepatic metabolism with ~90% by CYP 2C9 and 10% by CYP 2C19, drugs that inhibit or induce these enzymes might be expected to cause drug–drug interactions with phenytoin. It should be recognized that phenytoin might alter the effects of other drugs. As examples, cyclosporine, hormonal contraceptives and voriconazole all may have reduced effectiveness when phenytoin is added, presumably due to enzyme induction.

TABLE 19-7. DRUGS INFLUENCING PHENYTOIN PHARMACOKINETICS

Drug	Effect on Phenytoin Concentration	Mechanism
Amiodarone ^{69,70}	Increase	Inhibition of metabolism
Antacids ^{a,71,73}	Decrease	Decreased absorption
Carbamazepine ^{74,75}	Increase or decrease	Induction of metabolism
Chloramphenicol ⁷⁶	Increase	Inhibition of metabolism
Cimetidine ⁷⁷	Increase	Inhibition of metabolism
Ciprofloxacin ^{77,79}	Increase	Inhibition of metabolism
Disulfiram ^{80,81}	Increase	Inhibition of metabolism
Fluconazole ⁸²	Increase	Inhibition of metabolism
Fluoxetine ⁸³	Increase	Inhibition of metabolism
Folic acid ⁸⁴⁻⁸⁶	Decrease	Induction of metabolism
Isoniazid ^{78,88}	Increase	Inhibition of metabolism (most significant in phenotypically slow acetylators)
Phenobarbital ^{b,89,90}	Increase or decrease	Inhibition or induction of metabolism
Rifampin ⁹¹	Decrease	Induction of metabolism
Salicylates ^{c,92}	Decrease	Plasma protein displacement
Sertraline ⁹³	Increase	Inhibition of metabolism
Sulfonamides ^{94,95}	Increase	Inhibition of metabolism; plasma protein displacement
Ticlopidine ^{96,97}	Increase	Inhibition of metabolism
Trimethoprim ^{98,99}	Increase	Inhibition of metabolism
Valproate ^{d,37,100,101}	Decrease	Plasma protein displacement
Voriconazole ¹⁰²	Increase	Inhibition of metabolism

^aA decrease in absorption is not consistently observed. Both drugs should not be administered at the same time; antacid and phenytoin doses should be taken at least 2 hr apart whenever possible.

^bThe direction of change (if any) for the phenytoin concentration depends on which phenobarbital effect is predominant (i.e., induction or inhibition of metabolism).

^cPlasma protein displacement results in a decrease in the reported total phenytoin concentration but has little effect on the unbound phenytoin concentration or therapeutic effect. Single doses of 80 or 325 mg acetylsalicylic acid would have no effect on plasma binding of phenytoin.

^dValproate displaces phenytoin from its plasma protein binding. It is not clear, however, as to whether valproic acid also inhibits phenytoin metabolism.

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

As with drug-drug interactions, the effects of disease states on phenytoin therapy are difficult to quantify. The following are disease states that are known to alter the pharmacokinetics of phenytoin.

Hepatic disease—cirrhosis^{103,104}

Phenytoin is eliminated from the body primarily by hepatic metabolism. Therefore, patients with significant hepatic disease may require reduced maintenance doses. These patients frequently also have hypoalbuminemia, which alters the reported total phenytoin concentration. The reported phenytoin concentration can be “adjusted” by using Equation 4. The altered albumin has little effect on the loading dose required to achieve therapeutic unbound plasma and tissue concentrations (see Volume of Distribution).

Renal failure^{36,92,104,105}

Patients with end-stage renal failure (i.e., receiving dialysis) have a decreased plasma phenytoin binding affinity for albumin. They also usually have low serum albumin. These factors, which greatly affect the reported total concentration, have little influence on the unbound phenytoin concentration and the therapeutic effect. Therefore, patients with renal failure should initially receive normal loading and maintenance doses. A small amount of phenytoin is removed by hemodialysis, but it is generally considered to be negligible. Patients in critical care units receiving continuous renal replacement therapy (CRRT) may have more phenytoin removed. Data suggest that the phenytoin concentration in the CRRT effluent is approximately the same as the unbound phenytoin concentration in plasma. As an example, if a patient had an unbound phenytoin concentration of 1.5 mg/L ($C_{\text{normal binding}}$ of 15 mg/L) and a CRRT flow of 2 L/hr (48 L/day), the amount of phenytoin removed would be 72 mg/day (1.5 mg/L $\times$ 48 L/day). If CRRT is going to be maintained for more than a few days, phenytoin replacement doses, in addition to the usual maintenance dose, should probably be considered.

Equation 5 can be used to approximate the total phenytoin concentration that would be observed in end-stage renal failure patients on dialysis if they had normal plasma protein binding ($C_{\text{normal binding}}$). The $C_{\text{normal binding}}$ should be compared to the usual therapeutic range and the potential for phenytoin to produce either therapeutic or toxic effects.

Obesity^{33,106}

In obese patients, the ideal or nonobese weight probably correlates best with metabolism and, therefore, V_{max} and maintenance doses. Although using the nonobese weight to estimate the initial maintenance dose for the obese patient is recommended, plasma concentration monitoring is important, as significant variations have been observed. Loading doses require some adjustment because phenytoin has significant lipid solubility and an increased V in obese patients. As stated earlier (see Volume of Distribution), the V (in liters) in obese patients can be calculated using Equation 1.

Malabsorption^{18–21,25,29,107}

There is little direct evidence that phenytoin is incompletely absorbed (see Bioavailability of Dosage Forms). However, patients with diarrhea or rapid GI transit may have incomplete phenytoin absorption, especially if they take large single doses resulting in prolonged absorption. Because fosphenytoin appears to be the most rapidly orally absorbed phenytoin dosage form, it has been suggested that oral fosphenytoin be considered in patients where malabsorption is a possibility, such as with nasogastric feeding.

AIDS^{108,109}

Seizure disorders are common in patients with HIV/AIDS, and phenytoin is commonly used for control of seizures in this patient population. Many clinicians believe that patients with AIDS achieve low concentrations while receiving normal phenytoin doses. These observations may be because many patients with AIDS have a low serum albumin, GI disorders, and rapid GI transit due to other drug therapy or infectious disease processes resulting in decreased plasma binding, decreased bioavailability, or both.

Pregnancy and lactation^{85,86,110–120}

Most women (>90%) who have epilepsy and continue phenytoin throughout their pregnancy deliver normal babies. However, infants born to women with epilepsy and receiving phenytoin are about two to three times more likely to have some type of congenital defect. The benefits of continuing phenytoin usually outweigh the risks to the fetus if the mother develops uncontrolled seizures.

Decreases in phenytoin concentrations during pregnancy have been reported. The reason for the decrease is unclear, but proposed mechanisms include decreased bioavailability, decreased

plasma binding, and increased maternal and/or fetal metabolism. In addition, folate depletion or supplementation may also influence phenytoin metabolism. During pregnancy, phenytoin therapy should be monitored closely to ensure optimal therapeutic control of the seizure disorder.

Critically ill^{42,121–123}

Critically ill patients are complex and dynamic with regard to their clinical status and physiology. There is conflicting evidence as to whether or not this patient population has decreased, relatively normal, or increased metabolic capacity. In addition, these patients are likely to have altered renal function, hypoalbuminemia, and the presence of displacing drugs and, as a result, an alteration in phenytoin plasma binding. For these reasons, critically ill patients require frequent monitoring of phenytoin concentrations and may be candidates for measuring unbound phenytoin concentrations if exhibiting an unusual clinical response (see also Protein Binding).

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THEOPHYLLINE

Hanna Phan and John E. Murphy

Theophylline is a bronchial smooth muscle relaxant used in the treatment of asthma and other respiratory diseases. There are various proposed mechanisms of action of theophylline, including phosphodiesterase inhibition, adenosine receptor antagonism, histone deacetylase activation, apoptosis of inflammatory cells (e.g., neutrophils and T cells), and increased interleukin secretion.¹ As methylxanthines, theophylline and caffeine are also used to treat apnea, bradycardia, and weaning from the ventilator in neonates.^{2,3} The use of theophylline has decreased considerably over the past 25 yr due to the development and use of more effective treatments, particularly for asthma in children and adults. However, theophylline still continues to have a role when patients fail to respond to preferred agents such as inhaled corticosteroids and long-acting beta agonists for chronic management. Additionally, aminophylline is used as a tertiary alternative in cases of failed response to inhaled beta2-agonists and systemic corticosteroids for status asthmaticus.^{4,7} A series of Cochrane Collaborative reviews established that theophylline:

- is an effective preventive treatment for childhood asthma, although less effective and with a higher side-effect profile than inhaled corticosteroids⁸;
- should not be used in the treatment of exacerbations of chronic obstructive pulmonary disease (COPD)⁵; improves lung function and levels of oxygen and carbon dioxide in the blood of patients with COPD, who prefer it over placebo despite side effects⁶;
- is useful in extubating small preterm infants (<1000 g) in their first week of life⁹; and,
- has similar effects to caffeine for treating apnea in preterm infants, but has a narrower therapeutic range and shorter half-life and is thus potentially less useful once caffeine can be administered.¹⁰

Although some evidence from the Cochrane Collaborative demonstrates its use in the chronic management of childhood asthma, theophylline is not a preferred treatment for asthma for all ages.^{5,8} In fact, according to the National Asthma Education and Prevention Program, sustained-release theophylline (immediate release is not recommended) is considered a nonpreferred, alternative adjunctive maintenance treatment for asthma in older children (>5 yr) and adults.^{3,5} Additionally, methylxanthines such as aminophylline are not preferred alternative agents for treatment of asthma exacerbations compared to intravenous (IV) magnesium sulfate due to increased adverse effects and potential longer length of stay and time for symptom improvement.^{5,11} Data comparing efficacy and safety of aminophylline compared to IV beta2-agonists remain limited and do not provide evidence of an additive effect to acute therapy such as inhaled beta2-agonists.^{11,13}

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS¹⁴

The following dose recommendations are suggested to achieve theophylline concentrations of 5–10 mg/L in the neonate and approximately 10 mg/L in all other patient populations. Dosage adjustment should be based on an assessment of serum concentration and the patient's clinical status. For example, a concentration of 10 mg/L may be considered within normal limits; however, if a patient remains symptomatic, dosage increases may still be necessary to reach concentrations up to 15 mg/L for effect. Also noteworthy is that additional care is advised in individualizing dosing for neonates due to greater potential for toxicity secondary to age-dependent pharmacokinetic differences in metabolism and



clearance (CL). Caution is required when dosing patients who are unhealthy (e.g., critically ill), who smoke, or who are on other medications known to alter theophylline CL (see drug–drug interactions and drug–disease state or condition interactions sections).

Loading dose^{5,14}

The suggested loading dose of theophylline for patients without a history of theophylline use is 5 mg/kg/dose (~6 mg/kg/dose of aminophylline). If the patient has been receiving theophylline, it is advisable to first measure a concentration and then base the loading dose on the difference needed to achieve a desired concentration change. Generally, an increase of approximately 1 mg/L in concentration will occur with every 0.5 mg/kg/dose of theophylline in a loading dose, based on ideal body weight (IBW). This generalization is based on a V of 0.5 L/kg; however, note that V varies based on age, with reported ranges of 0.3–0.7 L/kg. Only rapid or immediate-release products should be used for oral loading doses, and IV doses are generally given over 20–30 min. The National Asthma Education and Prevention Program stated that in the emergency department “theophylline/aminophylline is not recommended because it appears to provide no additional benefit to optimal inhaled beta2-agonist therapy and may increase adverse effects.”⁵ Thus, at least for the emergency treatment of asthma, loading doses would not be warranted. The use of IV aminophylline has been noted in the critical care setting for management of acute asthma when conventional, preferred agents (i.e., inhaled short-acting beta2-agonist and systemic corticosteroid) and primary alternatives (i.e., magnesium sulfate) fail to provide sufficient response.^{5,7,11}

Maintenance dose^{14–16}

All doses in **Table 20-1** are expressed in terms of anhydrous theophylline and should be converted to the proper dosage if aminophylline or another salt form is administered. The doses suggested represent the recommended starting and usual maximum dose. Further dosing should be individualized based on the patient’s therapeutic response and measured steady state theophylline concentration. A patient’s theophylline CL can be calculated from a properly measured concentration and dosing history, and a patient-specific dose can then be determined based on the actual CL.

DOSAGE FORM AVAILABILITY^{14,19}

Theophylline products are available in different salt forms and different delivery forms (IV, oral liquids including syrups and elixirs, regular-release tablets and capsules, suppositories, and extended- and sustained-release tablets and capsules). When converting from one product to another, both theophylline salt (S) equivalence (**Table 20-2**) and bioavailability (**Table 20-3**) should be considered.

GENERAL PHARMACOKINETIC INFORMATION

Absorption

The bioavailability of theophylline depends on its formulation and route of administration.^{14,19–21} With few exceptions, the bioavailability for most theophylline products is quite good (90% to 100%). The absorption of theophylline can be delayed by intake of food; however, the extent of absorption is unchanged.¹⁴ When a patient is changed from IV to oral therapy, the maintenance infusion should be stopped and oral therapy should begin immediately.²¹ Table 20-3 provides the bioavailability percent [fraction (F) of dose] that is theophylline and comments for various products.

Distribution

Theophylline is not distributed into fatty tissue; therefore, for obese patients, IBW should be used in the calculation of doses. **Table 20-4** provides the population volumes of distribution for various age groups. Theophylline has been reported to distribute in the saliva with reports of saliva concentrations ranging from 50% to 100% of serum concentrations.^{14,22} Correlation of salivary and serum theophylline

TABLE 20-1. THEOPHYLLINE MAINTENANCE DOSES^{a,b,c}

Note: aminophylline dosage $\equiv$ theophylline dose $\div$ 0.8

Age	IV Maintenance Dose Continuous Infusion (mg/kg/hr)	Oral/IV Starting and Usual Maximum Maintenance Dose
Neonates		
(PNA $\leq$ 24 days)	N/A ^d	1 mg/kg every 12 hr
(PNA >24–<28 days)	N/A ^d	1.5 mg/kg every 12 hr
Infants (4–52 wk)	For ages 6–52 wk: mg/kg/hr = (0.008) $\times$ (age in wk) + 0.21	Total daily dose (mg) = [(0.2 $\times$ age in wk) + 5] $\times$ (weight in kg) PNA up to 26 wk: administer total daily dose divided every 8 hr ^e PNA > 26 wk: administer total daily dose divided every 6 hr ^e
1–9 yr	0.8–1 mg/kg/hr	Start with 10 mg/kg/day up to 16 mg/kg/day ^f (maximum 600 mg/day)
10–12 yr	0.7 mg/kg/hr	Start with 10 mg/kg/day up to 16 mg/kg/day ^f (maximum 600 mg/day)
13–16 yr (Non-smoking)	0.5 mg/kg/hr	Start with 10 mg/kg/day up to 16 mg/kg/day ^f (maximum 900 mg/day)
13–16 yr (Marijuana or cigarette smoking)	0.7 mg/kg/hr	Start with 10 mg/kg/day up to 16 mg/kg/day ^f
16 yr and adults (Non-smoking)	0.4 mg/kg/hr	10 mg/kg/day (usual maximum 900 mg/day) ^f
Young adult (Marijuana or cigarette smoking)	0.7 mg/kg/hr	Start with 10 mg/kg/day up to 16 mg/kg/day ^f
Older patients (>60 yr) and patients with cor pulmonale, congestive heart failure, liver failure, sepsis	0.2–0.3 mg/kg/hr (max 17 mg/hr)	Start with 6 mg/kg/day (do not exceed 400 mg/day) ^f

PNA = postnatal age.

^aUse ideal body weight for obese patients.

^bOne study suggests that the maintenance doses required to achieve therapeutic concentrations in patients with asthma decreased over approximately 15 yr, possibly due to the reduction in patients' passive smoke inhalation, a factor shown to increase CL.^{17,18} This might suggest more conservative dosing for the future.

^cAdapted from reference 14.

^dNot applicable; not usually dosed this way.

^eDosing interval refers to use of fast release oral product.

^fDosing interval in children and healthy adults can be divided and given every 8–12 hr with use of slow-release products.

concentrations has been clinically applied in therapeutic monitoring in apnea of prematurity; however the agent's utility has decreased since the availability of caffeine citrate.²³ Theophylline distributes into breast milk at approximately 70% of serum concentrations.¹⁴

Protein binding

Theophylline is approximately 40% bound to plasma proteins (i.e., albumin) in adults and 36% bound in neonates.^{5,14} Neonates have decreased protein binding due to greater percentage of fetal albumin.¹⁶ Due to the low percentage of theophylline bound to plasma proteins, changes in protein binding do not significantly affect theophylline CL or V.

TABLE 20-2. THEOPHYLLINE SALT EQUIVALENCE (S)^a

Drug	Anhydrous Theophylline Content (Mean ± SD)	S
Aminophylline anhydrous	85.7 ± 1.7	0.86
Aminophylline hydrous	78.9 ± 1.6	0.79
Theophylline monohydrate	90.7 ± 1.1	0.91

S = 1 for anhydrous theophylline.

^aAdapted from reference 14.

TABLE 20-3. BIOAVAILABILITY (F) OF DOSAGE FORMS^a

Dosage Form	Bioavailability Comments
IV aminophylline and theophylline	100% (F = 1)
Oral liquids	100% (F = 1)
Oral tablets and capsules (immediate release)	100% (F = 1); rate of absorption may be slowed when ingested with food or antacids
Oral tablets and capsules (enteric coated)	Incomplete and unpredictable, with no clinical indication for use
Oral tablets and capsules (extended release)	90% to 100% (F = 0.9–1) with extent and rate of absorption dependent on particular products
Suppositories (cocoa butter)	Slow and erratic
Suppositories (PEG)	90% to 100% (F = 0.9–1)
Rectal solution	90% to 100% (F = 0.9–1)

^aGenerally, products taken once a day exhibit incomplete absorption when ingested with food. Theo-Dur Sprinkle absorption is markedly impaired. Theo-24 has resulted in rapid release of a potentially toxic amount of theophylline. Along with the route, form, and particular product of theophylline, its salt equivalence must be considered. The theophylline salt equivalence (S) for each salt, compared to anhydrous theophylline (S = 1), is found in Table 20-2.

TABLE 20-4. VOLUME OF DISTRIBUTION

Age	Volume (L/kg)
Neonates (0–<4 wk)	0.8
Infants (4 wk–<1 yr)	0.5–0.7
Children (≥1 yr), adolescents, adults, and geriatrics	0.5

Metabolism and elimination

In adults, theophylline is 85% to 90% metabolized by hepatic biotransformation into relatively inactive metabolites primarily via demethylation by the cytochrome P450 1A2 (CYP 450 1A2) pathway and hydroxylation by the CYP 450 2E1 pathway. The only active metabolite, 3-methylxanthine, forms more slowly than its rate of excretion and, therefore, exhibits no pharmacologic effects. Due to the small percentage of a dose eliminated by renal excretion and the lack of significantly active metabolites, dosing adjustments are not required for renal dysfunction in adults.^{5,15} The role of pharmacogenomics with regard to use of theophylline, as with many medications, has yet to be fully defined. A polymorphism for the gene that encodes CYP 450 1A2, -2964 (G/A), has been associated with decreased theophylline CL compared to the G/G genotype. Identification of individuals with the G/A genotype may help prevent theophylline-associated toxicities.^{24,25} Thus, there is potential for application of pharmacogenomics in optimizing safe and effective use of theophylline, should this medication be used as alternate and/or adjunctive therapy for diseases such as asthma and COPD.

In neonates the N-demethylation pathway is absent, but this pathway is fully matured by 1 yr of age. The CYP 450 pathways appear to be almost absent in neonates. Approximately 50% of a theophylline

dose is excreted unchanged in the urine and 7% to 10% of the dose is converted to caffeine in neonates. Caffeine, an active metabolite, has a considerably longer half-life of approximately 100 hr, which leads to concentrations that are approximately 30% or more of theophylline concentrations. Dosing adjustments for renal dysfunction (urine output less than 2 mL/kg/hr) may be necessary in the neonate due to the higher fraction of unchanged theophylline excreted in the urine.^{14,26}

Clearance^{17,18}

The CL values in **Table 20-5** are for neonates, children, and healthy nonsmoking adults. The drug–disease state or condition interactions section provides CL adjustments or values of other patient populations.¹³ Additional monitoring in critically ill patients should be considered as renal and hepatic organ function can fluctuate, thereby potentially affecting theophylline CL.

TABLE 20-5. CLEARANCE RELATIVE TO AGE GROUPINGS

Population	Mean (± SD) Clearance ^a (L/hr/kg)
<i>Premature neonates</i>	
PNA 1–30 days	0.02 (± 0.01)
PNA 25–57 days	0.04 (± 0.02)
<i>Term infants</i>	
PNA 1 wk	0.03 (± 0.01)
PNA 6 months	0.06 (± 0.02)
PNA 9 months	0.09 (± 0.02)
<i>Children</i>	
1–8 yr	0.09 (± 0.03)
9–12 yr	0.07 (± 0.02)
13–15 yr	0.05 (± 0.02)
Adults (16–60 yr) healthy, nonsmoking asthmatics	0.04 (± 0.01)
Elderly (>60 yr) nonsmokers with normal cardiac, liver, and renal function	0.025 (± 0.01)

PNA = postnatal age.

^aAdapted from references 14, 19, 21, 27, and 28.

Half-life and time to steady state

The half-lives and estimated times-to-steady state for theophylline in neonates, children, and healthy non-smoking adults are listed in **Table 20-6**.

TABLE 20-6. THEOPHYLLINE HALF-LIVES AND ESTIMATED TIME-TO-STEADY STATE

Population	Mean (± SD) Half-Life ^a (hr)	Time to Steady State (hr) ^b
<i>Premature neonates</i>		
PNA 1–30 days	31 (± 12)	95–215
PNA 30–60 days	20 (± 5)	65–125
<i>Term infants</i>		
PNA 1 wk	18 (± 1)	85–95
PNA 6 months	7 (± 1)	30–40
PNA 9 months	4 (± 1)	15–25
<i>Children</i>		
1–<9 yr	3 (± 1)	10–20
9–15 yr	4 (± 2)	10–30

TABLE 20-6. cont'd

Population	Mean (± SD) Half-Life ^a (hr)	Time to Steady State (hr) ^b
Adults (16–60 yr) healthy, nonsmoking asthmatics	8 (± 2)	30–50
Elderly (>60 yr) nonsmokers with normal cardiac, liver, and renal function	10 (± 2)	40–60

PNA = postnatal age.

^aAdapted from references 14, 16, and 18.

^bAssuming five half-lives to reach steady state and using ± one standard deviation of the half-life.

DOSING STRATEGIES

The CL of theophylline varies considerably among age groups and is affected by both drug and disease/condition interactions. Furthermore, theophylline CL has not been directly correlated to specific laboratory tests of liver function; however, changes in these values can serve as a prompt for clinicians to assess potential pharmacokinetic changes in a specific patient. Thus, most dosing approaches rely on use of the average dose or average CL for age, disease state, or condition. When CL is used, a dosage regimen can be developed based on a clinician's desired therapeutic range for the patient. In either case (i.e., use of average dose or average CL), follow-up with measured theophylline concentrations can validate the initial dosing regimen chosen to ensure that a patient is in the desired range. If steady state concentrations are used, proportional changes in dosing should usually result in proportional concentration changes, unless the patient's condition changes.

When patients do not fit average CLs due to drug interactions or disease conditions, condition correction factors can be used to predict a patient's CL. When population-based CL is known for a condition or interaction, it may be used as well. For example, Table 20-9 gives a CL factor of 0.6 for patients on theophylline who are also receiving cimetidine. To estimate an adult patient's CL, the CL factor of 0.6 is multiplied times the average CL of 0.04 L/h/kg to yield a predicted CL of 0.024 L/h/kg.

One study evaluated the use of condition correction factors to predict theophylline CL in patients with single and multiple conditions or drug interactions.³⁴ The authors found that when patients had single factors, the prediction of CL was reasonable. As the numbers of conditions increased, the CL prediction was not as accurate, no matter how the factors were combined (i.e., multiplied, averaged, etc.). This may be due to the effect of multiple factors leading to increased variability in CL. Another study showed that the known interactions with theophylline of both cimetidine and ciprofloxacin are augmented when the two are used together with theophylline.³⁵ Thus, when correction factors are used to predict CL or dose in patients with multiple conditions and/or drug-drug interactions, greater caution should be exercised.

One study examined dosing equations for use in infants up to 1 yr of age and found that the following equation, which results in a mg/kg/day dose, tended to produce serum concentrations in the 5–10 mg/L range, a reasonable place to start therapy in infants being treated for apnea, bradycardia, and asthma. The authors recommended serum concentration monitoring 6–12 hr after start of therapy.³⁶

$$\text{Dose (mg/kg/day)} = (0.2 \times \text{postnatal age in wk}) + 5 \quad (\text{Eq. 1})$$

As an example of developing a dosing strategy for apneic premature neonates receiving intravenous theophylline, the authors of one study used nonlinear mixed effects modeling to predict V and CL.⁴³ The resulting population predictors were:

$$V \text{ (L)} = 0.63 \times Wt \quad (\text{Eq. 2})$$

$$\text{CL (L/h)} = 0.006 \times Wt^{0.75} \times P \quad (\text{Eq. 3})$$

Where Wt is weight in kg and P is 1.47 for neonates with oxygen support and 1 without support.

These parameters can then be used to develop a dosing regimen to produce desired concentrations in premature neonates, especially in the first week of life when theophylline pharmacokinetics can vary considerably.

For patients currently receiving theophylline, the approach to dose modification should take into account the patient's current serum concentration. Loading doses (mg/kg) for patients currently receiving theophylline (or aminophylline) can be estimated using the following equation:

$$\text{Loading dose} = (\text{desired serum concentration} - \text{measured serum concentration}) \times V \text{ (L/kg)} \quad (\text{Eq. 4})$$

The desired serum concentration should be set conservatively to allow for interpatient variability in V. The general population V is used (0.5 L/kg).¹⁴

THERAPEUTIC RANGE^{1,5,14,16,26,45-48}

Asthma. The therapeutic range was traditionally considered to be 10–20 mg/L. However, based on more recent data and the National Asthma Education and Prevention Program, a range of 5–15 mg/L enhances safety and with a balance of therapeutic benefit. For COPD, the therapeutic range is also 5–15 mg/L. Because it is debatable whether theophylline increases diaphragmatic contractility in these patients, its efficacy is questionable. However, as discussed earlier, COPD patients prefer it to placebo, and it improves lung function and levels of O₂ and CO₂ in the blood. Because COPD patients are usually elderly, may be on multiple medications, and their clinical status often changes in a manner that affects theophylline pharmacokinetics, serum concentrations should be monitored more frequently. One report described the anti-inflammatory activity of theophylline in low concentrations (i.e., 5–10 mg/L) compared to those required for bronchodilator activity, which would reduce risk for adverse effects.^{1,48} These actions enhance the anti-inflammatory effects of corticosteroids, making combination therapy potentially beneficial while reducing side effect potential at the lower concentrations.⁴⁸ In adult patients with asthma, preliminary data demonstrate potential benefit of a combination of theophylline (200 mg by mouth twice daily) and fluticasone propionate/salmeterol; however, additional data regarding safety and defined role in the current, stepwise asthma management guidelines have yet to be delineated.⁵⁰

Apnea or Bradycardia in Neonates. The therapeutic range is 6–12 mg/L. Although a wide range of concentrations has been suggested, many neonates respond at low concentrations. Therapy should be started at low concentrations and can be increased in increments of approximately 3 mg/L as necessary to effect.

Ventilator Weaning of Neonates. The therapeutic range is 5–20 mg/L with some data suggesting less benefit at concentrations less than 10 mg/L.⁵⁰ However, studies supporting the desired theophylline concentration for ventilator weaning are limited; other methylxanthines such as caffeine citrate can be used with decreased risk of adverse effects due to a wider therapeutic index.⁹ Some authors suggest that concentrations greater than 8 mg/L are required to enhance diaphragmatic contractility and promote relaxation of respiratory muscles.

THERAPEUTIC MONITORING

Per the National Asthma Education and Prevention Program, “routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic CL.”⁵ How frequently monitoring should occur depends on the relative stability or instability of the patient, changes in concurrent drug therapy, the apparent response or signs of possible toxicity, and whether there is potential of poor adherence.

Suggested sampling times and effect on therapeutic range

Therapeutic reference ranges often refer to concentrations drawn as peaks.⁵ Wherever concentration measurements are drawn in a dosing interval (e.g., peak, trough), it is important to be consistent with the timing of sampling on subsequent monitoring. One report showed circadian variation in theophylline CL with nighttime CL 13% higher than daytime, so altering between evening and morning may make changes in concentration more difficult to interpret.³³ There also appears to be diurnal variation in absorption rate (regular-release products) and extent (sustained-release products).⁵ Sampling times for the various age groups, along with the reasons for the timing, are listed below.

Neonates, Infants, and Children

- 2 hr after the first loading dose in neonates to calculate the V , if desired.
- 30 min after the first loading dose in infants and children, if administered intravenously, to calculate V for any additional loading doses that might be needed.
- 8–12 hr after initiation of maintenance dose to determine if adequate concentrations are being maintained or if the drug is accumulating rapidly, if deemed necessary. More frequent monitoring may be necessary in premature neonates given possible fluctuations in CL due to acute changes in clinical status and potential differences in CL due to age-dependent maturation of renal and hepatic function.
- 72 hr after initial dosing, if clinically stable. Check every 24–72 hr as needed to evaluate need for dosage adjustment in hospitalized patients. Check sooner for any acute changes in renal or hepatic function, with additional caution in critically ill patients.
- Every 1–6 months in stable, ambulatory patients, with more frequent evaluation for younger patients or patients with poor adherence, or history of adverse effects.
- When there are signs or symptoms of toxicity or lack of efficacy.
- In the emergency department, patients currently taking a theophylline-containing preparation may have a theophylline concentration measured to rule out theophylline toxicity.²⁶

Adults and Older Adults (Geriatrics)

- 30 min after the first loading dose, if administered intravenously, to calculate V for any additional loading doses that might be needed.
- 12–24 hr after initiation of maintenance dose to determine if adequate concentrations are being maintained or if the drug is accumulating rapidly, if deemed necessary.
- 72 hr after initial dosing and then every 24–72 hr as needed to evaluate need for dosage adjustment in hospitalized patients.
- Every 4–7 days once hospitalized patients are stabilized, unless otherwise indicated, to evaluate need for dosage adjustment and determine if CL is changing.
- Every 1–6 months in stable, ambulatory patients.
- When there are signs or symptoms of toxicity or lack of efficacy.
- In the emergency department, patients currently taking a theophylline-containing preparation may have a theophylline concentration measured to rule out theophylline toxicity.²⁶

Table 20-7 provides guidance on dosage adjustments based on a measured theophylline concentration.

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

The following are useful indicators of theophylline efficacy:

TABLE 20-7. GENERAL GUIDANCE ON ORAL AND IV DOSE ADJUSTMENT BASED ON PEAK SERUM THEOPHYLLINE CONCENTRATION

Serum Concentration (mg/L)	Oral Dosage Adjustment ^a	IV Dosage Adjustment ^a (assuming continuous infusion)
< 9.9	Assess clinical symptoms. If not improved, consider 25% daily dose increase. Reassess serum concentration after 3 days of new dosing.	Assess clinical symptoms. If symptoms not controlled and patient tolerating current dose, consider increase in infusion rate by 25%. Recheck serum concentration in 8–12 hr and 24 hr in pediatric and adult patients, respectively.
10–14.9	Assess clinical symptoms. If symptoms controlled, continue current dosage. If symptoms not well controlled, consider alternate/additional therapy if possible.	Assess clinical symptoms. If symptoms controlled, no adjustment recommended. If symptoms not well controlled consider alternate/additional therapy, if possible.
15–19.9	Assess for signs of toxicity. Consider 10% daily dose decrease to reduce risk of adverse effects, depending on treatment indication.	Assess for signs of toxicity. Consider decreasing infusion rate by 10% to reduce risk of adverse effects, depending on treatment indication.
20–24.9	Assess for signs of toxicity and treat if noted. Decrease daily dose by 25%. Reassess serum concentration after 3 days of new dosing.	Assess for signs of toxicity and treat if noted. Decrease infusion rate by 25% and recheck serum concentration in 8–12 hr and 24 hr for pediatric and adult patients, respectively.
25–30	Assess for signs of toxicity. If toxicities noted, treat symptoms. Skip next scheduled dose. If adverse effects not noted and drug continued, decrease subsequent doses by at least 25% and reassess concentration after 3 days of new dosing.	Assess for signs of toxicity. If toxicities noted, treat symptoms. Hold infusion for 12 hr and 24 hr in pediatric and adult patients, respectively. If adverse effects not noted and infusion to be restarted after hold, decrease infusion rate by at least 25% and recheck serum concentrations at 8–12 hr and 24 hr for pediatric and adult patients, respectively.
>30	Assess for signs of toxicity. If toxicities noted, treat symptoms. Hold doses until serum concentration is within therapeutic range and no symptoms of toxicity. If therapy is resumed, doses should be reduced by at least 50% and concentration reassessed after 3 days of new dosing.	Assess for signs of toxicity. If toxicities noted, treat symptoms. Hold infusion until serum concentration is within therapeutic range and no symptoms of toxicity. If therapy to be resumed, restart infusion at 50% or less of previous infusion rate and recheck serum concentrations at 8–12 hr and 24 hr for pediatric and adult patients, respectively.

^aAdapted with permission from Tables 3, 6, and 7, Theophyllines. In: McEvoy GK, ed. *AHFS Drug Information 2014*. Bethesda, MD: American Society of Health-System Pharmacists; copyright©2014. <http://online.statref.com/document.aspx?fxid=1&docid=1>. Accessed September 8, 2015.

Asthma or COPD

- Decrease in severity of wheezing and rales
- Respiration rate normalization
- Improvement of FEV₁
- Decrease in the ventilator support required

Apnea or bradycardia in neonates

- Decrease in number and depth of apneic and bradycardic episodes
- Heart rate normalization
- Decrease in the ventilator support required

Concentration-related toxicity

To reduce the potential for concentration-related toxicity, the following should be monitored when theophylline is used (see also **Table 20-8**):

- Liver function in patients receiving theophylline for asthma or COPD
- Liver and renal function in neonates receiving theophylline for apnea or bradycardia (urine output should be 2 mL/kg/hr or more)
- Drugs or disease states that may decrease theophylline CL

Seizures and death induced by theophylline can occur in the absence of any other adverse effect; therefore, theophylline concentrations should be monitored. In neonates receiving theophylline for apnea, bradycardia, or ventilator weaning, the following adverse effects may indicate toxicity: tachycardia (heart rate of more than 180 beats/min), irritability, seizures, and vomiting (e.g., appearance like “coffee grounds”).

TABLE 20-8. CONCENTRATION-RELATED ADVERSE EFFECTS

Concentration	Adverse Effect
>20 mg/L	Nausea, vomiting, diarrhea, headache, irritability, insomnia, tremor ^a
>35 mg/L ^b	Hyperglycemia, hyperkalemia, hypotension, ^c cardiac arrhythmias, hyperthermia, seizures, brain damage, and death

^aEffects have been reported with concentrations as low as 15 mg/L.
^bSide effects that occur at lower concentrations may also occur at higher concentrations.
^cMay also occur due to too rapid an infusion; infusion rate should not exceed 20 mg/min.

DRUG–DRUG INTERACTIONS

Many drug interactions have been reported with the use of theophylline. Most are related to alterations in theophylline CL, although some appear to have other mechanisms (Table 20-9).⁵¹ As with most pharmacokinetic drug-drug interactions, some patients may experience adverse effects due to changes in a drug’s CL and concentration, while others may be unaffected. Only interactions reported as moderately or highly clinically significant are listed in Table 20-9. Caution is advised when an interaction has been reported, but other factors must be considered as well (e.g., older patients may start with lower CL than younger patients and thus be at greater risk). Any drug that significantly inhibits or induces CYP 450 1A2 or CYP 450 2E1 should be suspect for potential impact on theophylline CL and concentrations. In addition to drug-drug interactions, caution should be taken with concurrent use of selected herbal supplements, such as St. John’s Wort, which has been reported to lead to reduced steady state theophylline concentrations.^{52,53}

TABLE 20-9. IMPACT OF SELECT DRUG–DRUG INTERACTIONS ON THEOPHYLLINE CLEARANCE^{a,b}

Drug	Mechanism	CL Impact	CL Factor ^c
Allopurinol (≥600 mg/day)	(?) Inhibit metabolism	Decrease	0.8
Beta blockers (nonselective)	Inhibit metabolism	Decrease	0.7 Propranolol
Caffeine	Inhibit metabolism	Decrease	0.7
Calcium channel blockers	Inhibit metabolism	Decrease	0.7–0.9 Verapamil
Carbamazepine ^d	Induce metabolism	Increase	N/A
Charcoal	Adsorption	Increase	Up to 1.9
Cimetidine	Inhibit metabolism	Decrease	0.6 (0.5–0.8)
Clarithromycin	Inhibit metabolism	Decrease	N/A
Corticosteroids	Inhibit metabolism	Decrease	N/A
Disulfiram	Inhibit metabolism	Decrease	0.8
Erythromycin	Inhibit metabolism	Decrease	0.7
Fluvoxamine	Inhibit metabolism	Decrease	0.3
Interferon, human alpha 2-a and 2-b	Inhibit metabolism	Decrease	0.2–0.7
Loop diuretics (furosemide) ^d	Unknown	Decrease	0.7

Mexiletine	Inhibit metabolism	Decrease	0.6
Phenobarbital	Induce metabolism	Increase	1.2
Phenytoin	Induce metabolism	Increase	1.6
Propafenone	Inhibit metabolism	Decrease	0.7
Rifampin	Induce metabolism	Increase	1.3 (to 1.8)
Quinolones	Inhibit metabolism	Decrease	0.7 (0.3–0.8)
Tacrine	Inhibit metabolism	Decrease	0.5
Terbinafine	Inhibit metabolism	Decrease	0.85
Ticlopidine	Inhibit metabolism	Decrease	0.65
Tobacco	Induce metabolism	Increase	1.6
Zafirlukast	Inhibit metabolism	Decrease	0.2
Zileuton	Inhibit metabolism	Decrease	0.5

^aAdapted from references 15, 16, 19, 20, and 29–33.
^bMany other pharmacokinetic and pharmacodynamic interactions have been reported with theophylline.
^cCL factors represent the average change in studies of multiple patients or the CL change in single patients in case reports. Wide variation should be expected when using these values to estimate the change in CL that might occur with an interaction.
^dMay increase or decrease theophylline concentrations.

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

Various disease states and conditions have been shown to alter theophylline CL (**Table 20-10**). As seen with drug–drug interactions, there can be considerable variability in the impact of a given disease state or condition on theophylline CL. Not only should one be aware of pharmacokinetic changes with the presence of conditions (e.g., smoking), but also the cessation or improvement of such conditions as this will affect drug CL.⁴⁰

TABLE 20-10. IMPACT OF DRUG–DISEASE STATE OR CONDITION INTERACTIONS ON CLEARANCE AND HALF-LIFE (t_{1/2})^a

Condition	Mean CL (L/hr/kg) (± SD)	Mean t _{1/2} (hr) (± 1 SD)	CL Factor ^b
Otherwise healthy adult nonsmokers (reference value)	0.04	8	1
Acute pulmonary edema	0.02	19	0.5
COPD, stable elderly nonsmokers	0.03 (± 0.01)	11 (± 1)	0.8
COPD with cor pulmonale	0.03 (± 0.01)	—	0.8
CHF	—	—	0.4
Cystic fibrosis (14–28 yr)	0.08 (± 0.02)	6 (± 2)	2
Fever associated with acute viral respiratory illness in (children 9–15 yr)	—	7 (± 3)	0.5
Pneumonia	—	—	0.4
<i>Liver disease</i>			
Acute hepatitis	0.02 (± 0.01)	19 (± 1)	0.5
Cholestasis	0.04 (± 0.02)	14 (6–32)	1
Cirrhosis	0.02 (± 0.01)	32 (10–56)	0.5
Child-Pugh Class B or C	—	23 (10)	—
<i>Pregnancy</i>			
1st trimester	—	9 (± 3)	—
2nd trimester	—	9 (± 3)	—
3rd trimester	—	13 (± 3)	—

TABLE 20-10. cont'd

Condition	Mean CL (L/hr/kg) ($\pm$ SD)	Mean $t_{1/2}$ (hr) ($\pm$ 1 SD)	CL Factor ^b
Sepsis with multiorgan failure	0.03	19 ($\pm$ 3)	0.7
<i>Thyroid disease</i>			
Hypothyroid	0.02 ($\pm$ 0.01)	12 ($\pm$ 4)	0.6
Hyperthyroid	0.05 ($\pm$ 0.01)	5 ($\pm$ 1)	1.2
Children with Down syndrome	Decreased	—	—
ECMO in neonates and infants	Decreased	—	—
<i>Smoking</i>			
Moderate cigarette use	—	4.1 $\pm$ 1	
Heavy cigarette use	0.06 $\pm$ 0.02	5.4 $\pm$ 1	1.5
Marijuana use	0.07 $\pm$ 0.03	4.3 $\pm$ 1	1.8
Cigarette and marijuana use	0.09 $\pm$ 0.02	4.3 $\pm$ 1	2.3
Past cigarette use	0.05 $\pm$ 0.001	6.4 $\pm$ 1	1.3
Elderly smokers	0.04 $\pm$ 0.01	5.9 $\pm$ 1	1
Passive smoking (children) ¹²	0.08 vs. 0.05 (in NE)	—	—
<i>Diet</i>			
Low carbohydrate and high protein	—	5.2 $\pm$ 1	—
High carbohydrate and low protein	0.05 $\pm$ 0.02	—	1.2
Charcoal-broiled beef (heavy consumption)	—	4.7 $\pm$ 0.4	—
Caffeine	—	Increased	—
Cabbage or Brussels sprouts (heavy consumption)	—	Decreased	—

NE = children not exposed to passive smoking.

^aAdapted from references 15, 26, 31, 34, and 37-40.

^bCompared to average adult CL of 0.04 L/h/kg. Note that the CL factor may not always have been based on head-to-head trials against average adults and variability may be considerable.

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VALPROATE

Barry E. Gidal

Valproate (VPA) is a carboxylic acid-derivative anticonvulsant used in the management of partial and generalized seizures including absence, tonic-clonic, and myoclonic seizures. In addition, VPA is used in patients with bipolar-affective disorder as well as for prophylaxis of migraine headaches. For seizures, VPA may be used as monotherapy or in combination with other antiepileptic drugs (AEDs).

USUAL DOSAGE RANGE IN THE ABSENCE OF CLEARANCE-ALTERING FACTORS

VPA is available as the acid and in two salts: valproate sodium and divalproex sodium. Dosages of all salt forms are expressed in terms of VPA (mw = 144.2 g/mol⁻¹, **S** = 1).¹ **Table 21-1** provides usual dosage ranges in the absence of clearance-altering factors (other than age).

TABLE 21-1. USUAL DOSAGE RANGE IN THE ABSENCE OF CLEARANCE-ALTERING FACTORS

Age Group	Dosage (Mean + SD) ^{a,b}
Neonates (<4 wk) ²	20 mg/kg/day
Infants (4 wk –<1 yr) ²	34 ± 14 mg/kg/day
Children	
1 –<5 yr	Not available ^c
5 –<10 yr ^{3,4}	28 ± 10 mg/kg/day
10 –<15 yr ³	19 ± 6 mg/kg/day
Adults (18 –<60 yr) ⁵	13 ± 5 mg/kg/day
Geriatrics (≥60 yr) ⁶	11 ± 4 mg/kg/day

^aDoses are for monotherapy to achieve mean $C_{ss,av}$ of ~60–70 mg/L.

^bOral (capsules, tablets, and solution).

^cInformation on this specific age range has not been established.

Table 21-2 provides information on available dosage forms of VPA.

TABLE 21-2. DOSAGE FORM AVAILABILITY¹

Dosage Form	Product
Valproic acid	Depakene (various generic)
Oral capsules: 250 mg	
Divalproex sodium	
Oral capsules (coated particles): 125 mg	Depakote Sprinkle
Oral tablets (enteric coated, delayed release): 125, 250, and 500 mg	Depakote (various generic)
Oral extended-release tablets: 500 mg	Depakote ER (various generic)
Valproate sodium	
Injection: 500 mg/5 mL ^a	Depacon
Oral solution: 250 mg/5 mL	Depakene syrup (various generic)

^aCurrent labeling information suggests that intravenous (IV) VPA should be administered slowly (maximum rate = 20 mg/min). However, faster rates of administration have been safely employed (6–10 mg/kg/min) in both children and adults.^{7–9} The parenteral formulation may be given intravenously only; intramuscular (IM) administration may result in tissue necrosis.



GENERAL PHARMACOKINETIC INFORMATION

Absorption

VPA is almost completely absorbed.^{6,10} The bioavailability of capsules and enteric-coated tablets is similar, although more variability apparently exists with the enteric-coated form.¹¹ The rate of absorption depends on the dosage form.

It is important for the clinician to recognize that all the available oral formulations of VPA have very different absorption patterns and should not be considered interchangeable.¹² For example, VPA (Depakene) capsules and syrup are absorbed quickly. Due to their enteric coatings, divalproex delayed-release (Depakote) products exhibit both improved gastrointestinal (GI) tolerability and delayed absorption, the latter resulting in a shift of the area under the serum concentration–time curve (AUC) to the right.^{11,13–15} Depakote tablets provide delayed, but not sustained release. Depakote Sprinkles exhibit a sustained-release profile and may be better tolerated because of decreased peak-trough variability compared to oral capsules and solution.

The delay in Depakote absorption may be 1–6 hr, with no change in the extent of absorption. This delay is dependent on gastric-emptying time and gastric pH, with the lag phase for absorption differing significantly between fed and fasted patients. For both regular and coated preparations, food decreases the rate, but not the extent of absorption. The time to achieve peak concentrations may be delayed to 3–8 hr because of dissolution rate changes. Once absorption starts, however, it is usually complete within 1–1.5 hr.¹⁵

Diurnal variations in VPA concentrations have been observed with the enteric-coated formulation and may result in nighttime concentrations that are ~40% of daytime concentrations. This day-night variation does not seem to occur with the extended-release formulation.

An extended-release preparation (Depakote ER) is also commercially available as a generic product and offers the potential of once-daily administration. It is important to recognize that the extended-release product differs from enteric-coated, delayed-release divalproex sodium with respect to both rate and extent of absorption. Depakote ER is not bioequivalent to Depakote, however. Pharmacokinetic studies suggest that when converting a patient from the delayed-release enteric-coated product (Depakote) to the extended-release formulation (Depakote ER), an increase in the total daily dose of ~15% (14% to 20%) is required to maintain equivalent AUC. In addition to once-daily dosing, a potential advantage of this formulation is a reduction in valproate concentration fluctuations over the dosage interval. Mean peak-to-trough concentration fluctuations are substantially less than with Depakote following conversion.¹⁶

Conversion from standard-release to extended-release formulation (i.e., twice-daily Depakote to once-daily Depakote ER) may be accomplished all at once and does not appear to require a prolonged dosage titration or conversion period. To minimize excessive VPA concentration fluctuations, substitution of the extended-release formulation should begin within 12 hr of the last dose of Depakote. Conversion from standard, delayed-release formulation of divalproex (Depakote) to the extended-release formulation will reduce peak-to-trough fluctuations in VPA concentrations. Although the ER formulation is acceptable for patients with epilepsy when given as a once-daily regimen, less peak-to-trough fluctuation (~22% less) will be seen if Depakote ER is given on an every 12-hr basis as compared to once daily.¹⁷ Whether this reduction in fluctuation is clinically meaningful in patients is unclear. An additional consideration for this formulation would be the impact of poor medication compliance. As would be expected, patients with missed doses of a once-daily extended-release formulation are likely to display greater fluctuations in concentrations as compared to patients taking the extended-release formulation twice daily or simply taking the standard, delayed-release preparation, who miss the same number of doses.¹⁸ Pharmacokinetic simulations have suggested that missed doses of extended-release divalproex may be replaced up to 12 hr following a missed dose.¹⁹

The bioavailability of the various dosage forms is provided in **Table 21-3**.

TABLE 21-3. BIOAVAILABILITY OF DOSAGE FORMS

Dosage Form	Bioavailability
IV	100% (F = 1)
IM	Not recommended; avoid use
Oral capsules and syrups	95%; range 90% to 100% (F ~ 0.95)
Enteric-coated tablets (Depakote)	95%; range 90% to 100% (F ~ 0.95)
Extended-release tablets (Depakote ER)	87% (F = 0.87)

Distribution

VPA is rapidly distributed into the central nervous system (CNS). VPA concentrations in cerebrospinal fluid (CSF) tend to be lower than unbound serum concentrations. Brain to total and unbound plasma concentration ratios are ~0.1 to 0.5, respectively; however, significant interpatient variability may be noted. The precise mechanism involved in the transport of VPA into, as well as efflux from, the brain remains uncertain. VPA distribution across the blood-brain barrier may be mediated by both passive diffusion and carrier transport mechanisms, with transport of VPA into the brain apparently mediated by a fatty acid selective anion exchanger and transport out mediated by a probenecid-sensitive active transport system.¹¹ VPA also distributes into breast milk, with typical serum concentrations in nursing infants ranging between 4% to 12% of corresponding maternal concentrations.^{11,20}

Estimating volume of distribution

Table 21-4 provides volume of distribution (V) values that can be assumed in the absence of disease or drug interactions when VPA is used in monotherapy. Single dose values were determined after a single dose and steady state volume determined under steady state conditions. The volume of distribution for VPA is relatively small, ranging from 0.12–0.19 L/kg in adults to 0.2–0.3 L/kg in children.

TABLE 21-4. VOLUME OF DISTRIBUTION

Age Group	Single-Dose Volume (Mean ± SD)	Steady State Volume (Mean ± SD)
Neonates (<4 wk) ²	0.28 L/kg	Not available ^a
Infants (4 wk –<1 yr) ^{21,22}	Not available ^a	0.32 L/kg
Children (3–16 yr) ^{3,23}	Not available ^a	0.22 ± 0.05 L/kg
Adults (18–<60 yr) ^{5,24,25}	0.12 ± 0.03 L/kg	0.15 ± 0.10 L/kg
Geriatrics (≥60 yr) ^{25,26}	0.16 ± 0.02 L/kg	Not available ^a

^aData not available on this age range.

Protein binding

VPA is 90% to 95% protein bound to albumin,^{5,11,27–31} and its protein binding is saturable.^{5,30,31} In adults, at total concentrations <75 mg/L, VPA percent unbound ranges between 7% and 10%. At total concentrations of 100–150 mg/L, however, percent unbound can be expected to increase to ~15% to 30% at either end of this range, respectively. This effect may be magnified in patients with significant hypoalbuminemia.³² Therefore, although unbound concentrations may increase proportionally with dose, total concentrations may exhibit curvilinear kinetics (i.e., less than proportional increases in concentrations with dose changes).³³ Clinicians must be mindful of this saturable binding when evaluating plasma concentration data in patients, where albumin concentrations may conceivably be altered. The percent unbound fluctuates more than the total concentration due to fluctuations in free fatty acid concentrations in the morning and diurnal differences in unbound concentrations and total clearance.^{5,34}

Elimination

VPA is primarily eliminated by the liver but has no clinically important first-pass metabolism. Because VPA is a low extraction drug, clearance is independent of blood flow. Only 3% to 7% of a dose is excreted unchanged in the urine.

The metabolism of VPA in the liver is extensive. The three main metabolic pathways, in order of importance, are

1. conjugation with glucuronic acid
2. mitochondrial β -oxidation
3. Ω -oxidation.¹¹

The most abundant metabolite, VPA-glucuronide accounts for ~60% of the recovered dose in the urine and VPA may competitively inhibit the metabolism of other drugs that form glucuronide conjugates. Several glucuronyltransferase (UGT) isozymes have been identified as participating in VPA metabolism, and include UGT1A3, 1A4, 1A6, 1A8, 1A9, and 1A10. These isozymes all appear to contribute to the formation of an acyl glucuronide conjugate that is inactive. Although human microsomal studies do not suggest a decline in VPA-glucuronide formation in elder patients, studies in nursing home patients suggest that elder females may have oral clearances that are ~27% less than male counterparts. Although cytochrome P450 isozymes are responsible for only a minority of VPA metabolism, they appear to be quite important in the generation of both active, and potentially toxic, metabolites. Approximately 10% of an administered dose of VPA is metabolized via CYP isozymes, including 2A6, 2B6, and 2C9.

Two of the desaturated metabolites, 2-ene-VPA and 4-ene-VPA, may possess anticonvulsant activity. The 2-ene-VPA metabolite will accumulate in the brain with chronic dosing.³⁵ One of VPA's potentially hepatotoxic metabolites, 4-ene, may be produced in larger quantities in patients on concomitant enzyme inducers, leading, in part, to the higher incidence of hepatotoxicity seen in children on polytherapy.³⁶ Both metabolites are generated via CYP isozymes, and, therefore, formation may be increased when VPA is given concomitantly with enzyme-inducing AEDs. CYP 2C9*1 appears responsible for the formation of 4-ene-VPA.³⁷ Unlike 4-ene-VPA, 2-ene-VPA does not appear to demonstrate embryotoxicity or hepatotoxicity. Although not proven, it is possible that loss of function mutations in CYP2C9 might lead to modest increases in VPA plasma concentrations.

Clearance depends primarily on the age of the patient and concomitant medications. Newborns eliminate VPA slower than children or adults. Although little is known in the elder population, in-vitro studies using human liver microsomes suggest no difference in VPA-glucuronide formation in elder versus younger livers.³⁸ As discussed previously the diurnal fluctuation in VPA concentration-time profiles is great, so clinicians should be mindful when monitoring apparent "trough" concentrations at varying times of day.³⁴

VPA exhibits concentration-related changes in apparent clearance, with lower clearance at higher concentrations. The lower apparent oral clearance of VPA at higher concentrations may reflect either saturable protein binding or partial saturation of intrinsic clearance. VPA is not removed efficiently by standard hemodialysis (<20%), but high-flux hemodialysis is effective.

The clearance values in **Table 21-5** can be assumed in the absence of disease or drug interactions when VPA is used in *monotherapy* (i.e., no influence of enzyme inducers).

Half-life and time to steady state

The half-life ($t_{1/2}$) values in **Table 21-6** can be assumed in the absence of disease interactions when VPA is used in monotherapy. Some drug-drug interactions alter the half-life and time to steady state.

TABLE 21-5. CLEARANCE BY AGE IN THE ABSENCE OF CLEARANCE-ALTERING FACTORS

Age Group	Clearance at Steady State ^a (Mean ± SD or Range)
Neonates (<4 wk) ²	0.011 to 0.018 L/hr/kg
Infants (4 wk –<1 yr) ^{2,21,22}	0.019 ± 0.008 L/hr/kg
Children (3–16 yr) ^{3,21,23}	0.018 ± 0.006 L/hr/kg
Adults (18 –<60 yr) ^{5,24}	0.009 ± 0.005 L/hr/kg
Geriatrics (≥60 yr) ^{11,25,26}	0.007 ± 0.005 L/hr/kg

^aUse ideal body weight in obese patients.

TABLE 21-6. VALPROATE HALF-LIFE AND TIME TO STEADY STATE BY AGE GROUP

Age	Half-Life (Mean ± SD)	Time to Steady State ^a
Neonates (<4 wk) ²	17–20 hr	86–100 hr
Infants (4 wk –<1 yr) ^{2,22}	12.5 ± 2.8 hr	49–77 hr
Children (3–16 yr) ^{3,4,23,39}	11 ± 4 hr	35–75 hr
Adults (18 –<60 yr) ^{5,24}	11.9 ± 5.7 hr	31–88 hr
Geriatrics (≥60 yr) ²⁶	15.3 ± 1.7 hr	68–85 hr

^aTime to steady state based on + and – 1 SD of the mean half-life or range and assuming steady state reached in five half-lives.

DOSING STRATEGIES

Initial dosing

The recommended initial target dose for VPA in adults is ~15 mg/kg/day. Typically, the VPA dose is gradually escalated to minimize initial adverse effects and enhance tolerability. A reasonable starting regimen would be VPA 250–500 mg once or twice daily. The dosage is gradually titrated upward (5–10 mg/kg/day) every 3–5 days. Eventual maintenance dosage depends primarily on clinical response (efficacy versus toxicity) and also on the impact of concomitant medication interactions. Maintenance doses typically range between 15 and 60 mg/kg/day. When using Depakene or the enteric-coated formulation Depakote, the typical dosage frequency is twice to three times daily. The extended-release product Depakote ER may be given once or twice daily.

Oral loading doses of VPA may produce unacceptable GI side effects in some patients. For the treatment of acute seizures, larger IV loading doses have been used (~20–25 mg/kg) and are generally well tolerated at rapid infusion rates. Loading doses of IV VPA of 25 mg/kg have been reported to result in total peak concentrations of 80–200 mg/L.^{7,8} Oral loading with the delayed-release formulation (Depakote) has been used in patients suffering from acute mania and in one small study was shown to be well tolerated.⁴⁰ Initial institution of Depakote ER following IV loading has also been employed in patients requiring prompt initiation of VPA therapy.⁴¹

Apparent oral clearance of VPA may correlate better with ideal body weight than with total body weight in obese patients. Thus, it may be prudent to use ideal body weight to estimate clearance and initial dosing needs in obese patients.

DOSAGE ADJUSTMENT

The simplest approach to dosage adjustment is based on the measurement of a trough concentration at steady state. Once this concentration is determined, VPA doses may be adjusted by a desired proportion, keeping in mind that as concentrations increase a curvilinear relationship between total concentration and dose is observed. Thus, at higher concentrations any given increase in the VPA dose

results in proportional increases in the unbound concentration but less than proportional increases in the total VPA concentration. At higher measured total concentrations an unexpected degree of response or toxicity may be seen.

THERAPEUTIC RANGE

Dose response to VPA is highly variable and dependent on the type and severity of seizure and an individual's pharmacokinetic parameters. Various seizure disorders or epileptic syndromes may require higher or lower average concentrations.

Studies correlating VPA concentrations with clinical response in patients with seizures have generally found that 40–50 mg/L is the minimum effective trough concentration for optimal seizure control. Seizure control tends to improve as the trough concentration increases from 40–120 mg/L. Monotherapy epilepsy trials suggest that higher concentrations (>80 mg/L) may be more effective than lower concentrations in treating complex-partial seizures.⁴² Seizure control may improve with prolonged therapy independent of changes in concentrations.

Whether the optimal concentration ranges for conditions such as migraine headache or bipolar-affective disorder are different than that for seizures has not been clearly established.⁴³

Depending on the clinical circumstances, some patients may benefit from trough concentrations greater than 120 mg/L, and they may not exhibit adverse effects. However, the incidence of adverse effects such as tremor and thrombocytopenia may well increase at higher concentrations.⁴⁴ Increased CNS toxicity is generally seen when concentrations reach 175–200 mg/L. Overall, regardless of clinical indication, there does not appear to be a clearly defined concentration–response relationship for this agent. For non-epilepsy conditions such as bipolar disorder, the range for total and unbound VPA tends to be broad, and routine use of plasma concentration monitoring may not be warranted.⁴³

An unbound VPA concentration range has not been established, although in some cases markedly elevated unbound concentrations have been associated with neurotoxicity. Determination of unbound VPA concentrations may be considered in patients with hypoalbuminemia.³²

Typical adverse events associated with VPA treatment include tremor, weight gain, hair loss, hyperammonemia, GI distress, and decreased cognitive functioning.³⁶ Patients with these reactions must be closely monitored. Adverse reactions associated with elevated concentrations of VPA, such as thrombocytopenia and platelet dysfunction, may not be readily detectable by patient history or physical assessment. Thus, potentially toxic concentrations may be present but not apparent from other side effects.

EFFECT OF AGE AND PREGNANCY ON THERAPEUTIC RANGE

Elderly patients may display an increased percent unbound as a result of lower serum albumin concentrations and may have a reduced unbound clearance (~40%) as compared to younger subjects.^{25,26} Measurement of unbound concentrations may therefore be reasonable in elderly patients, particularly for those with low serum albumin concentrations.

Alterations in VPA clearance and concentrations may also be expected in pregnancy. Total concentrations may begin to decline by the second trimester and can be expected to rise rapidly within 2–3 wk postpartum. Unbound concentrations are, however, largely unchanged during pregnancy. These changes are likely due to changes in maternal protein binding. Therefore, as with elderly patients, monitoring of unbound concentrations may be warranted in pregnant patients.

One study suggests that VPA concentrations may vary in women as a function of menstrual cycle.⁴⁵ Whether these fluctuations are clinically meaningful is unclear. Because of potential teratogenicity, VPA should be used with extreme caution (if at all) in women of child-bearing potential.

Data from children (8–11 yr of age) and adolescents (12–17 yr of age) suggest that Depakote ER used as a once daily administration will result in relatively small fluctuations in concentrations across a 24-hr dosage period.⁴⁶

THERAPEUTIC MONITORING

Suggested sampling times and effect on therapeutic range

Because the diurnal fluctuation in VPA concentration–time profiles is great,^{25,34} it is suggested that morning trough concentrations be used for monitoring. At a minimum, it is recommended that trough concentrations be consistently taken in the dosing interval (e.g., always before the morning dose or always before the afternoon dose). Trough VPA measurements should usually be obtained prior to a morning dose as these concentrations are the most consistent from day to day. Determination of peak concentrations is not typically employed. Timing of peak concentration measurements is highly dependent on the dosage form and the circumstances under which VPA is ingested. For example, the absorption of Depakote is highly dependent on administration in the fed or fasted state, and Depakene can potentially produce large differences between peak and trough concentrations.¹⁵ After any change in dosage or dosing interval, waiting 3 to 5 days prior to sampling should generally ensure that patients have achieved the new steady state.

With respect to optimal times for sampling VPA concentrations in patients receiving Depakote ER once daily in the morning, morning trough samples (21–24 hr following the previous dose) are typically considered to be the most reproducible. For patients taking this formulation in the evening, morning samples obtained 12–15 hr later can result in concentrations being 20% to 25% higher than expected trough concentrations.⁴⁷ Therefore, timing of serum sampling as close to trough times would be the most reasonable approach. Sampling around the expected peak time for this formulation (3–15 hr following dose administration) is unnecessary.

INITIAL AND FOLLOW-UP MONITORING

Because VPA clearance at low concentrations may be significantly different than at higher steady state concentrations, VPA concentrations generally should not be determined following the initial dose. The most cost-efficient strategy involves achieving steady state conditions before determining VPA concentrations. If serum concentrations are obtained following IV loading, particularly if rapid infusion rates are employed (e.g., setting of acute seizures), then clinicians should be cognizant of the impact of concentration-dependent protein binding. In this situation, percent unbound will decline as high initial peak concentrations decline.

Other indications for monitoring VPA concentrations include signs of toxicity, decreased seizure control, addition or withdrawal of AEDs or other interacting drugs, and suspected nonadherence.

PHARMACODYNAMIC MONITORING— CONCENTRATION-RELATED EFFICACY

Efficacy of VPA therapy is judged by a decrease in seizure activity. It may take several days to more than 1 week to achieve the full therapeutic effect at a given VPA concentration.¹ Little clinical or animal data exist to indicate specific synergistic or antagonistic pharmacodynamic interactions with other agents, although a potential synergistic effect of VPA and lamotrigine has been suggested in patients with refractory seizures resistant to pharmacotherapy.

The more common dose or concentration-related adverse effects of VPA therapy are GI in nature (e.g., nausea, vomiting, and diarrhea). Although hepatotoxicity has been reported in patients receiving VPA, a clear dose relationship is not established. Severe hepatotoxicity may be preceded by nonspecific symptoms such as loss of seizure control, malaise, and weakness.¹

Thrombocytopenia, platelet aggregation defects, and tremor also appear to be concentration related. Evidence from clinical trials with the AED lamotrigine suggests that pharmacodynamic interactions between this agent and VPA exist and may lead to an increased incidence of tremor and rash.

DRUG-DRUG INTERACTIONS

Pharmacokinetic interactions with VPA are common and clinically important. VPA is an enzyme inhibitor and is subject to enzyme induction. The concomitant administration of drugs that utilize enzyme metabolism may affect the actions of these drugs and of VPA. For example, VPA decreases the elimination of carbamazepine 10,11-epoxide (via inhibition of epoxide hydrolase),⁴⁸⁻⁵¹ phenobarbital (30% to 50%),^{52,53} and ethosuximide.⁵⁴ Because of protein-binding displacement, phenytoin total concentrations can decline during co-medication with VPA, while unbound concentrations can increase secondary to inhibition of intrinsic clearance. Clearance of lamotrigine is also markedly inhibited by VPA, resulting in significant prolongations in lamotrigine half-life.⁵⁵ VPA is a potent inhibitor of lamotrigine metabolism, with near maximal inhibition occurring at VPA daily doses of 250–500 mg.⁵⁶ The combination of VPA and lamotrigine increases the risk for potentially serious rash. The mechanism for this apparent interaction is unknown, but is likely due to inhibition of glucuronidation. This interaction is reversible and seems to be completely gone within 1 wk following VPA discontinuation. VPA also significantly reduces the clearance of lorazepam.⁵⁷ These interactions are presumably mediated via inhibition of glucuronyl transferase and can lead to clinically significant increases in serum concentrations of these compounds, with possible associated clinical toxicity. Enzyme inducers such as rifampin, phenytoin, carbamazepine, primidone, and phenobarbital increase the elimination of VPA, often requiring higher doses. Concomitant administration with AEDs such as gabapentin, pregabalin, levetiracetam, vigabatrin, perampanel, eslicarbazepine, or lacosamide would not be expected to result in significant pharmacokinetic interactions.

Co-administration of felbamate can reduce VPA clearance, possibly via inhibition of beta-oxidation. Through a similar mechanism, aspirin may also inhibit VPA metabolism.^{58,59} Cimetidine and ranitidine do not affect the clearance of VPA.⁶⁰ Among the newer generation AEDs, VPA can increase rufinamide concentrations by up to 70%. Co-administration with oral contraceptives may decrease VPA concentrations, possibly as a result of UGT induction by ethinyl estradiol.⁴⁵

Caution should be used when administering VPA concomitantly with CNS depressants, other anticonvulsants, monoamine oxidase inhibitors, and anticoagulants. It does not appear to alter the pharmacokinetics of oral contraceptive agents; however, VPA oral clearance is significantly increased in women taking oral contraceptive pills (21% to 45% increase in total and unbound oral clearance, respectively), presumably due to induction of UDP-glucuronyl transferase by ethinyl estradiol.⁶¹

Co-administration with other highly protein-bound drugs may result in protein-binding displacement interactions. In one study, concomitant treatment with naproxen resulted in an approximate 20% increase in VPA total plasma clearance. Unlike aspirin, naproxen does not appear to alter VPA intrinsic clearance, so unbound VPA concentrations are not affected.⁶²

Bidirectional interactions between VPA and several antiviral and antibiotic agents may also occur. For example, VPA may inhibit the metabolism of antiviral agents such as zidovudine while antibiotics in the carbapenem class have been shown to cause substantial reductions in concentrations of VPA, possibly via interference with its oral absorption.⁶³

Table 21-7 shows a number of potential drug-drug interactions between valproate and other AEDs, a number of which have no impact.

TABLE 21-7. IMPACT OF DRUG-DRUG INTERACTIONS ON THE CONCENTRATIONS OF THE INTERACTING AED AND VPA

AED	Effect on AED Concentration	Effect on VPA Concentration
Carbamazepine	Increased carbamazepine-epoxide	Decreased
Clobazam	No effect	No effect
Eslicarbazepine	No effect	No effect
Felbamate	Increased	Increased ($\geq 35\%$)
Gabapentin, pregabalin	No effect	No effect
Levetiracetam	No effect	No effect
Lamotrigine	Increased	No effect/slight decrease
Lacosamide	No effect	No effect
Oxcarbazepine	No effect	No effect
Perampanel	No effect	No effect
Phenytoin	Decreased total phenytoin Increased unbound phenytoin	Decreased
Phenobarbital	Increased	Decreased
Primidone	Increased Increased phenobarbital	Decreased
Tiagabine	No effect	No effect/slight decrease
Topiramate	No effect/slight decrease	No effect
Vigabatrin	No effect	No effect

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

In hepatic disease, renal impairment, and pregnancy, an increase in the volume of distribution and percent unbound can be expected due to changes in protein binding.⁶⁴ VPA is moderately dialyzable. With hepatic cirrhosis, the percent unbound increases to 29%; in renal failure, the percent unbound increases to 18%.¹¹ Head trauma may transiently increase VPA percent unbound and total clearance.⁶⁵

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VANCOMYCIN

Jeremiah J. Duby, Monica A. Donnelley, Chelsea L. Tasaka, and Brett H. Heintz

Vancomycin is a tricyclic glycopeptide antibiotic that is active against many Gram-positive organisms. It is used principally for the treatment of severe and/or resistant staphylococcal and enterococcal infections and may also be used for moderate infections in patients who may be allergic to first-line antibiotics (e.g., penicillins). Vancomycin is bactericidal and acts by binding to the C-terminal D-alanyl-D-alanine residue of the pentapeptide cell wall building block, thereby inhibiting cell wall synthesis. Renal excretion is the primary route of elimination, and kidney injury is the principle toxicity associated with vancomycin use.

Vancomycin represents parallel paradoxes in infectious disease and pharmacokinetics. First, it remains a first-line antibiotic for limb- and life-threatening infections due to multidrug resistant pathogens despite decades of use.¹ However, avoidance of selective antibiotic pressure is increasingly contradicted by reports of declining susceptibility through minimum inhibitory concentration (MIC) creep.² Second, vancomycin is the subject of more than 30 yr of intensive pharmacokinetic research and therapeutic drug monitoring; however, objectives for clinical management continue to evolve. The challenge is for practice changes to match the evolving threats of resistance and the slow pace of new antibiotic discovery. Clinicians must adapt to use of new dosing methods, targets, and tools (e.g., Bayesian estimation) as the potential risks and benefits of losing this critical antibiotic for patient care have never been greater.

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

Initiation of therapy

The foremost responsibility for initiation of therapy is determining why vancomycin is necessary. Antibiotic stewardship practices are essential to preserving the utility of the agent. The probability of multidrug resistant, Gram-positive infection must be investigated with a strong bias for discontinuation upon exclusion of a clear indication for therapy or resolution of infection. Consideration of patient-specific factors, source(s) of infection, pathogen, MIC, and potential kidney injury also play crucial roles in whether vancomycin is used, and how. Finally, individualized dosing is essential to maximize treatment success and mitigate the risks of toxicity.³

Dosing weight

Actual body weight (ABW) appears to represent the anthropometric measure with the closest correlation to steady state volume of distribution (V) and to total body clearance of vancomycin.⁴ Weight-based dosing based on ABW is especially important for markedly obese patients as standard empiric dosing (e.g., 1 g intravenous [IV] every 12 hr) is likely to result in concentrations below the accepted therapeutic range.⁵ Additional detail is provided in following sections.



Loading dose

The primary advantage of a vancomycin loading dose is earlier attainment of target concentrations.⁶ Loading doses of 25–30 mg/kg (ABW) may be used for patients with normal renal function; however, lower doses (e.g., 20 mg/kg) may be appropriate for patients with stage 4 or 5 chronic kidney disease (CKD) (see **Table 22-1**).¹

A clinical advantage to loading doses is indirectly inferred from a retrospective study of vancomycin pharmacodynamics. A more than 50% reduction in 30-day mortality rate and composite treatment failure was observed in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections that achieved an area under the concentration-time curve over 24 hr relative to minimum inhibitory concentration (AUC_{24}/MIC) > 521 mg × hr/L within the first 24 hr of therapy⁷ (the AUC/MIC ratio is the pharmacodynamic parameter that indexes total drug exposure or the AUC over 24 hr to the MIC of the pathogen). The potential benefit of loading doses is therefore especially important for patients with critical illness.⁸

Delay to therapeutic concentrations may occur for patients with a larger V (e.g., obesity, renal failure) or impaired elimination if an insufficient loading dose (or no loading dose) is given. Patients with poor renal function may experience a lag in achieving therapeutic concentrations without an adequate loading dose, particularly if maintenance dose size is adjusted downward due to poor renal function. The time to achieve steady state concentrations is three times greater for a patient with half-life of 24 hr than for a patient with a half-life of 8 hr.

There is no clinical evidence of a meaningful advantage to a loading dose with intermittent dosing in children with normal renal function, which is likely explained by the relatively high elimination rate and consequent short time to steady state.⁹ The focus for this population lies in providing a sufficient maintenance dose.

TABLE 22-1. SUGGESTED LOADING DOSES FOR ADULT PATIENTS

Renal Function (mL/min)	Suggested Load (mg/kg)	C _{peak} (mg/L) ^{a,b}
CrCl > 30	25–30	31–43
CrCl ≤ 30	20	25–29

^aEstimated $V = 0.7\text{--}0.8$ L/kg.

^bRange of peaks that would occur if the loading dose (or dose range in CrCl > 30) were matched with the range of V .

Maintenance dose

Elimination is dynamic because it is largely dependent on renal filtration, which is highly variable. Therefore, renal function represents the primary, clearance-altering factor for vancomycin dosing. The vancomycin package insert recommends 1 g every 12 hr for “patients with normal renal function.”¹⁰ Conventionally, normal renal function refers to creatinine clearance (CrCl) >60 mL/min as the standard for which renal dose adjustment is considered unnecessary. However, this assumption neglects a wide range of patients (i.e., CrCl of 90–250 mL/min), and may result in subtherapeutic dosing for young and hyperdynamic populations.

Because renal elimination is the primary clearance-altering factor for dosing, determining maintenance dose is principally about estimating renal function. Unfortunately, the most common biomarker used to estimate renal filtration, serum creatinine (S_{cr}), is commonly confounded by patient-specific factors such as age, chronic disease, nutrition, ethnicity, and body habitus. Further, S_{cr} is a lagging indicator of function and can lead to over- and underestimates of CrCl during the dynamic phases of acute kidney injury.

DOSAGE FORM AVAILABILITY¹¹

Vancomycin is available in oral and IV forms (see **Table 22-2**). Oral therapy is reserved for the treatment of pseudomembranous colitis. As systemic absorption is minimal, concentration monitoring is not warranted for most patients.

TABLE 22-2. AVAILABLE DOSAGE FORMS

Dosage Form	Product (Manufacturer)
<i>Powder for IV injection:</i>	
500 mg and 750 mg per vial	Vancomycin (multiple)
1 g, 5 g, and 10 g per vial	
<i>Solution for injection:</i>	
500 mg/100 mL	Vancomycin HCl (multiple)
750 mg/150 mL	
1,000 mg/200 mL	
<i>Oral capsules:</i>	
125 mg and 250 mg	Vancocin HCl (ANI Pharmaceutical)
125 mg and 250 mg	Vancomycin (multiple)
<i>Oral solution:</i>	
25 mg/mL	First-Vancomycin 25 (Cutis Pharma)
50 mg/mL	First-Vancomycin 50 (Cutis Pharma)
50 mg/mL	Vancomycin + SyrSpend SP PH4 (FAGRON)

GENERAL PHARMACOKINETIC INFORMATION

Absorption

The absolute bioavailability of orally administered vancomycin is generally poor in those with an intact gastrointestinal tract (<5%). However, elevated concentrations have been noted after oral dosing in patients with pseudomembranous colitis and/or severe renal failure.¹² Serum concentrations in the therapeutic range have been reported in these patients, so periodic monitoring should be considered, especially for patients receiving >2 g/day for ≥10 days. **Table 22-3** provides the bioavailability for the dosage forms.

TABLE 22-3. BIOAVAILABILITY OF DOSAGE FORMS

Dosage Form	Bioavailability	Comments
IV	100%	
Intramuscular (IM)	Not determined	Not recommended for IM use
Oral capsules and powder	<5%	Increased in pseudomembranous colitis

Volume of distribution

The disposition of vancomycin after IV administration is best characterized by a three-compartment pharmacokinetic model. The early distribution phases are generally not observed during clinical use due to the relatively long infusion rate used to administer the intermittent dose. Blood samples are also usually obtained after distribution is complete for practical reasons (i.e., to facilitate calculations based on one-compartment model). The half-life of the initial distribution phase is ~7 min and that of the second phase is ~0.5–1 hr. Population V values are provided in **Table 22-4**.

Protein binding

The plasma protein binding of vancomycin ranges from 30% to 55% and is dependent on the patient's albumin concentration. In patients with hypoalbuminemia, the protein binding is lower. For example, in end-stage renal disease and burn patients, mean protein binding values of 19% and 29%, respectively, have been reported.^{13,14}

TABLE 22-4. VOLUME OF DISTRIBUTION BY AGE GROUPING

Age	Volume L/kg (Mean ± SD) ^a
Premature neonates ^{15,16,b}	0.56 ± 0.02
Infants and full-term neonates ¹⁶⁻¹⁸	0.69–0.79 ^c
Infants (≥1 month–<1 yr) ¹⁷	0.69 ± 0.17
Children (2.5–11 yr) ¹⁹	0.63 ± 0.16
Adults (≥16–<65 yr) ²⁰⁻²⁵	0.62 ± 0.15
Obese adults (>30% over IBW) ²⁶	0.56 ± 0.18
Adults with severe renal impairment ^{23,24}	0.9 ± 0.21
Geriatrics (≥65 yr) ²⁰	0.76 ± 0.06
Critically ill adults (42–76 yr) ^{d,27,28}	1.32–1.68 ^{c,27,28}

^aActual body weight.
^bFrom 27 wk PCA (postconception age: the sum of the gestational age at birth and chronological age) to >37 wk PCA.
^cRange rather than ±SD.
^dMedical intensive care unit patients.
IBW = ideal body weight; SD = standard deviation.

Elimination

Vancomycin is primarily eliminated by glomerular filtration; ~80% to 90% of an IV administered dose is recovered unchanged in the urine of adult patients with normal renal function.¹² Therefore, dosage adjustment is necessary for those with disease- and/or age-related alterations in renal function. The nonrenal clearance of vancomycin ranges from <5% to as high as 20% of total body clearance. Vancomycin undergoes biliary excretion, but the typical amount of drug eliminated in bile has not been established.²⁹ There are no active or inactive metabolites of vancomycin, but crystalline degradation products (CDP-1) have been noted to form in a time- and temperature-dependent manner (see Assay Issues). Limited data in patients with hepatic impairment suggest that dosage adjustment is not warranted.

Clearance

Clearance values for various patient populations are shown in **Table 22-5**. Renal function is the primary determinant of a patient’s ability to clear vancomycin.

TABLE 22-5. AVERAGE CLEARANCE VALUES

Age	Clearance L/hr/kg (Mean ± SD)
Premature neonates ¹⁵	
27–30 wk PCA ^a	0.06 ± 0.004
31–36 wk PCA	0.07 ± 0.004
>37 wk PCA	0.079 ± 0.004
Infants and full-term neonates ¹⁸	0.067 ± 0.021
Children (2.5–11 yr) ¹⁹	0.11 ± 0.02
Adults (≥16–<65 yr) ^{20-25,30}	0.073 ± 0.025
Geriatrics (≥65 yr) ²⁰	0.053 ± 0.003
Critically ill adults (42–76 yr) ^{27,28}	0.052 ± 0.037

^aPCA = postconception age: the sum of the gestational age at birth and chronological age.

Half-life and time to steady state

The terminal elimination half-life ranges from 3 to 9 hr in adults with normal renal function (i.e., creatinine clearance of >80 mL/min/1.73 m²). **Table 22-6** shows the half-life values by age group and corresponding time to steady state values.

TABLE 22-6. HALF-LIFE AND TIME TO STEADY STATE BY AGE GROUPING

Age	Half-Life (Mean $\pm$ SD)	Time to Steady State (hr) ^a
Premature neonates ¹⁵		
27–30 wk PCA ^b	6.6 $\pm$ 0.4 hr	31–35
31–36 wk PCA	5.6 $\pm$ 0.4 hr	26–30
>37 wk PCA	4.9 $\pm$ 0.4 hr	23–27
Full-term neonates ¹⁷	6.7 hr	34
Infants (≥ 1 month–<1 yr) ¹⁷	4.1 hr	21
Children (2.5–11 yr) ¹⁷	5.6 $\pm$ 2.1 hr	18–39
Adults (≥ 16 –<65 yr) ^{20–25,30}	7 $\pm$ 1.5 hr	28–43
Adults with moderate to severe renal impairment (CrCl 10–60 mL/min) ^{23,24}	32 $\pm$ 19 hr	2.7–10.6 days
Geriatrics (≥ 65 yr) ²⁰	12.1 $\pm$ 0.8 hr	57–65

^aTime to steady state determined by assuming five half-lives for steady state and using $\pm$ one SD of the mean $t_{1/2}$.

^bPCA = postconception age.

DOSING STRATEGIES

Adult populations

There are many possible variations on the general techniques and practices for empiric dosing of vancomycin. Common methods include average doses from the package insert, nomograms based on various factors, and calculations based on population pharmacokinetic parameters. Vancomycin may be delivered by intermittent or continuous infusion. There are advantages and disadvantages of each strategy and method. The use of therapeutic drug monitoring as part of dosing strategies is discussed later.

Nomograms and pharmacokinetic population parameter estimations

Expediency and ease of use are the key advantages of nomograms. Essentially, they are tabular or graphical representations of pharmacokinetic calculations for a range of patient variables (e.g., CrCl or age). Each is defined by the values used for the pharmacokinetic parameters. A description of the process for developing a vancomycin nomogram is useful for understanding their use and limitations.

First, clinical studies are performed to determine the pharmacokinetic parameters (e.g., V , CL , k) from patient factors (e.g., height, weight, S_{Cr}) and vancomycin concentrations. The proportional relationship between CrCl and a parameter like CL_{vanco} is then plotted and expressed as an equation, which can then be used to determine doses and/or intervals.²³ An example of nomogram development is shown in **Figure 22-1**.

The potential disadvantages of nomograms and population parameter estimations are methodological limitations and misapplications. The seven most common population parameter estimation methods used in clinical practice were evaluated in a retrospective study that compared predicted and measured vancomycin concentrations in hospitalized patients ($n = 189$).³¹ The method with the least bias and greatest precision was predictive of the measured vancomycin concentration within 5 mg/L in only 66% of cases.²³ None of the methods provided estimations that were within 25%

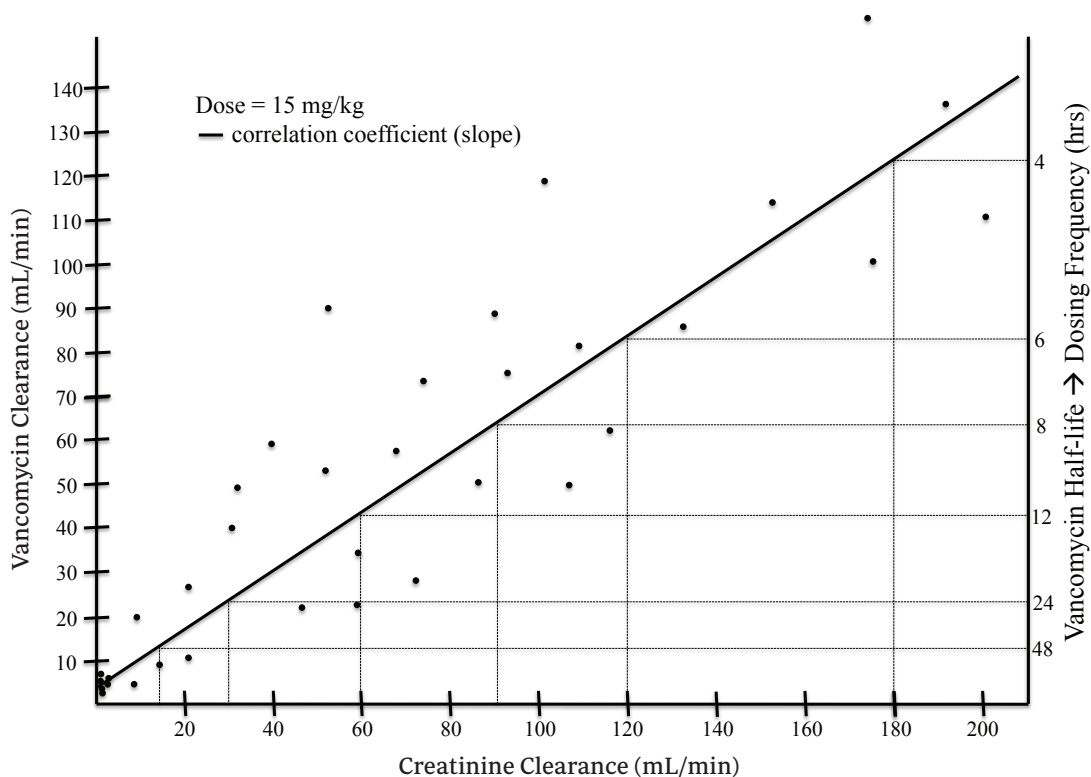


Figure 22-1. Example of graphical nomogram development. The correlation between vancomycin and creatinine clearance defines the line. Dosing frequency (and $t_{1/2}$) is determined by tracing from estimated CrCl to the correlation line and then to z axis.

of the measured concentration for greater than 50% of cases. The results are perhaps less surprising when the variability between the methods is compared (**Table 22-7**). A prevailing weakness of many methods is that the population pharmacokinetic parameters may represent the aggregation of data from various studies. Further, differences between any individual patient and the population averages will result in differences between the predicted and measured concentration. Another potential danger is that clinical studies and nomograms were developed when the target trough concentration was 5–10 mg/L.^{24,31-35} If a nomogram or dosing strategy was developed to target that concentration range, higher doses would be necessary to reach currently suggested target concentrations.

Continuous infusion dosing

The advantages of continuous infusion (CI) dosing of vancomycin compared to intermittent infusion (II) appear to be a lower risk of nephrotoxicity³⁶⁻³⁹ and a more rapid achievement of target concentrations.^{36,37,40,41} A meta-analysis of six studies demonstrated a significant reduction in the unadjusted relative risk for nephrotoxicity favoring CI (RR 0.6, 95% CI 0.4–0.9, $p = 0.002$).³⁸ Another study subsequently identified an eight-fold lower risk of nephrotoxicity with CI compared to II in critically ill patients based on multivariate analysis ($n = 1,430$).³⁶ The DALI study observed a significantly higher rate of target concentration (71% versus 39%, $p = 0.038$) and target $AUC_{24}/MIC > 400$ (88% versus 50%, $p = 0.008$) in patients that received CI.⁴⁰ A shorter time interval to achieve (2.04 versus 3.76 days, $p < 0.0001$) and greater fraction of time within (92.3% versus 30.8%, $p < 0.0001$) the target range was noted for a cohort of neurosurgical intensive case unit (ICU) patients that received CI versus II. Moreover, the mean AUC_{0-24}/MIC value (671.5 versus 354.4, $p < 0.0001$) and frequency of achieving the target of > 400 (92.3% versus 30.8%, $p < 0.0001$) strongly favored the CI group; there was no difference in the rate of nephrotoxicity (15.4% versus 21.5%, $p = 0.5$).³⁷

TABLE 22-7. PHARMACOKINETIC PARAMETERS USED FOR CALCULATING VANCOMYCIN DOSES

Method	V	Dosing Weight	CL _{vanco}	Weight for CrCl Estimation
Matzke ²³	CrCl > 60 mL/min: 0.72 L/kg CrCl 10–60 mL/min: 0.89 L/kg CrCl < 10 mL/min: 0.9 L/kg	ABW	(CrCl × 0.689) + 3.66 (mL/min) ^a	ABW
Burton ³²	0.47 L/kg	ABW < IBW ^b use ABW ABW > IBW ^b use BW _{adj}	(CrCl × 0.0075) + 0.04 (mL/min/kg) ^c	Dosing weight
Bauer ³⁵	0.7 L/kg	ABW < IBW ^d use ABW ABW < 1.3 × IBW ^d use ABW ABW > 1.3 × IBW ^d use BW _{adj}	(CrCl × 0.695) + 0.05 (mL/min/kg) ^e	Dosing weight
Ambrose ³⁴	[0.17 × age (yr)] + [0.22 × ABW (kg)] + 15	ABW	CrCl (mL/min) ^a	ABW ABW > 1.2 × IBW ^d use BW _{adj}
Birt ³³	0.54 L/kg	ABW	(CrCl × 0.674) + 13.45 (mL/min) ^a	ABW
Rodvold ²⁴	CrCl > 70 mL/min: 0.5 L/kg CrCl 40 – 70 mL/min: 0.59 L/kg CrCl 10 – 39 mL/min: 0.64 L/kg	ABW	(CrCl × 0.79) + 15.7 (mL/min) ^a	ABW

ABW = actual body weight; CrCl = creatinine clearance; IBW = ideal body weight; BW_{adj} = IBW + [0.4 × (ABW – IBW)].

^aCL_{vanco} and CrCl in mL/min.

^bIBW = 0.73 × ht (cm) – 59.42.

^cCL_{vanco} in mL/min/kg; CrCl in mL/min.

^dIBW_{males} = 50 kg + [2.3 × (Ht – 60)] kg, IBW_{females} = 45.5 kg + [2.3 × (Ht – 60)] kg.

^eCL_{vanco} and CrCl in mL/min/kg.

The chief limitation of CI vancomycin is the need for central venous access due to endothelial cell toxicity-associated with peripheral administration.⁴² Another practical consideration is providing an adequate loading dose. **Figure 22-2** illustrates a delay to therapeutic concentrations without a loading dose when CI is used. Equation 1 was developed to guide CI dosing based on target steady state concentrations and estimated CrCl.⁴³

Therapeutic drug monitoring of CI is simplified by the ability to monitor random rather than trough concentrations. The AUC₂₄/MIC over a 24-hr period for CI is simply the product of C_{ss} and 24 hr divided by the MIC of the organism being treated (Equation 2). Dose adjustments may be made in direct proportion to desired adjustments in measured steady state concentrations (Equation 3).

Continuous infusion dose calculation⁴³:

$$\text{CI rate (g/24 hr)} = [0.029 \times \text{CrCl (mL/min)} + 0.94] \times [\text{target } C_{ss} \times (24/1,000)] \text{ (Eq. 1)}$$

AUC₂₄/MIC for continuous infusion:

$$\text{AUC}_{24}/\text{MIC} = (C_{ss} \times 24 \text{ hr})/\text{MIC} \text{ (Eq. 2)}$$

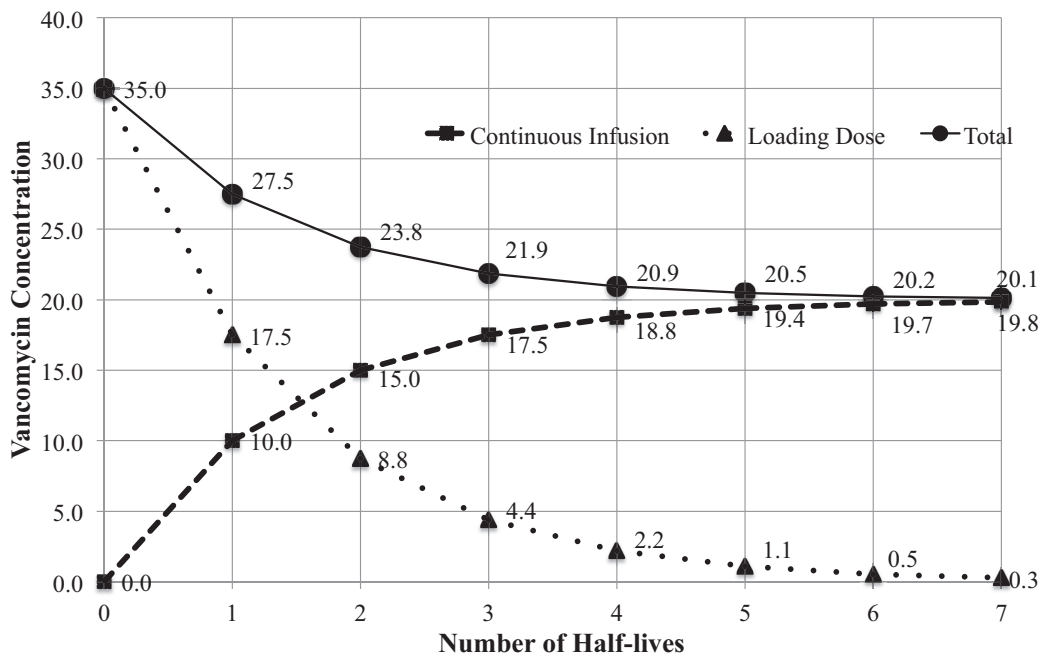


Figure 22-2. Importance of loading dose with continuous infusion.

Continuous infusion dose adjustment:

$$\text{new dose (mg/day)} = \frac{(\text{target concentration})}{(\text{measured concentration})} \times \text{current dose (mg/day)} \quad (\text{Eq. 3})$$

Pediatric populations

Dosing

The optimal dosing method for the pediatric population remains unclear despite extensive use. Current guidelines recommend vancomycin dosing 60 mg/kg/day for the treatment of presumed severe MRSA infections.⁴⁴ Empiric dosing in pediatric patients is confounded by the tremendous variability in age, weight, and renal function that occurs from birth to 18 yr of age. In a large, multicenter observational study of pediatric patients ($n = 702$), Le et al. determined that doses of 70 and 60 mg/kg/day were necessary for children < 12 and ≥ 12 yr of age, respectively, to achieve an $\text{AUC}_{0-24}/\text{MIC} > 400$.⁴⁵ The authors were careful to note that $\sim 25\%$ of patients failed to achieve the target $\text{AUC}_{0-24}/\text{MIC}$ due to individual variability in S_{cr} and age. In a review of the effects of age and weight on vancomycin trough concentrations in a relatively large retrospective cohort study, patients were divided into two groups based on vancomycin dose—40 mg/kg/day versus 60 mg/kg/day—and further stratified by age and weight.⁴⁶ Trough concentrations were significantly higher for children less than 2 yr or more than 6 yr of age; there were no observed differences for patients between 2 and 5 yr. Patients weighing more than 50 kg also had significantly higher trough concentrations when dosed at 60 mg/kg/day. The authors suggested considering age as well as weight in dosing vancomycin in contrast to current guideline recommendations.^{44,46}

Therapeutic targets in children

Vancomycin concentrations are used to guide therapy in most patients, with oral dosing as an exception. However, the therapeutic targets are unresolved in pediatric patients. $\text{AUC}_{0-24}/\text{MIC}$ appears to be the

best predictor of efficacy for vancomycin use in MRSA infections in adults,⁴⁷ but currently there are no outcomes studies comparing pharmacodynamics indices in the pediatric population. Trough concentrations of 7–10 mg/L appear adequate to achieve an $AUC_{0-24}/MIC > 400$ for pediatric patients based on pharmacokinetic modeling studies.^{45,48,49} Consequently, substantial overdosing is likely to result from targeting the higher trough concentrations suggested for adults.

Population pharmacokinetic parameters in children

Equation 4, below, allows prediction of clearance in neonates, which can then be matched with estimates of V to determine k (and half-life) to develop initial dosage regimens designed to produce desired vancomycin concentrations. Follow-up with measured concentrations may be necessary to ensure that desired concentrations are achieved. A population pharmacokinetic and covariate analysis, conducted in 214 premature neonates with an average postconceptional age of 30.4 wk, revealed that size, postconceptional age, and renal function explained 49.8%, 18.2%, and 14.1% of the variability observed in vancomycin clearance.⁵⁰ Several equations have been developed that relate vancomycin clearance to patient-specific variables including postconceptional age, body weight, and CrCl.^{18,51} Equation 4 was developed from a population pharmacokinetic analysis of vancomycin concentration/time data obtained from 374 infants with a median postnatal age of 70 days and a median gestational age of 33.5 wk.¹⁸

Clearance of vancomycin in neonates:

$$Cl_{\text{vanco}} (\text{L/hr}) = \left[W \times \left(\left(\frac{0.028}{S_{\text{Cr}}} \right) + (0.000127 \times \text{Age}) + (0.0123 \times \text{GA28}) \right) \right] + 0.006 \quad (\text{Eq. 4})$$

where W = weight (kg);

S_{Cr} = serum creatinine (mg/dL);

Age = postnatal age (days) if $S_{\text{Cr}} < 0.7$ mg/dL (62 $\mu\text{mol/L}$ in SI units) or age = 0 if $S_{\text{Cr}} \geq 0.7$ mg/dL (62 $\mu\text{mol/L}$);

GA28 is 1 if gestational age > 28 wk and 0 if gestational age ≤ 28 wk.

THERAPEUTIC RANGE

Minimum inhibitory concentration and efficacy

The Clinical and Laboratory Standards Institute (CLSI) changed the susceptibility breakpoint for the MIC of vancomycin for *Staphylococcus aureus* from ≤ 4 mg/L to ≤ 2 mg/L in 2006.^{54,55} It should be noted there are several methods to determine MIC. The CLSI reference standard is the *broth microdilution method*. The *Etest method* tends to report MICs 1 to 2 dilutions greater in comparison to broth microdilution.⁵⁶

Despite the reference MIC breakpoint, many studies suggest infection with $MIC > 1$ mg/L is associated with poor outcomes.⁵⁷⁻⁵⁹ One study found that treatment failure in MRSA bacteremia was associated with isolates with $MICs = 2$ mg/L (derived by broth microdilution) as compared to $MIC \leq 1$ mg/L (odds ratio 14.7).⁶⁰ Another found an association between an MIC breakpoint ≥ 1.5 mg/L (derived by Etest) and treatment failure.⁶¹

Two meta-analyses observed that greater MIC values (majority derived by Etest) were associated with increased mortality and treatment failure in patients with *Staphylococcus aureus* infections treated with vancomycin.^{62,63} Specifically, $MIC > 1$ mg/L but ≤ 2 mg/L was associated with higher mortality treatment failure relative to infections caused by isolates with $MIC \leq 1$ mg/L.⁶² In contrast to these results, another meta-analysis conducted in patients with *Staphylococcus aureus* bacteremia did not demonstrate an increased risk of mortality for patients with high as opposed to low MICs.⁶⁴ Although any association between MIC and poor outcomes is often attributed to increasing difficulty in achieving target $AUC_{0-24}/$

MIC, it should be noted that not all patients included in these meta-analyses received vancomycin as treatment for their infection.⁶²⁻⁶⁴ A separate subgroup analysis conducted in patients with methicillin-sensitive *Staphylococcus aureus* bacteremia treated with flucloxacillin and not vancomycin found a similar association between higher vancomycin MIC and mortality, suggesting that there may be factors irrespective of vancomycin pharmacodynamics that may also account for this relationship.⁶⁵

The role of vancomycin for infections due to MRSA with vancomycin MICs ≥ 2 mg/L appears to be limited. Conventional doses are unlikely to achieve the optimal AUC_{0-24}/MIC threshold for these isolates as the doses needed to achieve these thresholds are associated with an unacceptably high risk of nephrotoxicity.^{66,67} This is reflected in practice guidelines that recommend alternative therapy in this situation.¹

Peak concentration

Peak concentrations do not appear to correlate with safety or efficacy.^{68,69} The role of monitoring peaks is largely limited to estimating patient-specific pharmacokinetic parameters (k and V) for complex patients (e.g., those with critical illnesses, acute kidney injury, or stage 5 CKD). Peak concentrations should be drawn 1.5–2.5 hr after a 1-hr infusion or ~ 1 hr after a 2-hr infusion to allow for distribution to be complete.

Trough versus area under the curve

Historically, vancomycin has been classified as a concentration-independent and time-dependent killing agent, whereby the achievement of serum concentrations in excess of 4–5 times the MIC of the pathogen does not result in an enhanced bactericidal effect.⁵⁵ Optimization of time-dependent killing agents relies on maximizing the duration of time (T) the drug concentration exceeds the MIC of the pathogen ($T > MIC$). Vancomycin has been found to exhibit time-dependent killing in several in vitro studies, although other studies indicate that its effect is not typical of time-dependent killing agents due to a lack of association with the $T > MIC$.^{68,70-73} These studies revealed that vancomycin activity may be more appropriately predicted by the AUC/MIC ratio.^{71,72}

It is common practice to monitor trough concentrations to optimize dosing.^{1,57,74-77} The clinical practice guidelines for dosing and monitoring recommend targeting vancomycin trough concentrations of 15–20 mg/L for bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia.¹ Clinical studies investigating higher trough concentrations as the target index and range provide equivocal evidence of benefit.

Greater treatment success rate (60% versus 45%; $p = 0.034$) was observed in a retrospective study of propensity-matched patients ($n = 200$) treated for complicated MRSA bacteremia, endocarditis, osteomyelitis, or meningitis with target trough concentrations of 15–20 mg/L versus 5–20 mg/L.⁷⁸ A statistically significant relationship was not found between vancomycin trough concentration and clinical outcome in 98 patients with nosocomial pneumonia due to *Staphylococcus aureus*.⁷⁹ In this study, there was a greater incidence of multilobar involvement and previous antibiotic failure in patients that had higher trough concentrations, which may have confounded the results. Similarly, Lodise and colleagues⁷ did not observe a consistent relationship between C_{min}/MIC and treatment failure in patients with MRSA bacteremia, but they did observe a lower rate of treatment failure in patients that achieved a threshold $AUC_{24}/MIC \geq 521$ (MIC measured via broth microdilution) compared to patients that did not.

There are a growing number of studies that report AUC_{0-24}/MIC to be correlated with positive clinical outcomes. Patients ($n = 108$) with MRSA pneumonia that achieved AUC_{0-24}/MIC of ≥ 400 as compared to those with $AUC_{0-24}/MIC < 400$ had superior bacteriologic response.⁸⁰ The target AUC_{0-24}/MIC for less severe infections (i.e., skin and soft tissue, urinary tract infection) is not known, but is presumed to be no greater than 400. A meta-analysis of patients treated with vancomycin for *Staphylococcus aureus* bacteremia further supported an AUC_{0-24}/MIC threshold of 400 for reduced risk of treatment failure, persistent bacteremia, and mortality.⁸¹ Higher trough concentrations of 15 mg/L or greater were not

associated with improved outcomes compared to lower troughs. Two retrospective cohort studies also demonstrated an association between greater AUC_{0-24}/MIC on day 1 of vancomycin therapy and lower risk of treatment failure emphasizing the importance of achieving adequate AUC/MIC early in therapy.^{7,82} In concordance with these data, clinical practice guidelines cite $AUC_{0-24}/MIC \geq 400$ as a target to achieve clinical effectiveness.¹ **Table 22-8** describes several studies that focused on the impact of AUC/MIC on patient outcomes.

THERAPEUTIC DRUG MONITORING

Individualization of vancomycin therapy by means of monitoring serum or plasma concentrations may be necessary for certain patient groups, including those with fluctuating renal function, patients receiving concurrent treatment with known nephrotoxins (e.g., aminoglycosides or furosemide), patients requiring higher than usual doses (>4 g/day), obese patients (those whose ABW is $>30\%$ over IBW), patients receiving dialysis, and pediatric patients (especially premature neonates).⁸⁷⁻⁸⁹ Although there is some controversy regarding the need for monitoring concentrations, vancomycin pharmacokinetics may be unpredictable in these patient populations, so obtaining concentrations early in therapy helps ensure dose optimization. **Table 22-9** provides indications where monitoring vancomycin concentrations may be most helpful.

TABLE 22-9. INDICATIONS FOR MONITORING VANCOMYCIN CONCENTRATIONS

↑ Risk of treatment failure	- Critical illness, severe sepsis/septic shock - Deep-seated infections (i.e., central nervous system [CNS], osteomyelitis, endocarditis), pneumonia
↑ Risk of toxicity	- Chronic kidney disease, dynamic renal function - Critical illness - Obesity ($> 30\%$ above IBW) - Concurrent nephrotoxin (e.g., aminoglycosides, loop diuretics) - High-dose therapy (> 4 g/d) - Pediatric patients (especially premature neonates) - Elderly - Quadriplegic, paraplegic, amputees - Cachexia, wasting syndrome
Clinical course	- Substantial changes in renal function - Signs/symptoms of treatment failure - Signs/symptoms of toxicity

PHARMACODYNAMIC MONITORING

Concentration-related efficacy

Trough concentration

There is growing consensus that AUC_{0-24}/MIC provides the best pharmacodynamic predictor of efficacy, but calculation of AUC_{0-24}/MIC may be perceived as impractical as it requires multiple serum concentrations or pharmacokinetic software and the MIC.^{3,90} For this reason, monitoring of trough concentrations is commonly used as a surrogate measure of achieving adequate AUC_{0-24}/MIC .¹ **Table 22-10** provides suggested target concentrations and AUC_{0-24}/MIC values for various conditions. For isolates with $MIC \leq 1$ mg/L, maintaining vancomycin trough concentration of 15–20 mg/L will achieve $AUC_{0-24}/MIC > 400$ in ~90% of patients.³ Trough concentrations of 15–20 mg/L do not reliably achieve $AUC_{0-24}/MIC > 400$ for isolates with $MIC > 1$ mg/L.

TABLE 22-8. SELECT STUDIES INVESTIGATING EFFECT OF AUC₀₋₂₄/MIC ON CLINICAL OUTCOMES

Source	Study Population MRSA ^a	AUC Calculation	MIC Method	AUC ₂₄ /MIC Threshold (mg × hr/L)	Clinical Outcomes ^b
Moise-Brodeur ⁸⁰ (2004)	Pneumonia (n = 108)	AUC	Etest ^c	≥ 400	Increased clinical success; decreased time to infection eradication
Kullai ⁸³ (2011)	Bacteremia (n = 320)	$AUC_{24} = \frac{D}{[(CrCl \times 0.77) + 18.9]} \times 0.06$	Etest	≥ 421	Decreased rate of treatment failure
Brown ⁴⁷ (2012)	Complicated bacteremia, endocarditis (n = 50)	ADAPT II	Etest	≥ 211	Decreased attributable mortality
Gawronski ⁴⁷ (2013)	Osteomyelitis with bacteremia (n = 59)	ADAPT 5	Etest or Microscan	≥ 293	Decreased time to microbiological clearance
Holmes ⁸⁴ (2013)	<i>S. aureus</i> bacteremia (n = 182)	$AUC_{24} = \frac{D}{[(CrCl \times 0.79) + 15.4]} \times 0.06$	Etest or BMD ^d	≥ 373	Increased probability of survival
Zelenitsky ⁸⁵ (2013)	Bacteremia with septic shock (n = 35)	$AUC_{24} = \frac{D}{[(CrCl \times 0.79) + 15.4]} \times 0.06$	BMD	≥ 451 ≥ 578	Increased probability of survival
Jung ⁸⁶ (2014)	Bacteremia (n = 76)	PKS ^e	Etest and BMD	≥ 430 (Etest)	Increased rates of clinical success
Lodise ⁷ (2014)	Bacteremia (n = 123)	ADAPT 5	Etest and BMD	≥ 303 (Etest) ≥ 521 (BMD)	Decreased risk of treatment failure
Casapao ⁸² (2015)	Endocarditis (n = 139)	ADAPT 5i	Etest and BMD	≥ 600 (BMD)	Decreased risk of persistent bacteremia

^aMethicillin-resistant *Staphylococcus aureus*.
^bClinical outcome associated with AUC₂₄/MIC threshold.
^cEpsilometer test.
^dBroth microdilution.
^eAbbott's PKS software.
AUC = area under the inhibitory concentration-time curve. D = dose (mg) given over 24 hr.

Trough concentrations should be drawn within 30 min of the next scheduled dose. For patients with stable renal function, obtaining a trough concentration within 3–4 days of therapy is usually adequate if therapy is to be continued for 7–10 days or longer.⁸⁸ If the measured trough concentration is within 20% of the desired trough concentration and the patient is responding appropriately, the same regimen may be continued.

TABLE 22-10. THERAPEUTIC RANGES^{1,77,88,89}

Populations	Indications	Pharmacodynamic Indices		
		Trough (mg/L)	AUC ₀₋₂₄ /MIC (mg × hr/L)	C _{ss} (mg/L)
Adults	• Deep-seated infection ^a : (e.g., pneumonia, endocarditis, CNS infection, abscess)	15–20	>400	17–25 mg/L
	• Critical illness ^a			
	• <i>Staphylococcus aureus</i> bacteremia ^a			
	• Urinary tract infection	10–15	240–360	10–15
	• Skin and soft tissue infections, peritonitis			
	• MIC ≤ 0.5 mg/L			
Pediatric	• Serious infections ^a	> 10	>400 mg/L	17–25
	• MIC ≤ 0.5 mg/L	> 5	>200 mg/L	17–25

^a Presumes MIC ≤ 1 mg/L for *Staphylococcus aureus*; consider alternative therapy for MIC > 1 mg/L.

Area under the curve

Troughs may not reliably correlate with AUC₀₋₂₄ or clinical outcomes.^{7,67,79,82} Pharmacokinetic simulations estimate that 50% to 60% of patients with normal renal function and AUC₀₋₂₄/MIC > 400 mg × hr/L are not expected to have a trough concentration >15 mg/L.⁹¹ For these patients, trough-only monitoring could result in an unnecessary increase in dose.

AUC₀₋₂₄ can be estimated via population pharmacokinetics when initiating empiric therapy using Equation 6, where D is total dose (mg/day) and CrCl is the patient's creatinine clearance (mL/min).⁸⁰

AUC₂₄ estimation based on dose and CrCl⁸⁰:

$$\text{AUC}_{0-24} = \frac{D}{[(\text{CrCl} \times 0.79) + 15.4] \times 0.06} \quad (\text{Eq. 6})$$

Bayesian and other concentration-based estimates provide more precise and accurate predictions and calculations of AUC₀₋₂₄. The Bayesian approach requires the use of software and at least a single vancomycin concentration to provide an estimation of the patient's AUC and dosing recommendations to achieve the desired AUC₀₋₂₄. This method relies on a model derived from population pharmacokinetic data (Bayesian prior).³ A Bayesian approach is advantageous in that it can use a serum concentration obtained at any time during the treatment course and is adaptive in that it can incorporate dynamic changes (e.g., changes in creatinine clearance). The Bayesian approach is limited in that its accuracy is dependent on the Bayesian prior used. In a pharmacokinetic study that used models from richly sampled pharmacokinetic data sets as Bayesian priors, AUC estimations were within 97% of the true AUC (95% CI 93–102%; $p = 0.23$).⁹¹ In contrast, the pharmacokinetic model that was derived from peak or trough data only tended to underestimate the AUC by about 14% (95% CI 7% to 19%; $p < 0.001$).

Equations have been developed to calculate AUC that require at least two measured vancomycin concentrations. Equation 7 can be used to calculate the AUC_{0-24} irrespective of the dosing interval used.³ Calculation for AUC_{0-24} based on two concentrations and dosing frequency:

$$AUC_{0-24} = \left[\frac{t' \times (C_p + C_t)}{2} + \frac{C_p - C_t}{k} \right] \times \frac{24 \text{ hr}}{\tau}$$

(Eq. 7)

where t' is the infusion time

C_p is the vancomycin concentration at the end of the infusion (peak)

C_t is the trough concentration

τ is the dosage interval

k is the elimination rate constant calculated from the measured concentrations.

This equation simplifies AUC_{0-24} to two trapezoidal shapes—infusion and elimination. As a result, this method tends to underestimate true AUC_{0-24} as it does not account for the distribution phase and assumes a linear rise in concentration during the infusion. The resulting AUC_{0-24} is then divided by the measured MIC to yield the AUC_{0-24}/MIC . **Table 22-11** examines the advantages and limitations of different methods for calculating AUC_{0-24} .

TABLE 22-11. COMPARISON OF METHODS FOR CALCULATING AUC_{0-24}		
	Bayesian Method	Equation-Based Method
Serum Concentrations Required	1	2
Advantages	• Serum concentrations may be drawn at any time point • Adaptive—can account for dynamic renal function	• Could be programmed into electronic medical record to calculate automatically
Limitations	• Requires software • Reliance on population pharmacokinetic model for accuracy	• Serum concentrations must be drawn at steady state • Serum concentrations drawn during the distribution phase will result in overestimation of k and underestimation of AUC_{24}

Concentration-related toxicity

Vancomycin has been implicated as a nephrotoxic agent with a reported prevalence that varies from 5% to 43%.^{92,93} Vancomycin-induced nephrotoxicity is defined as the presence of at least two consecutive elevated serum creatinine concentrations (increase of 0.5 mg/dL or > 50% increase from baseline) documented after several days of vancomycin therapy in the absence of an alternative explanation.¹ Direct oxidative stress of the proximal renal tubule and allergic interstitial nephritis are the proposed mechanisms accounting for the nephrotoxic effects.⁹² These mechanisms correlate well with the reversibility of vancomycin-associated nephrotoxicity.^{94,93}

Greater doses, trough concentration, AUC_{0-24} , duration of therapy, and overall exposure have been demonstrated to be associated with risk of nephrotoxicity.^{36,69,79,92,95-97} Interpretation of observational studies demonstrating association of greater trough concentration with risk of nephrotoxicity is confounded by the fact that vancomycin clearance is dependent on renal function. Thus, reduced renal function is likely to result in higher trough concentrations. Thus it is difficult to attribute any observed association between trough concentration and nephrotoxicity to the nephrotoxic effects of vancomycin.

A retrospective cohort study stratified patients based on vancomycin exposure as measured by initial trough concentration.⁹⁸ The highest initial trough concentration within the first 96 hr of treatment was used to compare vancomycin exposure. The observed rates of nephrotoxicity were 5%, 21%, 20%, and 33% for patients with initial vancomycin trough concentrations of < 10, 10–15, 15–20, and > 20 mg/L, respectively. Of note, there was no difference in the rates of nephrotoxicity for patients with trough concentrations of 10–15 and 15–20 mg/L. A meta-analysis found that trough concentrations $\geq$ 15 mg/L were associated with a greater risk of nephrotoxicity.⁹³ This observed association persisted when the data were limited exclusively to studies that examined only the initial trough concentration. A prospective multicenter trial found a three-fold increase in nephrotoxicity in patients with troughs greater than 15 mg/L or race (black).⁹⁹ A recent meta-analysis agreed with this finding.⁹³

There is currently limited data to suggest an AUC_{0-24} threshold is associated with a greater risk of nephrotoxicity. Patients with $AUC_{0-24} \geq 1,300$ mg $\times$ hr/L in one study had a higher incidence of nephrotoxicity than patients with $AUC_{0-24} < 1,300$ mg $\times$ hr/L.⁹⁸ In contrast, patients that developed vancomycin-related nephrotoxicity in another study had AUC_{0-24} values ranging from 600–800 mg $\times$ hr/L as opposed to < 600 mg $\times$ hr/L in patients that did not.⁶⁹

Onset of nephrotoxicity typically occurs between 4 to 8 days after starting vancomycin therapy and is reversible in most patients if therapy is discontinued or doses properly adjusted.^{95,97,100} Obesity, preexisting renal dysfunction, critical illness, and concomitant administration of nephrotoxins have been identified as risk factors for vancomycin-related nephrotoxicity.^{92,98} Serum creatinine should be monitored every 3 days for patients with stable renal function and daily if the patient has unstable renal function or is receiving other nephrotoxic agents (e.g., aminoglycosides, loop diuretics, amphotericin B). Several observational studies suggest that concomitant administration of piperacillin-tazobactam may also be associated with a greater risk of vancomycin-induced nephrotoxicity.¹⁰¹⁻¹⁰³

Ototoxicity is a rare adverse effect associated with vancomycin therapy. The original association with ototoxicity was based on two cases reported in 1958 of patients who experienced hearing loss and had a vancomycin concentration of >80 mg/L. Additional case reports followed; however, evidence of a direct cause-and-effect relationship with vancomycin was lacking because most patients were receiving other agents known to be ototoxic (e.g., aminoglycosides, erythromycin). These early reports are the foundational premise for the suspected relationship between attainment of peak concentrations of > 30–50 mg/L and/or trough concentrations of > 10–20 mg/L and ototoxicity. Later studies did not reveal an association with vancomycin concentration, dose, or duration of therapy and ototoxicity.^{75,104}

Non-concentration-related toxicities

IV administration of vancomycin may result in a histamine-like reaction characterized by flushing, tingling, pruritus, tachycardia, and an erythematous macular rash involving the face, neck, upper trunk, back, and arms. This adverse effect is often referred to as *red man syndrome*. Systemic arterial hypotension or shock may also occur. This syndrome usually can be avoided by infusion of vancomycin at 15 mg/min or less or by pretreatment with an antihistamine. Thrombophlebitis has been associated with vancomycin and can be avoided by minimizing the concentration to 5 mg/mL or 10 mg/mL when given via a peripheral or central line, respectively.¹⁰ Lastly, eosinophilia, neutropenia, urticarial rashes, and drug fever have been reported.^{11,12}

DRUG–DRUG INTERACTIONS

No pharmacokinetic drug interactions have been reported with vancomycin. However, its concomitant use with other ototoxic and nephrotoxic drugs may increase the incidence of these toxicities. Data from several investigations indicate that vancomycin has the potential for producing nephrotoxicity, with the incidence ranging from 5% to 15%. When vancomycin was administered concomitantly with an aminoglycoside to adults, the incidence of nephrotoxicity increased in some, but not all, studies (range of 22% to 35%).^{12,105}

Concurrent use of a loop diuretic (e.g., furosemide) was associated with a five-fold increase in the risk of developing nephrotoxicity; the risk may be greatest in individuals over 60 yr of age.¹⁰⁶ Finally, concomitant amphotericin B was shown to increase the risk of nephrotoxicity by 6.7-fold.¹⁰⁶

There is evidence to suggest that the elimination half-life of vancomycin is prolonged and clearance is decreased in neonates receiving indomethacin to induce closure of a patent ductus arteriosus. Thus, empiric lengthening of the vancomycin dosing interval and concentration monitoring may be initially warranted.^{16,51}

DRUG–DISEASE STATE INTERACTIONS

Obesity

Obesity in the United States has more than doubled since vancomycin was brought to the market in the 1950s, with more than one-third of the population categorically obese.¹⁰⁷⁻¹⁰⁹ Vancomycin pharmacokinetics such as protein binding and renal clearance are altered in obesity.¹¹⁰

Current clinical practice guidelines recommend dosing based on ABW; however, these recommendations are based on limited data, and the population studied included young patients without kidney dysfunction ($\text{CrCl} > 100 \text{ mL/min}$).^{1,4} Moreover, clinicians commonly set limits on the empiric loading and maintenance doses given.¹¹¹ Obese patients appear to be at increased risk of elevated vancomycin trough concentrations when vancomycin is dosed mg/kg based on ABW and with similar frequency as nonobese patients.¹¹² Standard vancomycin dosing of 15 mg/kg every 8–12 hr was compared to a modified dosage regimen developed for obese patients. In the modified group, patients were given either 10 mg/kg every 12 hr or 15 mg/kg every 24 hr based on ABW. Patients with normal renal function in this group were given a loading dose of 20–25 mg/kg. The modified dosage regimen was selected based on modeling for target troughs of 10–20 mg/L and $\text{AUC}_{0-24}/\text{MIC}$ of > 400 when MIC was $\leq 1 \text{ mg/L}$. The modified regimen was associated with a higher frequency of goal trough attainment and a lower rate of supratherapeutic troughs.¹¹² A pre–post study ($n = 150$) compared trough-only guided dosing with a two-sample strategy—peak and trough following a loading dose—to determine the maintenance dose from calculation of k and V .¹¹¹ The two-sample method resulted in significantly more follow-up troughs in a vancomycin trough in the therapeutic range compared to the conventional, trough-only approach (65.2% versus 31%, $p = 0.024$).

Hyperdynamic populations

Patients with severe burns, trauma, traumatic brain injury, septic shock, and critical illness experience phases of hypermetabolic, hyperdynamic clearance of vancomycin. The likely etiology is augmented renal clearance and extrarenal elimination that results in an increased risk of subtherapeutic dosing.¹¹³⁻¹¹⁶ Careful consideration of renal function is, therefore, essential, especially for younger patients with these conditions. Conventional dosing (e.g., 1 g every 12 hr) is unlikely to achieve adequate concentrations of vancomycin for patients with $\text{CrCl} > 90 \text{ mL/min}$. Continuous infusion appears to be superior to intermittent dosing for rate (i.e., time and prevalence) of target concentration attainment in these populations.^{36,37,40,117}

The V of vancomycin is increased in critically ill patients.^{27,28} The larger volume may require the initial administration of higher than normal doses (i.e., $> 30 \text{ mg/kg/day}$ in adults) to achieve therapeutic concentrations. Vancomycin therapy should be guided in these patients on the basis of their renal function (CrCl) and volume status; serum concentration monitoring may be necessary because of the variability in clearance.

Hepatic insufficiency

Liver dysfunction has not been associated with alteration in the elimination of vancomycin. The degree of protein binding, however, is reduced (to $\sim 20\%$) and the unbound V increases by $\sim 8\%$ during serious infections.¹¹⁸ This has limited-to-no clinical significance.

Kidney disease

Acute kidney injury

The impact of acute renal impairment on the disposition of vancomycin is dependent on the severity and acuity of the insult.¹¹⁹ An adequate loading dose is essential to avoid prolonged subtherapeutic concentrations secondary to conservative maintenance doses. Elimination is highly dynamic during the injury and recovery phases. Biomarkers of renal function such as S_{Cr} tend to lag behind changes in function. Nonrenal clearance of 0.96–1.2 L/hr is generally preserved for up to 7–10 days after injury.¹¹⁵ However, the relationship between $CrCl$ and CL_{vanco} derived from patients with CKD cannot be used to project the degree of dosage adjustment that might be necessary to maintain desired concentrations among patients with acute kidney injury. Determining and adjusting the dosing frequency that achieves adequate target concentration attainment with minimal risk for toxicity may be extremely difficult in this clinical setting. Close concentration monitoring may be indicated during the injury and recovery phases.

Dialysis: dosing and concentration monitoring in hemodialysis patients and continuous renal replacement

Vancomycin is not substantially dialyzed by low-flux hemodialysis membranes made from cellulose acetate or cuprophane, but is by high-flux membranes such as polysulfone, cellulose triacetate and polymethylmethacrylate (30% to 40% over a standard 3- to 4-hr hemodialysis session).^{126–129} Vancomycin concentrations in patients with CKD undergoing chronic intermittent hemodialysis will decrease during the dialysis session. The vancomycin concentration will subsequently rise 3–6 hr after cessation of dialysis as vancomycin redistributes into serum from tissue. Thus, it is often recommended that concentrations are drawn 6 hr after dialysis. However, such postdialysis monitoring is difficult to coordinate. Predialysis concentrations that are scheduled to be drawn with other laboratory tests may reduce delays in therapy and unnecessary phlebotomy.^{128,130–134} The target vancomycin concentration in patients receiving hemodialysis is dependent on a number of variables, including the site and severity of infection. Typically, the goal is to maintain concentrations of 15–25 mg/L.

Vancomycin dosing in chronic hemodialysis patients is complicated by nonrenal clearance, which is difficult to quantify and generally reduced in renal impairment. The dialytic clearance is dependent on the dialyzer membrane, the duration of dialysis and the blood and dialysate flow rates.^{123,129,133,135–140} The intradialytic clearance and $t_{1/2}$ of vancomycin observed in chronic hemodialysis patients for some commonly utilized dialyzers are presented in **Table 22-12**. Comprehensive listings of vancomycin clearance values for various dialysis filters have been published.¹²¹

TABLE 22-12. INTRADIALYTIC CLEARANCE AND $T_{1/2}$ FOR COMMONLY USED DIALYZERS

Dialyzer	CL (L/hr)	$t_{1/2}$ (hr)
Cellulose/cellulose acetate ⁸⁹	0.25–3.6	N/A ^a
Cuprophane ⁸⁴	0.3–1	35.1
Cellulose triacetate ⁸⁷	6	4.5
Polymethylmethacrylate ⁸⁸	3.6–7.9	3.7–8
Polysulfone ^{80,84,86,92,93}	3.8–7.8	4.7

^aNot available.

A vancomycin dosing and monitoring algorithm for adult patients with end stage renal disease receiving high-flux intermittent hemodialysis for mild-to-moderate infections and severe and/or deep-seated infections is presented in **Table 22-13**.¹³⁴ In general, a 20-mg/kg loading dose (ABW) is

TABLE 22-13. SUGGESTED VANCOMYCIN DOSING IN SETTING OF INTERMITTENT HEMODIALYSIS

Loading dose	Actual Body Weight (kg)		Loading Dose (15–20 mg/kg)	
	<65		1,000 mg IV × 1	
	65–85		1,250 mg IV × 1	
	86–100		1,500 mg IV × 1	
	>100		1,750 mg IV × 1	
Maintenance dose	Mild-to-Moderate and Non-Deep-Seated Infections ^a			
	Vancomycin concentration (mg/L)		Maintenance dose given after dialysis	
			If concentration drawn predialysis	If concentration drawn postdialysis ^b
	<10		1,000 mg	750–1,000 mg
	10–15		500–750 mg	500 mg
	15–20		500 mg	HOLD ^c
	>20		HOLD ^c	
	Severe and/or Deep-Seated Infections ^d			
	Vancomycin concentration (mg/L)		Maintenance dose to be given after dialysis	
			If concentration drawn predialysis	If concentration drawn postdialysis ^b
	<10		1,000–1,500 mg	1,000 mg
	10–15		750–1,000 mg	500–750 mg
	15–20		500–750 mg	500 mg
	20–25		500 mg	HOLD ^c
	>25		HOLD ^c	

^aTarget pre-dialysis C_{min} = 10 – 20 mg/L.
^bConcentration –6 hr after completion of dialysis.
^cRepeat pre-dialysis vancomycin concentration prior to next scheduled dialysis session and re-dose accordingly.
^dTarget pre-dialysis C_{min} = 15 – 25 mg/L.

recommended for more severe infections and must not be delayed for hemodialysis. A supplemental dose of 500 mg after hemodialysis may be given if the loading dose is administered prior to hemodialysis. A predialysis vancomycin concentration should be drawn with morning laboratory tests prior to the next two hemodialysis sessions to guide further dosing. Doses are then given after dialysis. A weekly predialysis vancomycin concentration can be considered once a patient has two consecutive therapeutic predialysis concentrations. Routine monitoring of vancomycin concentrations prior to each dialysis session is not necessary in most cases. Vancomycin maintenance doses in this patient population, administered after dialysis, typically range from 500 to 1,000 mg depending on the vancomycin concentration determined prior to dialysis.^{123,134} A study conducted in patients (n = 55) undergoing chronic intermittent hemodialysis with a high-flux polysulfone membrane found a 500-mg dose administered with each dialysis session to be superior to 20 mg/kg every second dialysis session in achieving and maintaining vancomycin concentrations of 10–20 mg/L.¹⁴¹ Larger doses (e.g., vancomycin 750 mg IV postdialysis) may be needed in morbidly obese patients, in those with residual renal function, and when dosing occurs right before or during dialysis.^{128,130}

Continuous renal replacement therapy (CRRT) is increasingly used in the management of renal impairment among critically ill patients due to improved hemodynamic tolerability and limited need

to restrict fluids compared to intermittent dialysis. Variations of CRRT include continuous venovenous hemofiltration, continuous venovenous hemodialysis, and continuous venovenous hemodialfiltration (CVVHDF). CRRT may result in significant removal of vancomycin that can vary depending on the type used, the filter membrane used, and the resulting sieving coefficient (**Table 22-14**).

TABLE 22-14. EXAMPLES OF SIEVING COEFFICIENTS DURING CRRT

Filter Membrane	Sieving Coefficient
AN69 ¹²⁰	0.7
Polyamide ¹²⁴	0.73–0.79
Polymethylmethacrylate ¹²⁰	0.86
Polysulfone ^{120,125}	0.68–0.8

In general, it is recommended that adult patients receiving CRRT who are initiated on vancomycin should be given a 15–25-mg/kg loading dose followed by a maintenance dose of 10–15 mg/kg IV every 12–48 hr depending on a number of variables, including the site and severity of infection, evidence of residual renal function, the type of CRRT used, and the overall efficiency of drug removal, to maintain vancomycin target trough concentrations.¹³⁵ Vancomycin dosing in patients with renal impairment receiving CRRT should therefore be individualized. Vancomycin trough concentrations should be monitored regularly in this dynamic patient population to ensure adequate target attainment. A recent review found that vancomycin given as a 25-mg/kg loading dose followed by a continuous infusion of 60 mg/hr was more effective in achieving vancomycin concentrations in the target range (15–25 mg/L) when drawn at 24 hr of the initiation of therapy compared to an intermittent dosing approach in patients receiving CVVHDF.¹⁴²

ASSAY ISSUES

Vancomycin concentrations can be determined by a variety of methods including enzyme multiplied immunoassay (EMIT), fluorescence polarization immunoassay (FPIA), high performance liquid chromatography, and radioimmunoassay, with FPIA methods being used most often in clinical laboratories.¹² The FPIA methods used have similar reproducibility (precision), but differ significantly in accuracy due to cross-reactivity with inactive vancomycin crystalline degradation products (CDP-1).¹⁴³⁻¹⁴⁷ All of the FPIA methods are based on polyclonal antibodies (pFPIA), except for the Abbott AxSYM system, which is based on a murine monoclonal antibody (mFPIA). Vancomycin spontaneously degrades into CDP-1 in a time and temperature dependent manner due to prolonged exposure to body temperature. CDP-1 accumulates in patients with renal impairment, particularly CKD patients on dialysis, and results in falsely elevated concentrations when measured by pFPIA methods.¹⁴⁴ The overestimation of vancomycin concentration can be large enough to impact dosing decisions; a typical overestimation of 36% to 59% but as high as 127% has been reported.¹⁴⁵⁻¹⁴⁷ There is no cross-reactivity with the AxSYM mFPIA method or EMIT methods, which are also based on a monoclonal antibody.¹⁴⁵⁻¹⁴⁷ Recently cross-reactivity with telavancin has been reported. The PETIA systems (Synchron and Vista) and two CMIA systems (Architect and Advia Centaur XP) demonstrated cross-reactivity with telavancin. The FPIA Integra system and two EMIT assays (P-module and Olympus AU) did not appear to significantly cross-react with physiologic concentrations of telavancin.¹⁴⁸ Clinicians need to be aware of the immunoassay technique used in their institution and the quality assurance measures implemented to identify or eliminate cross-reactivity.

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WARFARIN

Ann K. Wittkowsky

In 1939, Professor Karl Link at the University of Wisconsin, supported by a grant from the Wisconsin Alumni Research Foundation, isolated a coumarin derivative, dicumarol (bishydroxywarfarin), from spoiled sweet clover. This compound was found to have been responsible for hemorrhagic deaths in cattle in the Midwestern United States and Western Canada for over a decade. A similar compound, warfarin, was later synthesized and marketed as a rodenticide. By 1955, this compound was commercially available as an anticoagulant.¹

Since then, warfarin has been established through clinical trials as a therapeutic agent for the prevention and treatment of venous and arterial thromboembolic disease. Unfortunately, a narrow therapeutic range and a vast array of drug, disease, and dietary interactions complicate safe use of warfarin. If not properly and respectfully used, this medication can lead to severe complications.

The antithrombotic effect of warfarin is the result of its interference with the hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. In addition, it interferes with the synthesis of the anticoagulant proteins C and S. In order for these clotting factors to become biologically active, glutamic acid residues at the NH₂-terminal region of clotting factor precursors must undergo gamma-carboxylation. This process requires the presence of vitamin KH₂, a reduced form of vitamin K. In the process of gamma-carboxylation, vitamin KH₂ is oxidized to vitamin KO, an inactive form of vitamin K which is then converted to vitamin K by vitamin K epoxide reductase (VKOR) and then to vitamin KH₂ by vitamin K₁ reductase. This vitamin K hepatic recycling process ensures a continuous supply of vitamin KH₂ for clotting factor synthesis.²

Warfarin inhibits VKOR and vitamin K₁ reductase, resulting in accumulation of biologically inactive vitamin KO and, thus, a reduction in vitamin K-dependent clotting factor synthesis. However, the biologic effects of warfarin are not apparent until the previously activated clotting factors are depleted. This depletion takes place according to the biologic half-life of each clotting factor (**Table 23-1**).³ Therefore, the full anticoagulant effect of warfarin does not occur for at least 3–7 days after beginning therapy or changing a dose. When warfarin therapy is discontinued, blood concentrations of the four vitamin K-dependent clotting factors gradually return to pretreatment levels.

Warfarin is monitored not by drug concentration measurements but by therapeutic response to the presence of the drug in serum. The prothrombin time (PT), or protime, expressed as an international normalized ratio (INR), describes the time to clot formation. The goal of warfarin therapy is to extend this time sufficiently to prevent pathologic clotting while minimizing the risk of hemorrhagic complications. An INR of 2–3 is suggested for most indications, although higher INRs may be necessary in other situations such as mechanical valve replacement.² The safety and effectiveness of warfarin therapy can be improved by thorough knowledge of the pharmacokinetic and pharmacodynamic factors that influence its anticoagulant effect.



TABLE 23-1. ELIMINATION HALF-LIVES OF VITAMIN K-DEPENDENT PROTEINS

Factor	Half-Life
II	42–72 hr
VII	4–6 hr
IX	21–30 hr
X	27–48 hr
Protein C	8 hr
Protein S	60 hr

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

Warfarin doses required to reach a therapeutic INR vary considerably among individuals. Although the average dose to reach an INR of 2–3 is 4 to 5 mg once daily, doses may range from as little as 0.5 mg daily to 20 mg or more.⁴ Numerous factors influence dosing requirements, including goal INR, interacting medications, dietary vitamin K intake, alcohol use, underlying disease states, age, genetic factors, and others.

A number of initiation and maintenance dosing strategies for adults and the elderly have been developed (see Dosing Strategies), all of which are based on assessment of INR response. Initiation therapy requires assessment of rate of increase in the INR after the first one to three doses of warfarin and until the INR reaches the lower limit of the therapeutic range, while maintenance therapy adjustments are based on an assessment of factors that may have led to changes in the INR. A weight-based loading protocol for infants and children has also been developed.⁵ Infants and children appear to require higher mg/kg warfarin doses than do adults.⁶ A general description of dosing requirements is provided in **Table 23-2**.

TABLE 23-2. USUAL DOSAGE RANGES

Age	Initiation Dose	Maintenance Dose
Infants 1 month–1 yr	0.2 mg/kg/day for 1–4 days	Average 0.33 mg/kg/day, based on INR response
Young children (1–6 yr)	0.2 mg/kg/day for 1–4 days	Average 0.15 mg/kg/day, based on INR response
Children (6–13 yr)	0.2 mg/kg/day for 1–4 days	Average 0.13 mg/kg/day, based on INR response
Teenagers (13–18 yr)	0.2 mg/kg/day for 1–4 days	Average 0.09 mg/kg/day, based on INR response
Adults (18–70 yr)	5–10 mg once daily for 1–4 days	5 mg (range 1–20 mg) once daily, based on INR response
Geriatrics (>70 yr)	2.5–5 mg once daily for 1–4 days	2.5 mg (range 1–20 mg) once daily, based on INR response. Often lower than for adults

DOSAGE FORM AVAILABILITY

Warfarin is currently available only as an oral tablet. Coumadin is the proprietary form of warfarin. Each dose strength of Coumadin is readily recognizable by its color (**Table 23-3**), and all Coumadin tablets are scored. The 10-mg tablet contains no dye and can be used to differentiate warfarin allergy from dye allergy in patients who present with mild allergic reactions after initiation of warfarin therapy.

Generic warfarin is available from many commercial sources, including a branded generic, Jantoven. The various manufacturers of generic warfarin have generally continued the same color scheme for tablet size identifications, but there are a few color modifications as well as tablet shape and size changes. Practitioners should exercise appropriate caution when counseling patients based on color schemes of the doses.

The U.S. Food and Drug Administration has given generic warfarin products an AB bioequivalence rating, meaning that the 90% confidence intervals of the rate and extent of absorption of the generic product are within 80% to 125% of the mean values of the innovator product.⁷ Randomized controlled trials and observational studies have typically found no difference in stability of anticoagulant therapy or in the rate of adverse events when patients are switched from brand to generic warfarin.^{8–12} Nevertheless, individual patients may experience changes in therapeutic response. Thus, patients should generally be treated with a single formulation of warfarin, and changes in product source should be considered when evaluating changes in therapeutic response.

TABLE 23-3. COUMADIN COLOR SCHEME^a

Coumadin Dose Size	Color
1 mg	Pink
2 mg	Lavender
2.5 mg	Green
3 mg	Tan
4 mg	Blue
5 mg	Peach
6 mg	Teal
7.5 mg	Yellow
10 mg	White

^aGeneric products follow the same color scheme, with possible variations in shade.

GENERAL PHARMACOKINETIC INFORMATION

Warfarin is a racemic mixture of R and S enantiomers, optical isomers that differ significantly with respect to their pharmacokinetic and pharmacodynamic properties (Table 23-4).^{13–15} S-warfarin is 2.7% to 3.8% more potent than R-warfarin, likely as a result of differences in receptor affinity to vitamin K reductase enzymes.^{14,16,17}

TABLE 23-4. PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERISTICS OF THE ENANTIOMERS OF WARFARIN

	R-warfarin	S-warfarin
Bioavailability	95% to 100%	95% to 100%
Volume of distribution	0.12–0.22 L/kg	0.11–0.19 L/kg
Protein binding	98.7% to 99.9%	98.9% to 100%
Elimination half-life	45 hr (20–70 hr)	29 hr (18–52 hr)
Hepatic metabolism	40% reduction; 60% oxidation CYP1A2>3A4>2C19	10% reduction; 90% oxidation CYP2C9>3A4
Clearance (single dose)	0.0005–0.0073 L/hr/kg	0.0009–0.0079 L/hr/kg
Clearance (multiple dose)	0.001–0.0052 L/hr/kg	0.0015–0.0131 L/hr/kg
Stereospecific potency	1 (reference)	2.7–3.8 × R warfarin

Absorption

Warfarin is nearly 100% bioavailable (F = 1) when taken orally.¹⁹ The drug is rapidly and completely absorbed from the stomach and proximal small intestine with peak blood concentrations within 0.3–4 hr.²⁰ Food decreases the rate but not the extent of absorption.²¹

Distribution

Volume of distribution

The volume of distribution (V) for racemic warfarin ranges from 0.11 to 0.18 L/kg, similar to that of albumin.^{22,23} The average V for both R and S warfarin is 0.15 L/kg.

Protein binding

Both R and S warfarin are highly (> 98%) bound to plasma proteins, primarily albumin.²⁴ Only the remaining free (unbound) concentration is pharmacologically active. The fraction of a given concentration that is unbound increases proportionately with decreasing plasma albumin concentrations and is accompanied by an increase in plasma clearance.^{25,26} Stereoselective protein binding has been demonstrated, with a range of 98.9% to 100% for S warfarin compared to 98.7% to 99.9% for R-warfarin.²⁷ However, these differences are unlikely to be clinically significant.

Elimination

Warfarin displays stereoselective metabolism, involving both oxidation by cytochrome p450 enzymes in the liver parenchyma and reduction to diastereomeric alcohols.^{28–33} S-warfarin is approximately 90% oxidized, primarily by CYP2C9 to S-6-hydroxywarfarin and S-7-hydroxywarfarin formed in a 3:1 ratio, and to a lesser extent by CYP3A4 to S-4'-hydroxywarfarin and S-10-hydroxywarfarin. R-warfarin is approximately 60% oxidized by CYP1A2 to R-6-hydroxywarfarin and R-7-hydroxywarfarin, by CYP3A4 to R-10-hydroxywarfarin and R-4'-hydroxywarfarin, and by CYP2C19 to R-8-hydroxywarfarin.

These inactive oxidative metabolites and reduced alcohol derivatives of warfarin are eliminated by urinary excretion. Approximately 50% of a dose of racemic warfarin administered orally is recovered in the urine over 9 days, with recovery of 31% of S-warfarin metabolites and 19% of R-warfarin metabolites and only trace amounts of unchanged drug.³¹ Table 23-4 shows clearance values for S- and R-warfarin.^{14,34}

A number of genetic variants of CYP2C9 have been identified, and their influence on warfarin dose requirements reviewed in detail.³⁵ In comparison to patients who are homozygous for the wild-type allele (CYP2C9*1*1), patients with a heterozygous (CYP2C9*1*2, CYP2C9*1*3, CYP2C9*2*3) or homozygous (CYP2C9*2*2, CYP2C9*3*3) presentation of a variant allele display significant reductions in the metabolism of S-warfarin to 7-hydroxywarfarin. In *in vivo* studies, the clearance of S-warfarin is 8% to 42% lower in CYP2C9*1/*2 heterozygotes compared to the homozygous wild-type, and subjects with the CYP2C9*1/*3 genotype have 38% to 63% lower clearance. Comparatively, heterozygous *2/*3 patients had 70% to 77% lower clearance, and homozygous *2*2 and *3/*3 patients had 68% lower and 38% to 91% lower clearance rates, respectively.^{36–40}

In response to reduced S-warfarin clearance, patients with variant expression of CYP2C9 have lower warfarin dosing requirements than patients with the wild-type allele.^{41–43} Their risk of overanticoagulation is higher during initiation therapy and during maintenance therapy, and they are more likely to experience bleeding complications of warfarin.^{43–46}

The genetic expression of vitamin K epoxide reductase complex subunit 1 (VKORC1) also influences warfarin dosing requirements. A number of single nucleotide polymorphisms of VKORC1 have been shown to be associated with interindividual and interethnic warfarin dosing requirements. The most significant of these are 1173C>T in intron 1 (expressed as CC, CT, or TT) and 3730G>A (expressed as GG, GA, or AA) in the 3' untranslated region, as well as -1639G>A (expressed as AA, AG, or GG).⁴⁷

Initial work in 147 patients followed from initiation of warfarin therapy found that regardless of the presence of confounding variables, the mean adjusted daily dose of warfarin required to maintain a stable INR was higher (6.2 mg) among patients with the VKORC1 1173 CC genotype than patients carrying the CT (4.8 mg) or the TT genotype (3.5 mg).⁴⁸ Subsequently, 10 common noncoding VKORC1 SNPs were identified, with 5 major haplotypes inferred in 368 patients (119 white, 96 of African descent, 120 of Asian descent), declaring a low-dose haplotype group (A) and a high-dose haplotype group (B).⁴⁹ The mean maintenance dose of warfarin for the 3 haplotype group combinations was 2.7 mg/d for A/A, 4.9

mg/d for A/B, and 6.2 mg/d for B/B. The A haplotype represents more warfarin sensitivity (i.e., less VKOR expressed), and the B haplotype represents less warfarin sensitivity. Asians had a higher proportion of group A haplotypes, and Africans had a higher proportion of group B haplotypes.

Half-life and time to steady state

The average elimination half-life of S-warfarin is 29 hr and of R-warfarin is 45 hr.^{13–15,23} Although it takes approximately five half-lives to reach steady state warfarin concentrations after initiation of therapy or dosage adjustments, therapeutic steady state is not achieved until the vitamin K-dependent clotting factors have also reached a new equilibrium.

Dosing strategies

Initiation dosing

Because of wide variability in dosing requirements among patients, the initial dosing of warfarin therapy is based on the presence or absence of factors that may influence dosing requirement and on the INR response to initial doses. Large fixed loading doses (10 mg–15 mg daily for several days) and loading doses based on body weight (1.5 mg/kg), although once favored, are no longer recommended as they increase the risk of both overanticoagulation and hemorrhage.^{50,51} Instead, two general methods for initiation with moderate warfarin doses are used. These are the average daily dosing method and flexible initiation.

Average daily dosing method

In an evaluation of over 2000 patients taking stable doses of warfarin for a variety of indications, the geometric mean dose was 4.57 mg daily, and the arithmetic mean dose was 5.13 mg daily.⁴ Patients who do not meet specific criteria that indicate either high or low sensitivity to the effects of warfarin can be initiated with a dose of 5 mg daily, with INR values checked within 3–5 days. Subsequent doses are based on the response to the INR and the INR is checked again in another 3–5 days. This pattern continues until the INR is above the lower limit of the therapeutic range, at which time a maintenance dose is selected based on the doses given to this point.

Patients who are expected to be more sensitive to the effects of warfarin are described in **Table 23-5**. In these patients, the average warfarin dosing requirement is likely to be reduced to 1–3 mg daily. Using the average daily dosing method, patients with any of these characteristics should be initiated with a lower dose (2.5 mg is often used), with subsequent dosing based on INR response as measured within 3–5 days.

TABLE 23-5. FACTORS LIKELY TO INCREASE SENSITIVITY TO WARFARIN

- Age >75
 - Clinical congestive heart failure
 - Clinical hyperthyroidism
 - Diarrhea
 - Decreased overall oral intake
 - Drug–drug interactions that decrease clearance or increase pharmacodynamic response
 - Elevated baseline INR
 - End stage renal failure
 - Fever
 - Following heart valve replacement
 - Hepatic disease
 - Known CYP2C9 variant
 - Hypoalbuminemia
 - Malignancy
 - Malnutrition
-

Several algorithms have been developed to assist with dosing decisions after the first few doses of warfarin have been administered. Pengo et al.⁵² found that after four doses of warfarin 5 mg daily, the INR on day 5 could be used to predict weekly warfarin maintenance doses. Siguret et al.⁵³ administered warfarin 4 mg daily for three doses and used the INR on day 4 to predict maintenance dose in elderly patients. Comparatively, Oates et al.⁵⁴ found that the INR on day 15 after 2 wk of warfarin 2 mg daily could be used to predict maintenance dose requirements in elderly patients.

Two algorithms have been developed that use two INR values to predict warfarin maintenance dose. Tait et al. administered warfarin 5 mg daily for 4 days, and used the INR on day 5 to select warfarin doses for days 5–7.⁵⁵ The subsequent INR on day 8 was then used to predict the maintenance dose. Kovacs et al. developed a similar algorithm using warfarin 10 mg daily for 2 days.⁵⁶ At day 3, the INR was used to guide dosing on days 3 and 4, and the INR on day 5 was used to guide the next 3 doses. In a study comparing this algorithm to a previously published 5-mg initiation algorithm, patients who received the 10-mg starting doses reached the therapeutic range more rapidly than those initiated with 5-mg starting doses, with no difference in the risk of major bleeding or overanticoagulation.⁵⁷ However, the patients in this study were relatively young and healthy outpatients with acute venous thrombosis. Warfarin initiation with 10 mg may lead to overanticoagulation and increased bleeding risk in older and less healthy patients with other indications for oral anticoagulation.⁵⁸ In addition, initiation with 10 mg can cause a rapid depletion of protein C, which may induce a relatively hypercoagulability.⁵⁹

Each of these algorithms differs not only in method used to achieve stable dosing, but also in validation sample size, population studied, time to achieve a therapeutic INR, risk of under- and overanticoagulation during initiation therapy, and success in predicting the maintenance dose. None is a preferred method, but all demonstrate the importance of assessment of change in INR as a predictor of eventual warfarin maintenance dose requirement and the significance of evaluation of underlying factors that may influence warfarin dosing requirement in individual patients.

Flexible initiation

Hospitalized patients who are available for daily INR testing may benefit from flexible initiation of warfarin. Several flexible initiation algorithms have been developed, each of which considers the rate of increase in the INR on a daily basis to inform daily warfarin dose and to predict the maintenance dosing requirements.

The earliest nomogram by Fennerty et al. started with a 10-mg dose followed by daily INR and daily warfarin adjustments to reach a predicted maintenance dose by day 4.⁶⁰ This method was successfully applied in relatively young patients with thromboembolic disease (mean age 52) and in older patients with other indications for oral anticoagulation (mean age 66).^{60,61} However, concerns about the use of 10-mg starting doses, particularly in the elderly, have persisted.

A low-dose flexible initiation nomogram was associated with a lower risk of overanticoagulation in elderly patients (age >65) compared to a modification of the Fennerty nomogram.⁶² More recently, an age-adjusted flexible warfarin initiation protocol was found to be superior to either the Fennerty nomogram or empiric dosing.⁶³ Further modifications of this age-adjusted flexible initiation protocol have since been published.⁶⁴

Crowther et al.^{65,66} compared flexible initiation nomograms that started with either 5- or 10-mg starting doses followed by daily INR determination and prediction of the maintenance dose by day 6. These authors concluded that the 10-mg initiation was more likely to result in overanticoagulation on each day that INR was evaluated.

Initiation nomograms that incorporate genetic information

Numerous algorithms that incorporate CYP2C9 and VKORC1 genetic information to predict warfarin dosing requirement have been published. In a homogenous, racially and ethnically diverse population, they explain only 37% to 55% of the variation in warfarin dose requirements.⁶⁷ During the first week of therapy, genotype alone accounts for 12% of therapeutic dose variability, but over the first several weeks of therapy becomes less relevant as INR and prior doses increasingly predict therapeutic dose,

and genotype information.⁶⁸ In fact, much of the information provided by including genetic information in a dose-prediction model is captured by early INR response.⁶⁹

A systematic review of small clinical trials that compared genotype-based warfarin dosing to a non-genotype strategy found no statistically significant difference in bleeding rates, time within therapeutic range, or time to achieve a stable warfarin dose.⁷⁰ Large-scale, randomized controlled trials are underway to determine whether pharmacogenomic-based dosing will improve clinical outcomes. However, genotyping is unlikely to be cost-effective in most patients.⁷¹

Maintenance dosing

Once a patient has reached the lower limit of the therapeutic range and is at relative steady state, maintenance dosing adjustments are frequently required to maintain the INR within the therapeutic range. Numerous factors influence the stability of therapy, including drug and disease state interactions, dietary vitamin K intake, alcohol use, activity, stress, and many others. These factors and the INR must be evaluated regularly. The frequency of monitoring and assessment is described in **Table 23-6**. Dosing adjustments are based on INR results and the presumed explanation for out-of-range INRs. For example, a transient cause of under-anticoagulation, such as a missed dose, may be most appropriately managed by simply continuing the usual maintenance dose or giving a one-time “booster dose” (1.5–2 times the daily maintenance dose) to replace the missed dose. Comparatively, a more persistent cause of underanticoagulation such as the addition of an interacting enzyme inducer that will be continued more than just a few days will require a more permanent dosing increase. Similarly, a transient cause of overanticoagulation such as acute illness may require holding a dose of warfarin without any change in the long-term maintenance dose. A more persistent cause of overanticoagulation such as addition of an interacting enzyme inhibitor for more than a few days will require a more permanent dosing reduction.

When dosing adjustments are required, they are generally in the range of 5% to 20% of the daily dose, or 5% to 20% of the total weekly dose.⁷² The tablet size(s) available to the patient and the patient’s own concerns regarding same daily dosing (e.g., 4 mg daily or 28 mg weekly) or alternate-day dosing (2.5 mg Mondays, Wednesdays, and Fridays, and 5 mg on all other days, or 27.5 mg/week) must also be considered.⁷³

A maintenance dosing adjustment guideline for a patient with a goal INR of 2–3 is presented in **Table 23-7**. However, it is imperative that the adjustments only be made in patients who have already reached the therapeutic range. The use of maintenance dosing adjustments (e.g., small 5% to 15% changes every 7 days rather than more aggressive initiation doses) during initiation therapy will significantly prolong the time to reach the lower limit of the therapeutic range.

TABLE 23-6. FREQUENCY OF INR MONITORING AND PATIENT ASSESSMENT

Initiation Therapy	
Flexible initiation method	Daily through day 4, then within 3–5 days
Average daily dosing method	Every 3–5 days until INR > lower limit of therapeutic range, then within 1 week
After hospital discharge	If stable, within 3–5 days; if unstable, within 1–3 days
First month of therapy	At least weekly
Maintenance Therapy	
Dose held today in patient with significant overanticoagulation	In 1–2 days
Dosage change today	Within 1–2 wk
Dosage change made ≤2 wk ago	Within 2–4 wk
Routine follow-up of medically stable and reliable patients	Every 4–6 wk
Routine follow-up of medically unstable or unreliable patients	Every 1–2 wk

TABLE 23-7. WARFARIN DOSING ADJUSTMENT GUIDELINES FOR INR GOAL OF 2–3

INR	Dosage Adjustment Guidelines
<1.5	Consider a booster dose of 1.5–2 × daily maintenance dose Consider resumption of prior maintenance dose if factor causing decreased INR is transient [e.g., missed warfarin dose(s)] If dosage adjustment needed, increase maintenance dose by 10% to 20%
1.5–1.8	Consider a booster dose of 1.5–2 times daily maintenance dose Consider resumption of prior maintenance dose if factor causing decreased INR is considered [e.g., missed warfarin dose(s)] If dosage adjustment needed, increase maintenance dose by 5% to 15%
1.8–2	No dosage adjustment may necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does not represent an increased risk of thromboembolism for the patient Consider a booster dose of 1.5–2 × daily maintenance dose Consider resumption of prior maintenance dose if factor causing decreased INR is transient [e.g., missed warfarin dose(s)] If dosage adjustment needed, increase maintenance dose by 5% to 10%
2–3	Desired range
3–3.2	No dosage adjustment may be necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does not represent an increased risk of hemorrhage for the patient Consider continuation of prior maintenance dose if factor causing elevated INR is transient [e.g., acute alcohol ingestion] If dosage adjustment needed, reduce maintenance dose by 5% to 10%
3.5–3.9	Consider holding one dose Consider resumption of prior maintenance dose if factor causing elevated INR is transient [e.g.: acute alcohol ingestion] If dosage adjustment needed, decrease maintenance dose by 5% to 15%
> 4	Hold until INR < upper limit of therapeutic range Consider use of mini dose (1–2.5 mg) oral vitamin K Consider resumption of prior maintenance dose if factor causing elevated INR is transient [e.g.: acute alcohol ingestion] If dosage adjustment needed, decrease maintenance dose by 5%– 15%

THERAPEUTIC RANGE

Many clinical trials evaluating the effectiveness and safety of warfarin have helped to establish specific INR ranges for the prevention and treatment of venous and arterial thromboembolism. The American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy meets every few years to summarize available literature and develop graded, evidence-based guidelines.⁷⁴ The therapeutic range for various indications, as recommended by the 9th ACCP Conference, are listed in **Table 23-8.**²

TABLE 23-8. OPTIMAL THERAPEUTIC RANGE BY INDICATION

Indication	Target INR (Range)
Atrial fibrillation	2.5 (2–3)
Atrial flutter	2.5 (2–3)
Cardioembolic stroke	2.5 (2–3)
Left ventricular dysfunction	2.5 (2–3)
Myocardial infarction	2.5 (2–3)
Venous thromboembolism	2.5 (2–3)
Valvular heart disease	2.5 (2–3)
Valve replacement, bioprosthetic	2.5 (2–3)
Valve replacement, mechanical	
Aortic, bileaflet	2.5 (2–3)
Aortic, other	3 (2.5–3.5)
Mitral, all	3 (2.5–3.5)

THERAPEUTIC MONITORING

Warfarin therapy suppresses the vitamin K dependent clotting factors to different extents. In stable anticoagulated patients, factor II (mean activity 19%; range 9% to 54%) and factor X (mean activity 18%; range 9% to 45%) are suppressed to the greatest extent, compared to factor VII (mean activity 33%; range 16% to 57%) and factor IX (mean activity 48%; range 26% to 94%).⁷⁵ But despite considerable variability, mean activity of all clotting factors is highly predictive of INR.

The intensity of warfarin therapy is monitored by evaluation of the PT, expressed as the INR.⁷⁶ The PT is prolonged by deficiencies in plasma concentrations of clotting factors II, V, VII, and X. It is measured by adding both calcium and a tissue thromboplastin to plasma, which accelerates activation of the extrinsic pathway of the clotting cascade. Time-to-clot formation is read in seconds using various technologies.

Thromboplastins are extracted from various tissue sources and prepared for use as commercial reagents. Because of lack of standardization among manufacturers of thromboplastins, each reagent is assigned an International Sensitivity Index (ISI) that describes its comparison to an international reference thromboplastin derived from human brain. The ISI is listed in the product information for each lot of thromboplastin.⁷⁷ The ISI is used to convert prothrombin time in seconds to the INR, using the formula:

$$\text{INR} = \left(\frac{\text{PT}_{\text{patient}}}{\text{PT}_{\text{mean normal}}} \right)^{\text{ISI}}$$

The mean normal PT is typically about 12 seconds for most thromboplastin reagents and is measured by averaging the PT of nonanticoagulated subjects. The INR is the value that would have been obtained if the reference preparation had been used in the test. In this way, results obtained at different laboratories can be compared and results from different lots of the same manufacturer of thromboplastin can also be compared.

Variations in thromboplastin sensitivity are due to differences in manufacturing, source, and method of preparation. More sensitive thromboplastins with ISI values close to 1 produce less rapid stimulation of factor X, resulting in greater prolongation of the PT for a given reduction in clotting factors.⁷⁸ Less sensitive thromboplastins activate residual factor X more rapidly and result in a less prolonged PT, despite a comparable reduction in clotting factors. ISI values range from 0.95 to 2.9, with a higher ISI number indicating a less sensitive reagent.

Although manufacturers carefully calibrate the ISI values of their thromboplastins, they do not, in most cases, provide ISI values that are specific to the instrumentation that will be used to measure INR at individual laboratories. One means of overcoming this problem is the use of calibrating plasma provided by reagent manufacturers.⁷⁹ By using plasma samples with carefully calculated INR values, a laboratory can verify the correct ISI value for its system.

Although PT is intended to be measured using plasma samples obtained by venipuncture, a number of point-of-care INR devices have been developed that use whole blood for rapid measurement of INR.⁸⁰ These test systems are used in anticoagulation clinics, physician offices, and hospital nursing units, and can be used for patient self-testing at home.⁸¹

PHARMACODYNAMIC MONITORING

Patients treated with warfarin should be routinely monitored for signs and symptoms of the development, progression, or recurrence of venous or arterial thromboembolism. They should also be assessed regularly for the development of hemorrhagic complications to warfarin therapy. In addition, factors that influence the stability of the INR should be assessed on a regular basis. These include changes in dietary vitamin K intake, prescription and nonprescription medications and dietary supplements, underlying disease states, alcohol use, activity, the development of acute illness, and others.² Changes in any of these parameters can influence the intensity of anticoagulant therapy and increase the risk of hemorrhagic or thromboembolic complications.

INR-related efficacy

After initiation of warfarin therapy, initial elevations in the INR represent depletion of factor VII due to its short elimination half-life.⁸² However, the antithrombotic effect of warfarin requires adequate depletion of factors II and X.⁸³ Since protein C also has a relatively short elimination half-life, initial warfarin doses can induce a relative hypercoagulable state as the anticoagulant effect of protein C is depleted more rapidly than clotting factors II and X.⁵⁹ For these reasons, in addition to the known pharmacokinetic properties of warfarin, the antithrombotic effect of warfarin is delayed for 4–5 days after initiation. For treatment of acute venous thromboembolism, warfarin therapy must therefore be overlapped with unfractionated heparin, a low molecular weight heparin, a direct thrombin inhibitor, or an indirect factor Xa inhibitor during initiation therapy.⁸⁴ Current guidelines suggest that this overlap continue for a minimum of 5 days and until the INR is stable and above the lower limit of the therapeutic range.⁸⁵

The INR is designed for monitoring long-term anticoagulation therapy and is less reliable during the induction phase of oral anticoagulant therapy. It is also less reliable for patients with significant liver dysfunction, hereditary factor deficiencies, or for screening for bleeding disorders. These conditions require evaluation of other measures of hemostasis.

The INR can be increased by the presence of heparin or low molecular weight heparin in the sample, as well as by direct thrombin inhibitors and factor Xa inhibitors.^{86,87} Hemolysis and elevated hematocrit also influence the INR.^{88,89} Specimens must be handled differently by laboratory personnel in each of these situations.

Antiphospholipid antibody (APA) syndrome is a condition associated with venous and arterial thromboembolism requiring chronic anticoagulation with warfarin and routine INR monitoring.⁹⁰ Because the INR is a phospholipid-dependent test, it may be invalid in patients with APA syndrome whether monitored by standard methodology or point-of-care testing.^{91,92} In these patients, an alternative monitoring strategy that is independent of phospholipids may be preferable. One option is the use of chromogenic factor X.⁹³ An INR of 2–3 is roughly equivalent to suppression of factor X to 35% to 45% of normal.

Time spent within the therapeutic range (time-in-therapeutic range; TTR) is a measure of the quality of anticoagulant control and is a predictor of both the efficacy and the safety of oral anticoagulation.⁹⁴ Increased TTR is associated with a reduction in both thromboembolic complications and hemorrhage. TTR can be measured as the fraction of INRs in range, as a cross section of INRs on a given day, or by a linear interpolation method.⁹⁵ Each method has advantages and limitations, but all allow an overall examination of the quality of anticoagulation control. The fraction of INRs in range is commonly used as a quality assurance measure in anticoagulation clinics, while linear interpolation of TTR is frequently used in clinical trials to describe the quality of anticoagulation control.

INRs below the therapeutic range are associated with an increased risk of thromboembolic events. The risk of stroke in patients with atrial fibrillation increases dramatically with INRs <2.⁹⁶ Similarly, there is a steep increase in the risk of stroke at INRs <2.5 in patients with mechanical heart valve replacement.⁹⁷ In patients with a first episode of idiopathic venous thromboembolism (VTE) treated for a minimum of 3 months, the risk of recurrent VTE in the 21 months following discontinuation of warfarin was lower in patients who spent more time within the therapeutic INR range of 2–3 and higher in patients who spent more time with an INR <1.5.⁹⁸ Thus, the quality of oral anticoagulant control directly influences clinical outcomes.

INRs below the therapeutic range occur frequently during long-term oral anticoagulation and may be the result of various dosing issues (initiation therapy, withholding warfarin for invasive procedures, noncompliance, response to dosing adjustments), or of interactions (with drugs, disease states, diet, alcohol, etc.).⁹⁹ However, up to 30% of INRs <2 cannot be explained despite extensive patient assessment.

INR-related toxicity

Bleeding is the primary adverse effect associated with warfarin.¹⁰⁰ Bleeding is typically referred to as either minor or major depending on the site of bleeding, its clinical consequences, and/or the interventions required for control. The risk of bleeding is dependent on the intensity of anticoagulation, underlying patient characteristics, concomitant use of drugs that impact hemostasis, and the length of anticoagulant therapy.

Intensity of anticoagulation is a major determinant of the risk of major bleeding complications in patients taking warfarin. Outpatients taking warfarin who develop INRs >6 are at a significantly greater risk of developing major bleeding within the next 2 wk compared to patients with INRs within the therapeutic range of 2–3.¹⁰¹ The risk of intracranial hemorrhage increases significantly when the INR is >4.^{97,102} Bleeding risk is also increased by variability in the INR, which is an indicator of poor management of warfarin therapy.^{102,103}

When warfarin therapy is managed in a designated anticoagulation clinic setting, the risk of major bleeding can be minimized in comparison to warfarin management by routine medical care.^{104,105} However, advanced age appears to increase the risk of warfarin-related intracranial hemorrhage, even when patients are managed by anticoagulation clinics.^{106,107}

Prediction methods that are based on the presence of risk factors for bleeding can be used to estimate bleeding risk associated with warfarin therapy. One popular method assigns a point score (total 0–4 points) for the presence of age >65, history of stroke, history of gastrointestinal bleeding (1 point each), and any one of four other comorbid conditions (recent myocardial infarction, elevated serum creatinine >1.5 mg/dL, hematocrit <30% or diabetes) (1 point for any or all).¹⁰⁸ Application of this Bleeding Risk Index to warfarin patients managed in an anticoagulation clinic setting found that major bleeding occurred at a rate of 0.8%/patient-year in patients with a low risk score (0 points), 2.5%/patient-year in patients with an intermediate risk score (1–2 points), and 10.6%/patient-year in patient with a high risk score (3–4 points).¹⁰⁹

Reversing INR-related toxicity

Reversal of overanticoagulation is accomplished by withholding warfarin, administering vitamin K, and/or administering blood products.² These strategies may be used alone or in combination, guided by the INR, the patient’s bleeding risk and bleeding status, and the time needed for reversal. Blood products, such as fresh frozen plasma (FFP), act rapidly, have a short duration of effect, and are reserved for active bleeding. Prothrombin complex concentrates and recombinant factor VIIa have also been used to manage life-threatening warfarin-induced bleeding. High dose vitamin K (10 mg by IV infusion) is often used in conjunction with blood products in patients who are bleeding. The onset of effect is relatively rapid and the duration of effect is prolonged, but can lead to extended warfarin resistance.

Lower doses of vitamin K can be used to reverse overanticoagulation when no bleeding is present. The oral route is preferred as subcutaneous administration can lead to a delay in onset of effect and both subcutaneous and intramuscular administration can lead to hematoma formation.¹¹⁰⁻¹¹³ Vitamin K doses in the range of 1–2.5 mg will reduce the INR back to within the therapeutic range within 24 hr without causing complete reversal or prolonged warfarin resistance.

There are currently two formulations of vitamin K₁ available in the United States, a scored 5-mg tablet (Mephyton) and an injectable preparation available as a 2-mg/mL or 10-mg/mL aqueous dispersion (Aquamephyton) that can also be administered orally. When a more rapid reversal is needed (for example, prior to invasive procedures), the IV route can be used. Rapid IV administration of vitamin K has been associated with anaphylactic reactions, so a prolonged infusion in 50–100 mL of diluent over 30–60 minutes is necessary.¹¹⁴ Recommendations for reversal of warfarin in the setting of overanticoagulation are described in **Table 23-9**.¹⁰⁰

TABLE 23-9. RECOMMENDATIONS FOR REVERSAL OF WARFARIN

INR	Clinical Scenario	Management
<4.5	No bleeding	Hold warfarin until INR in therapeutic range
	Rapid reversal required	Hold warfarin
		Consider vitamin K 2.5 mg oral
4.5–10	No bleeding	Hold warfarin until INR in therapeutic range
	Rapid reversal required	Consider vitamin K 2.5 mg oral
		Hold warfarin
>10	No bleeding	Give vitamin K 2.5 mg oral or 1 mg IV infusion
	Rapid reversal required	Hold warfarin
		Give vitamin K 2.5 mg oral or 1–2 mg IV infusion, and repeat every 24 hr as needed
Any INR	Serious or life threatening bleeding	Hold warfarin
		Give vitamin K 1–2 mg IV infusion and repeat every 6–24 hr as needed
		Give vitamin K 10 mg IV infusion
		Give 4 units FFP or consider 4-factor PCC

DRUG–DRUG INTERACTIONS

Warfarin is highly susceptible to interactions with prescription and nonprescription drugs as well as with herbal and other natural products.¹¹⁵ Through a variety of mechanisms these interactions may elevate or reduce the INR, increasing the risk of hemorrhagic or thromboembolic complications, respectively. Pharmacokinetic interactions are those that influence the absorption, distribution,

metabolism, or excretion of warfarin. Pharmacodynamic interactions influence response to warfarin without altering its pharmacokinetics. Clinically significant warfarin drug interactions are listed in **Table 23-10**.^{115–120} Clinically significant interactions between warfarin and dietary supplements are listed in **Table 23-11**.^{115,120–124}

The impact of drug interactions on INR, bleeding risk, or risk of thromboembolism may be seen when interacting drugs are initiated, discontinued, or when there is a change in dose. Patient susceptibility to drug interactions is highly variable, as is the magnitude of the response, the time of onset, and the duration of the interaction once the interacting drug is discontinued.¹²⁵ These variables are influenced by numerous underlying patient characteristics that may influence clotting factor synthesis and degradation, the pharmacokinetics and/or pharmacodynamics of the interacting drug, and the pharmacokinetics and/or pharmacodynamics of the R and S enantiomers of warfarin.¹²⁶ Genetic expression of CYP2C9 influences warfarin dosing requirements and may also influence the risk and/or severity of warfarin drug interactions.¹²⁷

Interacting drugs are not often strictly contraindicated in patients taking warfarin, though appropriate therapeutic alternatives with little or no interaction potential should be used when possible. When noninteracting alternatives are not available or not appropriate, the interacting drugs can be used concurrently as long as the frequency of INR monitoring and the dosing of warfarin are adjusted appropriately. These interventions should be guided by the pharmacokinetic and pharmacodynamic characteristics of warfarin and of the interacting drug, known characteristics of the interaction in similar patients, the expected time course associated with the known or presumed mechanism of the interaction, and the underlying thromboembolic or hemorrhagic risk of the patient involved. For example, enzyme inhibition interactions typically occur rapidly, so the INR should be checked 2–3 days after the interacting agent is added to warfarin therapy. Enzyme induction interactions tend to occur more slowly, so the INR should be checked within the first week after addition of the interacting drug. However, no guidelines for drug interaction management exist, and appropriately so, since each case must be handled individually due to expected variability in response.

DRUG–DISEASE STATE OR CONDITION INTERACTIONS

A number of disease states influence the therapeutic response to warfarin. The influence of these conditions should be considered during initiation of therapy when they may influence the starting dose of warfarin, as well as later in therapy when new onset, exacerbation, or improvement in these conditions may influence INR response and the maintenance dosing requirements for warfarin.

Advanced age

Warfarin dosing requirements decline with advanced age.¹²⁸ There do not appear to be differences in the pharmacokinetics of warfarin in young versus elderly patients, however.¹²⁹ The elderly may have reduced availability of vitamin K stores and lower plasma concentrations of vitamin K dependent clotting factors, both of which could contribute to this observation.^{129,130} Age may be the most important readily available predictor of warfarin dosing requirement.¹³¹

Pregnancy and lactation

Warfarin is a teratogen and is associated with congenital abnormalities such as stippled calcifications and nasal cartilage hypoplasia, particularly when exposure occurs during weeks 6–12 of pregnancy.¹³² Other abnormalities as well as fetal hemorrhage can occur throughout pregnancy. Accordingly, warfarin is considered contraindicated in pregnancy. Alternative anticoagulants such as heparin and low molecular weight heparin should be used instead of warfarin in pregnant women. Warfarin is not excreted in breast milk and can be used safely post-partum by nursing mothers.¹³³

TABLE 23-10. CLINICALLY SIGNIFICANT WARFARIN DRUG INTERACTIONS

Mechanism	Effect on INR	Drugs/Drug Classes
Increased synthesis of clotting factors	Decreased	Vitamin K
Reduced catabolism of clotting factors	Decreased	Methimazole Propylthiouracil
Induction of warfarin metabolism	Decreased	Alcohol (chronic use) Aminoglutethimide Aprepitant <i>Barbiturates</i> Bosentan Carbamazepine Dicloxacillin Ethchlorvynol Fosphenytoin Glutethimide Griseofulvin Mitotane Nafcillin Phenytoin Primidone <i>Rifamycins</i> Terbinafine
Reduced absorption of warfarin	Decreased	Cholestyramine Colestipol Sucralfate
Unexplained mechanisms	Decreased	Ascorbic acid Azathioprine <i>Corticosteroids</i> Cyclosporine Mercaptopurine <i>Protease Inhibitors</i> Ribavirin
Increased catabolism of clotting factors	Increased	<i>Thyroid hormones</i>
Protein binding displacement	Increased	Chloral Hydrate
Decreased synthesis of clotting factors	Increased	<i>Cephalosporins</i> Vitamin E
Impaired vitamin K production by gut flora	Increased	<i>Aminoglycosides</i> <i>Tetracyclines</i>
Inhibition of warfarin metabolism	Increased	Acetaminophen Alcohol (acute use) Allopurinol Amiodarone <i>Azole Antifungals</i> Capecitabine Celecoxib Chloramphenicol Cimetidine Delavirdine Disulfiram Efavirenz <i>Fluoroquinolone antibiotics</i> Fluorouracil Fosphenytoin Ifosfamide

		Isoniazid Leflunomide <i>Macrolide antibiotics</i> Metronidazole Omeprazole Orlistat Phenytoin Propafenone Quinidine Quinine Rofecoxib <i>Selective Serotonin Reuptake Inhibitors</i> <i>Statins</i> (not atorvastatin/ pravastatin) <i>Sulfa antibiotics</i> Zafirlukast
Additive anticoagulant	Increased response	<i>Direct thrombin inhibitors</i> Heparin <i>Low molecular weight heparins</i> <i>Thrombolytic agents</i>
	Unexplained mechanisms	Acarbose <i>Androgens</i> Carboplatin Clofibrate <i>Corticosteroids</i> Cyclophosphamide Etoposide Fenofibrate Gefitinib Gemcitabine Gemfibrozil Influenza virus vaccine Isotretinoin Mesalamine Paclitaxel Tamoxifen Testosterone Tolterodine Tramadol Trastuzumab
Increased bleeding risk	No effect	Aspirin/acylated salicylates Clopidogrel/ticlopidine <i>Glycoprotein IIB/IIIA inhibitors</i> <i>Nonsteroidal anti-inflammatory drugs</i> Prasugrel

Italics = drug class.

Source: Adapted with permission from Wittkowsky AK. Drug interactions with oral anticoagulants. In: Colman RW, Marder VJ, Clowes AW, et al., eds. *Hemostasis and Thrombosis. Basic Principles and Clinical Practice*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; © 2006.

TABLE 23-11. CLINICALLY SIGNIFICANT INTERACTIONS BETWEEN WARFARIN AND DIETARY SUPPLEMENTS

Mechanism	Effect	Supplements
Inhibition of warfarin metabolism	Increased INR	Chinese wolfberry Cranberry juice Grapefruit juice Mango
Contain coumarin derivatives	Increased INR	Danshen/methyl salicylate Dong quai Boldo/fenugreek
Unknown	Increased INR	Curbicin Devil's claw Fish oil Glucosamine-chondroitin Melatonin Papaya extract Guilinggao Vitamin E
Inhibition of platelet aggregation	Increased bleeding	Garlic Ginger Ginkgo
Contain vitamin K/derivatives	Decreased INR	Avocado Coenzyme Q10 Foods high in vitamin K Green tea Some multivitamins Sushi containing seaweed
Induction of CYP3A4	Decreased INR	St. John's wort
Unknown	Decreased INR	Ginseng Melatonin Soy

Source: Adapted with permission from Wittkowsky AK. Drug interactions with oral anticoagulants. In: Colman RW, Marder VJ, Clowes AW, et al., eds. *Hemostasis and Thrombosis. Basic Principles and Clinical Practice*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; © 2006.

Alcoholism

Acute alcohol ingestion can elevate the INR by inhibiting warfarin metabolism.¹³⁴ Patients who binge drink are at increased bleeding risk from overanticoagulation and from risk of falls. Conversely, chronic alcohol use is associated with CYP enzyme induction and causes higher warfarin dosing requirements in alcoholic patients. Patients taking warfarin should be encouraged to moderate their alcohol intake.

Liver disease

Hepatic disease is often accompanied by coagulopathy due to a reduction in clotting factor synthesis.¹³⁵ These patients may appear to be “auto-anticoagulated” with baseline elevated INRs. However, the degree of factor suppression in liver disease does not mimic that of Hepatics treated with warfarin; thus, these patients are not protected from thromboembolism.¹³⁶ Hepatic disease may reduce the clearance of warfarin.

Renal disease and hemodialysis

End stage renal disease is associated with reduced activity of CYP2C9, leading to lower warfarin dosing requirements.¹³⁷ Hypoalbuminemia associated with nephrotic syndrome increases the free fraction of warfarin, but there is also an associated increase in plasma clearance.¹³⁸ When INR is monitored in

patients undergoing hemodialysis, blood draws should be taken from peripheral sites rather than from the dialysis graft as heparin can influence INR results.¹³⁹ It may also be necessary for the sample to be deheparinized with a heparin absorbent to eliminate any potential risk of contamination by heparin from the dialysis circuit.

Congestive heart failure

Exacerbations of heart failure can cause an increased responsiveness to warfarin and elevate the INR.¹⁴⁰ The likely mechanism of this effect is hepatic congestion leading to a reduction in warfarin metabolism.

Cardiac valve replacement

Patients commencing warfarin therapy after cardiac valve replacement appear to have increased response to warfarin.¹⁴¹ This enhanced sensitivity diminishes over time and several weeks after surgery patients typically require higher doses than initially suspected. Hypoalbuminemia, age, diet, physical activity and reductions in clotting factor concentrations as a result of cardiopulmonary bypass all likely contribute to this phenomenon.

Nutritional status

Changes in dietary intake of vitamin K containing foods have a profound impact on warfarin dosing requirements and INR response.¹²⁴ Diets modified intentionally or as a result of disease, surgery, or other exogenous factors are likely to influence the therapeutic response to warfarin.

Thyroid disease

Hypothyroidism decreases the catabolism of clotting factors, leading to increased warfarin dosing requirements to maintain a therapeutic INR.¹⁴² Conversely, hyperthyroidism increases sensitivity to warfarin.¹⁴³ Patient who start or stop thyroid replacement therapy or who undergo treatment for hyperthyroidism require careful INR monitoring and dosing adjustments to maintain safe and effective oral anticoagulation.

Smoking and tobacco use

Constituents of cigarette smoke may induce cytochrome P450 enzymes, including CYP1A2, a minor contributor to the metabolism of R-warfarin.¹⁴⁴ Warfarin dosing requirements have been observed to decline after smoking cessation.¹⁴⁵ Chewing tobacco contains high quantities of vitamin K and can suppress INR response.¹⁴⁶

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APPENDIX A. THERAPEUTIC RANGES OF DRUGS IN TRADITIONAL AND SI UNITS

Drug	Traditional Range	Conversion Factor ^a	SI Range
Acetaminophen	>5 mg/dL toxic	66.16	>330 µmol/L toxic
N-acetylprocainamide	4–10 mg/L	3.606	14–36 µmol/L
Amitriptyline	75–175 ng/mL	3.605	270–630 nmol/L
Carbamazepine	4–12 mg/L	4.23	17–51 µmol/L
Chlordiazepoxide	0.5–5 mg/L	3.336	2–17 µmol/L
Chlorpromazine	50–300 ng/mL	3.136	150–950 nmol/L
Chlorpropamide	75–250 mcg/mL	3.613	270–900 µmol/L
Clozapine	250–350 ng/mL	0.003	0.75–1.05 µmol/L
Cyclosporine	100–200 ng/mL ^b	0.832	80–160 nmol/L
Desipramine	100–160 ng/mL	3.754	375–600 nmol/L
Diazepam	100–250 ng/mL	3.512	350–900 nmol/L
Digoxin	0.9–2.2 ng/mL	1.281	1.2–2.8 nmol/L
Disopyramide	2–6 mg/L	2.946	6–18 µmol/L
Doxepin	50–200 ng/mL	3.579	180–720 nmol/L
Ethosuximide	40–100 mg/L	7.084	280–710 µmol/L
Fluphenazine	0.5–2.5 ng/mL	2.11	5.3–21 nmol/L
Glutethimide	>20 mg/L toxic	4.603	>92 µmol/L toxic
Gold	300–800 mg/L	0.051	15–40 µmol/L
Haloperidol	5–15 ng/mL	2.66	13–40 nmol/L
Imipramine	200–250 ng/mL	3.566	710–900 nmol/L
Isoniazid	>3 mg/L toxic	7.291	>22 µmol/L toxic
Lidocaine	1–5 mg/L	4.267	4–22 µmol/L
Lithium	0.5–1.5 mEq/L	1	0.5–1.5 µmol/L
Maprotiline	50–200 ng/mL	3.605	180–720 µmol/L
Meprobamate	>40 mg/L toxic	4.582	>180 µmol/L toxic
Methotrexate	>2.3 mg/L toxic	2.2	>5 µmol/L toxic
Nortriptyline	50–150 ng/mL	3.797	190–570 nmol/L
Pentobarbital	20–40 mg/L	4.419	90–170 µmol/L
Perphenazine	0.8–2.4 ng/mL	2.475	2–6 nmol/L
Phenobarbital	15–40 mg/L	4.306	65–172 µmol/L
Phenytoin	10–20 mg/L	3.964	40–80 µmol/L
Primidone	4–12 mg/L	4.582	18–55 µmol/L
Procainamide	4–8 mg/L	4.249	17–34 µmol/L
Propoxyphene	>500 ng/mL toxic	2.946	>1,500 ng/mL
Propranolol	50–200 ng/mL	3.856	190–770 nmol/L
Protriptyline	100–300 ng/mL	3.797	380–1,140 nmol/L
Quinidine	2–6 mg/L	3.082	6–18 µmol/L
Salicylate (acid)	15–25 mg/dL	0.072	1.1–1.8 mmol/L



APPENDIX A. (CONT'D)

Drug	Traditional Range	Conversion Factor ^a	SI Range
Theophylline	10–20 mg/L	5.55	55–110 μmol/L
Thiocyanate	>10 mg/dL toxic	0.172	>1.7 mmol/L toxic
Valproic acid	50–100 mg/L	6.934	350–700 μmol/L

^aTraditional units are multiplied by conversion factor to get SI units.

^bWhole blood assay.

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APPENDIX B. NONDRUG REFERENCE RANGES FOR COMMON LABORATORY TESTS IN TRADITIONAL AND SI UNITS^a

Laboratory Test	Reference Range Traditional Units	Conversion Factor	Reference Range SI Units	Comment
Alanine aminotransferase (ALT)	0–30 International Units/L	0.01667	0–0.5 μ kat/L	SGPT
Albumin	3.5–5 g/dL	10	35–50 g/L	
Ammonia	30–70 mcg/dL	0.587	18–41 μ mol/L	
Aspartate aminotransferase (AST)	8–42 International Units/L	0.01667	0.133–0.7 μ kat/L	SGOT
Bilirubin (direct)	0.1–0.3 mg/dL	17.1	1.7–5.1 μ mol/L	
Bilirubin (total)	0.3–1 mg/dL	17.1	5–17 μ mol/L	
Calcium	8.5–10.8 mg/dL	0.25	2.1–2.7 mmol/L	
Carbon dioxide (CO ₂)	24–30 mEq/L	1	24–30 mmol/L	Serum bicarbonate
Chloride	96–106 mEq/L	1	96–106 mmol/L	
Cholesterol (HDL)	>40 mg/dL	0.026	>1.05 mmol/L	Desirable
Cholesterol (LDL)	<130 mg/dL	0.026	<3.36 mmol/L	Desirable
Creatinine kinase (CK)	25–90 International Units/L (males)	0.01667	0.42–1.5 μ kat/L	Males
	10–70 International Units/L (females)		0.17–1.17 μ kat/L	Females
Creatinine clearance (CrCl)	90–140 mL/min/1.73 m ²	0.017	1.53–2.38 mL/sec/1.73 m ²	
Folic acid	150–540 ng/mL	2.266	340–1,223 nmol/L	
Gamma-glutamyl transpeptidase	0–30 units/L (but varies)	0.01667	0–0.5 μ kat/L (but varies)	GGT/GGTP
Globulin	2–3 g/dL	10	20–30 g/L	
Glucose (fasting)	70–110 mg/dL	0.056	3.9–6.1 mmol/L	Fasting
Hemoglobin (Hgb)	14–18 g/dL (males)	0.622	8.7–11.2 mmol/L	
	12–16 g/dL (females)		7.4–9.9 mmol/L	
Iron	50–150 mcg/dL	0.179	9–26.9 μ mol/L	
Iron-binding capacity (total)	250–410 mcg/dL	0.179	45–73 μ mol/L	TIBC
Lactate dehydrogenase	100–210 International Units/L	16.67 0.01667	1667–350 nmol/L, 1.7–3.5 μ kat/L	LDH
Magnesium	1.5–2.2 mEq/L	0.5	0.75–1.1 mmol/L	
5' nucleotidase	1–11 units/L (but varies)	0.01667	0.02–0.18 μ kat/L (but varies)	
Phosphate	2.6–4.5 mg/dL	0.329	0.85–1.48 mmol/L	
Potassium	3.5–5 mEq/L	1	3.5–5 mmol/L	
Serum creatinine (SCr)	0.7–1.5 mg/dL	88.4	62–133 μ mol/L	Adults
Serum lactate (arterial)	0.5–2 mEq/L	1	0.5–2 mmol/L	
Serum lactate (venous)	0.5–1.5 mEq/L	1	0.5–1.5 mmol/L	Lactic acid



APPENDIX B. (CONT'D)

Laboratory Test	Reference Range Traditional Units	Conversion Factor	Reference Range SI Units	Comment
Sodium	136–145 mEq/L	1	136–145 mmol/L	
Total serum thyroxine (T ₄)	4–12 mcg/dL	12.86	51–154 nmol/L	Total T ₄
Triglycerides	<200 mg/dL	0.0113	<2.26 mmol/L	Adults >20 yr
Total serum triiodothyronine (T ₃)	78–195 ng/dL	0.0154	1.2–3 nmol/L	Total T ₃
Urea nitrogen, blood	8–20 mg/dL	0.357	2.9–7.1 mmol/L	BUN
Uric acid (serum)	3.4–7 mg/dL	59.48	202–416 μmol/L	

^aSome laboratories are maintaining traditional units for enzyme tests.
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