Emergency Drug Therapy

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WILLIAM G. BARSAN, M.D.
Associate Professor
Department of Emergency Medicine
University of Cincinnati Medical Center
Cincinnati, Ohio

MICHAEL S. JASTREMSKI, M.D.
Professor and
Director of Program in
Critical Care and Emergency Medicine
SUNY Health Science Center at Syracuse
Syracuse, New York

SCOTT A. SYVERUD, M.D.
Assistant Professor
Department of Emergency Medicine
University of Cincinnati Medical Center
Cincinnati, Ohio

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Contributors

William G. Barsan, M.D.
Associate Professor, Department of Emergency Medicine, University of Cincinnati College of Medicine; Attending Physician, University of Cincinnati Hospital, Cincinnati, Ohio
Respiratory Drugs; Anticoagulants and Thrombolytics

Michelle H. Biros, M.S., M.D.
Senior Associate Staff Physician, Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota
Anticonvulsants

Bryan Blackwelder, Pharm.D.
Clinical Assistant Professor, College of Pharmacy, University of Florida Health Science Center/Jacksonville; Pediatric Practitioner, Department of Pharmacy, University Medical Center, Jacksonville, Florida
Considerations in the Dosing of Pediatric Patients

Steven C. Carleton, M.D., Ph.D.
Chief Resident, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio
Endocrine and Miscellaneous Agents

Lynnette Doan-Wiggins, M.D., FACEP
Assistant Professor of Medicine, Loyola University Stritch School of Medicine; Associate Director, Emergency Department, Loyola University Medical Center, Maywood, Illinois
Drug Therapy During Pregnancy and Lactation; Obstetric and Gynecologic Emergency Drug Therapy

Steven C. Dronen, M.D.
Associate Professor of Emergency Medicine, University of Cincinnati College of Medicine; Staff Physician, University of Cincinnati Hospital, Cincinnati, Ohio
Plasma and Volume Expanders

Susan M. Dunmire, M.D., FACEP
Assistant Professor of Medicine, Division of Emergency Medicine, University of Pittsburgh School of Medicine; Attending Physician and Academic Coordinator, Emergency Department, Presbyterian–University Hospital, Pittsburgh, Pennsylvania
Analgesics

Frederick B. Epstein, M.D., FACEP
Assistant Clinical Professor of Surgery and Emergency Medicine, University of Florida College of Medicine, Gainesville; Director, Department of Emergency Medicine, Bay Medical Center, Panama City, Florida
Endocrine and Miscellaneous Agents

Douglas Evans, M.D.
Assistant Instructor, Department of Ophthalmology, State University of New York Health Science Center at Syracuse, Syracuse, New York; Captain, United States Air Force Ophthalmology Clinic, Lakenheath, Great Britain
Ophthalmic Agents

John I. Gerson, M.D.
Associate Professor, Department of Anesthesiology, State University of New York Health Science Center at Syracuse, Syracuse, New York
Injected Anesthetics

W. Brian Gibler, M.D., FACEP
Assistant Professor of Emergency Medicine, Department of Emergency Medicine, University of Cincinnati College of Medicine; Attending Emergency Physician, Department of Emergency Medicine and Center for Emergency Care, University of Cincinnati Hospital, Cincinnati, Ohio
Antiarrhythmics

John Hoepner, M.D.
Chairman, Department of Ophthalmology, State University of New York Health Science Center at Syracuse, Syracuse, New York
Ophthalmic Agents

Michael S. Jastremski, M.D.
Associate Professor, State University of New York Health Science Center at Syracuse; Director of Program in Critical Care and Emergency Medicine, University Hospital, Syracuse, New York
Antihypertensives

Louis J. Ling, M.D.
Medical Director, Hennepin Regional Poison Center; Assistant Director, Emergency Medicine Residency Program, Hennepin County Medical Center, Minneapolis, Minnesota
Antidotes

Mariane McLaughlin, Pharm.D.
Clinical Coordinator, Pharmacy Department, University Hospital, State University of New York Health Science Center at Syracuse, Syracuse, New York
Basic Clinical Pharmacokinetics

Edward J. Otten, M.D.
Associate Professor, University of Cincinnati College of Medicine; Director of Prehospital Care, University of Cincinnati Hospital, Cincinnati, Ohio
Antivenins and Antitoxins

Paul M. Paris, M.D., FACEP
Associate Professor and Chief, Division of Emergency Medicine, University of Pittsburgh School of Medicine; Chief, Division of Emergency Medicine, Presbyterian–University Hospital; Attending, Children's Hospital of Pittsburgh, Western Pennsylvania Hospital, and Mercy Hospital, Pittsburgh, Pennsylvania
Analgesics

Leo C. Rotello, M.D.
Assistant Professor, Program in Critical Care and Emergency Medicine, State University of New York Health Science Center at Syracuse, Syracuse, New York
Osmotic Agents

Charles E. Saunders, M.D., FACP
Associate Professor of Clinical Medicine, University of California, San Francisco; Director, Paramedic Division, Department of Health, City and County of San Francisco; Attending Physician, Emergency Services, San Francisco General Hospital, San Francisco, California
Vasoactive Agents

Daniel L. Savitt, M.D.
Assistant Clinical Professor of Surgery, Brown University; Attending Physician, Department of Emergency Medicine, Rhode Island Hospital, Providence, Rhode Island
Therapeutic Gases

Jay L. Schauben, Pharm.D., FABAT
Clinical Associate Professor, College of Pharmacy and Division of Emergency Medicine, College of Medicine, University of Florida Health Science Center/Jacksonville; Director, Clinical Toxicology Services, University Medical Center, Jacksonville, Florida
Considerations in the Dosing of Pediatric Patients

Clifton A. Sheets, M.D., FACEP
Assistant Clinical Professor, Wright State University; Attending Physician, Miami Valley Hospital, Dayton, Ohio
Emetics and Antiemetics

Bonita Singal, M.D.
Assistant Professor, Department of Emergency Medicine, Wright State University; Attending Physician, Good Samaritan Hospital, Dayton, Ohio
Acidifying and Alkalizing Agents

Mark S. Smith, M.D.
Professor and Chairman, Department of Emergency Medicine, George Washington University Medical Center, Washington, D.C.
Anticoagulants and Thrombolytics

William H. Spivey, M.D.
Associate Professor and Chief, Division of Research, Department of Emergency Medicine, Medical College of Pennsylvania, Philadelphia, Pennsylvania
Routes of Drug Administration

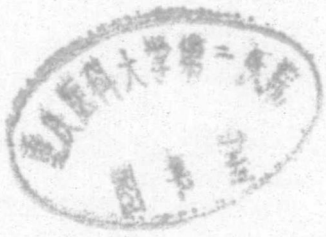
Scott A. Syverud, M.D.
Assistant Professor, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio; Attending Physician, University of Cincinnati Hospital, Cincinnati, Ohio, and St. Luke West Hospital, Florence, Kentucky
Muscle Relaxants

Thomas E. Terndrup, M.D.
Assistant Professor, Critical Care and Emergency Medicine and Pediatrics, State University of New York Health Science Center at Syracuse; Attending Physician, Emergency Department, and Research Director, Emergency Medicine, University Hospital, Syracuse, New York
Sedative-Hypnotics

Alexander Trott, M.D.
Associate Professor, Department of Emergency Medicine, University of Cincinnati College of Medicine; Attending Physician, University of Cincinnati Hospital, Cincinnati, Ohio
Antimicrobials

Peter Van Ligten, M.D.
Assistant Professor, Department of Emergency Medicine, Ohio State University, Columbus, Ohio
Endocrine and Miscellaneous Agents

Jonathan Warren, M.D.
Assistant Professor, Critical Care and Emergency Medicine and Medicine, State University of New York Health Science Center at Syracuse; Attending Physician, University Hospital, Syracuse, New York
Fluid and Electrolyte Therapy



Preface

All physicians involved in the care of acutely ill patients are faced with decisions regarding drug therapy. When treating a common condition with which one has extensive experience, the choice of drug therapy is usually not difficult. Problems can arise (1) when treating uncommonly encountered conditions, (2) when treating commonly encountered conditions in patients who have unusual characteristics (e.g., pregnancy, liver failure), and (3) when standard therapy is not having the desired therapeutic effect and more intensive (and possibly less familiar) therapy is needed. This text is designed to lend guidance and give solid guidelines and dosing information for the tough cases, although it will also be useful when treating the easy cases.

Typically, when one encounters a condition with which one has had little experience, an expert can be consulted for help. There are, however, emergent situations where treatment must be given and expert help is not immediately available. In these cases, one may consult several different texts for information regarding the diagnosis, indications for treatment, and actual dosage and method of drug administration. However, specific indications and end-points for drug treatment are often difficult to find in standard texts. It is also frequently difficult to decide what to do next when your first drug choice does not have the desired effect. We have attempted to address these issues in one text so that the physician does not have to consult several different references and *still* be in doubt as to the next step.

Chapters 1 through 4 discuss the basics of drug therapy and special considerations that affect drug therapy. Chapters 5 to 26 discuss specific drug types. Each of these chapters first lists **Conditions** for which treatment with the type of drug is indicated. The text for each condition is divided into **Diagnosis, Indications for Treatment, a Drug Treatment Outline,** and **Discussion.** The **Diagnosis** section is not meant to be a complete discussion of the condition, but rather an attempt to point out the salient differential features of that condition or to hit the high points in diagnosis. The **Indications** section gives *specific* indications for drug treatment for each condition. When specific indications are unclear, this section will usually present a consensus opinion. Although not all authorities will agree with all the specific indications for treatment given in this book, we anticipate that our recommendations represent a majority view. This text gives very specific criteria for treatment with different drugs.

The **Drug Treatment Outline** provides a quick reference for initial dosage, repeat dosage, end-points, and second- and third-line treatment for each condition discussed. These outlines can be used alone, especially when a fast answer is needed, or with the textual material. Significant cautions are usually listed in the outlines (e.g., pretreat children with atropine prior to succinylcholine use). Although the outlines make more sense when used with the text, they can also stand alone.

The Discussion section gives a brief rationale for the preferred use of one drug over another and offers tips and advice based on clinical experience. The discussion section fills in any gaps not covered in the drug treatment outline.

At the end of each chapter, each drug covered in the chapter is outlined separately under the heading Specific Agents. Information on distribution, elimination, and dosing is given, as is information on toxicity and treatment of toxicity. Dosing adjustments for organ failure and Food and Drug Administration categories for use in pregnancy are given for each drug.

It is important to understand that this book addresses, for the most part, only *emergency* drug therapy, and, more specifically, parenteral drug therapy. The outpatient treatment of nonemergent conditions is not covered in most instances. Drug treatment that needs to be given within the first 1 to 2 hours, and often within the first 1 to 2 minutes, is under the purview of this text. Hence, this book is written for those physicians who deal with such conditions. Physicians involved in the day-to-day care of critically ill patients will find useful information, as will the clinician who only occasionally deals with critically ill patients. To reflect this wide audience, the contributors to this text range from intensivists to ophthalmologists, anesthesiologists, emergency physicians, and pediatric pharmacologists.

We have attempted to be up to date with our drug selections, but the lag time between writing and final publication always ensures that something will be out of date by the time of publication. This is especially true in a technologically advanced area like drug treatment. We hope, however, that the reader will find this book useful not only when decisions must be made rapidly, but also when time is available to read in more detail. If this book can be used to enhance patient care in critical situations and at the same time be user friendly, our goal for this text will have been reached.

William G. Barsan, M.D.
Michael S. Jastremski, M.D.
Scott A. Syverud, M.D.

Contents

CHAPTER 1

Basic Clinical Pharmacokinetics

MARIANE McLAUGHLIN, PHARM.D.

Over the past 20 years the science of clinical pharmacokinetics has evolved from simple observation of how a drug is handled by the body to complex monitoring of drug concentration on an individual patient basis. The many advances made in this discipline apply to the relatively small number of pharmacologic agents for which a relationship between serum concentration and desired (or adverse) effect has been established. In general, a basic knowledge of pharmacokinetic principles has become a necessity to the clinician in order to effectively initiate and adjust the dosage regimens of patients receiving pharmacologic treatment. This chapter addresses pharmacokinetic principles, individual variability, and drug concentration monitoring. The pharmacokinetic information presented here is introductory, and the reader is referred to the pharmacokinetics texts in the References following this chapter for more detailed information. Specific pharmacologic agents are addressed in subsequent chapters.

Pharmacokinetics is defined as the time course of drug absorption, distribution, metabolism, and excretion. The effect of these functions on drug concentration is of major importance because an alteration in any one of them has the capacity to drastically change the concentration of active drug reaching its receptor site. In addition, the dosage form itself can delay or enhance drug entry into the systemic circulation. A separate discipline known as biopharmaceutics is devoted to the study of product formulation and its effect on the release and absorption of the active drug. Yet another discipline, pharmacodynamics, is concerned with the study of biochemical and physiologic effects of drugs, or, in other words, their mechanism of action. Last, clinical pharmacokinetics is the science that relates the biopharmaceutic, pharmacokinetic, and pharmacodynamic information to patient care (Fig. 1–1).

LADME

The acronym LADME, which stands for *l*iberation, *a*bsorption, *d*istribution, *m*etabolism, and *e*xcretion, is used to represent the pharmacokinetic processes that occur after administration of a medication. *Liberation* refers to the release of the active drug from the dosage form following oral administration. *Absorption* is defined as the transfer of the drug from the site of administration to the general circulation. *Distribution* refers to the movement of the drug from the circulation to various body fluids and tissues. *Metabolism* is defined as the biotransformation of the drug, usually to inactive, excretable forms. *Excretion* is the elimination of the

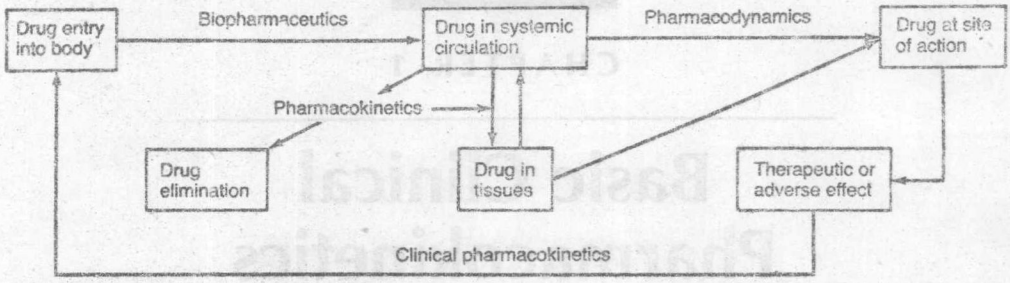


FIGURE 1–1. Interrelationship of biopharmaceutics, pharmacodynamics, pharmacokinetics, and clinical pharmacokinetics.

drug by the kidneys, bile, or lungs, in active or inactive forms.

The effect of these functions on drug concentrations is easily demonstrated using concentration versus time curves. Figure 1–2 represents the changes in serum drug concentration, as effected by LADME, following a single oral dose of a drug.

LIBERATION AND ABSORPTION

Liberation refers to the disintegration of the dosage form of the drug in the gastrointestinal (GI) tract and subsequent dissolution of the active drug in GI fluids. It is generally considered after oral administration of tablets and capsules. Once the drug is released from the dosage form and is in solution, it can be absorbed. Liberation and absorption can be altered by patient factors and/or product formulation factors. Product formulation plays a critical role in these processes, since it can cause changes in the rate and/or extent of absorption and thus ultimately affects the serum concentrations achieved.

Problems with formulation can result in a detrimental decrease in serum concentration due to poor tablet disintegration, binding of the active drug to inert ingredients, and other such factors. However, many benefits are also gained from altered product formulation, such as those provided by the many sustained-release dosage forms developed over the past 10 years. Physiologic factors also have an important role in drug liberation and absorption. Factors such as GI motility, pH of GI fluids, disease states, and food and drug interactions can affect drug liberation and absorption.

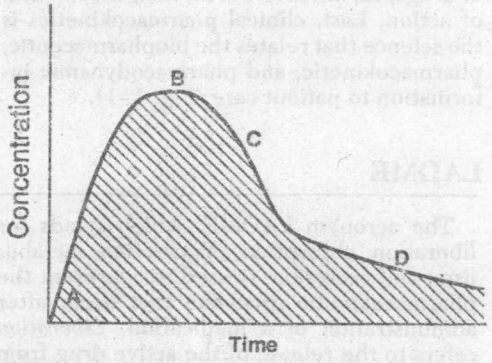


FIGURE 1–2. Graph representing changes in serum drug concentration following a single oral dose of a drug. Section *A* represents the initial absorption of the drug, resulting in increasing serum concentrations. Section *B* reflects the combination of continuing absorption and distribution; thus the serum concentration tends to level off as absorption decreases and distribution commences. Section *C* represents continued distribution and initiation of elimination. Finally, in Section *D*, all other functions are completed, and the concentration versus time curve reflects only elimination. The area under the curve (AUC) represents the total amount of drug reaching the systemic circulation *(shaded area)*.

RATE AND EXTENT OF ABSORPTION

The rate of absorption of a drug directly affects the peak concentration attained. A drug that is absorbed quickly will attain its peak concentration earlier than a drug that is absorbed more slowly. Figure 1–3 represents the concentration versus time curves of two formulations of the same drug, administered at the same dosage. Formulation *A* is rapidly absorbed and attains a high peak concentration (C_{max}) at 1 hour after administration. Formulation *B* is absorbed more slowly and therefore has a lower C_{max} and a greater time to reach that C_{max}. However, the sys-

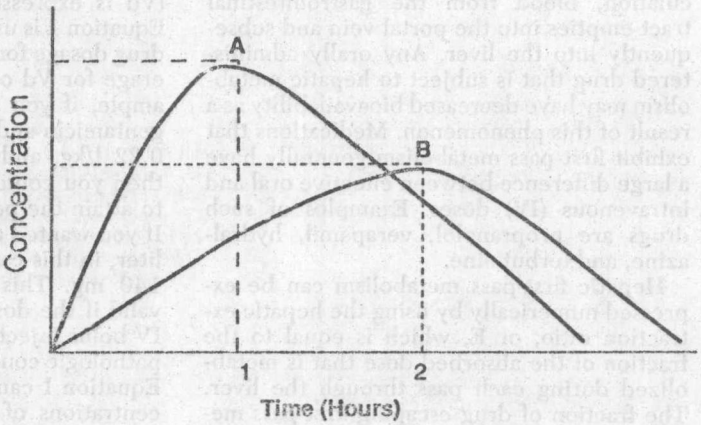


FIGURE 1–3. Effect of the rate of absorption on the concentration versus time curve. Formulation *A* is rapidly absorbed and attains a high peak concentration (or C_{max}) at 1 hour after administration. Formulation *B* is absorbed more slowly and therefore has a lower C_{max} and a greater time to reach that C_{max}. However, the systemic availability of the two formulations, as reflected by the AUC, is identical.

temic availability of the two formulations, as reflected by the AUC, is identical.

Alterations in the rate of absorption can become clinically significant when a minimum concentration must be attained in order for the drug to elicit its desired effect. In such a case, a rapidly absorbed formulation, such as formulation *A* in Figure 1–3, might be more desirable. In general, changes in the extent of absorption have more clinical significance than do changes in the rate of absorption because they can cause the amount of drug in the body to vary greatly. Figure 1–4 represents the concentration versus time curves of two formulations of the same drug, with equal dosages and equal rates of absorption. However, formulation *D* is not completely absorbed and therefore may not reach the minimally effective concentration. In addition, the AUCs of the two formulations in Figure 1–4 are quite different.

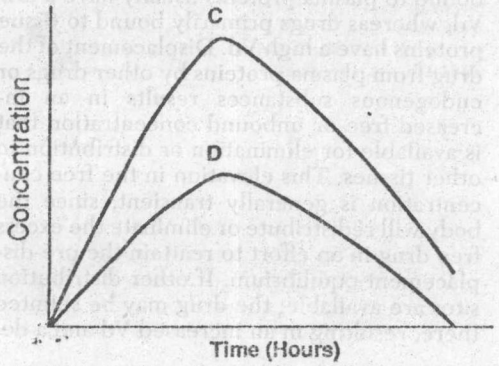


FIGURE 1–4. Effect of the extent of absorption on the concentration versus time curve.

BIOAVAILABILITY

Bioavailability is defined as the rate and extent of drug movement from the site of administration to the systemic circulation. Drugs administered intravascularly are used as a reference point, since 100% of the dose reaches the systemic circulation. The bioavailability of drugs given by other routes of administration is generally less than 100% and reflects the effect of numerous factors on the drug and its dosage form. For example, the bioavailability of medications administered orally reflects the liberation of drug from the dosage form, absorption across the gastrointestinal mucosa, and the effect of hepatic first-pass metabolism (discussed in the following section). In addition, drug solubility, gastric pH, gastric emptying time, intestinal motility, disease states, and interacting substances may all affect a drug's bioavailability. The cumulative effect of all these factors is conveniently reflected numerically as the bioavailable fraction, or f. Drugs administered intravascularly have a bioavailable fraction of one (1), since the entire dose is systemically available, whereas drugs administered extravascularly generally have a bioavailability of less than 100% and a bioavailable fraction of less than one.

HEPATIC FIRST-PASS METABOLISM

Hepatic first-pass metabolism refers to the biotransformation of active drug by the liver prior to the drug's reaching the systemic circulation. Before reaching the systemic cir-

culation, blood from the gastrointestinal tract empties into the portal vein and subsequently into the liver. Any orally administered drug that is subject to hepatic metabolism may have decreased bioavailability as a result of this phenomenon. Medications that exhibit first-pass metabolism generally have a large difference between effective oral and intravenous (IV) doses. Examples of such drugs are propranolol, verapamil, hydralazine, and terbutaline.

Hepatic first-pass metabolism can be expressed numerically by using the hepatic extraction ratio, or E, which is equal to the fraction of the absorbed dose that is metabolized during each pass through the liver. The fraction of drug escaping first-pass metabolism is referred to as (1 − E). The hepatic extraction ratio can also be used to calculate the bioavailable fraction, using the following equation:

$$f = \text{fraction absorbed} \times (1 - E)$$

For example, if 90% of a drug is absorbed after oral administration, and 20% of the absorbed dose is metabolized during first pass, the bioavailable fraction is 0.72. This means that 72% of the dose administered reaches the systemic circulation, or f × the dose.

DISTRIBUTION/VOLUME OF DISTRIBUTION

Once the drug reaches the systemic circulation, it mixes in the plasma, binds to erythrocytes and plasma proteins, and diffuses from the plasma to other body fluids and tissues. The plasma and rapidly equilibrating tissues are referred to as the *central compartment*. Any movement of drug from this central compartment to peripheral or more slowly equilibrating tissues is known as *distribution*. The term *volume of distribution* (Vd) is useful in relating the peak concentration and the dose of drug, as noted in Equation 1.

$$\text{Equation 1: } C_{max} = \frac{\text{dose}}{Vd}$$

The Vd does *not* represent an anatomic moiety but rather the volume of serum that would be required to accommodate all of the drug present in the body, *if* it were present in all tissues at the same concentration at which it is present in the serum or plasma. (Vd is expressed in liters/kilogram [l/kg]). Equation 1 is useful for calculating the initial drug dosage for patients if the population average for Vd of the drug is known. For example, if you are giving a loading dose of gentamicin and know that the average Vd is 0.22 l/kg, and your patient weighs 80 kg, then you could calculate the dose required to attain the peak concentration you desire. If you wanted a peak concentration of 8 mg/liter, in this case the loading dose would be 140 mg. This equation, however, is only valid if the dose of drug is administered by IV bolus injection, and if the patient has no pathologic condition that could alter the Vd. Equation 1 can be modified to estimate concentrations of orally administered medications by including the bioavailable fraction (f) as in Equation 2.

$$\text{Equation 2: } C_{max} = f \times \frac{\text{dose}}{Vd}$$

The two major factors that can alter the Vd of a drug are a change in the medium in which it is distributed and a change in its protein binding. In the case of water-soluble medications, which are primarily distributed in extracellular fluids (ECF), any disease state or condition resulting in a change in the ECF volume alters the Vd. Examples include dehydration, which generally results in a decreased volume of drug distribution, and congestive heart failure, liver disease, ascites, and iatrogenic fluid overload, all of which result in an increased Vd. The Vd of lipid-soluble drugs is not as easily altered, but obesity is one factor that can cause a large increase in their Vd.

Any change in the plasma or tissue protein binding of a drug has the potential to alter the Vd of that drug and subsequently the serum concentration. Drugs that are highly bound to plasma proteins usually have a low Vd, whereas drugs primarily bound to tissue proteins have a high Vd. Displacement of the drug from plasma proteins by other drugs or endogenous substances results in an increased free or unbound concentration that is available for elimination or distribution to other tissues. This elevation in the free concentration is generally transient, since the body will redistribute or eliminate the excess free drug in an effort to reattain the pre-displacement equilibrium. If other distribution sites are available, the drug may be shunted there, resulting in an increased Vd and a de-