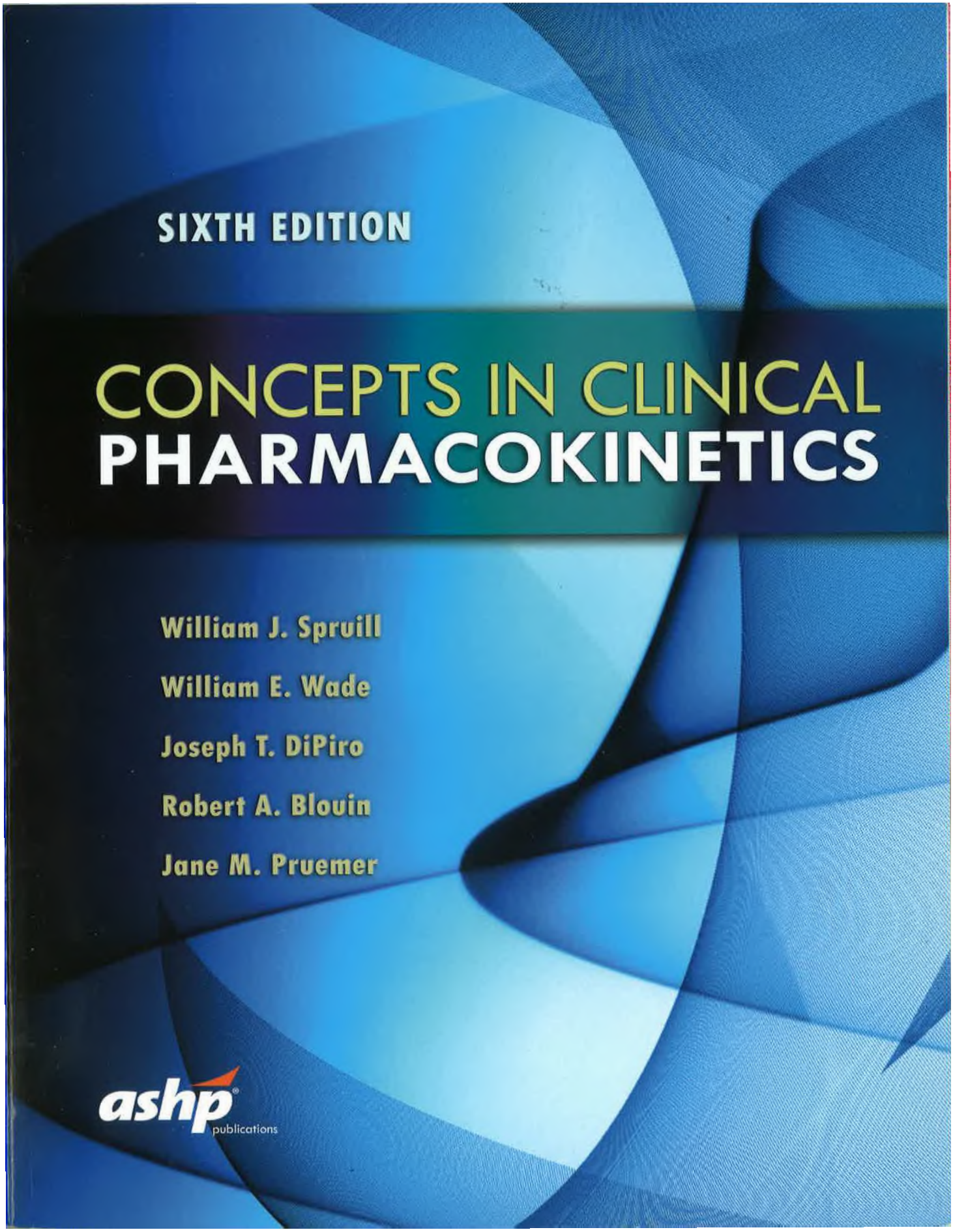

Concepts in Clinical Pharmacokinetics

SIXTH EDITION

William J. Spruill, PharmD, FASHP, FCCP
Associate Professor
Department of Clinical and Administrative Sciences
University of Georgia, College of Pharmacy
Athens, Georgia

William E. Wade, PharmD, FASHP, FCCP
Professor
Department of Clinical and Administrative Sciences
University of Georgia, College of Pharmacy
Athens, Georgia

Joseph T. DiPiro, PharmD
Executive Dean
South Carolina College of Pharmacy
Charleston, South Carolina

Robert A. Blouin, PharmD
Professor and Dean
UNC Eshelman School of Pharmacy
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Jane M. Pruemer, PharmD, BCOP, FASHP
Professor of Clinical Pharmacy Practice
James L. Winkle College of Pharmacy
University of Cincinnati
Cincinnati, Ohio

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Preface

For students just entering the world of pharmacy or seasoned practitioners, the study of pharmacokinetics and the mathematical equations required for drug dosing can be quite intimidating. Combined with the terminology of the science, this may make a course in pharmacokinetics a considerable challenge. In this sixth edition of *Concepts in Clinical Pharmacokinetics*, we continue to focus on the fundamental pharmacokinetic concepts. These concepts, along with the mathematical equations, are broken down to their simplest forms, and a step-by-step approach is adopted to explain the "how to" of the discipline. We believe that such an approach allows the student to gain greater comprehension of the subject matter, which allows adaptation of concepts to specific clinical drug dosing situations.

Pharmacokinetic concepts are further illustrated by application to clinical dosing cases, including aminoglycosides, vancomycin, theophylline, digoxin, and phenytoin. These cases are designed to show the easily understandable, step-by-step approach for performing appropriate clinical dosing consults. All cases provide the complete mathematical solutions for each calculation, allowing readers to "check their math." Equations are explained in detail, and all similar equations used throughout the text are cross-referenced to the basic concept. In addition there is a valuable appendix containing basic and drug-specific pharmacokinetic equations.

This edition expands on several concepts including proper estimation of renal function, extended-interval aminoglycoside dosing, pharmacogenomic effects on drug metabolism, a phenytoin "cheat sheet" to help you through the calculations maze, and new vancomycin cases based on higher desired vancomycin levels and trough-only dose estimations. As with past editions the reader will find numerous clinical correlates throughout the text to further highlight specific clinical or mathematical explanations.

The goal for this edition, as with the previous five editions, remains the same—to provide the student or practitioner with the concepts and clinical applications needed for a better understanding of this complicated, yet vital, subject.

William J. Spruill
William E. Wade
Joseph T. DiPiro
Robert A. Blouin
Jane M. Pruemer

February 2014

Acknowledgments

We are indebted to our wives Paula Spruill, Theresa Wade, and Cecily DiPiro for their love and patience during the preparation of this sixth edition.

A Note from the Authors on Using This Edition

This book teaches the basic biopharmaceutic concepts, mathematical models, and clinical applications needed to determine such values as dose, interval, steady-state concentration, etc. Specific conceptual and mathematical formulas are combined to solve more complex dosing situations. Eleven chapters contain a practice quiz to chart your progress, and there are three practice sets of questions with answers. The last four chapters are completely devoted to clinical cases that fully explain, step-by-step, how to dose several drugs that generally require serum drug concentrations. We strongly encourage you to attempt to solve these cases without looking at the step-by-step answers, and then when finished, check to see if you got them right.

—WS, WW, JD

A complete online course based on this book with four enrollment options is available through the University of Georgia Center for Continuing Education. To learn more go to:

http://www.georgiacenter.uga.edu/courses/healthcare-pharmacy

Abbreviations

- **α** : distribution rate constant for two-compartment model
- **AUC** : area under plasma drug concentration versus time curve
- **AUMC** : area under the (drug concentration × time) versus time (moment) curve
- **β** : terminal elimination rate constant
- **C** : concentration
  - $\overline{C}$ average steady-state concentration
  - C_0, C_1, C_2 initial (just after infusion), first, second concentrations
  - C_{in} concentration in blood on entering organ
  - C_{last} last measured concentration
  - C_{max} maximum concentration
  - C_{max1}, C_{max2} first, second maximum concentrations
  - $C_{max\,(steady\,state)}$ steady-state maximum concentration
  - $C_{min\,(steady\,state)}$ steady-state minimum concentration
  - C_{min} minimum concentration
  - C_{out} concentration in blood on leaving organ
  - C_{peak} peak concentration
  - C_{ss} steady-state concentration
  - C_t concentration at time *t*
  - C_{trough} trough concentration
- **Cl** : clearance
  - Cl_b biliary clearance
  - Cl_h hepatic (liver) clearance
  - Cl_i intrinsic clearance
  - Cl_m clearance by metabolism (mainly liver)
  - $Cl_{other\ organs}$ clearance by other organs
  - $Cl_{P \to mX}$ formation clearance for a given metabolite *X*
  - $Cl_{P \to m1}$ fractional clearance of parent drug (*P*) to form metabolite 1 (m_1)
  - Cl_r renal clearance
  - Cl_t total body clearance
- **conc** : concentration
- **Δ** : change in
- ***E*** : extraction ratio

continued on next page

- **e** : base of natural logarithm
- **F** : fraction of drug absorbed that reaches systemic circulation (bioavailability)
  - F_{m1} fraction of m_1 formed from a single dose of the parent drug
  - F_p fraction of unbound drug in plasma
  - F_t fraction of unbound drug in tissue
- **GFR** : glomerular filtration rate
- **GI** : gastrointestinal
- **K** : elimination rate constant
  - K_0 rate of drug infusion
  - K_{12} rate constant for transfer of drug from compartment 1 to compartment 2
  - K_{21} rate constant for transfer of drug from compartment 2 to compartment 1
  - K_a absorption rate constant
  - K_m Michaelis–Menten constant (drug concentration at which elimination rate = ½ Vmax)
- **λ** : terminal elimination rate constant
- m_1, m_2, m_3 : metabolites 1, 2, and 3
- $m_{1,u}, m_{2,u}, m_{3,u}$: amount of m_1, m_2, or m_3 excreted in the urine
- **MRT** : mean residence time
- **n** : number of doses
- **Q** : bloodflow
  - Q_h hepatic bloodflow
- **S** : salt form of drug
- **SST** : serum separator tube
- **τ** : dosing interval
- **t** : time (after dose)
  - t' time after end of infusion ($t' = \tau - t$ for trough concentration)
  - t'' time (duration) of loading infusion
  - t_0 time zero
  - $T½$ half-life
  - $t_{90\%}$ time required to reach 90% of steady-state concentration
- **V** : volume; volume of distribution
  - V_{area} volume of distribution by area
  - V_c volume of central compartment
  - V_{extrap} extrapolated volume of distribution
  - V_p plasma volume
  - V_{ss} steady-state volume of distribution
  - V_t tissue volume
  - V_{max} maximum rate of the elimination process
- **X** : amount of drug
  - X_0 dose (or initial dose) of drug
  - X_1, X_2 amount of drug at different times
  - X_c amount of drug in central compartment
  - X_d daily dose of drug
  - X_p amount of drug in peripheral compartment

LESSON 1

Introduction to Pharmacokinetics and Pharmacodynamics

OBJECTIVES

After completing Lesson 1, you should be able to:

1. Define and differentiate between *pharmacokinetics* and *clinical pharmacokinetics*.
2. Define *pharmacodynamics* and relate it to pharmacokinetics.
3. Describe the concept of the therapeutic concentration range.
4. Identify factors that cause interpatient variability in drug disposition and drug response.
5. Describe situations in which routine clinical pharmacokinetic monitoring would be advantageous.
6. List the assumptions made about drug distribution patterns in both one- and two-compartment models.
7. Represent graphically the typical natural log of plasma drug concentration versus time curve for a one-compartment model after an intravenous dose.

Pharmacokinetics is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. *Clinical pharmacokinetics* is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.

A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practical. For example, the receptor sites for digoxin are thought to be within the myocardium. Obviously we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids (**Figure 1-1**). *Kinetic homogeneity* describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect (**Figure 1-2**). Changes in the plasma drug concentration reflect changes in drug concentrations

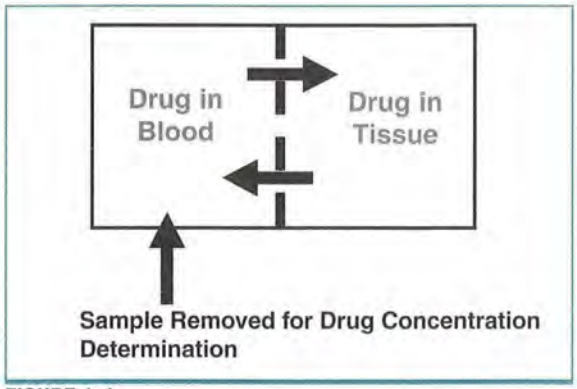

FIGURE 1-1.
Blood is the fluid most often sampled for drug concentration determination.

at the receptor site, as well as in other tissues. As the concentration of drug in plasma increases, the concentration of drug in most tissues will increase proportionally.

Similarly, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. **Figure 1-3** is a simplified plot of the drug concentration versus time profile after an intravenous drug dose and illustrates this concept.

The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics. It is the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

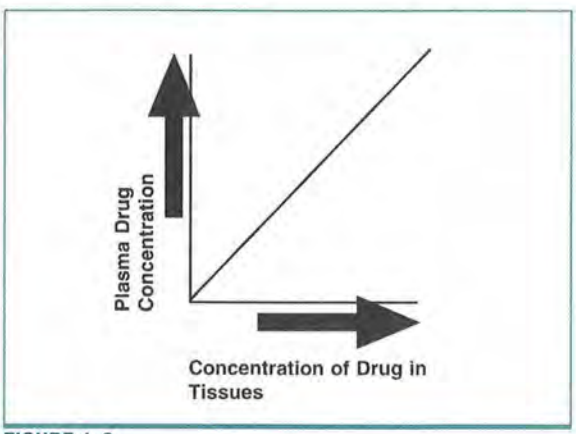

FIGURE 1-2.
Relationship of plasma to tissue drug concentrations.

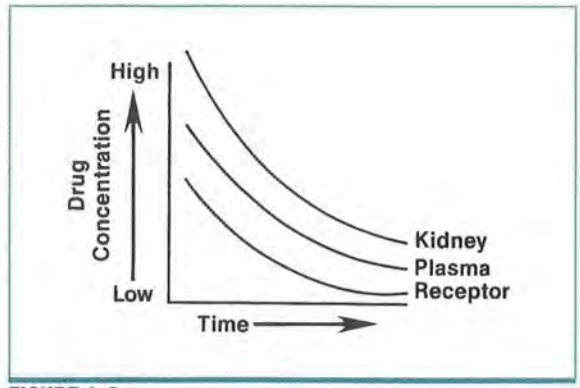

FIGURE 1-3.
Drug concentration versus time.

Clinical Correlate

Drugs concentrate in some tissues because of physical or chemical properties. Examples include digoxin, which concentrates in the myocardium, and lipid-soluble drugs, such as benzodiazepines, which concentrate in fat.

Basic Pharmacodynamic Concepts

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. Receptors may be present on neurons in the central nervous system (i.e., opiate receptors) to depress pain sensation, on cardiac muscle to affect the intensity of contraction, or even within bacteria to disrupt maintenance of the bacterial cell wall.

For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect (**Figure 1-4**). However, other factors affect drug response as well. Density of receptors on the cell surface, the mechanism by which a signal is transmitted into the cell by second messengers (substances within the cell), or regulatory factors that control gene translation and protein produc-

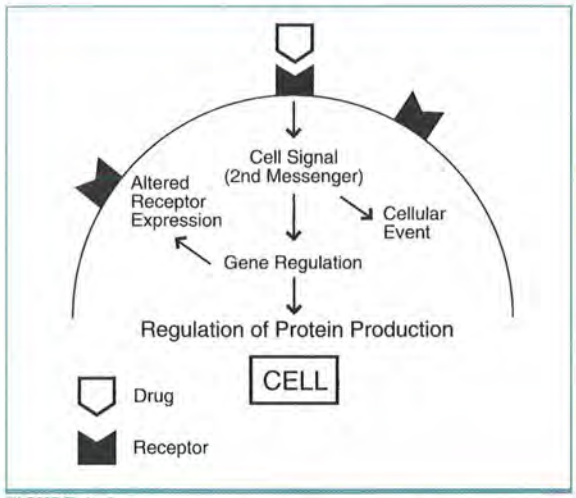

FIGURE 1-4.
Relationship of drug concentration to drug effect at the receptor site.

tion may influence drug effect. This multilevel regulation results in variation of sensitivity to drug effect from one individual to another and also determines enhancement of, or tolerance to, drug effects.

In the simplest examples of drug effect, there is a relationship between the concentration of drug at the receptor site and the pharmacologic effect. If enough concentrations are tested, a maximum effect (E_{max}) can be determined (**Figure 1-5**). When the logarithm of concentration is plotted versus effect (Figure 1-5), one can see that there is a concentration below which no effect is observed and a concentration above which no greater effect is achieved.

One way of comparing *drug potency* is by the concentration at which 50% of the maximum effect is achieved. This is referred to as the *50% effective concentration* or *EC_{50}*. When two drugs are tested in the same individual, the drug with a lower EC_{50} would be considered more potent. This means that a lesser amount of a more potent drug is needed to achieve the same effect as a less potent drug.

The EC_{50} does not, however, indicate other important determinants of drug response, such as the duration of effect. Duration of effect is determined by a complex set of factors, including the time that a drug is engaged on the receptor as well as intracellular signaling and gene regulation.

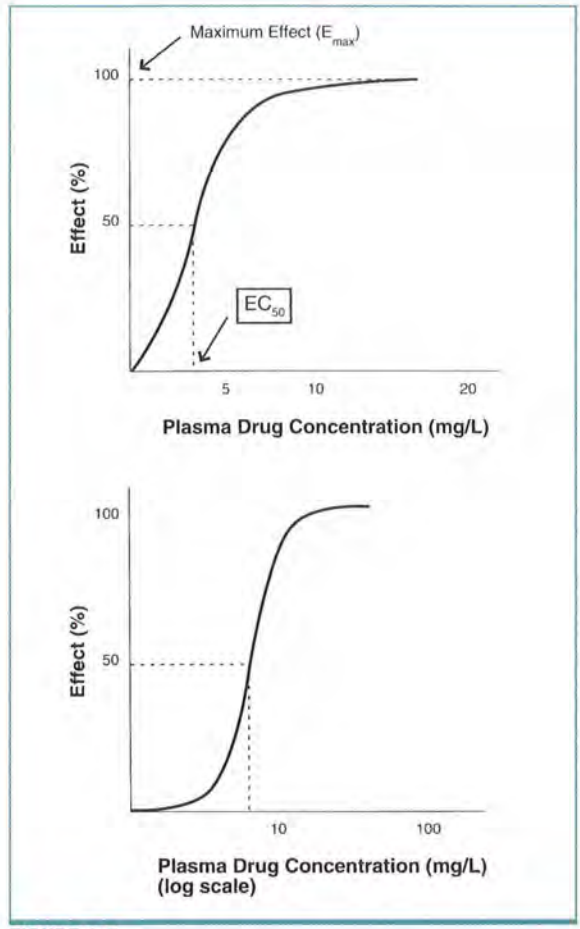

FIGURE 1-5.
Relationship of drug concentration at the receptor site to effect (as a percentage of maximal effect).

For some drugs, the effectiveness can decrease with continued use. This is referred to as *tolerance*. Tolerance may be caused by pharmacokinetic factors, such as increased drug metabolism, that decrease the concentrations achieved with a given dose. There can also be pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure. An example of drug tolerance is the use of opiates in the management of chronic pain. It is not uncommon to find these patients requiring increased doses of the opiate over time. Tolerance can be described in terms of the dose–response curve, as shown in **Figure 1-6**.

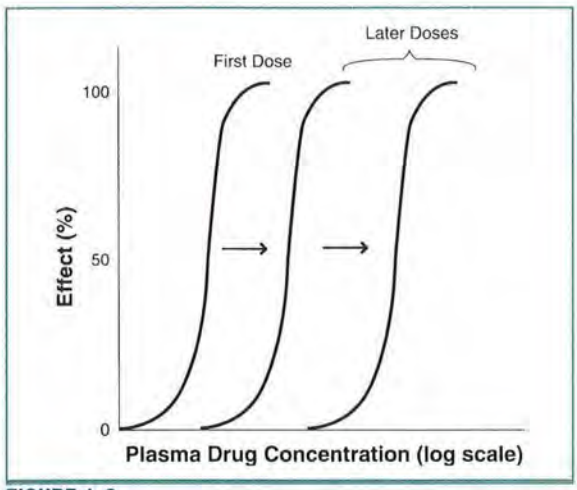

FIGURE 1-6.
Demonstration of tolerance to drug effect with repeated dosing.

To assess the effect that a drug regimen is likely to have, the clinician should consider pharmacokinetic and pharmacodynamic factors. Both are important in determining a drug's effect.

Clinical Correlate

Tolerance can occur with many commonly used drugs. One example is the hemodynamic tolerance that occurs with continued use of organic nitrates, such as nitroglycerin. For this drug, tolerance can be reversed by interspersing drug-free intervals with chronic drug use.

Clinical Correlate

One way to compare potency between two drugs that are in the same pharmacologic class is to compare EC_{50}. The drug with a lower EC_{50} is considered more potent.

Therapeutic Drug Monitoring

Therapeutic drug monitoring is defined as the use of assay procedures for determination of drug concentrations in plasma, and the interpretation and application of the resulting concentration data to develop safe and effective drug regimens. If performed properly, this process allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes. Together with observations of the drug's clinical effects, it should provide the safest approach to optimal drug therapy.

The usefulness of plasma drug concentration data is based on the concept that pharmacologic response is closely related to drug concentration at the site of action. For certain drugs, studies in patients have provided information on the plasma concentration range that is safe and effective in treating specific diseases—the therapeutic range (**Figure 1-7**). Within this therapeutic range, the desired effects of the drug are observed. Below it, there is greater probability that the therapeutic benefits are not realized; above it, toxic effects may occur.

No absolute boundaries divide subtherapeutic, therapeutic, and toxic drug concentrations. A gray area usually exists for most drugs in which these concentrations overlap due to variability in individual patient response.

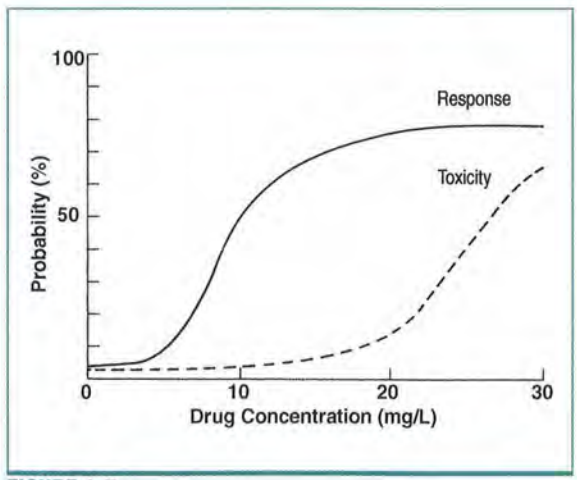

FIGURE 1-7.
Relationship between drug concentration and drug effects for a hypothetical drug.

Source: Adapted with permission from Evans WE, editor. General principles of applied pharmacokinetics. In: *Applied Pharmacokinetics*, 3rd ed. Vancouver, WA: Applied Therapeutics; 1992. pp.1–3.

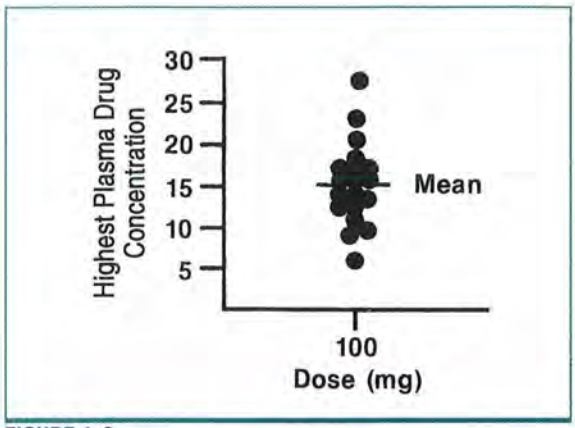

FIGURE 1-8.
Example of variability in plasma drug concentration among subjects given the same drug dose.

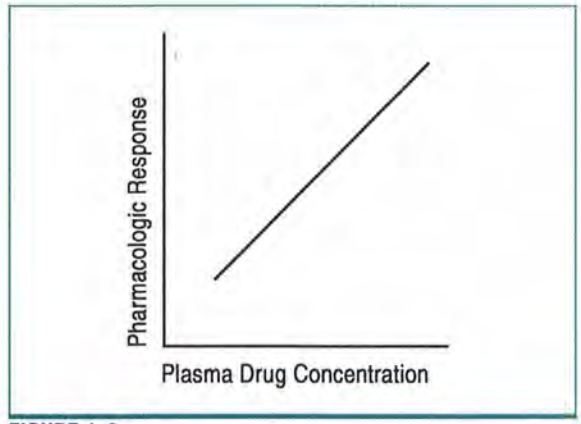

FIGURE 1-9.
When pharmacologic effects relate to plasma drug concentrations, the latter can be used to predict the former.

Numerous pharmacokinetic characteristics of a drug may result in variability in the plasma concentration achieved with a given dose when administered to various patients (**Figure 1-8**). This interpatient variability is primarily attributed to one or more of the following:

- Variations in drug absorption
- Variations in drug distribution
- Differences in an individual's ability to metabolize and eliminate the drug (e.g., genetics)
- Disease states (renal or hepatic insufficiency) or physiologic states (e.g., extremes of age, obesity) that alter drug absorption, distribution, or elimination
- Drug interactions

Therapeutic monitoring using drug concentration data is valuable when:

- A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. This relationship allows us to predict pharmacologic effects with changing plasma drug concentrations (**Figure 1-9**).
- Wide intersubject variation in plasma drug concentrations results from a given dose.
- The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).
- The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensives).

The value of therapeutic drug monitoring is limited in situations in which:

- There is no well-defined therapeutic plasma concentration range.
- The formation of pharmacologically active metabolites of a drug complicates the application of plasma drug concentration data to clinical effect unless metabolite concentrations are also considered.
- Toxic effects may occur at unexpectedly low drug concentrations as well as at high concentrations.
- There are no significant consequences associated with too high or too low levels.

Theophylline is an excellent example of a drug in which significant interpatient variability in pharmacokinetic properties exists. This is important from a clinical standpoint as subtle changes in serum concentrations may result in marked changes in drug response. **Figure 1-10** shows the relationship between theophylline concentration (*x*-axis, on a logarithmic scale) and its pharmacologic effect (changes in pulmonary function [*y*-axis]). This figure illustrates that as the concentration of theophylline increases, so does the intensity of the response for some patients. Wide interpatient variability is also shown.

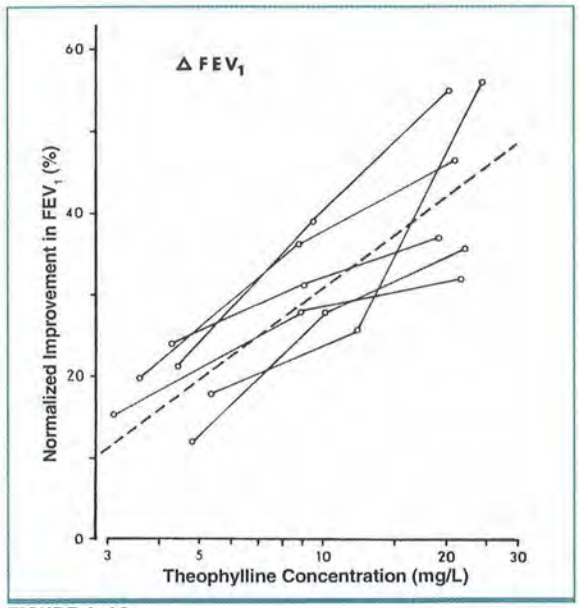

FIGURE 1-10.
Relationship between plasma theophylline concentration and change in forced expiratory volume (FEV) in asthmatic patients. **Source:** Reproduced with permission from Mitenko PA, Ogilvie RI. Rational intravenous doses of theophylline. *N Engl J Med* 1973;289:600–3. Copyright 1973, Massachusetts Medical Society.

Figure 1-11 outlines the process clinicians may choose to follow in making drug dosing decisions by using therapeutic drug monitoring. **Figure 1-12** shows the relationship of pharmacokinetic and pharmacodynamic factors.

Examples of therapeutic ranges for commonly used drugs are shown in **Table 1-1**.

As can be seen in this table, most drug concentrations are expressed as a unit of mass per volume.

Clinical Correlate

A drug's effect may also be determined by the amount of time that the drug is present at the site of action. An example is with beta-lactam antimicrobials. The rate of bacterial killing by beta-lactams (the bacterial cell would be considered the site of action) is usually determined by the length of time that the drug concentration remains above the minimal concentration that inhibits bacterial growth.

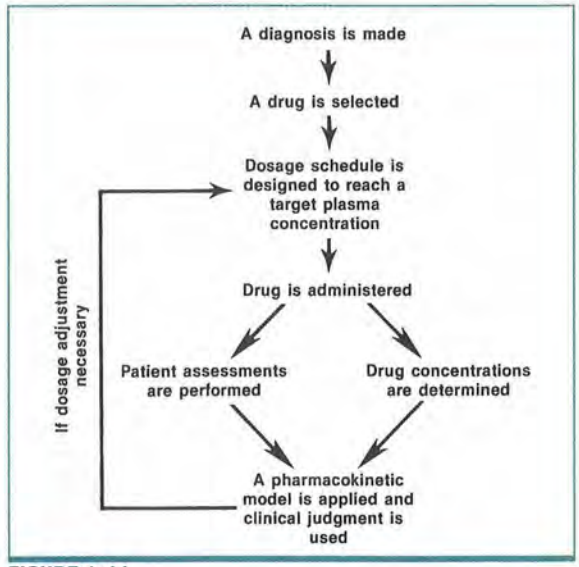

FIGURE 1-11.
Process for reaching dosage decisions with therapeutic drug monitoring.

TABLE 1-1. Therapeutic Ranges for Commonly Used Drugs

Drug	Range
Digoxin	0.5–2.0 ng/mL
Lidocaine	1.5–5.0 mg/L
Lithium	0.6–1.4 mEq/L
Phenobarbital	15–40 mg/L
Phenytoin	10–20 mg/L
Quinidine	2–5 mg/L
Cyclosporine	150–400 ng/mL
Valproic acid	50–100 mg/L
Carbamazepine	4–12 mcg/L
Ethosuximide	40–100 mg/L
Primidone	5–12 mg/L

Source: Adapted with permission from Bauer LA. Clinical pharmacokinetics and pharmacodynamics. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. *Pharmacotherapy: a Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill; http://Accesspharmacy.com

Pharmacokinetic Models

The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Simplifications of body processes are necessary to

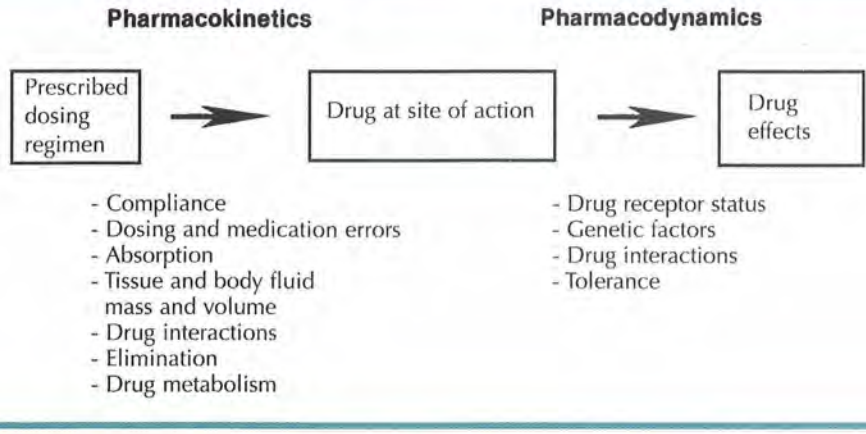

FIGURE 1-12.
Relationship of pharmacokinetics and pharmacodynamics and factors that affect each.

predict a drug's behavior in the body. One way to make these simplifications is to apply mathematical principles to the various processes.

To apply mathematical principles, a model of the body must be selected. A basic type of model used in pharmacokinetics is the *compartmental model.* Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body. There are one-compartment, two-compartment, and multicompartment models. The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids. These models can be used to predict the time course of drug concentrations in the body (**Figure 1-13**).

Compartmental models are termed *deterministic* because the observed drug concentrations determine the type of compartmental model required to describe the pharmacokinetics of the drug. This concept will become evident when we examine one- and two-compartment models.

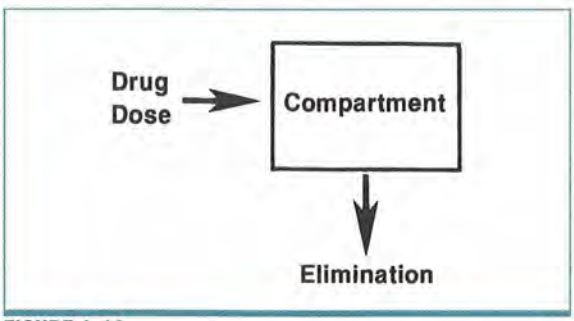

FIGURE 1-13.
Simple compartmental model.

To construct a compartmental model as a representation of the body, simplifications of body structures are made. Organs and tissues in which drug distribution is similar are grouped into one compartment. For example, distribution into adipose tissue differs from distribution into renal tissue for most drugs. Therefore, these tissues may be in different compartments. The highly perfused organs (e.g., heart, liver, and kidneys) often have similar drug distribution patterns, so these areas may be considered as one compartment. The compartment that includes blood (plasma), heart, lungs, liver, and kidneys is usually referred to as the *central compartment* or the *highly blood-perfused compartment* (**Figure 1-14**). The other compartment that includes fat tissue, muscle tissue, and cerebrospinal fluid is the peripheral compartment, which is less well perfused than the central compartment.

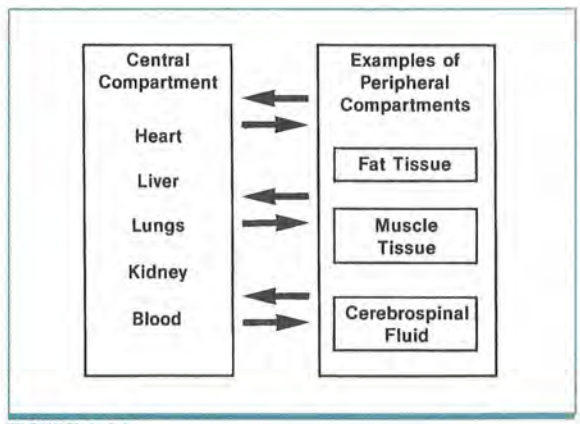

FIGURE 1-14.
Typical organ groups for central and peripheral compartments.

Another simplification of body processes concerns the expression of changes in the amount of drug in the body over time. These changes with time are known as *rates*. The *elimination rate* describes the change in the amount of drug in the body due to drug elimination over time. Most pharmacokinetic models assume that elimination does not change over time.

The value of any model is determined by how well it predicts drug concentrations in fluids and tissues. Generally, it is best to use the simplest model that accurately predicts changes in drug concentrations over time. If a one-compartment model is sufficient to predict plasma drug concentrations (and those concentrations are of most interest to us), then a more complex (two-compartment or more) model is not needed. However, more complex models are often required to predict tissue drug concentrations.

Clinical Correlate

Drugs that do not extensively distribute into extravascular tissues, such as aminoglycosides, are generally well described by one-compartment models. Extent of distribution is partly determined by the chemistry of the agents. Aminoglycosides are polar molecules, so their distribution is limited primarily to extracellular water. Drugs extensively distributed in tissue (such as lipophilic drugs like the benzodiazepines) or that have extensive intracellular uptake may be better described by the more complex models.

Compartmental Models

The one-compartment model is the most frequently used model in clinical practice. In structuring the model, a visual representation is helpful. The compartment is represented by an enclosed square or rectangle, and rates of drug transfer are represented by straight arrows (**Figure 1-15**). The arrow pointing into the box simply indicates that drug is put into that compartment; the arrow pointing out of the box indicates that drug is leaving the compartment.

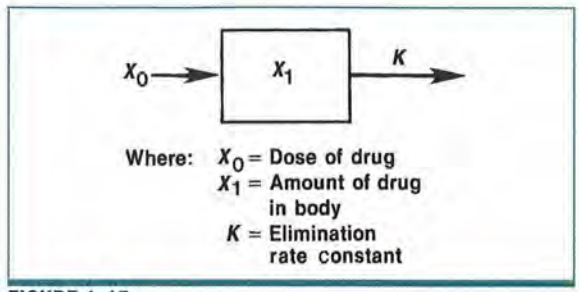

FIGURE 1-15.
One-compartment model.

This model is the simplest because there is only one compartment. All body tissues and fluids are considered a part of this compartment. Furthermore, it is assumed that after a dose of drug is administered, it distributes instantaneously to all body areas. Common abbreviations are shown in Figure 1-15.

Some drugs do not distribute instantaneously to all parts of the body, however, even after intravenous bolus administration. *Intravenous bolus dosing* means administering a dose of drug over a very short time period. A common distribution pattern is for the drug to distribute rapidly in the bloodstream and to the highly perfused organs, such as the liver and kidneys. Then, at a slower rate, the drug distributes to other body tissues. This pattern of drug distribution may be represented by a two-compartment model. Drug moves back and forth between these compartments to maintain equilibrium (**Figure 1-16**).

Figure 1-17 simplifies the difference between one- and two-compartment models. Again, the one-compartment model assumes that the drug is distributed to tissues very rapidly after intravenous administration.

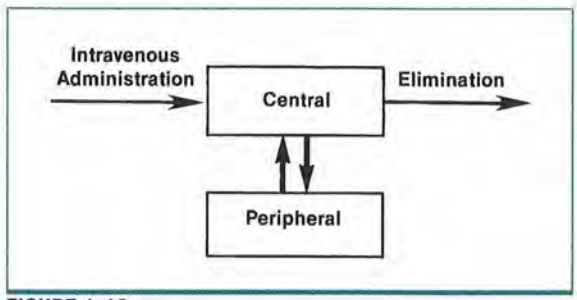

FIGURE 1-16.
Compartmental model representing transfer of drug to and from central and peripheral compartments.

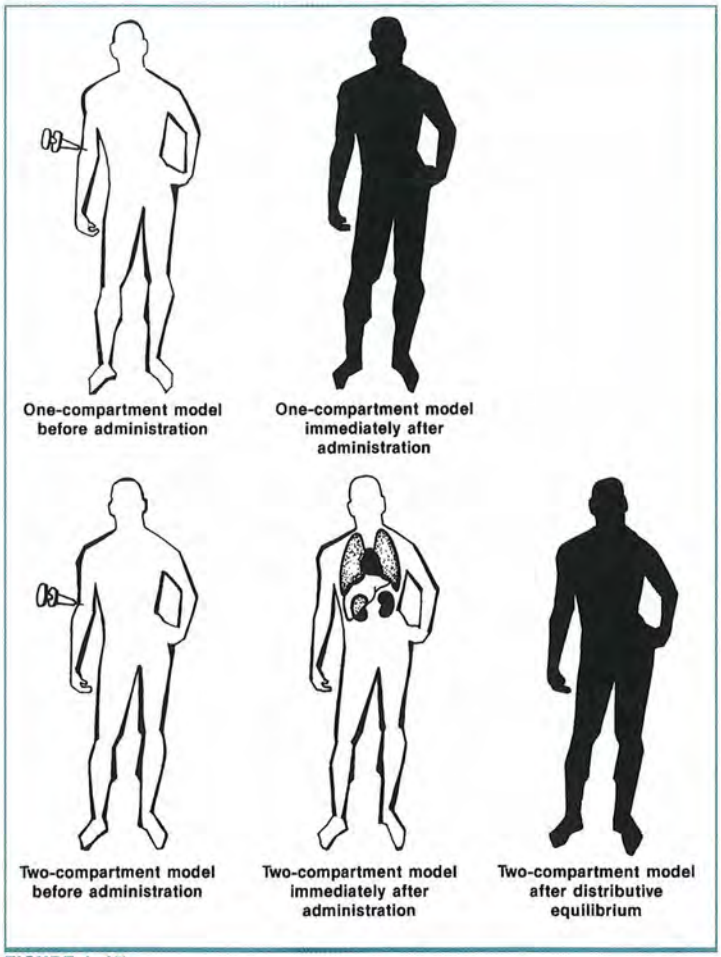

FIGURE 1-17.
Drug distribution in one- and two-compartment models.

The two-compartment model can be represented as in **Figure 1-18**, where:

- X_0 = dose of drug
- X_1 = amount of drug in central compartment
- X_2 = amount of drug in peripheral compartment
- K = elimination rate constant of drug from central compartment to outside the body
- K_{12} = elimination rate constant of drug from central compartment to peripheral compartment
- K_{21} = elimination rate constant of drug from peripheral compartment to central compartment

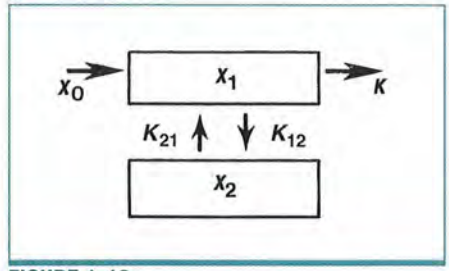

FIGURE 1-18.
Two-compartment model.

Clinical Correlate

Digoxin, particularly when given intravenously, is an example of a drug that is well described by two-compartment pharmacokinetics. After an intravenous dose is administered, plasma concentrations rise and then rapidly decline as drug distributes out of plasma and into muscle tissue. After equilibration between drug in tissue and plasma, plasma concentrations decline less rapidly (**Figure 1-19**). The plasma would be the central compartment, and muscle tissue would be the peripheral compartment.

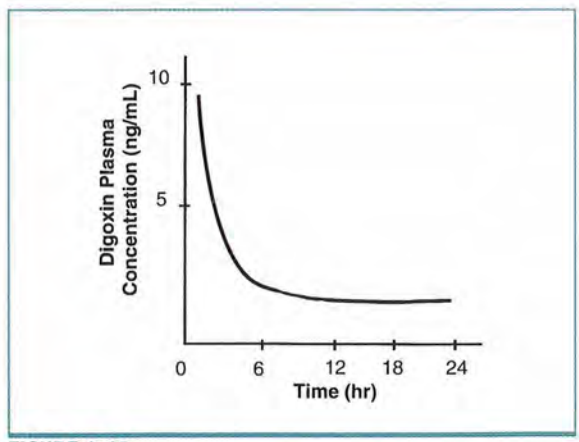

FIGURE 1-19.
Plasma concentrations of digoxin after an intravenous dose.

Volume of Distribution

Until now, we have spoken of the amount of drug (X) in a compartment. If we also consider the volume of the compartment, we can describe the concept of drug concentration. *Drug concentration* in the compartment is defined as the amount of drug in a given volume, such as mg/L:

$$\text{concentration} = \frac{\text{amount of drug in body}}{\text{volume in which drug is distributed}} = \frac{X}{V} \quad \text{1-1}$$

Volume of distribution (usually expressed as V, Vd, or V_D) is an important indicator of the extent of drug distribution into body fluids and tissues. V relates the amount of drug in the body (X) to the measured concentration in the plasma (C). Thus, V is the volume required to account for all of the drug in the body if the concentrations in all tissues are the same as the plasma concentration:

$$\text{volume of distribution} = \frac{\text{amount of drug}}{\text{concentration}}$$

A large volume of distribution usually indicates that the drug distributes extensively into body tissues and fluids. Conversely, a small volume of distribution often indicates limited drug distribution.

Volume of distribution indicates the extent of distribution but not the tissues or fluids into which the drug distributes. Two drugs can have the same volume of distribution, but one may distribute primarily into muscle tissues, whereas the other may concentrate in adipose tissues. Approximate volumes of distribution for some commonly used drugs are shown in **Table 1-2**.

TABLE 1-2. Approximate Volumes of Distribution of Commonly Used Drugs

Drug	Volume of Distribution (L/kg)
Amlodipine	16.0 ± 4
Ganciclovir	1.1 ± 0.2
Ketorolac	0.21 ± 0.04
Lansoprazole	0.35 ± 0.05
Montelukast	0.15 ± 0.02
Sildenafil	1.2 ± 0.3
Valsartan	0.23 ± 0.09

Source: Brunton LL, Lazo JS, Parker KL (editors). *The Pharmacologic Basis of Therapeutics*, 11th edition. New York: McGraw-Hill; 2006. pp. 1798, 1829, 1839, 1840, 1851, 1872, 1883.

When V is many times the volume of the body, the drug concentrations in some tissues should be much greater than those in plasma. The smallest volume in which a drug may distribute is the plasma volume.

To illustrate the concept of volume of distribution, let us first imagine the body as a tank filled with fluid as the body is primarily composed of water. To calculate the volume of the tank, we can place a known quantity of substance into it and then measure its concentration in the fluid (**Figure 1-20**). If the amount of substance (X) and the resulting concentration (C) is known, then the volume of distribution (V) can be calculated using the simplified equations:

$$X = VC \text{ or } C = \frac{X}{V} \text{ or } V = \frac{X}{C}$$

X = amount of drug in body

V = volume of distribution

C = concentration in the plasma

As with other pharmacokinetic parameters, volume of distribution can vary considerably from one person to another because of differences in physiology or disease states. *Something to note:* The dose of a drug (X_0) and the amount of drug in the body (X) are essentially the same thing because all of the dose goes into the body.

In this example, important assumptions have been made: that instantaneous distribution occurs and that it occurs equally throughout the tank. In the closed tank, there is no elimination. This example is analogous to a one-compartment model of the body after intravenous bolus administration. However, there is one complicating factor—during

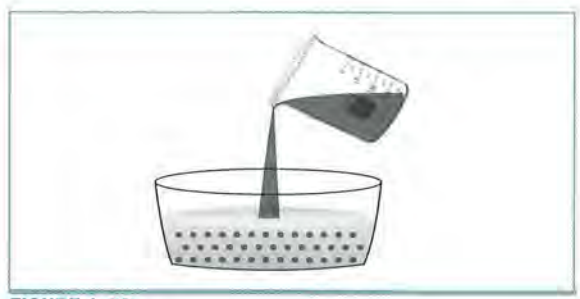

FIGURE 1-20.
The volume of a tank can be determined from the amount of substance added and the resulting concentration.

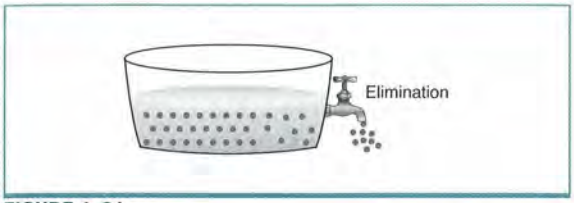

FIGURE 1-21.
Drug elimination complicates the determination of the volume of the body from drug concentrations.

the entire time that the drug is in the body, elimination is taking place. So, if we consider the body as a tank with an open outlet valve, the concentration used to calculate the volume of the tank would be constantly changing (**Figure 1-21**).

We can use the relationship given in **Equation 1-1** for volume, amount of drug administered, and resulting concentration to estimate a drug's volume of distribution in a patient. If we give a known dose of a drug and determine the concentration of that drug achieved in the plasma, we can calculate a volume of distribution. However, the concentration used for this estimation must take into account changes resulting from drug elimination, as discussed in Lessons 3 and 9.

For example:

If 100 mg of drug X is administered intravenously and the plasma concentration is determined to be 5 mg/L just after the dose is given, then:

$$\text{volume of distribution } (V) = \frac{\text{dose}}{\text{resulting concentration}} = \frac{X_0}{C} = \frac{100 \text{ mg}}{5 \text{ mg/L}} = 20 \text{ L}$$

Clinical Correlate

The volume of distribution is easily approximated for many drugs. For example, if the first 80-mg dose of gentamicin is administered intravenously and results in a peak plasma concentration of 8 mg/L, volume of distribution would be calculated as follows:

$$\text{volume of distribution } (V) = \frac{\text{dose}}{\text{resulting concentration}} = \frac{X_0}{C} = \frac{80 \text{ mg}}{8 \text{ mg/L}} = 10 \text{ L}$$

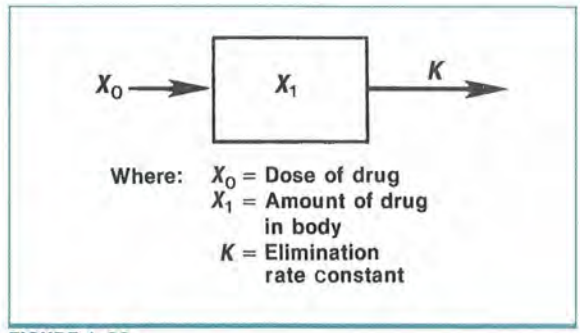

FIGURE 1-22.
One-compartment model.

Clinical Correlate

Drugs that have extensive distribution outside of plasma appear to have a large volume of distribution. Examples include digoxin, diltiazem, imipramine, labetalol, metoprolol, meperidine, and nortriptyline.

Plasma Drug Concentration Versus Time Curves

With the one-compartment model (**Figure 1-22**), if we continuously measure the concentration of a drug in the plasma after an intravenous bolus dose and then plot these plasma drug concentrations against the times they are obtained, the curve shown in **Figure 1-23** would result. Note that this plot is a curve and that the plasma concentration is highest just after the dose is administered at time zero (t_0).

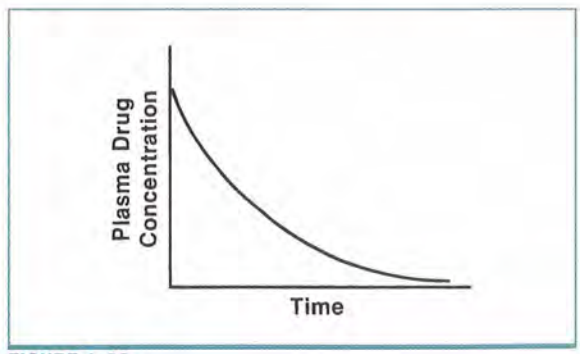

FIGURE 1-23.
Typical plasma drug concentration versus time curve for a one-compartment model.

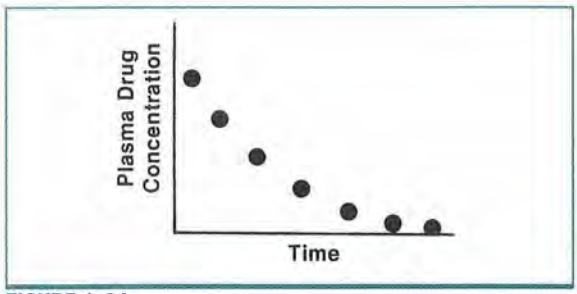

FIGURE 1-24.
Plasma drug concentrations determined at specific time points.

Because of cost limitations and patient convenience in clinical situations, only a small number of plasma samples are usually obtained for measuring drug concentrations (**Figure 1-24**). From these known values, one is able to predict plasma drug concentrations at times when no samples are available (**Figure 1-25**). In clinical situations, it is rare to collect more than two samples after a dose.

The prediction of drug concentrations based on known concentrations can be subject to multiple sources of error. However, if we realize the assumptions used to make the predictions, some errors can be avoided. These assumptions are pointed out as we review the one-compartment system.

From a mathematical standpoint, the prediction of plasma concentrations is easier if we know that the concentrations are all on a straight line rather than a curve. This conversion can be accomplished for most drugs by plotting the natural logarithm (ln) of the plasma drug concentration versus time. The plot of a curve (Figure 1-25) is, in effect, converted to a straight line by using the natural log of the plasma drug concentration (**Figure 1-26**).

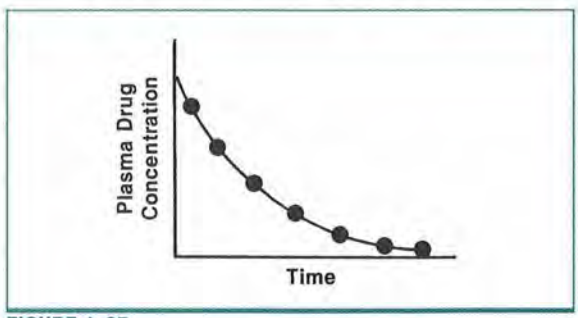

FIGURE 1-25.
Plasma drug concentrations can be predicted for times when they were not determined. Concentrations on the line drawn through the measured concentrations are predicted concentrations.

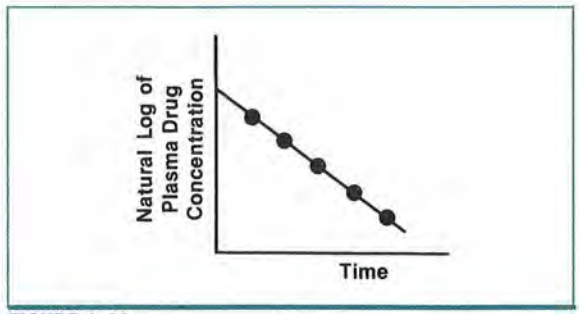

FIGURE 1-26.
With a simple one-compartment, intravenous bolus model, a plot of the natural log of plasma concentration versus time results in a straight line.

A straight line is obtained from the natural log of plasma drug concentration versus time plot only for drugs that follow first-order elimination processes and exhibit one-compartment distribution. First-order elimination occurs when the amount of drug eliminated from the body in a specific time is dependent on the amount of drug in the body at that time. This concept is explained further in Lesson 2.

An alternative to calculating the natural log values is to plot the actual concentration and time values on semilogarithmic (or semilog) paper (**Figure 1-27**), a special graph paper that automatically adjusts for the logarithmic relationship by altering the distance between lines on the *y*-axis. The lines on the *y*-axis are not evenly spaced but rather

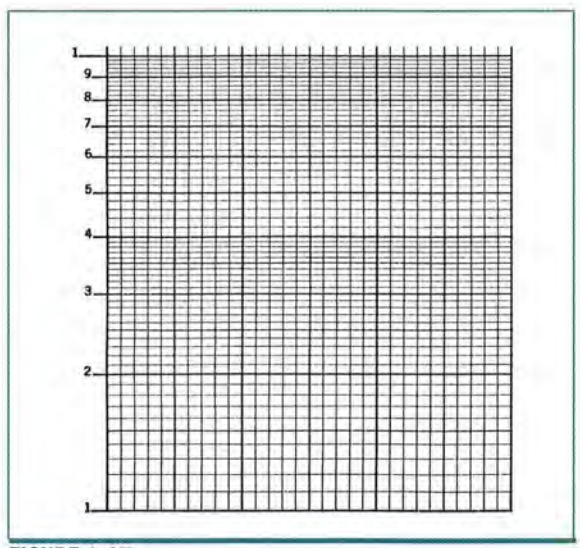

FIGURE 1-27.
Paper with one log-scale axis is called semilog paper.

are logarithmically related within each log cycle (or multiple of 10). So when the actual values of plasma drug concentrations are plotted against the time values, a straight line results. The *x*-axis has evenly spaced lines; there is no logarithmic conversion of those values. (The term *semilogarithmic* indicates that only one axis is converted.) The numbers on the *y*-axis may be used to represent 0.1 through 1, 1 through 10, 10 through 100, or any series with a 10-fold difference in the range of values.

Clinical Correlate

Semilog graph paper can be found via google.com

If a series of plasma concentration versus time points are known and plotted on semilog paper, a straight line can be drawn through the points by visual inspection or, more accurately, by linear regression techniques. *Linear regression* is a mathematical method used to determine the line that best represents a set of plotted points. From this line, we can predict plasma drug concentrations at times for which no measurements are available (**Figure 1-28**).

Clinical Correlate

For a typical patient, plasma concentrations resulting from an 80-mg dose of gentamicin may be as shown in **Table 1-3**. The plasma concentrations plotted on linear and semilogarithmic graph paper are shown in **Figure 1-29**. With the semilog paper, it is easier to predict what the gentamicin plasma concentration would be 10 hours after the dose is administered.

TABLE 1-3. Time Course of Plasma Gentamicin Concentration

Concentration (mg/L)	Time after Dose (hours)
6	1
4.4	2
2.4	4
0.70	8

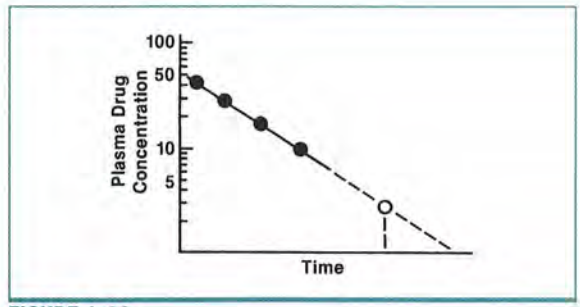

FIGURE 1-28.
When plasma concentration versus time points fall on a straight line, concentrations at various times can be predicted simply by picking a time point and matching concentration on the line at that time.

Math Principle

The *log of a number* is the power to which a given base number must be raised to equal that number. With natural logarithms, the base is 2.718. For example, the natural logarithm of 8.0 is *x*, where $2.718^x = 8.0$ and x = 2.08. Natural logarithms are used because they relate to natural processes such as drug elimination, radioactive decay, and bacterial growth. Instead of 2.718 to indicate the base of the

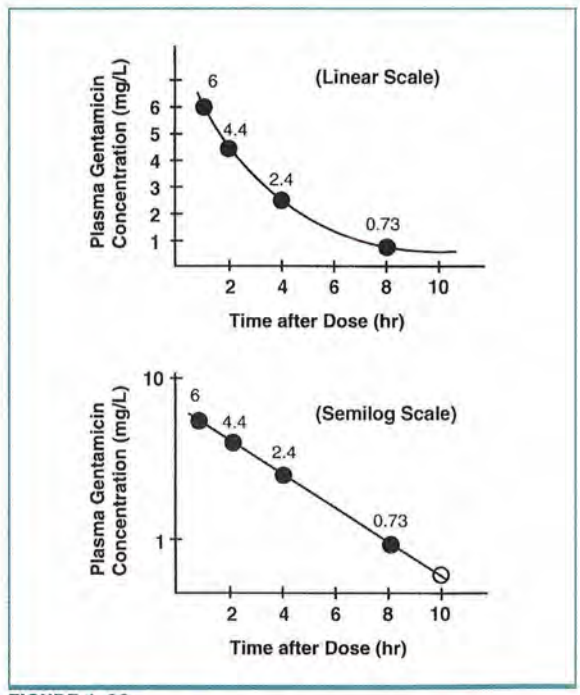

FIGURE 1-29.
Predicting plasma drug concentrations with semilog scale.

natural log function, the abbreviation *e* is used. Also, instead of writing natural logarithm of 8.0, we shall use the abbreviation *ln 8.0*.

Natural logarithms can be related to common logarithms (base 10 logarithms) as follows:

$$\text{log base } 10 = \frac{\text{log base e}}{2.303}$$

Using the Calculator with Natural Log and Exponential Keys

There are two major keys that will be used to calculate pharmacokinetic values from either known or estimated data. These are the *ln* key and the e^x key. Certain calculators do not have the e^x key. Instead, they will have an *ln* key and an *INV* key or a *2nd* key. Pressing the *INV* key or the *2nd* key and then the *ln* key will give e^x values.

Clinically Important Equations Identified in This Chapter

1. $C = X/V$
2. $V = X/C$

REVIEW QUESTIONS

1-1. The study of the time course of drug absorption, distribution, metabolism, and excretion is called:

A. pharmacodynamics.
B. drug concentration.
C. pharmacokinetics.
D. kinetic homogeneity.

1-2. The application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient is known as:

A. pharmacodynamics.
B. clinical pharmacokinetics.

1-3. Because we cannot practically measure drug concentration in specific tissues, we measure it in the plasma and assume that this concentration is the same as that in tissue.

A. True
B. False

1-4. *Pharmacodynamics* refers to the relationship of drug:

A. dose to drug concentration in plasma.
B. dose to drug concentration at the receptor site.
C. concentrations to drug effect.
D. dose to drug effect.

1-5. Drug pharmacodynamics are affected by the drug concentration at the site of the receptor, density of receptors on the target cell surface, mechanism by which a signal is transmitted into the cell by second messengers, and regulatory factors that control gene translation and protein production.

A. True
B. False

1-6. The EC_{50} refers to the drug concentration at which:

A. one-half the maximum response is achieved.
B. the maximal effect is achieved.
C. tolerance is likely to be observed.

1-7. The therapeutic range is the range of plasma drug concentrations that clearly defines optimal drug therapy and where toxic effects cannot occur.

A. True
B. False

1-8. Therapeutic drug concentration monitoring with plasma drug concentration data assumes that pharmacologic response is related to the drug concentration in plasma.

A. True
B. False

1-9. One factor that may result in variability in plasma drug concentrations after the same drug dose is given to different patients includes variations in:

A. drug absorption.
B. the EC_{50} of the drug.

1-10. An example of a situation that would not support therapeutic drug monitoring with plasma drug concentrations would be one in which:

A. a wide variation in plasma drug concentrations is achieved in different patients given a standard drug dose.
B. the toxic plasma concentration is many times the therapeutic concentration range.
C. correlation between a drug's plasma concentration and therapeutic response is positive.

1-11. For a drug with a narrow therapeutic index, the plasma concentration required for therapeutic effects is near the concentration that produces toxic effects.

A. True
B. False

1-12. Highly perfused organs and blood comprise what is usually known as the peripheral compartment.

A. True
B. False

1-13. The most commonly used model in clinical pharmacokinetic situations is the:

A. one-compartment model.
B. two-compartment model.
C. multicompartment model.

1-14. Instantaneous distribution to most body tissues and fluids is assumed in which of the following models?

A. one-compartment model
B. two-compartment model
C. multicompartment model

1-15. The amount of drug per unit of volume is defined as the:

A. volume of distribution.
B. concentration.
C. rate.

1-16. If 3 g of a drug are added and distributed throughout a tank and the resulting concentration is 0.15 g/L, calculate the volume of the tank.

A. 10 L
B. 20 L
C. 30 L
D. 200 L

1-17. For a drug that has first-order elimination and follows a one-compartment model, which of the following plots would result in a curved line?

A. plasma concentration versus time
B. natural log of plasma concentration versus time

1-18. A drug that follows a one-compartment model is given as an intravenous injection, and the following plasma concentrations are determined at the times indicated:

Plasma Concentration (mg/L)	Time after Dose (hours)
81	1
67	2
55	3

Using semilog graph paper, determine the approximate concentration in plasma at 6 hours after the dose.

A. 18 mg/L
B. 30 mg/L
C. < 1 mg/L

ANSWERS

1-1. A. *Incorrect answer.* Pharmacodynamics deals with the relationship between the drug concentration at the site of action and the resulting effect.

B. *Incorrect answer.* Drug concentrations in plasma and tissues result from pharmacokinetic processes.

C. CORRECT ANSWER

D. *Incorrect answer.* Kinetic homogeneity describes the relationship between plasma drug concentration and concentration at a receptor or site of action.

1-2. A. *Incorrect answer.* Pharmacodynamics alone is not sufficient for effective therapeutic management, as it does not account for absorption, distribution, metabolism, and excretion.

B. CORRECT ANSWER

1-3. A. *Incorrect answer.* The plasma drug concentration is not the same as that in the tissue but rather is related to the tissue concentration by the volume of distribution (*V*). Plasma drug concentrations are commonly used because blood, being readily accessible via venipuncture, is the body fluid most often collected for drug measurement.

B. CORRECT ANSWER

1-4. A, B. *Incorrect answers.* These statements are definitions of pharmacokinetics.

C. CORRECT ANSWER

D. *Incorrect answer.* This statement refers to the effect of pharmacokinetic and pharmacodynamic processes.

1-5. A. CORRECT ANSWER

B. *Incorrect answer*

1-6. A. CORRECT ANSWER

B. *Incorrect answer.* The "50" in EC_{50} refers to 50% of the maximal effect.

C. *Incorrect answer.* The term EC_{50} refers to pharmacologic effect and not to tolerance.

1-7. A. *Incorrect answer.* Although the therapeutic range of a drug describes a range of plasma drug concentrations generally considered safe and effective in a patient population, no absolute boundaries divide subtherapeutic, therapeutic, and toxic drug concentrations for an individual patient. Both pharmacodynamic and pharmacokinetic factors influence a patient's response.

B. CORRECT ANSWER

1-8. A. CORRECT ANSWER

B. *Incorrect answer.* This statement is the basic assumption underlying the use of plasma drug concentrations.

1-9. A. CORRECT ANSWER

B. *Incorrect answer.* The EC_{50} is a way of comparing drug potency. The EC_{50} is the concentration at which 50% of the maximum effect of the drug is achieved.

1-10. A. *Incorrect answer.* A wide variation in plasma drug concentrations would be a good justification for therapeutic drug level monitoring.

B. CORRECT ANSWER. When the toxic plasma concentration is much greater than the therapeutic concentration range, there is less need for drug level monitoring.

C. *Incorrect answer.* A positive correlation between concentration and response makes therapeutic drug level monitoring more useful.

1-11. A. CORRECT ANSWER. For a drug with a narrow therapeutic index, the plasma concentration required for therapeutic effects is near the concentration that produces toxic effects. The dosage of such a drug must be chosen carefully.

B. *Incorrect answer*

1-12. A. *Incorrect answer.* The peripheral compartment is generally made up of less well-perfused tissues, such as muscle and fat.

B. CORRECT ANSWER

1-13. A. CORRECT ANSWER

B. *Incorrect answer.* Although a two-compartment model is often used, it is not used as commonly as a one-compartment model.

C. *Incorrect answer.* Multicompartment models are used occasionally for research purposes but are not normally used in clinical pharmacokinetics.

1-14. A. CORRECT ANSWER

B. *Incorrect answer.* In a two-compartment model, it is assumed that drug distribution to some tissues proceeds at a lower rate than for other tissues.

C. *Incorrect answer.* In a multicompartment model, it is also assumed that drug distribution to some tissues proceeds at a lower rate than for other tissues.

1-15. A. *Incorrect answer.* The volume of distribution refers to the dose over the resulting concentration.

B. CORRECT ANSWER

C. *Incorrect answer.* The amount per unit of volume is a static value and would not change over time; therefore, it would not be considered a rate.

1-16. A, C, D. *Incorrect answers.* A math error must have been made. The answer can be found by dividing 3 g by 0.15 g/L.

B. CORRECT ANSWER

1-17. A. CORRECT ANSWER

B. *Incorrect answer.* This plot would be a straight line (see Figure 1-29).

1-18. A, C. *Incorrect answers.* These results might have been determined if linear graph paper was used or if the points were plotted incorrectly.

B. CORRECT ANSWER

Discussion Points

D1. An H_2-receptor antagonist is given to control gastric pH and prevent stress bleeding. The following gastric pHs were observed when steady-state concentrations of the drug were achieved. What are the E_{max} and EC_{50} of this drug?

Plasma Concentration (mg/L)	Resulting pH
0.25	1.0
0.5	1.0
1	1.4
2	2.6
3	3.8
4	4.8
5	4.8

D2. The relationship shown in **Figure 1-30** is observed from a clinical study. What are some of the likely reasons for this result?

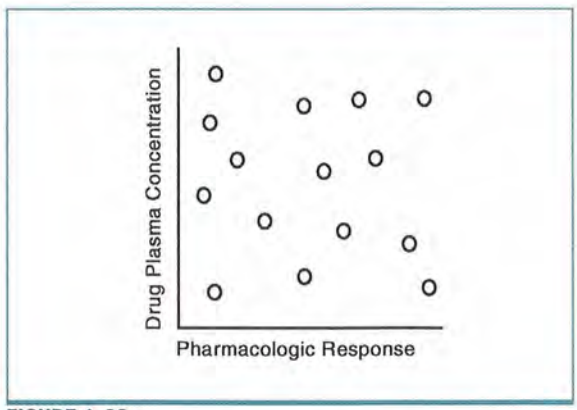

FIGURE 1-30.
Pharmacologic response versus drug plasma concentration.

D3. The models shown in **Figure 1-31** both well represent actual plasma concentrations of a drug after a dose. Which one should be preferred to predict plasma levels? Provide a justification for your answer.

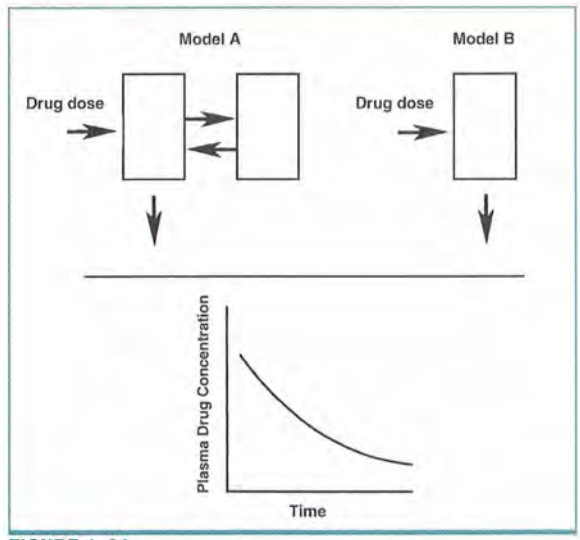

FIGURE 1-31.
Models for predicting plasma drug concentrations over time.

D4. Would you expect a large drug molecule that does not cross physiologic membranes very well and is not lipid soluble to have a relatively high or low volume of distribution? Explain your answer.

D5. When plotting plasma drug concentration (*y*-axis) versus time (*x*-axis), what are the advantages of using a natural log scale for the y-axis rather than a linear scale?

LESSON 2
Basic Pharmacokinetics

OBJECTIVES

After completing Lesson 2, you should be able to:

1. Define the concept of apparent volume of distribution and use an appropriate mathematical equation to calculate this parameter.
2. Identify the components of body fluids that make up extracellular and intracellular fluids and know the percentage of each component.
3. Describe the difference between whole blood, plasma, and serum.
4. Define drug clearance.
5. Describe the difference between first- and zero-order elimination and how each appears graphically.

To examine the concept of volume of distribution further, let's return to our example of the body as a tank described in Lesson 1. We assumed that no drug was being removed from the tank while we were determining volume. In reality, drug concentration in the body is constantly changing, primarily due to elimination. This flux makes it more difficult to calculate the volume in which a drug distributes.

One way to calculate the apparent volume of drug distribution in the body is to measure the plasma concentration immediately after intravenous administration before elimination has had a significant effect. The concentration just after intravenous administration (at time zero, t_0) is abbreviated as C_0 (**Figure 2-1**). The volume of distribution can be calculated using the equation:

$$\text{volume of distribution} = \frac{\text{amount of drug administered (dose)}}{\text{initial drug concentration}} \quad or \quad V(\text{L}) = \frac{X_0(\text{mg})}{C_0(\text{mg/L})}$$

(See **Equation 1-1**.)

C_0 can be determined from a direct measurement or estimated by back-extrapolation from concentrations determined at any time after the dose. If two concentrations have been determined, a line containing the two values and extending through the y-axis can be drawn on semilog paper. The point where that line crosses the y-axis gives an estimate of C_0. Both the direct measurement and back-extrapolation approaches assume that the drug distributes instantaneously into a single homogeneous compartment.

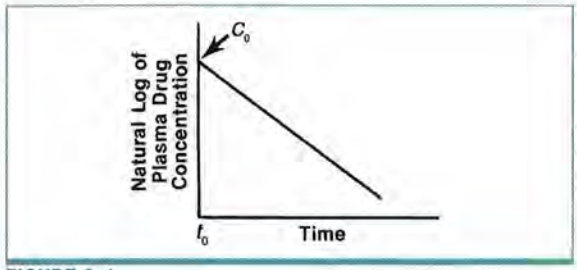

FIGURE 2-1.
Concentration resulting immediately after an intravenous injection of a drug is referred to as C_0.

The volume of distribution is an important parameter for determining proper drug dosing regimens. Often referred to as the *apparent* volume of distribution, it does not have an exact physiologic significance, but it can indicate the extent of drug distribution and aid in determination of dosage requirements. Generally, dosing is proportional to the volume of distribution. For example, the larger the volume of distribution, the larger a dose must be to achieve a desired target concentration.

To understand how distribution occurs, you must have a basic understanding of body fluids and tissues (**Figure 2-2**). The fluid portion (water) in an adult makes up approximately 60% of total body weight and is composed of intracellular fluid (35%) and extracellular fluid (25%). Extracellular fluid is made up of plasma (4%) and interstitial fluid (21%). Interstitial fluid surrounds cells outside the vascular system. These percentages vary somewhat in a child.

If a drug has a volume of distribution of approximately 15–18 L in a 70-kg person, we might assume that its distribution is limited to extracellular fluid, as that is the approximate volume of extracellular fluid in the body. If a drug has a volume of distribution of about 40 L, the drug may be distributing into all body water because a 70-kg person has approximately 40 L of body water (70 kg × 60%). If the volume of distribution is much greater than 40–50 L, the drug probably is being concentrated in tissue outside the plasma and interstitial fluid.

If a drug distributes extensively into tissues, the volume of distribution calculated from plasma concentrations could be much higher than the actual physiologic volume in which it distributes. For example, by measuring plasma concentrations, it appears that digoxin distributes in approximately 440 L in an adult. Because digoxin binds extensively to muscle tissue, plasma levels are fairly low relative to concentrations in muscle tissue. For other drugs, tissue concentrations may not be as high as the plasma concentration, so it may appear that these drugs distribute into a relatively small volume.

It is also important to distinguish among blood, plasma, and serum. *Blood* refers to the fluid portion in combination with formed elements (white cells, red cells, and platelets). *Plasma* refers only to the fluid portion of blood (including soluble proteins but not formed elements). When the soluble protein fibrinogen is removed from plasma, the remaining product is *serum* (**Figure 2-3**).

These differences in biologic fluids must be recognized when considering reported drug concentrations. The plasma concentration of a drug may be much less than the whole blood concentration if the drug is preferentially sequestered by red blood cells.

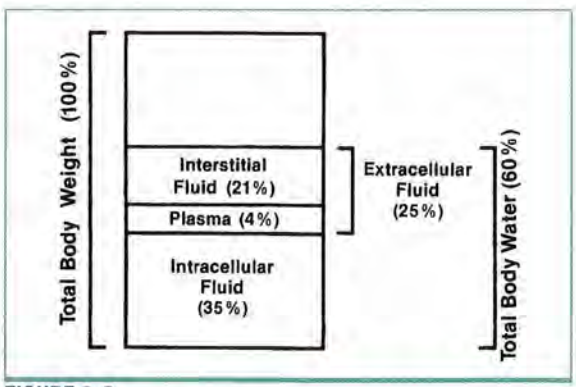

FIGURE 2-2.
Fluid distribution in an adult.

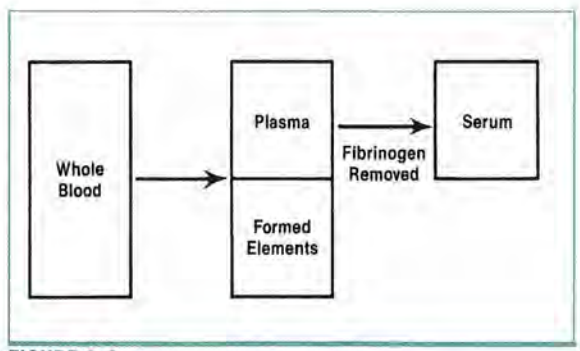

FIGURE 2-3.
Relationship of whole blood, plasma, and serum.

Clinical Correlate

Most drug concentrations are measured using plasma or serum that usually generate similar values. It is more relevant to use plasma or serum than whole blood measurements to estimate drug concentrations at the site of effect. However, some drugs, such as antimalarials, are extensively taken up by red blood cells. In these situations, whole blood concentrations would be more relevant, although they are not commonly used in clinical practice.

Clearance

Another important parameter in pharmacokinetics is clearance. *Clearance* is a measure of the removal of drug from the body. Plasma drug concentrations are affected by the rate at which drug is administered, the volume in which it distributes, and its clearance. A drug's clearance and the volume of distribution determine its half-life. The concept of half-life and its relevant equations are discussed in Lesson 3.

Clearance (expressed as volume/time) describes the removal of drug from a volume of plasma in a given unit of time (drug loss from the body). Clearance does not indicate the amount of drug being removed. It indicates the volume of plasma (or blood) from which the drug is completely removed, or cleared, in a given time period. **Figures 2-4** and **2-5** represent two ways of thinking about drug clearance. In Figure 2-4, the amount of drug (the number of dots) decreases but fills the same volume, resulting in a lower concentration. Another way of viewing the same decrease would be to calculate the volume that would be drug-free if the concentration were held constant.

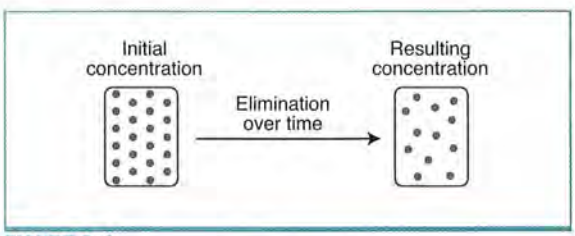

FIGURE 2-4.
Decrease in drug concentration due to drug clearance.

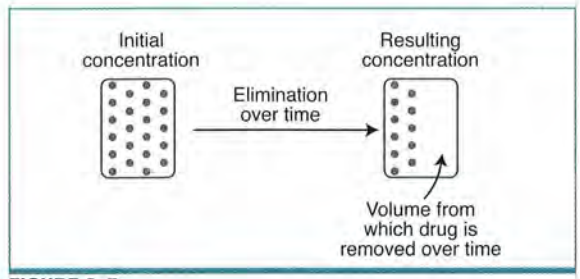

FIGURE 2-5.
Clearance may be viewed as the volume of plasma from which drug is totally removed over a specified period.

Drugs can be cleared from the body by many different mechanisms, pathways, or organs, including hepatic biotransformation and renal and biliary excretion. *Total body clearance* of a drug is the sum of all the clearances by various mechanisms.

2-1 $$Cl_t = Cl_r + Cl_m + Cl_b + Cl_{other}$$

where

- Cl_t = total body clearance (from all mechanisms, where t refers to total);
- Cl_r = renal clearance (through renal excretion);
- Cl_m = clearance by liver metabolism or biotransformation;
- Cl_b = biliary clearance (through biliary excretion); and
- Cl_{other} = clearance by all other routes (gastrointestinal tract, pulmonary, etc.).

For an agent removed primarily by the kidneys, renal clearance (Cl_r) makes up most of the total body clearance. For a drug primarily metabolized by the liver, hepatic clearance (Cl_m) is most important.

A good way to understand clearance is to consider a single well-perfused organ that eliminates drug. Blood flow through the organ is referred to as Q (mL/minute) as seen in **Figure 2-6**, where C_{in} is the drug concentration in the blood entering the organ and C_{out} is the drug concentration in the exiting blood. If the organ eliminates some of the drug, C_{in} is greater than C_{out}.

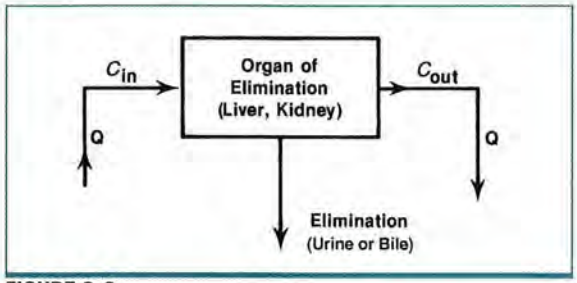

FIGURE 2-6.
Model for organ clearance of a drug.

We can measure an organ's ability to remove a drug by relating C_{in} and C_{out}. This extraction ratio (E) is:

$$E = \frac{C_{in} - C_{out}}{C_{in}}$$

This ratio must be a fraction between zero and one. Organs that are very efficient at eliminating a drug will have an extraction ratio approaching one (i.e., 100% extraction). **Table 2-1** is used as a general guide.

The drug clearance of any organ is determined by blood flow and the extraction ratio:

$$\text{organ clearance} = \text{blood flow} \times \text{extraction ratio}$$

or:

2-2 $$Cl_{organ} = Q \times \frac{C_{in} - C_{out}}{C_{in}} \text{ or } Cl_{organ} = QE$$

If an organ is very efficient in removing drug (i.e., extraction ratio near one) but blood flow is low, clearance will also be low. Also, if an organ is inefficient in removing drug (i.e., extraction ratio close to zero) even if blood flow is high, clearance would again be low. See **Table 2-2**.

The equations noted previously are not used routinely in clinical drug monitoring, but they describe the concept of drug clearance. Examination of a single well-perfused organ to understand clearance is a noncompartmental approach; no assumptions about the number of compartments have to be made. Therefore, *clearance* is said to be a model-independent parameter. Clearance also can be related to the model-dependent parameters volume of distribution and elimination rate (discussed in Lesson 3).

TABLE 2-1. Rating of Extraction Ratios

Extraction Ratio (E)	Rating
> 0.7	High
0.3–0.7	Intermediate
< 0.3	Low

Clearance may also be a useful parameter for constructing dosage recommendations in clinical situations. It is an index of the capacity for drug removal by the body's organs.

Clinical Correlate

Blood flow and the extraction ratio will determine a drug's clearance. Propranolol is a drug that is eliminated exclusively by hepatic metabolism. The extraction ratio for propranolol is greater than 0.9, so most of the drug presented to the liver is removed by one pass through the liver. Therefore, clearance is approximately equal to liver blood flow ($Cl = Q \times E$: when $E \sim 1.0$, $Cl \sim Q$). One indication of the high extraction ratio is the relatively high oral dose of propranolol compared with the intravenous dose; an oral dose is 10–20 times the equivalent intravenous dose. The difference reflects the amount of drug removed by first-pass metabolism after absorption from the gastrointestinal tract and before entry into the general circulation.

The average clearances of some commonly used drugs are shown in **Table 2-3**. These values can vary considerably between individuals and may be altered by disease.

TABLE 2-2. Effect on Clearance

Extraction Ratio (E)	Blood Flow (Q) (L/hour)	Clearance (Cl) (L/hour)
High (0.7–1.0)	Low	Low
Low (< 0.3)	High	Low
High (0.7–1.0)	High	High
Low (< 0.3)	Low	Low

TABLE 2-3. Average Clearances of Common Drugs

Amlodipine	5.9 ± 1.5 mL/min/kg
Ganciclovir	3.4 ± 0.5 mL/min/kg
Ketorolac	0.50 ± 0.15 mL/min/kg
Lansoprazole	6.23 ± 1.60 mL/min/kg
Montelukast	0.70 ± 0.17 mL/min/kg
Sildenafil	6.0 ± 1.1 mL/min/kg
Valsartan	0.49 ± 0.09 mL/min/kg

Source: Brunton LL, Lazo JS, Parker KL (editors), *The Pharmacologic Basis of Therapeutics*, 11th edition. New York: McGraw-Hill; 2006. pp. 1798, 1829, 1839, 1840, 1851, 1872, 1883.

First-Order and Zero-Order Elimination

The simplest example of drug elimination in a one-compartment model is a single intravenous bolus dose of a drug. It is first assumed that:

1. Distribution and equilibration to all tissues and fluids occurs instantaneously so a one-compartment model applies.
2. Elimination is first order.

Most drugs are eliminated by a first-order process, and the concept of first-order elimination must be understood. With *first-order elimination*, the amount of drug eliminated in a set amount of time is directly proportional to the amount of drug in the body. The amount of drug eliminated over a certain time period increases as the amount of drug in the body increases; likewise, the amount of drug eliminated per unit of time decreases as the amount of drug in the body decreases.

With the first-order elimination process, although the amount of drug eliminated may change with the amount of drug in the body, the fraction of a drug in the body eliminated over a given time remains constant. In practical terms, the fraction or percentage of drug being removed is the same with either high or low drug concentrations. For example, if 1000 mg of a drug is administered and the drug follows first-order elimination, we might observe the patterns in **Table 2-4**.

TABLE 2-4. First-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated over Preceding Hour (mg)	Fraction of Drug Eliminated over Preceding Hour
0	1000	—	—
1	880	120	0.12
2	774	106	0.12
3	681	93	0.12
4	599	82	0.12
5	527	72	0.12
6	464	63	0.12
7	408	56	0.12

The actual amount of drug eliminated is different for each fixed time period depending on the initial amount in the body, but the fraction removed is the same, so this elimination is first order. Because the elimination of this drug (like most drugs) occurs by a first-order process, the amount of drug eliminated decreases as the concentration in plasma decreases. The actual fraction of drug eliminated over any given time (in this case 12%) depends on the drug itself and the individual patient's capacity to eliminate the drug.

On the other hand, with *zero-order elimination*, the amount of drug eliminated does not change with the amount or concentration of drug in the body, but the fraction removed varies (**Figure 2-7**). For example, if 1000 mg of a drug is administered and the drug follows zero-order elimination, we might observe the patterns in **Table 2-5**.

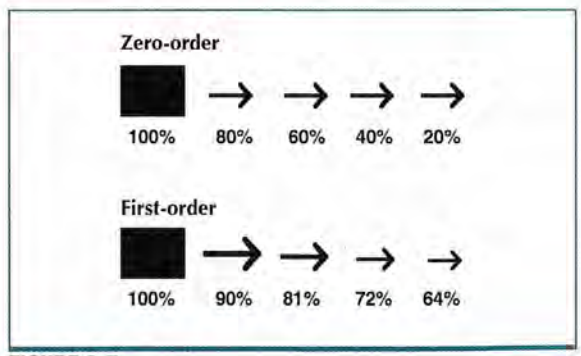

FIGURE 2-7.
Zero- versus first-order elimination. The size of the arrow represents the amount of drug eliminated over a unit of time. Percentages are the fraction of the initial drug amount remaining in the body.

TABLE 2-5. Zero-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated over Preceding Hour (mg)	Fraction of Drug Eliminated over Preceding Hour
0	1000	—	—
1	850	150	0.15
2	700	150	0.18
3	550	150	0.21
4	400	150	0.27
5	250	150	0.38

Now that we have examined zero- and first-order elimination, let's return to our simple one-compartment, intravenous bolus situation. If the plasma drug concentration is continuously measured and plotted against time after administration of an intravenous dose of a drug with first-order elimination, the plasma concentration curve shown in **Figure 2-8** would result. To predict concentrations at times when we did not collect samples, we must linearize the plot by using semilog paper (**Figure 2-9**).

Clinical Correlate

Most antimicrobial agents (e.g., aminoglycosides, cephalosporins, and vancomycin) display first-order elimination when administered in usual doses. The pharmacokinetic parameters for these drugs are not affected by the size of the dose given. As the dose and drug concentrations increase, the amount of drug eliminated per hour increases while the fraction of drug removed remains the same.

Some drugs (e.g., phenytoin), when given in high doses, display zero-order elimination. Zero-order elimination occurs when the body's ability to eliminate a drug has reached its maximum capability (i.e., all transporters are being used). As the dose and drug concentrations increase, the amount of drug eliminated per hour does not increase, and the fraction of drug removed declines.

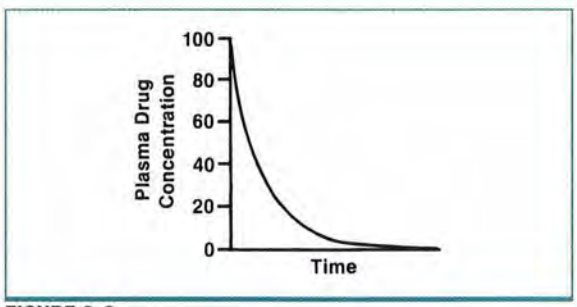

FIGURE 2-8.
Plasma drug concentration versus time after an intravenous (bolus) drug dose, assuming a one-compartment model with first-order elimination (linear *y*-scale).

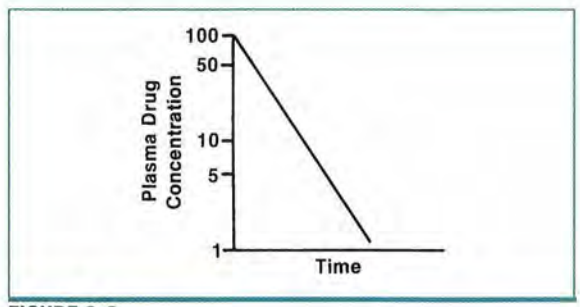

FIGURE 2-9.
As in Figure 2-8, but with a log scale *y*-axis.

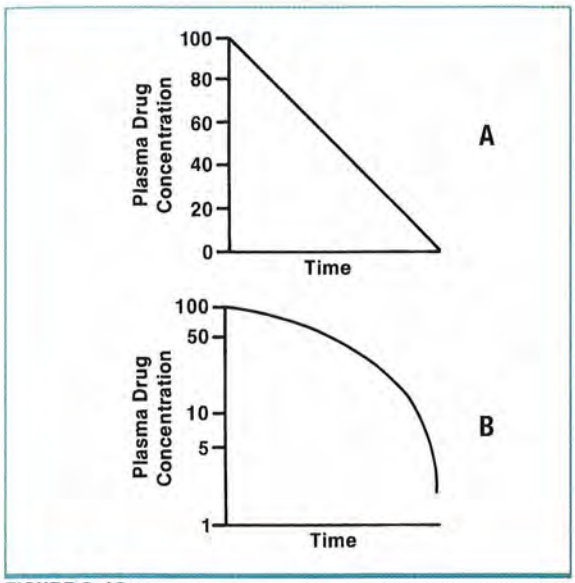

FIGURE 2-10.
Plasma drug concentrations versus time after an intravenous (bolus) drug dose, assuming a one-compartment model with zero-order elimination (**A**, linear plot; **B**, log plot).

For a drug with first-order elimination, the natural log of plasma concentration versus time plot is a straight line. Conversely, plots with zero-order elimination would be as shown in **Figure 2-10**. Note that for a drug with zero-order elimination, the plot of the plasma concentration versus time is linear (plot A in Figure 2-10), whereas on semilog paper (representing the natural log of plasma concentration versus time) it is a curve (bottom plot in Figure 2-10). If the natural log of a plasma drug concentration versus time plot is linear, it generally can be assumed that the drug follows first-order elimination.

REVIEW QUESTIONS

2-1. The volume of distribution equals _____ divided by initial drug concentration:

A. clearance
B. initial drug concentration
C. half-life
D. dose

2-2. A dose of 1000 mg of a drug is administered to a patient, and the following concentrations result at the indicated times below. Assume a one-compartment model.

Plasma Concentration (mg/L)	Time after Dose (hours)
100	2
67	4
45	6

An estimate of the volume of distribution would be:

A. 10 L.
B. 22.2 L.
C. 6.7 L.
D. 5 L.

2-3. If a drug is poorly distributed to tissues, its apparent volume of distribution is probably:

A. large.
B. small.

2-4. For the body fluid compartments below, rank them from the lowest volume to the highest, in a typical 70-kg person.

A. Plasma < extracellular fluid < intracellular fluid < total body water
B. Extracellular fluid < intracellular fluid < plasma < total body water
C. Intracellular fluid < extracellular fluid < plasma < total body water
D. Total body water < plasma < intracellular fluid < extracellular fluid

2-5. *Plasma* refers only to the fluid portion of blood, including soluble proteins but not formed elements.

A. True
B. False

2-6. The units for clearance are:

A. concentration/half-life.
B. dose/volume.
C. half-life/dose.
D. volume/time.

2-7. Total body clearance is the sum of clearance by the kidneys, liver, and other routes of elimination.

A. True
B. False

2-8. To determine drug clearance, we must first determine whether a drug best fits a one- or two-compartment model.

A. True
B. False

2-9. With a drug that follows first-order elimination, the amount of drug eliminated per unit time:

A. remains constant while the fraction of drug eliminated decreases.
B. decreases while the fraction of drug eliminated remains constant.

ANSWERS

2-1. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. You can determine the correct answer from the units in the numerator and denominator. They should cancel to yield a volume unit. *Grams* divided by *grams per liter* would leave you with *liter* as the unit. The

volume is therefore determined from the dose, or amount of drug given, and the resulting initial concentration.

2-2. A. *Incorrect answer*. You may have used 100 mg/L as the initial concentration.

B. *Incorrect answer*. You may have used an incorrect initial concentration.

C. CORRECT ANSWER. To find the initial concentration, plot the given plasma concentration and time values on semilog paper, connect the points, and read the value of the *y*-axis (concentration) when *x* (time) = 0. This should be 150 mg/L. You can then determine the volume of distribution using the equation volume of distribution = dose/initial concentration.

D. *Incorrect answer*. You may have used an incorrect initial concentration, or you may have used linear graph paper instead of semilog paper.

2-3. A. *Incorrect answer*. Drug concentrations are generally measured in plasma. When drug distributes poorly into tissues, the plasma level will be increased. Examining the equation volume of distribution = dose/initial concentration, as the initial concentration increases, the volume will decrease.

B. CORRECT ANSWER

2-4. A. CORRECT ANSWER. See Figure 2-2. Plasma would be 2.8 L, extracellular fluid would be 18 L, intracellular fluid would be 25 L, and total body water would be 42 L.

B, C, D. *Incorrect answers*

2-5. A. CORRECT ANSWER

B. *Incorrect answer*

2-6. A, B, C. *Incorrect answers.* The units for clearance are volume/time.

D. CORRECT ANSWER

2-7. A. CORRECT ANSWER. Total body clearance can be determined as the sum of individual clearances from all organs or routes of elimination.

B. *Incorrect answer*

2-8. A. *Incorrect answer*

B. CORRECT ANSWER. It is not necessary to specify a model to determine drug clearance.

2-9. A. *Incorrect answer*

B. CORRECT ANSWER. With first-order elimination, the amount of drug eliminated in any time period is determined by the amount of drug present at the start. Although the amount of drug eliminated in successive time periods may decrease, the fraction of the initial drug that is eliminated remains constant.

Discussion Points

D1. Drug Y is given by an intravenous injection and plasma concentrations are then determined as follows:

Time after Injection (hours)	Concentration (mg/L)
0	12
1	9.8
2	7.9
3	6.4
4	5.2
5	4.2
6	3.4
7	2.8
8	2.2

Is this drug eliminated by a first- or zero-order process? Defend your answer.

D2. Which of the following patient scenarios is associated with a smaller volume of distribution?

A. Dose = 500 mg and initial serum concentration is 40 mg/L

B. Dose = 20 mg and initial serum concentration is 1.5 mg/L

D3. Explain how a person who weighs 70 kg can have a volume of distribution for a drug of 700 L.

D4. For drug X, individual organ clearances have been determined as follows:

Renal clearance	180 mL/minute
Hepatic clearance	22 mL/minute
Pulmonary clearance	5.2 mL/minute

How would you describe the clearance of drug X?

LESSON 3

Half-Life, Elimination Rate, and AUC

OBJECTIVES

After completing Lesson 3, you should be able to:

1. Calculate the elimination rate constant given a natural log (ln) of plasma drug concentration versus time curve.
2. Define *half-life*.
3. Calculate a drug's half-life given a natural log of plasma drug concentration versus time curve.
4. Define the relationship between half-life and elimination rate constant.
5. Calculate a drug's half-life given its elimination rate constant.
6. Define *drug clearance* and relate it to the area under the plasma drug concentration curve and drug dose.
7. Calculate a drug's volume of distribution, concentration at time zero, and area under the plasma concentration versus time curve (AUC), given plasma concentration data after an intravenous bolus drug dose.

In Lesson 2, we learned that for most drugs (those following first-order elimination) a straight line can describe the change in natural log of plasma concentration over time. Recognizing this relationship, we can now develop mathematical methods to predict drug concentrations.

Whenever you have a straight line such as that in **Figure 3-1**, the line is defined by the equation:

$$Y = mX + b$$

where m is the slope of the line and b is the intercept of the y-axis. If you know the slope and the y-intercept, you can find the value of Y for any given X value.

As the value for the y-intercept may be obtained easily by visual inspection, the only part of the equation that must be calculated is the slope of the line. A slope is calculated from the change in the y-axis (the vertical change) divided by the change in the x-axis (the horizontal change), as in **Figure 3-2**:

$$\text{slope} = \frac{\Delta Y}{\Delta X} \text{ or slope} = \frac{Y_2 - Y_1}{X_2 - X_1}$$

where Δ means "change in."

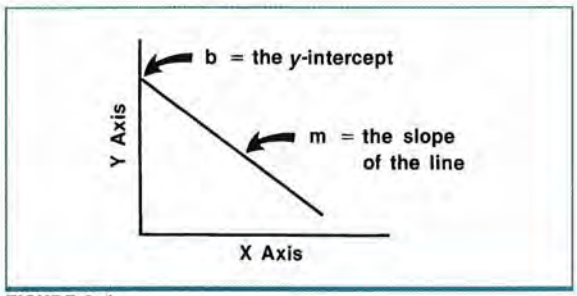

FIGURE 3-1.
Straight-line plot showing slope and *y*-intercept.

The slope is obtained by selecting two different points on the line and calculating the difference between their values. We can apply these same mathematical principles to the natural log of plasma concentration versus time plot (**Figure 3-3**). The *slope* is the change in the natural log of plasma concentrations divided by the change in time between the concentrations:

$$\text{slope} = \frac{\Delta \ln \text{conc}}{\Delta \text{ time}} \text{ or slope} = \frac{\ln C_1 - \ln C_0}{t_1 - t_0}$$

If, for example, 10 mg/L is the first concentration (C_0) drawn immediately after administration (t_0 = 0 hour) and 1 mg/L is the second concentration (C_1) drawn 2.5 hours after administration (t_1 = 2.5 hours):

$$\text{slope} = \frac{\ln C_1 - \ln C_0}{t_1 - t_0}$$

$$= \frac{\ln 1 - \ln 10}{2.5 \text{ hr} - 0 \text{ hr}} = \frac{0 - 2.303}{2.5 \text{ hr}}$$

$$= -0.92 \text{ hr}^{-1}$$

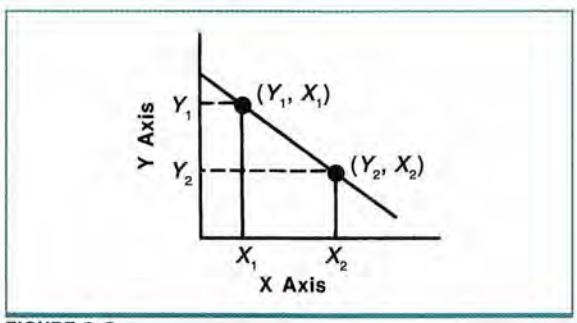

FIGURE 3-2.
The slope of a straight line can be determined from any two points on the line.

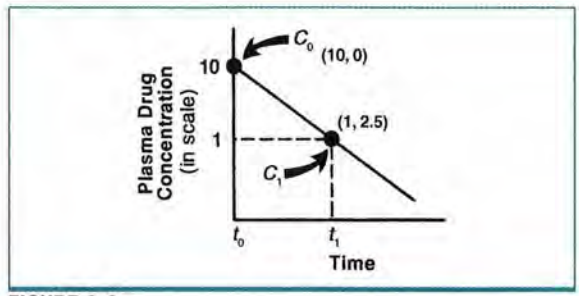

FIGURE 3-3.
The slope of the natural log of plasma concentration versus time curve can be determined if two plasma concentrations and their corresponding times are known.

Note that the slope is calculated using $\ln C_1 - \ln C_0$ or $\ln (C_1/C_0)$ and not $\ln (C_1 - C_0)$. The latter would give an incorrect result. A negative slope indicates that the natural log of concentration declines with increasing time.

When the natural log of drug concentration is plotted versus time and a straight line results, as in the previous example, the slope of that line indicates the rate of drug elimination. A steeper slope (**Figure 3-4**, top graph) indicates a faster rate of elimination than does a flatter slope (Figure 3-4, bottom graph). For first-order processes, the rate of elimination (expressed as the fraction of drug in the body removed over a unit of time) is the same at high or low concentrations and is therefore called an *elimination rate constant*.

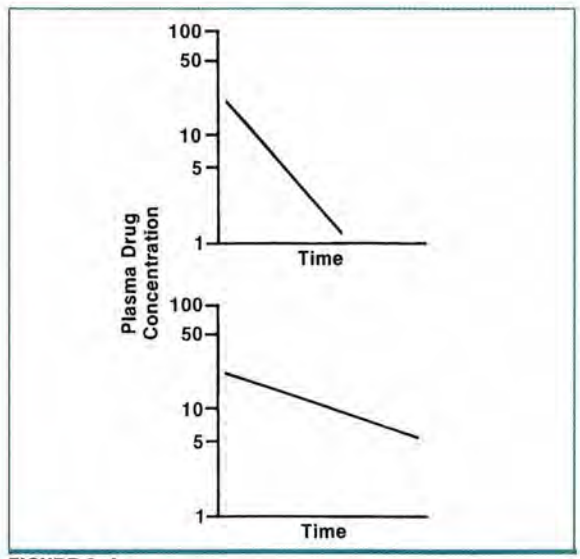

FIGURE 3-4.
A steeper slope (top) indicates a faster rate of elimination.

Therefore, when drug elimination is first order, the negative slope of the natural log of drug concentration versus time plot equals the drug's elimination rate constant:

$$\text{slope} = -\text{elimination rate constant}$$

or:

$$-\text{slope} = \text{elimination rate constant}$$

One must carefully examine the mathematical differences in positive and negative slope and elimination rate constant (K) values as they apply to various dosing equations. The slope value from two plasma drug concentrations is always a negative number; however, K can be used in either its positive or negative form by simple application of one of the rules of logarithms: Log [A/B] = Log A – Log B.

Remember that the elimination rate constant is the fraction of drug removed over a unit of time. If the elimination rate constant is 0.25 hr^{-1}, then 25% of the drug remaining in the body is removed each hour.

Because we know that a plot of the natural log of drug concentration over time is a straight line for a drug following first-order elimination, we can predict drug concentrations for any time after the dose if we know the equation for this line. Remember that all straight lines can be defined by:

$$Y = mX + b$$

As shown in Figure 3-3:

- Y axis = natural log of drug concentration in plasma
- X axis = time after dose
- m = slope of line, or negative elimination rate constant
- b = intercept on natural log of plasma drug concentration axis (y-intercept)

Now, when we convert to our new terms:

$$\ln \text{ drug concentration} = (-\text{elimination rate constant} \times \text{time}) + \ln \text{ concentration at } y\text{-intercept}$$

If we know the slope of the line and the intercept of the y-axis, we can predict the natural log of drug concentration at any time after a dose.

Drug concentrations can be predicted using these mathematical methods instead of the previously described graphical methods. With mathematical methods, our predictions of drug concentrations over time are more accurate. So, if the negative slope of the natural log of drug concentration versus time plot equals the elimination rate constant, our equation for the line:

$$Y = mX + b$$

becomes:

$$\ln (\text{drug concentration}) = (-\text{elimination rate constant} \times \text{time}) + \ln y\text{-intercept}$$

To simplify our terminology here, let:

$\ln C$ = natural log of drug concentration,

K = elimination rate constant, and

t = time after dose.

Also, we shall call the y-intercept "$\ln C_0$," the drug concentration immediately after a dose is administered (at time zero, or t_0). Therefore, our equation becomes:

$$\ln C = (-K \times t) + \ln C_0 \text{ or } -K = \frac{\ln C - \ln C_0}{t}$$

This last equation is valuable in therapeutic drug monitoring. If two plasma drug concentrations and the time between them are known, then the elimination rate can be calculated. If one plasma drug concentration and the elimination rate are known, then the plasma concentration at any later time can be calculated. Note that this equation above can also be expressed to solve for K as a positive value as shown below:

$$K = \frac{\ln C_0 - \ln C}{t}$$

Note C_0 and C have changed locations. Last, either version of this equation can now be re-written in a calculator friendly version by applying the log rule, Log [A/B] = Log A – Log B, yielding

$$K = \frac{\ln[C_0/C]}{t} \text{ or } K = \frac{\ln[C/C_1]}{t}$$

Clinical Correlate

The concepts presented in this lesson can be used to predict plasma concentrations in some situations. For example, if a patient with renal dysfunction received a dose of vancomycin and plasma concentrations were determined 24 and 48 hours after the dose, then two plasma concentrations could be plotted on semilog paper to determine when the concentration would reach 10 mg/L (**Figure 3-5**). This would be approximately 88 hours after the infusion. This information can be used to determine when the next dose should be given.

Elimination Rate Constant

As stated in the previous section, the elimination rate constant (K) represents the fraction of drug removed per unit of time and has units of reciprocal time (e.g., minute^{-1}, hour^{-1}, and day^{-1}). These units are evident from examination of the calculation of K. For example, in **Figure 3-6**, C_0 is the first plasma drug concentration measured just after the dose is given, and C_1 is the second plasma drug concentration measured at a later time (t_1). From our previous discussion, we know that the equation for this line ($y = mX + b$) is:

$$\ln C_1 = -Kt + \ln C_0$$

Furthermore, we know that the slope of the line equals $-K$, and we can calculate this slope:

3-1 $$\text{slope} = -K = \frac{\ln C_1 - \ln C_0}{t_1 - t_0}$$

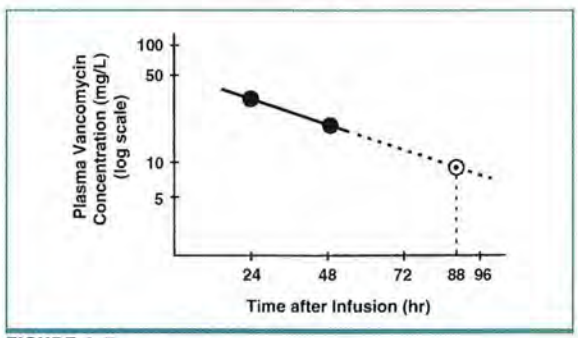

FIGURE 3-5.
Predicting plasma drug concentrations.

It is a property of logarithms that:

$$\ln C_1 - \ln C_0 = \ln \frac{C_1}{C_0}$$

Then, using numbers from Figure 3-6:

$$-K = \frac{\ln \frac{C_1}{C_0}}{t_1 - t_0} = \frac{\ln\left(\frac{5\ \text{mg/L}}{12.3\ \text{mg/L}}\right)}{6\ \text{hr} - 0\ \text{hr}}$$

So, $-K = -0.15\ \text{hr}^{-1}$, or $K = 0.15\ \text{hr}^{-1}$.

In this case, the elimination rate constant is $0.15\ \text{hr}^{-1}$. This means that 15% of the drug remaining in the body is removed each hour, so an initial plasma concentration of 10 mg/L will decrease 15% (0.15 × 10 mg/L = 1.5 mg/L) to 8.5 mg/L by the end of the first hour. By the end of the second hour, the concentration will be 7.2 mg/L, a 15% reduction from 8.5 mg/L (0.15 × 8.5 mg/L = 1.3).

The equation $\ln C = -Kt + \ln C_0$ is important because it allows the estimation of the concentration at any given time. Remember that it is in the form of an equation for a line, $Y = mX + b$. Remembering the rule of logarithms that $\ln X^p = P \ln X$, if we take the antilog of each part of this equation, we get:

3-2 $$C = C_0 e^{-Kt}$$

where:

- C = plasma drug concentration at time = t,
- C_0 = plasma drug concentration at time = 0,
- K = elimination rate constant,
- t = time after dose, and
- e = base of the natural log (approximately 2.718).
- e^{-Kt} = percent or fraction remaining after time (t)

In "plain English," this equation is saying that a concentration at some time (C) is equal to some previous concentration (C_0) "time" e^{-Kt}, the fraction of C_0 remaining after t hours. To determine the e^{-Kt} portion on a calculator, enter the value for $-Kt$ and then the function for e^x, or inverse natural log, or raise 2.718 to the power of the value of $-Kt$. The antilog of a number is equal to e (or 2.718) raised to

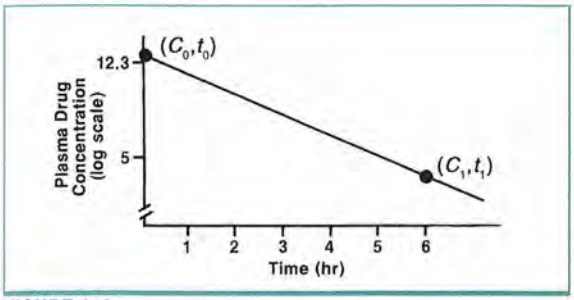

FIGURE 3-6.
Determination of a line (log scale) from two known plasma drug concentrations.

a power equal to that number. The preceding equation can also be used to predict the concentration at any time, given an initial concentration of C_0 and an elimination rate of K.

Clinical Correlate

If we know that the plasma drug concentration just after a gentamicin dose is 8 mg/L and the patient's elimination rate constant is 0.25 hr^{-1}, we can predict what the concentration will be 8 hours later:

$$C = C_0 e^{-Kt}$$

where:

$C_0 = 8$ mg/L,

$K = 0.25\ hr^{-1}$, and

$t = 8$ hours.

$$C_{at\ 8\ hr} = 8\ mg/L \times e^{-0.25\ hr^{-1}(8\ hr)}$$

$$= 8\ mg/L\ (0.135)$$

$$= 1.1\ mg/L$$

Note that the term e^{-Kt} indicates the fraction of the initial dose of drug that remains in the body at time t; 0.135 (or 13.5%) remains in the body 8 hours after the initial dose in this example. Conversely, the term $1 - e^{-Kt}$ would indicate the percent or fraction excreted after time (t).

Half-Life

Another important parameter that relates to the rate of drug elimination is half-life ($T½$). The *half-life* is the time necessary for the concentration of drug in the plasma to decrease by one-half. A drug's half-life is often related to its duration of action and also may indicate when another dose should be given.

One way to estimate the half-life is to visually examine the natural log of plasma drug concentration versus time plot and note the time required for the plasma concentration to decrease by one-half. For example, in **Figure 3-7**, the decrease from 10 to 5 mg/L takes approximately 1.5 hours. It also takes 1.5 hours for the concentration to decrease from 5.0 to 2.5 mg/L, from 7.0 to 3.5 mg/L, etc. At any point, the decrease in concentration by one-half takes approximately 1.5 hours, even when the decrease is from a concentration as low as 0.05 to 0.025 mg/L. Thus, the half-life can be estimated to be 1.5 hours.

There is another way to estimate the half-life from two known concentrations. Because the half-life is the time for a concentration to decrease by one-half, $T½$ can be estimated by halving the initial concentration, then taking one-half of that concentration to get a second concentration, and so on until the final concentration is reached. The number of halves required to reach the final desired concentration, divided into the time between the two concentrations, is the *estimated half-life*. For example, the

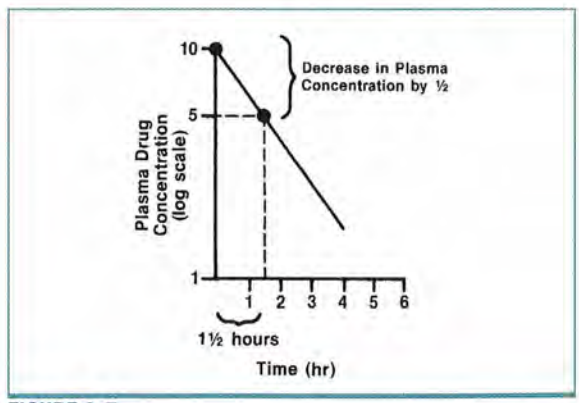

FIGURE 3-7.
Half-life can be determined from the natural log of plasma concentration versus time plot.

following two concentrations were determined at the times stated after a dose was administered:

C (mg/L)	8.0	4.0
t (hour)	0	6

Because the concentration drops from 8.0 to 4.0 mg/L in 6 hours, the half-life is 6 hours. Consider a case in which concentrations and times were as follows:

C (mg/L)	12.0	3.0
t (hour)	8	12

The concentration drops from 12 mg/L to 3 mg/L in 4 hours. To get from 12 to 3 requires a halving of 12 to 6 and a halving of 6 to 3, representing two half-lives in 4 hours, or one half-life of 2 hours.

The half-life and the elimination rate constant express the same idea. They indicate how quickly a drug is removed from the plasma and, therefore, how often a dose has to be administered.

If the half-life and peak plasma concentration of a drug are known, then the plasma drug concentration at any time can be estimated. For example, if the peak plasma concentration is 100 mg/L after an intravenous dose of a drug with a 2-hour half-life, then the concentration will be 50 mg/L 2 hours after the peak concentration (a decrease by half). At 4 hours after the peak concentration, it will have decreased by half again, to 25 mg/L, and so on as shown in **Table 3-1**.

Half-life may be mathematically calculated with the following equation:

3-8 $$T\frac{1}{2} = \frac{0.693}{K}$$

The equation represents the important relationship between the half-life and the elimination rate constant shown by mathematical manipulation. We already know that:

$$\ln C = C_0 - Kt$$

TABLE 3-1. Example of Half-Life

Time after Peak Concentration (half-life)	Plasma Concentration (mg/L)
0	100
2	50
4	25
6	12.5
8	6.25
10	3.125

By definition, the concentration (C) at the time (t) equal to the half-life ($T½$) is half the original concentration (C_0). Therefore, at one half-life, the concentration is half of what it was initially. So we can say that at $t = T½$, $C = ½C_0$. For simplicity, let's assume that $C_0 = 1$. Therefore:

$$\ln 0.5C_0 = \ln C_0 - K(T\tfrac{1}{2})$$

$$\ln 0.5 = \ln 1 - K(T\tfrac{1}{2})$$

Transforming this equation algebraically gives:

$$K(T\tfrac{1}{2}) = \ln 1 - \ln \tfrac{1}{2}$$

$$T\tfrac{1}{2} = \frac{0-(-0.693)}{K}$$

$$T\tfrac{1}{2} = \frac{0.693}{K}$$

and

$$K = \frac{0.693}{T\tfrac{1}{2}}$$

Therefore, the half-life can be determined if we know the elimination rate constant and, conversely, the elimination rate constant can be determined if we know the half-life. This relationship between the half-life and elimination rate constant is important in determining drug dosages and dosing intervals.

Clinical Correlate

Half-life can be calculated from two plasma concentrations after a dose is given. First, the elimination rate constant (K) is calculated as shown previously. For example, if a dose of gentamicin is administered and a peak plasma concentration is 6 mg/L after the infusion is completed and is 1.5 mg/L 4 hours later, the elimination rate constant is calculated as follows:

$$K = -\frac{\ln C_1 - \ln C_0}{t_1 - t_0}$$

$$= -\frac{\ln 1.5 - \ln 6}{4\ \text{hr} - 0\ \text{hr}}$$

$$= -\frac{-1.39}{4\ \text{hr}}$$

$$= 0.348\ \text{hr}^{-1}$$

Then:

$$T\frac{1}{2} = \frac{0.693}{K} = 2.0\ \text{hr}$$

Clinical Correlate

The average plasma half-lives of some commonly used drugs are shown in **Table 3-2**. These may vary considerably between individuals and may be altered by disease. Note that drug effects may persist for a period of time longer than would be predicted by a drug's half-life. The greater the value of the half-life, the longer the drug stays in the body. As an example from Table 3-2, half of a dose of vancomycin takes approximately 5.6 hours to be eliminated from the body (no matter the size of the dose). Also, half of a dose of cefazolin is eliminated in approximately 2.2 hours after administration, and so on.

TABLE 3-2. Half-Lives of Common Drugs

Drug	Half-Life (hours)
Enoxaparin	3.8
Cefazolin	2.2
Digoxin	39
Gentamicin	2–3
Atorvostatin	20
Lithium	22
Vancomycin	5.6
Levofloxacin	7

Source: Brunton LL, Lazo JS, Parker KL (editors), *The Pharmacologic Basis of Therapeutics*, 11th edition. New York: McGraw-Hill; 2006. pp. 1800, 1806, 1817, 1821, 1830, 1842, 1843, 1883.

Relationships among Pharmacokinetic Parameters

In previous lessons, we discussed elimination rate, volume of distribution, and clearance. These important parameters aid in calculating a drug dosage regimen. All three relate to how fast a drug effect will terminate. There are significant relationships among these parameters, the drug dose, and plasma drug concentrations. In this lesson, we begin to explore these relationships so that we can better predict plasma drug concentrations achieved with drug doses.

Although clearance is a model-independent pharmacokinetic parameter and is not physiologically dependent only on elimination rate, it is sometimes useful to relate it to such parameters as the elimination rate constant (K) and the volume of distribution (V). Mathematically, systemic clearance (Cl_t) is related to V and K by:

$$Cl_t / V = K$$

or:

3-4 $$Cl_t = V \times K$$

Clearance and volume are independent factors that together determine K (and $T½$). Because V has units of volume (milliliters or liters) and clearance has units of volume/time (usually milliliters per minute), K has units of reciprocal time ($minute^{-1}$, $hour^{-1}$, or day^{-1}). It is important to understand that the elimination rate constant and plasma drug concentration versus time curve are determined by drug clearance and volume of distribution.

Clearance can be related to drug dose by first evaluating the plasma drug concentration versus time curve after a dose. In examining this curve (**Figure 3-8**), we see that there is a definite area under the curve, referred to as the *area under the plasma drug concentration versus time curve* or *AUC*.

The AUC is determined by drug clearance and the dose given:

3-5 $$\text{AUC} = \frac{\text{dose administered}}{\text{drug clearance}}$$

When clearance remains constant, the AUC is directly proportional to the dose administered. If the dose doubled, the AUC would also double. Another way to think about this concept is that clearance is the parameter relating the AUC to the drug dose.

We usually know the dose of drug being administered and can determine plasma drug concentrations over time. From the plasma concentrations, the AUC can be estimated and drug clearance can be determined easily by rearranging the previous equation to:

$$\text{drug clearance} = \frac{\text{dose administered}}{\text{AUC}}$$

With a one-compartment model, first-order elimination, and intravenous drug administration, the AUC can be calculated easily:

$$\text{AUC} = \frac{\text{initial concentration } (C_0)}{\text{elimination rate constant } (K)}$$

C_0 has units of concentration, usually milligrams per liter (mg/L), and K is expressed as reciprocal time (usually $hour^{-1}$), so the AUC is expressed as milligrams per liter times hours (mg/L × hr). These units make sense graphically as well because when we multiply length times width to measure area, the product of the axes (concentration in milligrams per liter, and time in hours) would be expressed as milligrams per liter times hours.

AUC can be calculated by computer modeling of the above AUC equation, or by applying the *trapezoidal rule*. The trapezoidal rule method is rarely used, but provides visual means to understand AUC. If a line is drawn vertically to the x-axis from each measured concentration, a number of smaller areas are described (**Figure 3-9**). Because we are using the determined concentrations rather than their natural logs, the plasma drug concentration versus time plot is curved. The tops of the resulting shapes are curved as well, which makes their areas difficult to calculate. The area of each shape can be estimated, however, by drawing a straight line between adjacent concentrations and calculating the area of the resulting trapezoid (**Figure 3-10**).

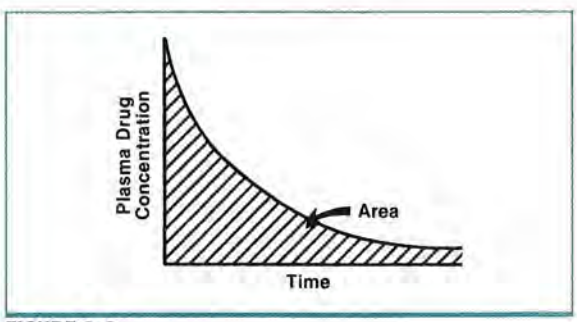

FIGURE 3-8.
Area under the plasma drug concentration versus time curve.

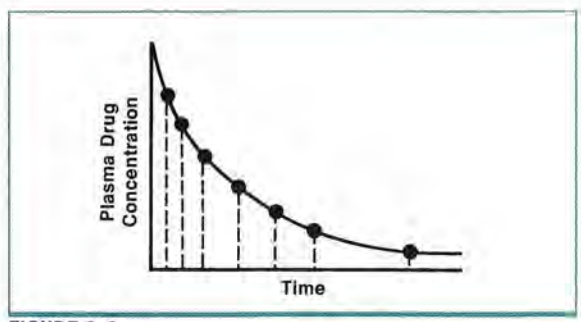

FIGURE 3-9.
A plasma drug concentration versus time curve can be divided into a series of trapezoids.

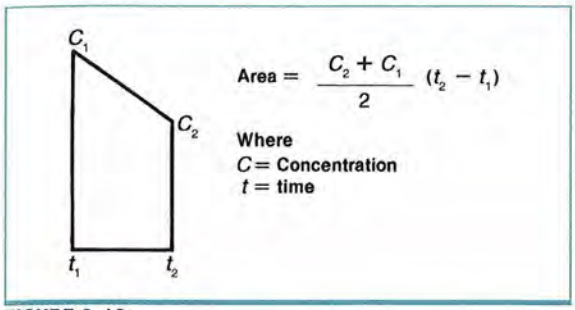

FIGURE 3-10.
Calculation of the area of a trapezoid.

If the time between measurements (and hence the width of the trapezoid) is small, only a slight error results. These smaller areas can be summed to estimate the AUC, as shown in the following equation.

$$\text{AUC} = \left[\left(\frac{C_2 + C_1}{2}\right)(t_2 - t_1)\right] + \left[\left(\frac{C_3 + C_2}{2}\right)(t_3 - t_2)\right] \ldots \text{etc.}$$

To calculate drug clearance, however, we need the AUC from time zero to infinity, and the preceding method only estimates the AUC to the final measured drug concentration.

The terminal part of the AUC is estimated by dividing the last measured plasma concentration by the elimination rate constant (**Figure 3-11**):

$$\text{terminal area} = \frac{C_{\text{last}}}{K}$$

Add the terminal area to the value of AUC from the preceding equation to find the value of AUC from zero to infinity.

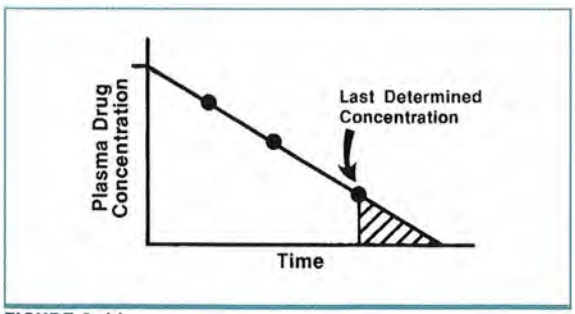

FIGURE 3-11.
Terminal area.

Clinical Correlate

The AUC can be used to determine a drug's clearance. For an individual patient, when the same drug dose is given over a period of time and the volume of distribution remains constant, changes in clearance can be assessed by changes in the AUC. For example, a doubling of the AUC would result if clearance decreased by half. For orally administered drugs, this would only be true if the fraction of drug absorbed from the gastrointestinal tract remained constant. AUC is only rarely used in clinical situations to determine clearance. It is used more frequently in clinical research.

To calculate drug clearance, divide drug dose by AUC. By knowing how to calculate clearance by the area method, it is not necessary to decide first which model (i.e., one, two, or more compartments) best fits the observed plasma levels.

Clinically Important Equations Identified in This Chapter

1. $K = \frac{\ln C_0 - \ln C}{t}$
2. $C = C_0 e^{-Kt}$ Equation 3-2
3. $T_{1/2} = \frac{0.693}{K}$ Equation 3-3
4. $\text{Cl}_t = V \times K$ Equation 3-4

REVIEW QUESTIONS

3-1. Which of the following is the equation for a straight line?

A. $X = mY + b$

B. $b = mY + X$

C. $Y = mX + b$

D. $mX + Y = b$

3-2. Which of the following would be the slope (and hence the negative elimination rate constant) of the straight line in **Figure 3-12**?

A. $\ln (C_0 - C_1)$

B. $t_0 - t_1$

C. $C_0 - t_0$

D. $(\ln C_1 - \ln C_0)/(t_1 - t_0)$

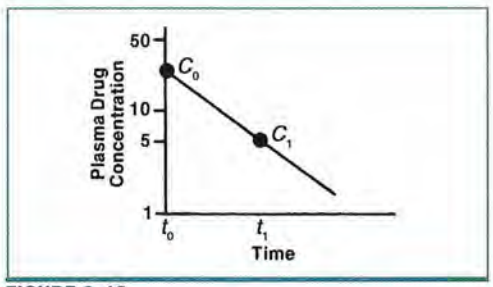

FIGURE 3-12.
Plasma drug concentration versus time.

3-3. Which of the following is the elimination rate constant for **Figure 3-13**?

A. –0.173

B. 0.52

C. 0.231

D. 0.173

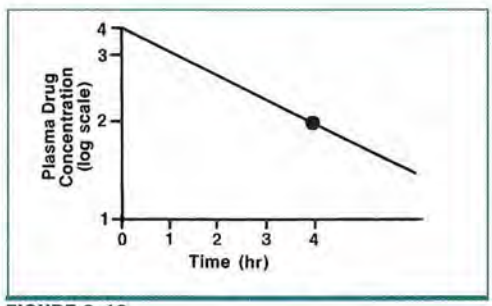

FIGURE 3-13.
Plasma drug concentration versus time.

3-4. If two patients receive the same drug and the plots in **Figure 3-14** result, which patient has the larger elimination rate constant (faster elimination)?

A. Patient A

B. Patient B

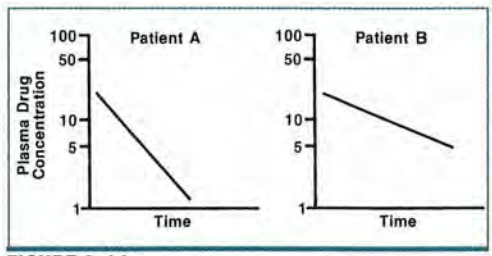

FIGURE 3-14.
Plasma drug concentration versus time.

3-5. A patient with renal dysfunction received a dose of vancomycin. Plasma concentrations were 22 and 15 mg/L at 24 and 48 hours after infusion, respectively. Plot these two plasma concentrations on semilog paper and determine when the concentration would reach 10 mg/L.

A. 54 hours

B. 72 hours

C. 96 hours

D. 128 hours

3-6. Using the equation $C = C_0 e^{-Kt}$, determine the plasma concentration of a drug 24 hours after a peak level of 10 mg/L is observed if the elimination rate constant is 0.05 hr^{-1}.

A. 3.01 mg/L

B. 33.2 mg/L

C. 18.1 mg/L

3-7. Which of the following is a proper unit for the elimination rate constant?

A. minutes

B. mg/minute

C. hr^{-1}

D. mg/L

3-8. If the elimination rate constant is 0.2 hr^{-1} the percent of drug removed per hour is:

A. 20%.

B. 1%.

C. 0.1%.

D. 10%.

3-9. If the plasma concentration just after a gentamicin dose is 10 mg/L and the patient's elimination rate constant is 0.15 hr^{-1}, predict what the plasma concentration will be 8 hours later.

A. 6.0 mg/L

B. 3.0 mg/L

C. 1.5 mg/L

D. 1.0 mg/L

3-10. For a drug that has an initial plasma concentration of 120 mg/L and a half-life of 3 hours, what would the plasma concentration be 12 hours after the initial concentration?

A. 15 mg/L

B. 112.5

C. 7.5 mg/L

D. 60

3-11. From **Figure 3-15**, the approximate $T½$ is:

A. 5 hours.

B. 10 hours.

C. 20 hours.

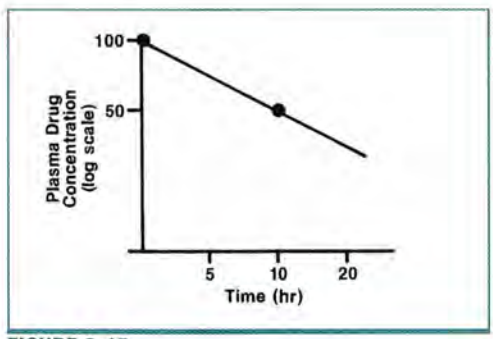

FIGURE 3-15.
Plasma drug concentration versus time.

3-12. If a drug has an elimination rate constant of 0.564 hr^{-1}, what is the half-life?

A. 1.23 hours

B. 0.81 hour

C. 1.77 hours

3-13. To calculate drug clearance by the area method, it is necessary to first determine whether the drug best fits a one- or two-compartment model.

A. True

B. False

3-14. In the trapezoid shown in **Figure 3-16**, what is the area?

A. 150 (mg/L) × hour

B. 300 (mg/L) × hour

C. 100 (mg/L) × hour

D. 25 (mg/L) × hour

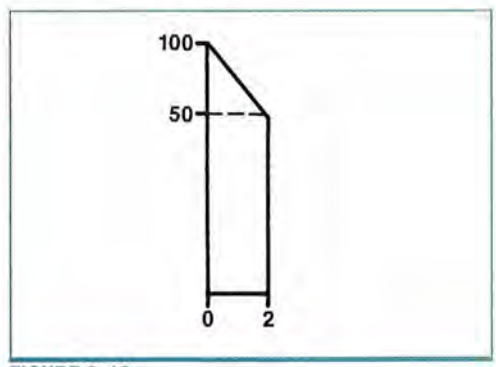

FIGURE 3-16.
Trapezoid.

3-15. If the dose (X_0) and AUC are known, the clearance (area method) is calculated by:

A. AUC/dose.

B. dose/AUC.

C. plasma concentration/AUC.

D. K/AUC.

3-16. Using **Figure 3-17** and knowing that a 500-mg dose was given intravenously, calculate clearance by the area method.

A. 42 L/hour

B. 8.4 L/hour

C. 3 L/hour

D. 4.2 L/hour

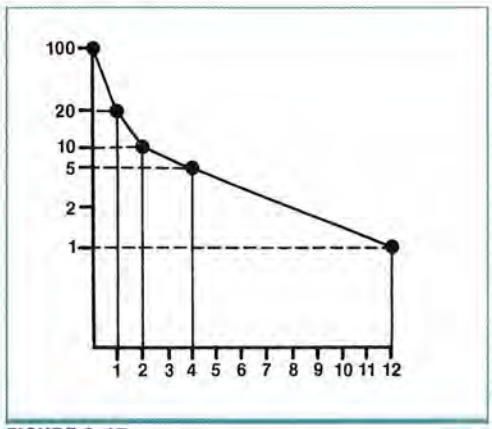

FIGURE 3-17.
Plasma drug concentration versus time.

ANSWERS

3-1. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. The slope is m, and b is the y-intercept.

3-2. A. *Incorrect answer.* This value should be $(\ln C_1 - \ln C_0)$ and should be divided by the change in time $(t_1 - t_0)$.

B. *Incorrect answer*. The numerator $[(\ln C_1 - \ln C_0)]$ hasn't been included.

C. *Incorrect answer*

D. CORRECT ANSWER. The slope is the natural log of change in concentration divided by the change in time: $(\ln C_1 - \ln C_0)/(t_1 - t_0)$.

3-3. A. *Incorrect answer*. The elimination rate constant would not have a negative value; this is merely the slope of the line.

B. *Incorrect answer*. You may have added ln 2 and ln 4 rather than subtracted ln 4 from ln 2.

C. *Incorrect answer*. You may have used 3 hours in the denominator rather than 4 hours for change in time.

D. CORRECT ANSWER

3-4. A. CORRECT ANSWER. The larger the slope of the line is (i.e., the steeper the line is), the larger the elimination rate constant will be.

B. *Incorrect answer.* Note that the slope of the line is smaller (i.e., the line is less steep).

3-5. A, C, D. *Incorrect answers.* Be sure your points are plotted on paper that has a log scale for y (concentration) values. Double-check the placement of your points.

B. CORRECT ANSWER

3-6. A. CORRECT ANSWER

B. *Incorrect answer.* You may have used Kt and not $-Kt$.

C. *Incorrect answer.* Check the $-Kt$ term, which should be $-0.05\ hr^{-1} \times 24$ hours (or -1.2).

3-7. A. *Incorrect answer.* A rate constant is a unit change per time expressed as reciprocal time units (e.g., $minute^{-1}$).

B. *Incorrect answer.* The elimination rate constant does not include mass units.

C. CORRECT ANSWER

D. *Incorrect answer*. These are the proper units for concentration.

3-8. A. CORRECT ANSWER

B, C, D. *Incorrect answers.* The elimination rate constant is 0.2 hr^{-1}, meaning one fifth (or 20%) per hour.

3-9. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. $C_{8\ hr} = C_0e^{-Kt}$, where C_0 = 10 mg/L, K = 0.15 hr^{-1}, and t = 8 hours.

3-10. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. $C_{12\ hr} = C_0e^{-Kt}$, where C_0 = 120 mg/L, K = 0.231 hr^{-1}, and t = 12 hours. K is calculated from half-life ($K = 0.693/T½$). Also, 12 hours represents four half-lives. We would expect the concentration to decrease from 120 mg/L to 60 mg/L, then to 30 mg/L, 15 mg/L, and finally, to 7.5 mg/L.

3-11. A, C. *Incorrect answers*

B. CORRECT ANSWER. To find the $T½$ of 10 hours, find the interval of time necessary for the concentration to decrease from 100 to 50.

3-12. A. CORRECT ANSWER

B. *Incorrect answer.* You may have used $T½ = K/0.693$ rather than $T½ = 0.693/K$.

C. *Incorrect answer.* You may have used $T½ = 1/0.564$ rather than $T½ = 0.693/K$.

3-13. A. *Incorrect answer*

B. CORRECT ANSWER. When using the area method, it does not matter if the drug best fits any particular model.

3-14. A. CORRECT ANSWER

B. *Incorrect answer.* You may have neglected to divide the sum of 100 plus 50 by 2 before then multiplying by the width of 2.

C, D. *Incorrect answers.* Be sure you calculated the height correctly as the average of 50 and 100.

3-15. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. Remember, clearance has units of volume/time, so the units in the equation must result in volume/time. Dose/AUC has units of mg/(mg/L) × hour, which reduces to L/hour.

3-16. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. To calculate clearance, the AUC from time zero to infinity must be used. The AUC from time zero to 12 hours can be calculated, and to this area is added the estimated area from 12 hours to infinity. This area is estimated by dividing the drug concentration at 12 hours, 1 mg/L, by the elimination rate constant, 0.20 hr^{-1} (estimated by the slope of the line between the last two points), thereby obtaining an area of 5 (mg/L) × hour from 12 hours to infinity. Clearance = dose/AUC. Dose is 500 mg. AUC is 119 mg/L, which is the sum of 114 mg/L (from 0 to 12 hours) and 5 mg/L (from 12 hours to infinity).

Discussion Points

D-1. Drug X is given by intravenous administration to two patients. Two plasma concentrations are then determined, and the slope of the plasma concentration versus time curve is calculated. Determine which patient (A or B) has the greater elimination rate constant.

	Patient A	Patient B
Slope of plasma concentration versus time curve	−0.55	−0.23

D-2. Drug X is given to two patients, and two plasma drug concentrations are then determined for each patient. Determine which patient has the greater elimination rate constant.

Time after Dose (hours)	Plasma Concentration (mg/L)	
	Patient A	Patient B
8	22	30
16	5	8

D-3. Why is the half-life of most drugs the same at high and low plasma concentrations?

D-4. The plasma concentration versus time curves for two different drugs are exactly parallel; however, one of the drugs has much higher plasma concentrations. What can you say about the two drugs' half-lives?

D-5. For drug X, the AUC determines the intensity of drug effect. Explain why a reduction of drug clearance by 50% would result in the same intensity of effect as doubling the dose.

D-6. Discuss the mathematical consequences of using a negative versus a positive value for elimination rate constant (k). How do the rules of logarithms affect the arrangements of the equations used to calculate elimination rate constant and desired dosing interval (τ)?

Practice Set 1

The following problems are for your review. Definitions of symbols and key equations are provided here:

X_0 = dose administered

K = elimination rate constant

V = volume of distribution

$T½$ = half-life

t_0 = time immediately after drug administration

C_0 = concentration of drug in plasma at t_0

C_t = C_0e^{-Kt} = concentration of drug in plasma at any time (t) after drug administration

AUC = area under plasma concentration versus time curve

Cl_t = total drug clearance from body = dose/AUC

$$K = \frac{\ln C_0 - \ln C_1}{t_1 - t_0}$$

QUESTIONS

The following applies to **Questions PS1-1 to PS1-3**. A 1-gram dose of drug X is administered by intravenous injection, and the following plasma concentrations result (a one-compartment model is assumed):

Time after Dose (hours)	Plasma Concentration (mg/L)
2	15
4	9.5
6	6

PS1-1. The plasma concentration at 9 hours after the dose estimated from a plot of the points on semilog graph paper* is:

A. < 0.1 mg/L.

B. 0.7 mg/L.

C. 3.1 mg/L.

D. 4.8 mg/L.

*Hint: 3-cycle semilog graph paper can often be found free via an Internet search.

PS1-2. An estimate for the volume of distribution would be:

A. 67 L.

B. 43 L.

C. 53 L.

PS1-3. For this same example, the half-life would be:

A. 1.3 hours.

B. 1.5 hours.

C. 3.1 hours.

D. 4.6 hours.

The following applies to **Questions PS1-4 to PS1-6**. An 80-mg dose of drug Y is administered as an intravenous bolus, and the following plasma concentrations result:

Time after Dose (hours)	Plasma Concentration (mg/L)
0	6.7
0.5	6.0
1	5.3
2	4.2
4	2.6
8	1.0

PS1-4. Using the plasma concentrations at 4 and 8 hours, K is:

A. 0.118 hr^{-1}.

B. 0.239 hr^{-1}.

C. 0.478 hr^{-1}.

D. 0.960 hr^{-1}.

PS1-5. Using the trapezoidal rule, calculate the area under the curve from 0 to 8 hours (AUC_{0-8}). Then calculate it from 0 hours to infinity (∞). *Remember*: $AUC_{0\rightarrow 8}$ equals AUC_{0-8} plus the area under the curve after 8 hours. This

terminal area is calculated by taking the final concentration (at 8 hours) and dividing by K above.

A. 4.2 (mg/L) × hour
B. 24.8 (mg/L) × hour
C. 28.9 (mg/L) × hour
D. 53.7 (mg/L) × hour

PS1-6. For this same example, the clearance calculated by the area method would be:

A. 0.36 L/hour.
B. 0.78 L/hour.
C. 1.52 L/hour.
D. 2.76 L/hour.

ANSWERS

PS1-1. A, B. *Incorrect answers.* You may have used linear graph paper rather than semilog paper.

C. CORRECT ANSWER

D. *Incorrect answer.* Be sure your x-scale for time is correct and that you extrapolated the concentration for 9 hours.

PS1-2. A, C. *Incorrect answers*

B. CORRECT ANSWER. First, estimate C_0 by drawing a line back to time = 0 (t_0) using the three plotted points. This should equal 23 mg/L. Then, V = dose/C_0 = 1000 mg/23 mg/L = 43 L.

PS1-3. A. *Incorrect answer.* You may have calculated the numerator incorrectly.

B, D. *Incorrect answers.* You may have used the wrong time interval.

C. CORRECT ANSWER. Half life = 0.693/K, where: K = (ln 6 − ln 15)/(6 hours − 2 hours) = 0.23 hr^{-1}. So, half-life = 0.693/0.23 = 3.1 hours.

PS1-4. A, C, D. *Incorrect answers*

B. CORRECT ANSWER

$$K = \frac{\ln 1 - \ln 2.6}{8\ \text{hr} - 4\ \text{hr}} = \frac{0 - 0.96}{4\ \text{hr}}$$

$$= 0.239\ \text{hr}^{-1}$$

PS1-5. A. *Incorrect answer.* You may have included just the area from 8 hours to infinity.

B. *Incorrect answer.* You may not have included the area from 8 hours to infinity.

C. CORRECT ANSWER.

For AUC from 0 to 8 hours:

$$\frac{6.7 + 6.0}{2}(0.5) = 3.18$$

$$\frac{6.0 + 5.3}{2}(0.5) = 2.82$$

$$\frac{5.3 + 4.2}{2}(1) = 4.75$$

$$\frac{4.2 + 2.6}{2}(2) = 6.80$$

$$\frac{2.6 + 1.0}{2}(4) = 7.20$$

$$3.18 + 2.82 + 4.75 + 6.80 + 7.20 = 24.8\ (\text{mg/L}) \times \text{hr}$$

For AUC from 8 hours to infinity:

$$C_{8\ \text{hr}} = \frac{1.0\ \text{mg/L}}{0.239\ \text{hr}^{-1}} = 4.18\ (\text{mg/L}) \times \text{hr}$$

Therefore, the AUC from time zero to infinity equals:

$$24.8\ (\text{mg/L}) \times \text{hr} + 4.18\ (\text{mg/L}) \times \text{hr} = 28.93\ (\text{mg/L}) \times \text{hr}$$

D. *Incorrect answer.* You may not have multiplied by 1/2 when calculating the area from 8 hours to infinity.

PS1-6. A. *Incorrect answer.* You may have inverted the formula.

B, C. *Incorrect answers*

D. CORRECT ANSWER

$$\text{clearance} = \frac{\text{dose}}{\text{AUC}} = \frac{80 \text{ mg}}{28.93 \text{ (mg/L)} \times \text{hr}}$$

$$= 2.76 \text{ L/hr}$$

LESSON 4

Intravenous Bolus Administration, Multiple Drug Administration, and Steady-State Average Concentrations

OBJECTIVES

After completing Lesson 4, you should be able to:

1. Describe the principle of superposition and how it applies to multiple drug dosing.
2. Define *steady state* and describe how it relates to a drug's half-life.
3. Calculate the estimated peak plasma concentration after multiple drug dosing (at steady state).
4. Calculate the estimated trough plasma concentration after multiple drug dosing (at steady state).
5. Understand the equation for accumulation factor at steady state.

In clinical practice, most pharmacokinetic dosing is performed with one-compartment, intermittent infusion models at steady state. Using these models, we can obtain, from population estimates or patient-specific calculation, an elimination rate constant (K) and a dosing interval (τ) based on this K value. Volume of distribution (V) can likewise be either estimated or calculated from patient-specific values. So far, our discussion has been limited to a single intravenous (IV) bolus dose of drug; however, most clinical situations require a therapeutic effect for time periods extending beyond the effect of one dose. In these situations, multiple doses of drug are given. The goal is to maintain a therapeutic effect by keeping the amount of drug in the body, as well as the concentration of drug in the plasma, within a fairly constant range (the therapeutic range). In this lesson, we construct equations for predicting drug concentrations after multiple IV bolus (i.e., IV push) doses. Intermediate equations are used simply to illustrate the derivation of the final equations that can be applied clinically. Full understanding of this simpler IV bolus model will aid in the understanding of the slightly more complicated yet more clinically relevant IV intermittent infusion equations used later in this book.

Clinical Correlate

This lesson describes a one-compartment, first-order, IV bolus pharmacokinetic model. It is used only to illustrate certain math concepts that will be further explored with the more commonly used IV intermittent infusion (i.e., IV piggyback) models described in Lesson 5. Consequently, read this IV bolus section only for general conceptual understanding, knowing that it is seldom applied clinically.

Intravenous Bolus Dose Model

Although not used often clinically, the simplest example of multiple dosing is the administration of rapid IV doses (IV boluses) of drug at constant time intervals, in which the drug is represented by a one-compartment model with first-order elimination (i.e., one-compartment, first-order model).

The first dose produces a plasma drug concentration versus time curve like the one in **Figure 4-1**. C_0 is now referred to as C_{max}, meaning maximum concentration, to group it with the other peak concentrations that occur with multiple dosing.

If a second bolus dose is administered before the first dose is completely eliminated, the maximum concentration after the second dose (C_{max2}) will be higher than that after the first dose (C_{max1}) (**Figure 4-2**). The second part of the curve will be very similar to the first curve but will be higher (have a greater concentration) because some drug remains from the first dose when the second dose is administered.

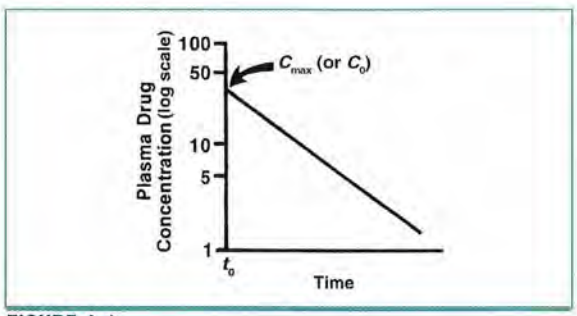

FIGURE 4-1.
Plasma drug concentrations after a first dose.

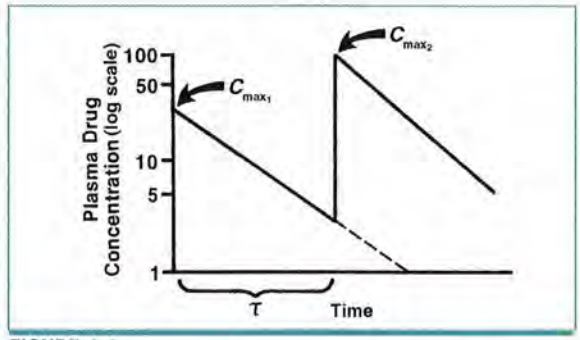

FIGURE 4-2.
Plasma drug concentrations resulting from a second dose.

The *dosing interval* is the time between administration of doses. The dosing interval, symbolized by the Greek letter tau (τ), is determined by a drug's half-life. Rapidly eliminated drugs (i.e., those having a short half-life) generally have to be given more frequently (shorter τ) than drugs with a longer half-life.

If a drug follows first-order elimination (i.e., the fraction of drug eliminated per unit of time is constant), then plasma drug concentrations after multiple dosing can be predicted from concentrations after a single dose. This method uses the principle of superposition, a simple overlay technique.

If the early doses of drug do not affect the pharmacokinetics (e.g., absorption and clearance) of subsequent doses, then plasma drug concentration versus time curves after each dose will look the same; they will be superimposable. The only difference is that the actual concentrations may be higher at later doses because drug has accumulated.

Recall that the y-intercept is called C_0 and the slope of the line is $-K$. Furthermore, the drug concentration at any time (C_t) after the first IV bolus dose is given by:

$$\ln C_t = \ln C_0 - Kt \quad \text{(See Equation 3-2.)}$$

or

$$C_t = C_0 e^{-Kt}$$

A second IV bolus dose is administered after the dosing interval (τ), but before the first dose is completely eliminated. Because $C_t = C_0e^{-Kt}$ at any time (t) after the first dose, it follows that:

$$C_{min1} = C_{max1}e^{-K\tau}$$

where C_{min1} is the concentration just before the next dose is given and τ, the dosing interval, is the time from C_{max} to C_{min}.

C_{max2} is the sum of C_{min1} and C_{max1} (**Figure 4-3**), as the same dose is given again:

$$C_{max2} = C_{max1} + C_{min1}$$

We showed that:

$$C_{min1} = C_{max1}e^{-K\tau}$$

so:

$$C_{max2} = C_{max1} + C_{max1}e^{-K\tau}$$

By rearranging, we get:

$$C_{max2} = C_{max1}(1 + e^{-K\tau})$$

A third IV bolus dose can be administered after the same dosing interval (τ). The plasma drug concentration versus time profile reveals a further increase in the maximum concentration immediately after the third dose, as shown in **Figure 4-4**. Just as after the first dose:

$$C_{min2} = C_{max2}e^{-K\tau}$$

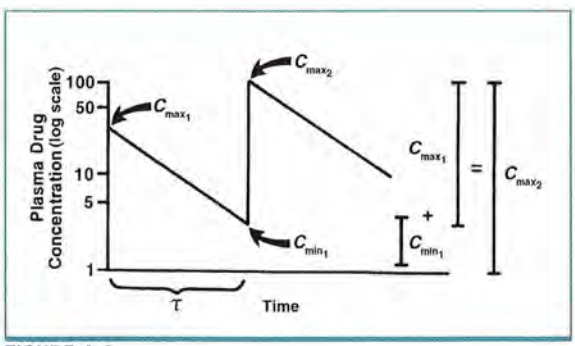

FIGURE 4-3.
C_{max2} calculation.

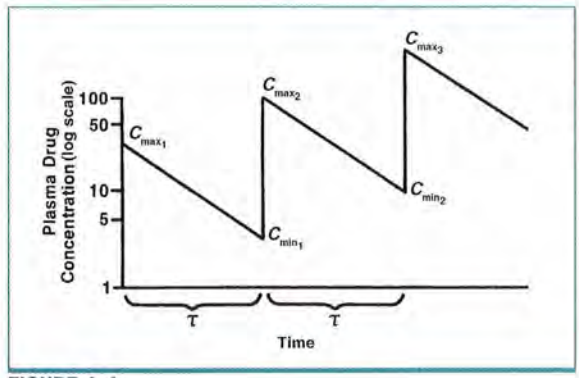

FIGURE 4-4.
Increase in C_{max}.

which, by substitution for $C_{max2} = C_{max1}(1+e^{-K\tau})e^{-K\tau}$. Moreover:

$$C_{max3} = C_{max2} + C_{max1}$$

which, substituting for $C_{min2} = C_{max1}(1+e^{-K\tau})e^{-K\tau} + C_{max1}$. This simplifies as follows:

$$C_{max3} = C_{max1}[(1+e^{-K\tau})(e^{-K\tau}) + 1]$$
$$= C_{max1}[e^{-K\tau} + e^{-2K\tau} + 1]$$
$$= C_{max1}[1 + e^{-K\tau} + e^{-2K\tau}]$$

As we can see, a pattern emerges—after any number of dosing intervals, the maximum concentration will be:

$$C_{max\,n} = C_{max1}[1 + e^{-K\tau} + e^{-2K\tau} + \ldots + e^{-(n-1)K\tau}]$$

where n is the number of doses given. This equation can be simplified by mathematical procedures to a more useful form:

$$C_{max\,n} = C_{max1}\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}$$

where $C_{max\,n}$ is the concentration just after n number of doses are given. So, if we know C_{max1}, the elimination rate, and the dosing interval, we can predict the maximum plasma concentration after any number (n) of doses.

We also know that $C_{\min n}$ (concentration just before a dose is given) equals $C_{\max n}e^{-K\tau}$. Therefore:

$$C_{\min n} = C_{\max 1}\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}e^{-K\tau}$$

and because $C_{\max 1} = X_0/V$ (i.e., dose divided by volume of distribution):

$$C_{\min n} = \frac{X_0}{V}\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}e^{-K\tau}$$

This latter change allows us to calculate $C_{\min}$ if we know the dose and volume of distribution, a likely situation in clinical practice.

In each of the preceding equations, the term $(1-e^{-nK\tau})/(1-e^{-K\tau})$ appears. It is called the *accumulation factor* because it relates drug concentration after a single dose to drug concentration after n doses with multiple dosing. This factor is a number greater than 1, which indicates how much higher the concentration will be after n doses compared with the first dose. For example, if 100 doses of a certain drug are given to a patient, where $K = 0.05\ hr^{-1}$ and $\tau = 8$ hours, the accumulation factor is calculated as follows:

$$\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})} = \frac{(1-e^{-100(0.05\ hr^{-1})8\ hr})}{(1-e^{-(0.05\ hr^{-1})8\ hr})} = 3.03$$

This means that the peak (or trough) concentration after 100 doses will be 3.03 times the peak (or trough) concentration after the first dose.

The accumulation factor for two or three doses can also be calculated to predict concentrations before achievement of steady state. Remember:

4-1 $$\text{accumulation factor} = \frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}$$

So for the second IV bolus dose:

$$\text{accumulation factor (two doses)} = \frac{(1-e^{-2(0.05\ hr^{-1})8\ hr})}{(1-e^{-(0.05\ hr^{-1})8\ hr})}$$

$$= \frac{(1-0.449)}{(1-0.670)}$$

$$= 1.67$$

For the third IV bolus dose:

$$\text{accumulation factor (three doses)} = \frac{(1-e^{-3(0.05\ hr^{-1})8\ hr})}{(1-e^{-(0.05\ hr^{-1})8\ hr})}$$

$$= \frac{(1-0.301)}{(1-0.670)}$$

$$= 2.12$$

Therefore, after two or three doses, the observed peak drug concentration will be 1.67 or 2.12 times the peak concentration after the first dose, respectively. The concept of accumulation factor is discussed in more detail in the Accumulation Factor section later in this lesson.

These equations will be used later to predict drug concentrations for given dosage regimens. For certain drugs (e.g., aminoglycosides), it is important to predict peak ($C_{\max}$) and trough ($C_{\min}$) concentrations in various clinical situations.

Clinical Correlate

If a drug has a very short half-life (much less than the dosing interval), then the plasma concentrations resulting from each dose will be the same and accumulation of drug will not occur (as shown in **Figure 4-5**). An example would be a drug such as gentamicin given every 8 hours intravenously to a patient whose excellent renal function results in a drug half-life of 1.0–1.5 hours.

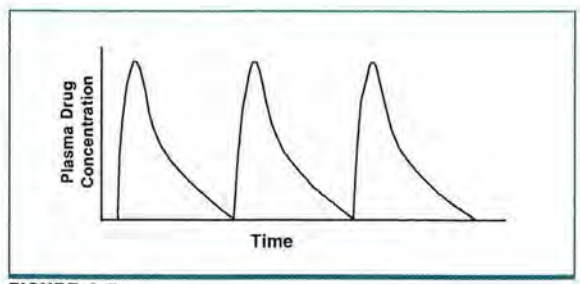

FIGURE 4-5.
Plasma drug concentration versus time.

Intravenous Bolus Equations at Steady State

As successive doses of a drug are administered, the drug begins to accumulate in the body. With first-order elimination, the amount of drug eliminated per unit of time is proportional to the amount of drug in the body. Accumulation continues until the rate of elimination approaches the rate of administration:

rate of drug going in = rate of drug going out

As the rate of drug elimination increases and then approaches that of drug administration, the maximum (peak) and minimum (trough) concentrations increase until equilibrium is reached. After that point, there will be no additional accumulation; the maximum and minimum concentrations will remain constant with each subsequent dose of drug (**Figure 4-6**).

When this equilibrium occurs, the maximum (and minimum) drug concentrations are the same for each additional dose given (assuming the same dose and dosing interval are used). When the maximum (and minimum) drug concentrations for successive doses are the same, the amount of drug eliminated over the dosing interval (rate out) equals the dose administered (rate in) and the condition of *steady state* is reached.

Steady state will always be reached after repeated drug administration at the same dosing interval if the drug follows first-order elimination. However, the time required to reach steady state varies from drug to drug, depending on the elimination rate constant. With a higher elimination rate constant (a shorter half-life), steady state is reached sooner than with a lower one (a longer half-life) (**Figure 4-7**).

Steady state is the point at which the amount of drug administered over a dosing interval equals the amount of drug being eliminated over that same period, and it is totally dependent on the elimination rate constant. Therefore, when the elimination rate is higher, a greater amount of drug is eliminated over a given time interval; it then takes a shorter time for the amount of drug eliminated and the amount of drug administered to become equivalent (and, therefore, achieve steady state). If the half-life of a drug is known, the time to reach steady state can be determined. If repeated doses of drug are given at a fixed interval, then in one half-life the plasma concentrations will reach 50% of those at steady state. By the end of the second half-life, the concentrations will be 75% of steady state, and so on as shown in **Table 4-1**. The plasma concentrations will increase by progressively smaller increments. *For all practical purposes, steady state will be reached after approximately four or five half-lives*; the concentrations at steady state may be abbreviated as C_{ss}.

For a drug such as gentamicin, with a 1- to 4-hour half-life in patients with normal renal function, steady-state concentration is achieved within 10–20 hours. For agents with longer half-lives, such as digoxin and phenobarbital, however, a week or longer may be needed to reach steady state.

With multiple drug doses (**Figure 4-8**), steady state is reached when the drug from the first dose is almost entirely eliminated from the body. At this point, the amount of drug remaining from the first dose does not contribute significantly to the total

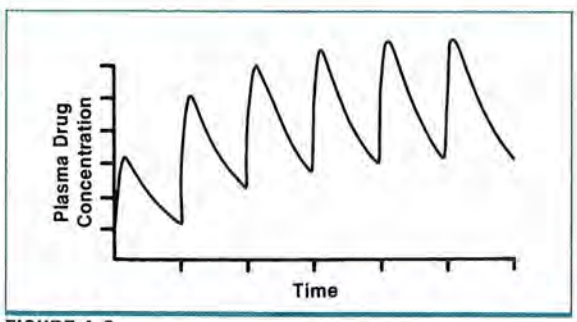

FIGURE 4-6.
Multiple-dose drug administration.

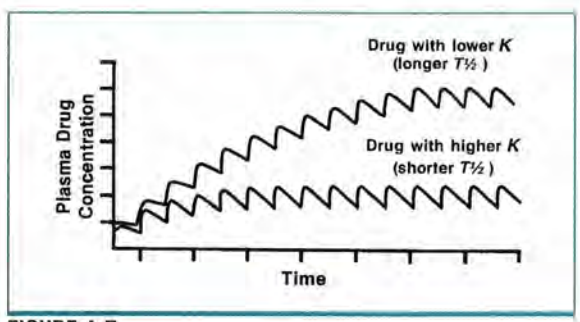

FIGURE 4-7.
Steady state is reached sooner with a drug having a shorter half-life.

TABLE 4-1. Percentage of Steady-State Concentration Reached

Duration of Drug Administration (half-lives)	Steady-State Concentration Reached (%)
1	50
2	75
3	87.5
4	93.75
5	96.875
6	98.4735
7	99.25

TABLE 4-2. Time to Reach Steady State for Commonly Used Drugs[a]

Drug	Time to Reach Steady State (hours)
Enoxaparin	19
Cefazolin	11
Digoxin	195
Gentamicin	10–15
Atorvastatin	100
Lithium	110
Vancomycin	28
Levofloxacin	35

[a]Calculated from average drug half-lives, Table 3-2.

amount of drug in the body. After a single dose, approximately four or five half-lives are required for the body to eliminate the amount of drug equivalent to the one dose. However, at steady state, the amount of drug equivalent to one dose is eliminated over one dosing interval. This apparently faster elimination is a result of accumulation of drug in the body. Although the same percentage of drug is eliminated per hour, the greater amount of drug in the body at steady state causes a greater amount to be eliminated over the same time period.

The average times to reach steady state for some commonly used drugs are shown in **Table 4-2**. These values may vary considerably between individuals and may be altered by disease. For some drugs (e.g., aspirin, ranitidine, and gentamicin), the therapeutic effects will begin before steady-state plasma concentrations are reached. For others (e.g., zidovudine or lovastatin), a much longer time period than that needed to reach steady state is necessary for full therapeutic benefits.

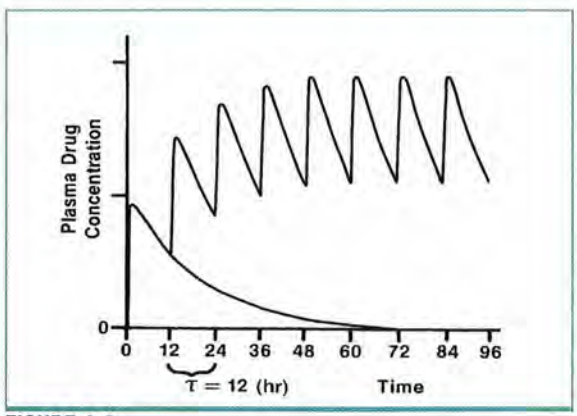

FIGURE 4-8.
At steady state, the time required to eliminate one dose of drug is one dosing interval.

Clinical Correlate

Time to achieve steady state is a physiologic function based solely on the drug's K or half-life, and the amount of time it takes to achieve steady state cannot be increased or decreased. However, administration of a loading dose for drugs that take many hours to reach steady state is commonly used to achieve a concentration within the therapeutic range from the outset of therapy.

The time to reach steady state is determined by the drug's elimination rate constant (K), but what determines the actual plasma drug concentrations achieved? At steady state, the levels achieved depend on the drug's clearance, volume of distribution, dose, and dosing interval (τ). When equivalent doses are given, a drug with a low elimination rate constant and small volume of distribution should achieve higher steady-state plasma concentrations than an otherwise similar agent with a high elimination rate constant and large volume of distribution. In the remainder of this lesson, we examine some aspects of multiple drug dosing.

Steady-state concentrations are commonly increased in two ways:

- Method 1—Increase the drug dose but maintain the same dosing interval (τ), as shown in **Figure 4-9**, which results in wider fluctuations between the maximum (peak) and minimum (trough) concentrations after each dose.
- Method 2—Keep the same dose but give it more frequently, as shown in **Figure 4-10**, which reduces the differences between the peak and trough concentrations.

Note that the time to achieve steady state is the same in both figures.

Clinical Correlate

You may wish to change a patient's steady-state drug concentrations. For example, the patient is not receiving maximal benefits because the steady-state concentrations are relatively low or the steady-state levels are high, causing the patient to experience toxic effects. Remember from earlier in this lesson that repeated doses of drug require approximately four or five half-lives to reach steady state. Clinically, this means that each time a dose or dosing interval is changed, four or five half-lives are needed to reach a new steady state. Of course, a drug with a long half-life will require a longer time to achieve the new steady state than a drug with a relatively short half-life. For example, Drug A has a half-life of 6 hours; if the dose or dosing interval is changed, steady state will not be reached for 24–30 hours after the change. If Drug B has a half-life of 3 hours, steady state will be reached in 12–15 hours after a change in the dose or dosing interval.

In deciding on a specific dosing regimen for a patient, the goal is to achieve a certain plasma concentration of drug at steady state. Ideally, peak and trough concentrations will both be within the therapeutic range (**Figure 4-11**).

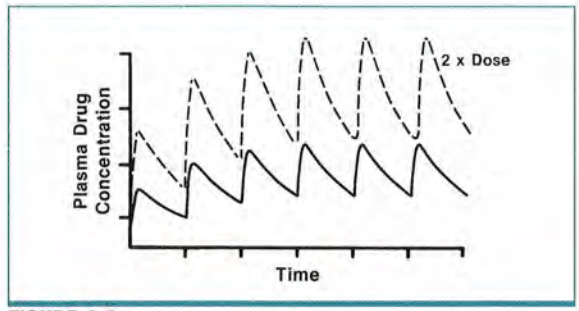

FIGURE 4-9.
Dose increase with no change in dosing interval to achieve higher concentrations.

Accumulation Factor

Equations can describe the plasma concentrations and pharmacokinetics of a drug at steady state. Remember, steady state will be reached only after four or five half-lives.

Recall that with an IV bolus injection of a drug fitting a one-compartment model and first-order elimination, the drug concentration at any time (t) after any number of doses (n), not necessarily at steady state, can be described by:

$$C_{n(t)} = \frac{X_0}{V}\left(\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}\right)e^{-Kt}$$

accumulation factor

Note the inclusion of the accumulation factor from **Equation 4-1** as part of this equation.

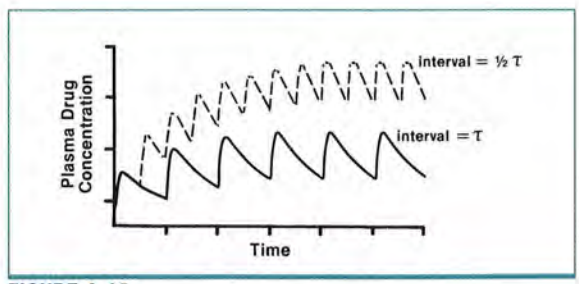

FIGURE 4-10.
Dosing interval decrease with no change in dose to achieve higher concentrations.

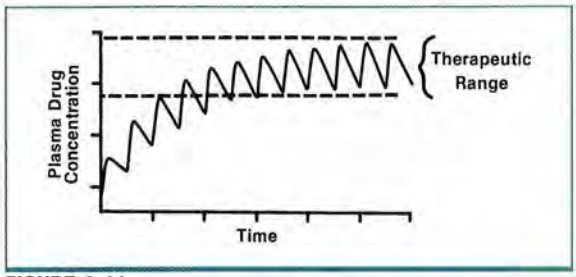

FIGURE 4-11.
Maintenance of plasma drug concentrations within the therapeutic range.

To predict the plasma concentration of a drug at any time t after n number of doses, we therefore need to know four values:

- drug dose (X_0),
- volume of distribution (V),
- elimination rate constant (K), and
- dosing interval (τ).

If we wish to predict the steady-state peak concentration immediately after an IV bolus dose, where $t = 0$ and $e^{-0} = 1$, the equation above for $C_{n(t)}$ becomes:

$$C_{peak(n)} = \frac{X_0}{V}\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}$$

because time after the dose equals zero ($t = 0$, and $e^{-0} = 1$).

As multiple drug doses are administered and n becomes sufficiently large (> 4 or 5 doses), n increases and approaches infinity (abbreviated as $n\rightarrow\infty$). The preceding equation can then be simplified. As n becomes a large number, $e^{-nK\tau}$ approaches $e^{-\infty}$, which approaches zero, so $1 - e^{-nK\tau}$ approaches 1. As $1 - e^{-nK\tau}$ approaches 1, the value of this numerator becomes 1, and the resultant numerator/denominator combination is termed the *accumulation factor at steady state*:

4-2 $$\frac{1}{(1-e^{-K\tau})}$$

The equation for $C_{peak(n)}$ now becomes the equation for $C_{peak\ ss}$ and can be written as:

$$C_{peak(steady\ state)} = \frac{X_0}{V}\left[\frac{1}{(1-e^{-K\tau})}\right]$$

We can estimate the minimum or trough concentration at steady state. The trough concentration occurs just before the administration of the next dose (at $t = \tau$). In this situation, the general equation for the equation for $C_{n(t)}$ becomes:

$$C_{trough(steady\ state)} = \frac{X_0}{V}\left[\frac{1}{(1-e^{-K\tau})}\right]e^{-K\tau}$$

Clinical Correlate

In most clinical situations, it is preferable to wait until a drug concentration is at steady state before obtaining serum drug concentrations. Use of steady-state concentrations is more accurate and makes the numerous required calculations easier.

Note the similarity between the equations for $C_{peak(steady\ state)}$ and $C_{trough(steady\ state)}$. The expression for $C_{trough(steady\ state)}$ simplifies to $C_{peak(steady\ state)}$ times e^{-Kt}. An almost identical equation (below) can be used to calculate the concentration at any time after the peak. The only difference is that t is replaced by the time elapsed since the peak level. Therefore:

$$C_{(t)} = C_{peak(steady\ state)}e^{-Kt}$$

where t is the time after the peak.

This last relationship is very useful in clinical pharmacokinetics. It is really the same as an equation presented earlier. (See **Equation 3-2.**)

$$C_t = C_0e^{-Kt}$$

The preceding equation, stated in words, means a concentration at any time (C_t) is equal to some previous concentration (C_0) multiplied by the fraction (or percent) of that previous concentration (i.e., e^{-Kt}) remaining after it has been allowed to be eliminated from the body for a number of hours represented by t.

If two drug concentrations and the time between them are known, K can be calculated. If one concentration after a dose (e.g., a peak concentration) and K are known, then other concentrations at any time after a dose (but before the next dose) can be estimated.

Average Steady-State Concentration with Intravenous Bolus Dosing

We now have examined both the maximum and minimum concentrations that occur at steady state. Another useful parameter in multiple IV dosing situations is the average concentration of drug in the plasma at steady state ($\overline{C}$) (**Figure 4-12**). Because $\overline{C}$ is independent of any pharmacokinetic model, it is helpful to the practicing clinician (model assumptions do not have to be made). $\overline{C}$ is not an arithmetic or geometric mean.

Several mathematical methods may be used to calculate the average drug concentration, but only one is presented here. A plasma drug concentration versus time curve, after steady state has been achieved with IV dosing, is illustrated in **Figure 4-13**. By knowing the dose given (X_0) and the dosing interval (τ), we can determine the average concentration if we also know the area under the plasma drug concentration versus time curve (AUC) over τ. Therefore:

$$\overline{C} = \frac{\text{AUC}}{\tau}$$

and since:

$$\text{AUC} = \frac{\text{dose}}{\text{drug clearance}}$$

$$\overline{C} = \frac{\text{dose}}{\text{drug clearance} \times \tau}$$

The equation:

$$\overline{C} = \frac{\text{dose}}{\text{Cl}_t \times \tau} \quad \text{4-3}$$

is very useful, particularly with drugs having a long half-life, in which the difference between peak and trough steady-state levels may not be large.

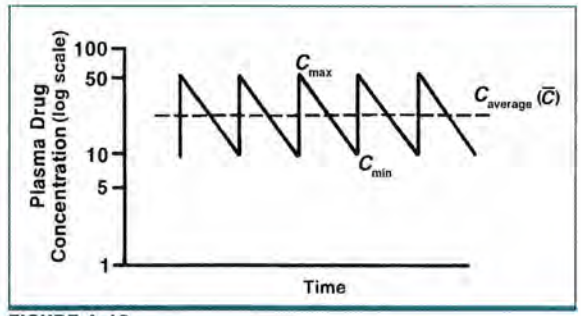

FIGURE 4-12.
Average plasma drug concentration at steady state.

It is important to recognize from the equations that $\overline{C}$ at steady state is determined by the clearance and drug dose (dose/τ). If the dose remains the same [n = a time period such as a day (e.g., 80 mg every 8 hours [80 × 3] or 120 mg every 12 hours [120 × 2])] while τ is changed, $\overline{C}$ would remain the same. Also, changes in V or K that are not related to a change in clearance would not alter $\overline{C}$. With multiple drug dosing at steady state, changes in τ, K, or V (with no change in clearance) would alter the observed peak and trough drug concentrations but not $\overline{C}$.

In dealing with such equations, it is helpful to remember that the units of measure on both sides must be the same. For example, in the equation above, $\overline{C}$ should be in micrograms per milliliter, milligrams per liter, or similar concentration units. Therefore, the right side of the equation must have the same units, as is the case when:

- dose is in a consistent mass unit, such as milligrams,
- clearance is in liters per hour or milliliters per minute, and
- dosing interval is in hours.

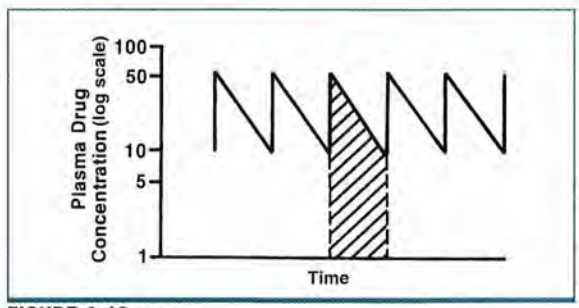

FIGURE 4-13.
AUC for one dosing interval.

So, dose/(Cl × τ) has the following units:

$$\frac{\text{amount}}{(\text{volume/time}) \times \text{time}}$$

Then, as both hour terms cancel out, we see that amount per volume (concentration) is left.

Predicting Steady-State Concentration

The equation for $C_{peak(steady\ state)}$ derived above (and shown below) is valuable because it allows us to predict the peak plasma concentration achieved when a drug is given in a specified dose (X_0) at a consistent and repeated interval (τ). To predict peak concentration at steady state, however, we also must have an estimate of the elimination rate (K) and the volume of distribution (V); therefore, the following equation is used only for IV bolus dosing:

$$C_{peak(steady\ state)} = \frac{X_0}{V}\left[\frac{1}{(1-e^{-K\tau})}\right]$$

It is possible to estimate a patient's K and V from published reports of similar patients. For example, most patients with normal renal function will have a gentamicin V of 0.20–0.30 L/kg and a K of 0.035–0.2 hr^{-1}. In a clinical setting in which a drug is administered and plasma concentrations are then determined, it is possible to calculate a patient's actual K and V using plasma concentrations. Such calculations can be performed as follows.

Example 1

A patient receives 500 mg of drug X intravenously every 6 hours until steady state is reached. Just after the dose is administered, a blood sample is drawn to determine a peak plasma concentration. Then, 5 hours later, a second plasma concentration is determined. Using the two plasma concentrations, we first calculate K, as described previously:

$$K = \frac{\ln C_{peak} - \ln C_{5hr}}{5\ hr}$$

Then we insert the known C_{peak}, K, X_0, and τ values in the equation for C_{peak}. By rearranging the equation to isolate the only remaining unknown variable, we can then use it to calculate V:

$$V = \frac{X_0}{C_{peak(steady\ state)}}\left[\frac{1}{(1-e^{-K\tau})}\right]$$

Now we know the values of all the variables in the equation (V, K, C_{peak}, X_0, and τ) and can use this information to calculate a new C_{peak} if we change the dose (e.g., if the previous C_{peak} is too high or too low). For example, if we want the peak level to be higher and wish to calculate the required dose to reach this new peak level, we can rearrange our equation:

$$X_0 = V \times C_{peak(steady\ state)}(1-e^{-K\tau})$$

and substitute our calculated V and K and the desired C_{peak}. Or we can choose a new dose (X_0) and calculate the resulting C_{peak} by inserting the calculated K and V with τ into the original equation:

$$C_{peak(steady\ state)} = \frac{X_0}{V}\left[\frac{1}{(1-e^{-K\tau})}\right]$$

Remember that each time we calculate a peak plasma level (C_{peak}), the trough plasma level also can be calculated if we know K and τ:

$$C_{trough} = C_{peak}e^{-K\tau}$$

If the dosing interval is not changed, new doses and concentrations are directly proportional if nothing else changes (i.e., K or V).

So,

$$X_{0\ (new)} = \frac{C_{peak(steady\ state)new}}{C_{peak(steady\ state)old}} \times X_{0\ (old)}$$

and,

$$C_{peak(steady\ state)new} = \frac{X_{0\ (new)}}{X_{0\ (old)}} \times C_{steady\ state(old)}$$

Clinically Important Equations Identified in This Chapter

1. $$C_{peak(steady\ state)} = \frac{X_0}{V}\left[\frac{1}{(1-e^{-K\tau})}\right]$$

   This equation is developed from the equation in Lesson 1:

   $$C = X/V$$

   by attaching the steady-state accumulation factor.

2. $$C_{trough} = C_{peak}e^{-K\tau}$$

   This equation is similar to **Equation 3-2** in Lesson 3.

3. $$\bar{C} = \frac{dose}{Cl_t \times \tau}$$ Equation 4-3

REVIEW QUESTIONS

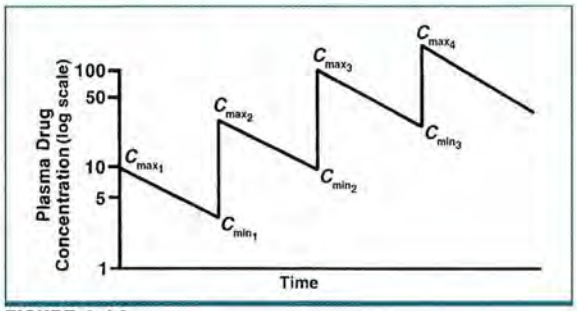

FIGURE 4-14.
Plasma drug concentration versus time.

Note: Refer to **Figure 4-14** when answering questions 4-1 through 4-3.

4-1. If C_{max1}, K, and τ are 100 mg/L, 0.40 hr^{-1}, and 6 hours, respectively, what is the value of C_{max2}?

A. 109.1 mg/L
B. 9.1 mg/L
C. 100 mg/L
D. 110 mg/L

4-2. For the example given in the previous question, what is the value of C_{min2}?

A. 9.1 mg/L
B. 43.6 mg/L
C. 85.3 mg/L
D. 9.9 mg/L

4-3. What is the maximum concentration after 15 doses if the dose (X_0) is 800 mg and the volume of distribution (V) is 20 L? Assume that τ equals 6 hours and K equals 0.50 hr^{-1}.

A. 42.1 mg/L
B. 66.7 mg/L
C. 52.9 mg/L
D. 156.8 mg/L

4-4. When multiple drug doses are given and steady state is reached, the amount of drug eliminated during one dosing interval (τ) is equal to the drug dose.

A. True
B. False

4-5. A drug with a relatively small K (long $T½$) takes a longer time to reach steady state than a drug with a large K.

A. True
B. False

4-6. If a drug with a $T½$ of 12 hours is given every 6 hours and a peak concentration at steady state is 10 mg/L, what will be the approximate peak concentration just after the fifth dose is administered?

A. 5 mg/L
B. 7.5 mg/L
C. 10 mg/L

4-7. A 100-mg dose of drug X is given to two different patients every 8 hours. Which patient (A or B) is likely to achieve higher steady-state plasma concentrations?

Patient	Elimination Rate (hr^{-1})	Volume of Distribution (L)
A	0.2	10
B	0.4	20

A. Patient A
B. Patient B

4-8. Decreasing the dosing interval while keeping the dose constant will result in lower steady-state concentrations.

A. True
B. False

4-9. Which of the following dosage techniques results in the greatest difference between maximum (peak) and minimum (trough) concentrations after a dose?

A. Small doses given at a short dosing interval

B. Large doses given at a long dosing interval

4-10. What is the peak drug X concentration attained at steady state if 100 mg is given by IV injection every 6 hours, the patient's $K = 0.35\ hr^{-1}$, and $V = 20$ L? (Assume a one-compartment distribution.)

A. 3.4 mg/L

B. 5.7 mg/L

C. 16.3 mg/L

D. 41 mg/L

4-11. What would be the trough level for the example in question 4-10?

A. 0.41 mg/L

B. 0.7 mg/L

C. 2 mg/L

D. 5 mg/L

4-12. A 500-mg dose of drug X is given every 6 hours until steady-state levels are reached. At steady state, the AUC for one dosing interval is 42 (mg/L) × hour. What is the average concentration over that dosing interval?

A. 3.1 mg/L

B. 7 mg/L

C. 12.5 mg/L

D. 22 mg/L

4-13. A patient receives an antimicrobial dose of 400 mg IV every 8 hours. After steady state is reached, a peak level of 15 mg/L is determined; the level 4 hours after the peak is 4.5 mg/L. What dose is required to attain a peak plasma level of 35 mg/L? (Assume IV bolus drug administration.)

A. 400 mg

B. 800 mg

C. 933 mg

D. 3108 mg

4-14. For the example given in the last question, when the peak plasma level is 35 mg/L, what will the trough plasma level be?

A. 2.3 mg/L

B. 3.2 mg/L

C. 4.8 mg/L

D. 32 mg/L

ANSWERS

4-1. A. CORRECT ANSWER

B. *Incorrect answer.* This value is the minimum concentration after the first dose. Remember to add the value of C_{max1}, which was 100 mg/L.

C. *Incorrect answer.* This is the value of C_{max1}. C_{max2} is calculated as the sum of C_{max1} and C_{min1}.

D. *Incorrect answer.* This is close to the C_{max2} but is actually the steady-state C_{max}. C_{max2} is calculated as the sum of C_{max1} and C_{min1}.

4-2. A. *Incorrect answer.* This is C_{min1}.

B, C. *Incorrect answers*

D. CORRECT ANSWER. C_{min2} can be found from C_{max2} as follows: $C_{min2} = C_{max2}\,(e^{-Kt})$, so $C_{min2} = 109.1\ mg/L(e^{-0.4/hr \times 6\ hr}) = 109.1 \times 0.091 = 9.9\ mg/L$.

4-3 A. CORRECT ANSWER.

$$C_{max\,n} = C_{max1}\frac{(1-e^{-nK\tau})}{1-e^{-K\tau}}$$

$$C_{max1} = \frac{X_0}{V} = \frac{800\ mg}{20\ L}$$

Then

$$C_{max\,15} = \left(\frac{800\ mg}{20\ L}\right)\left[\frac{(1-e^{-15(0.5\ hr^{-1})6\ hr})}{(1-e^{-(0.5\ hr^{-1})6\ hr})}\right]$$

$$C_{max\,15} = 42.1\ mg/L$$

B, C, D. *Incorrect answers*

4-4. A. CORRECT ANSWER. When steady state is reached, the amount of drug eliminated over one dosing interval is equal to the dose.

B. *Incorrect answer*

4-5. A. CORRECT ANSWER. The half-life directly relates to the time required to reach steady state. Approximately five half-lives are required to reach steady state. A longer half-life (lower K) will mean that more time is required to reach steady state.

B. *Incorrect answer*

4-6. A, C. *Incorrect answers*

B. CORRECT ANSWER. Administration of five doses would take 24 hours, which is two drug half-lives. After one half-life, the peak concentration would be 50% of steady-state concentration; at two half-lives, it would be 75%. So the peak concentration just after the fifth dose would be approximately 7.5 mg/L.

4-7. A. CORRECT ANSWER. Higher concentrations would result with a lower K and V.

B. *Incorrect answer*

4-8. A. *Incorrect answer*

B. CORRECT ANSWER. By decreasing the dosing interval the amount of drug administered per unit of time will increase and steady-state concentrations will increase.

4-9. A. *Incorrect answer.* A small dose given very frequently results in a smaller change from peak to trough concentrations.

B. CORRECT ANSWER

4-10. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The peak concentration is calculated as follows:

$$C_{peak} = X_0/V(1/[1-e^{-K\tau}])$$

$$= 100\ mg/20\ L(1/[1-e^{-0.35\ hr^{-1} \times 6\ hr}])$$

$$= 5.7\ mg/L$$

4-11. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The trough concentration is calculated as follows:

$$C_{trough} = C_{peak} \times e^{-K\tau}$$

$$= 5.7\ mg/L \times e^{-0.35\ hr^{-1} \times 6\ hr}$$

$$= 0.7\ mg/L$$

In this case, the elapsed time t is equal to τ.

4-12. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The average plasma concentration is determined as follows:

$$C = AUC/\tau$$

$$= 42\ (mg/L) \times hr/6\ hr$$

$$= 7\ mg/L$$

4-13. A. *Incorrect answer*. Giving the same dose would result in the same peak concentration of 15 mg/L.

B. *Incorrect answer*. Doubling the dose would result in a doubling of the steady-state peak concentration to 30 mg/L.

C. CORRECT ANSWER

D. *Incorrect answer*. This dose would result in a steady-state peak concentration of 117 mg/L.

4-14. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. To answer this question, K must first be calculated:

$$K = (\ln C_{4\ hr} - \ln C_{peak})/4 = 0.3\ hr^{-1}$$

Then, use the following to calculate the trough plasma concentration:

$$C_{trough} = C_{peak} \times e^{-K} = 35\ mg/L \times e^{-0.30\ hr^{-1} \times 8\ hr}$$

$$= 35\ mg/L \times 0.091 = 3.2\ mg/L$$

Discussion Points

D-1. Explain why, for most drugs, the increase in drug plasma concentrations resulting from a single dose will be the same magnitude whether it is the first or tenth dose.

D-2. Explain why the plasma concentrations (maximum or minimum) remain the same for each dose after steady state is reached.

D-3. Explain why changing the dose or the dosing interval does not affect the time to reach steady state.

D-4. The peak plasma concentration achieved after the first IV dose of drug X is 25 mg/L. The drug's half-life is 3.5 hours, and it is administered every 12 hours. What will be the peak plasma concentration at steady state?

D-5. Discuss why the equations for the IV bolus model may not be relevant in clinical practice.

D-6. Discuss the advantages and disadvantages of using the one-compartment first-order model before steady state is attained.

LESSON 5

Relationships of Pharmacokinetic Parameters and Intravenous Intermittent and Continuous Infusions

OBJECTIVES

After completing Lesson 5, you should be able to:

1. Explain the relationships of pharmacokinetic parameters and how changes in each parameter affect the others.
2. Describe the relationship between the rate of continuous intravenous (IV) drug infusion, drug clearance, and steady-state plasma concentration.
3. Calculate plasma drug concentrations during and after continuous IV infusion.
4. Calculate an appropriate loading dose to achieve therapeutic range at onset of infusion.
5. Calculate peak and trough concentrations at steady state after intermittent IV infusions.

Relationships of Pharmacokinetic Parameters

Understanding the relationships of pharmacokinetic parameters is important to determine what will occur to the plasma concentration versus time curve when changes in any of the parameters arise. If we administer multiple IV doses of a drug that exhibits one-compartment, first-order elimination kinetics, we might find a plasma drug concentration versus time curve that resembles **Figure 5-1**. A thorough understanding of the basic components of the IV bolus and continuous infusion model will lead to a better understanding of the more commonly used steady-state IV intermittent model equations. Consequently, study this lesson with the knowledge that many of these equations will later be combined and changed to yield the final, more commonly used dosing equations as shown in the cases presented later.

Changes in Elimination Rate Constant

If the dose, the volume of distribution, and the dosing interval (τ) all remain the same but the elimination rate constant (K) decreases (as with decreasing renal or

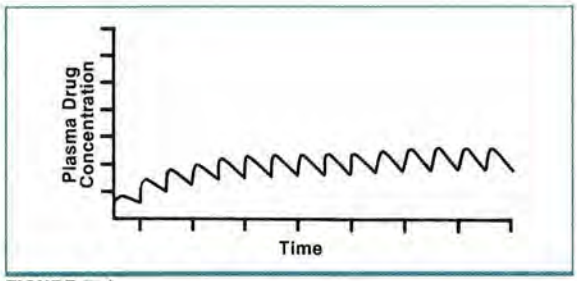

FIGURE 5-1.
Plasma drug concentrations after multiple intravenous doses.

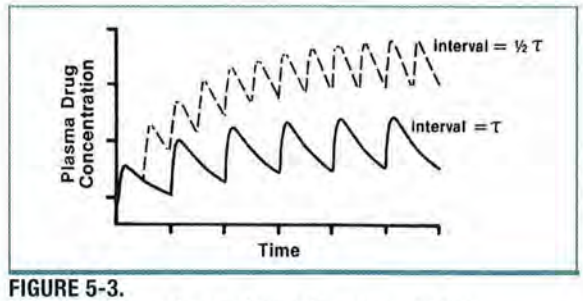

FIGURE 5-3.
Effect of decreased τ on plasma drug concentrations.

hepatic function), the curve should change as shown in **Figure 5-2**. With a lower *K*, we would see that:

1. Peak and trough concentrations at steady state are higher than before.
2. The difference between peak and trough levels at steady state is smaller because the elimination rate is lower.

Because *K* is decreased in this situation, the half-life ($T½$) is increased and, therefore, the time to reach steady state ($5 \times T½$) is also lengthened. This concept is important in designing dosing regimens for patients with progressing diseases of the primary organs of drug elimination (kidneys and liver).

Changes in Dosing Interval

For another example, suppose everything, including the elimination rate, remains constant but the dosing interval (τ) is decreased. The resulting plasma drug concentration versus time curve would be similar to that in **Figure 5-3**. The peak and trough concentrations at steady state are increased. Also, the difference between peak and trough plasma concentrations at steady state is smaller (only because the body is allowed less time to eliminate drug before receiving the next dose). Because *K* (and therefore $T½$) is the same, the time to reach steady state remains unchanged.

Changes in Dose

Now, suppose that *K*, *V*, and τ remain constant but the dose (X_0) is increased. The plasma concentration versus time curve shown in **Figure 5-4** would result. The drug concentrations at steady state are higher, but there is no difference in the time required to reach steady state, as it is dependent only on $T½$ (and *K*).

With some drugs, it is preferable to give a smaller dose at more frequent intervals; with other drugs, the reverse is true. The disadvantage of larger, less frequent dosing is that the fluctuation from peak to trough concentrations is greater. Thus, the possibility of being in a toxic range just after a dose is given and in a subtherapeutic range before the next dose is given is also greater. The problem with smaller, more frequent doses is that such administration may not be practical, even though plasma concentrations may be within the therapeutic range for a greater portion of the dosing interval.

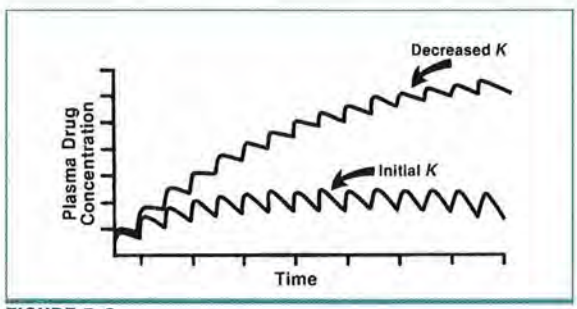

FIGURE 5-2.
Effect of decreased *K* (and therefore increased $T½$) on plasma drug concentrations.

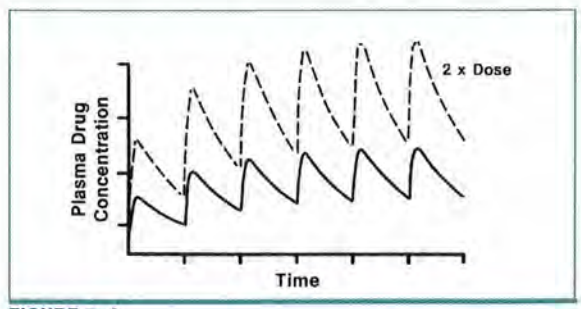

FIGURE 5-4.
Effect of increased dose on plasma drug concentrations.

Changes in Clearance and Volume of Distribution

A drug's half-life and elimination rate constant are determined by its clearance and volume of distribution (discussed in Lessons 2 and 3). These last two pharmacokinetic parameters determine the plasma drug concentrations that result from a dosing regimen, so changes in clearance or volume of distribution result in changes in steady-state plasma drug concentrations.

Volume of distribution and clearance may change independently. However, some disease states may alter both the clearance and the volume of distribution. An example is the effect of renal failure on aminoglycoside concentrations. The renal clearance of aminoglycosides decreases in patients with renal failure, and the volume of distribution may increase because of the fluid accumulation that occurs with oliguric renal failure.

There are a number of conditions that may increase or decrease volume of distribution. The volume of distribution of drugs that distribute primarily in body water increases in patients with conditions that cause fluid accumulation (e.g., renal failure, heart failure, liver failure with ascites, and inflammatory processes such as sepsis). As one would expect, dehydration results in a decreased volume of distribution for drugs of this type. Drugs that are highly bound to plasma protein (such as phenytoin) have a greater volume of distribution when protein binding is decreased by hypoalbuminemia or phenytoin-displacing agents. If fewer proteins are available for binding, then to maintain equilibrium with the tissues, free drug moves from the plasma to the tissues, thus increasing the "apparent" volume of distribution.

Changes in the volume of distribution directly affect steady-state plasma drug concentrations. In general, if the drug dose, dosing interval (τ), and drug clearance are all unchanged but the volume of distribution decreases, there will be greater fluctuation of plasma concentrations with higher peak concentrations. Conversely, if the volume of distribution increases, there will be less fluctuation of plasma concentrations with a lower peak (**Figure 5-5**).

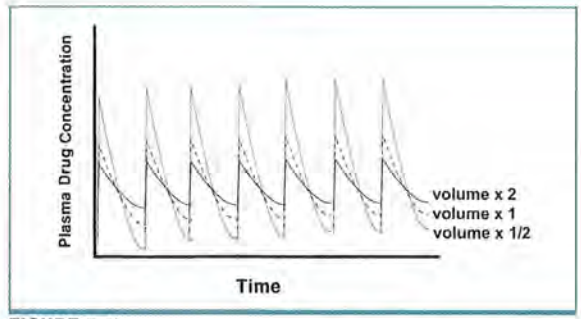

FIGURE 5-5.
Effect of changes in volume of distribution on plasma drug concentrations.

The effect of volume of distribution changes on plasma drug concentrations can be easily estimated for most drugs. When the volume of distribution increases, assuming there are no other changes, peak steady-state plasma drug concentrations decrease. Conversely, if the volume of distribution decreases, peak steady-state plasma drug concentrations increase. This can also be demonstrated by the following equation:

$$C_{ss} = K_0 / KV$$

$$K_0 = X_0 / t$$

where K_0 = the rate of drug infusion (or administration). (Note: This equation is derived in the section Continuous Infusion later in this lesson.)

There are a number of conditions that may increase or decrease drug clearance. Agents that change renal blood flow directly affect the clearance of drugs excreted by the kidneys. Renal clearance may decrease when agents that compete for active renal secretion are administered concomitantly (such as penicillin with probenecid). For drugs that are eliminated hepatically, clearance may be altered by drugs or conditions that increase or decrease liver blood flow. Some conditions (such as hepatitis or cirrhosis) also may decrease the capability of liver enzymes to metabolize drugs. Drug clearance may increase when organ function improves after healing, with concomitant drug administration, or under conditions that increase organ blood flow or the activity of metabolic enzymes.

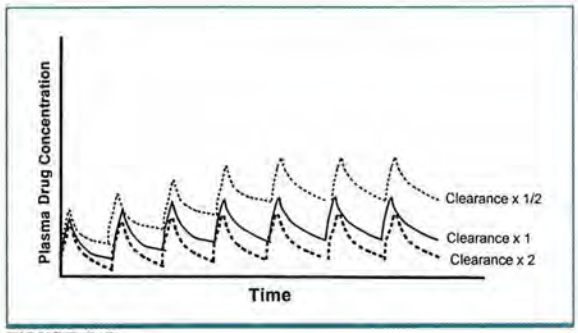

FIGURE 5-6.
Effect of changes in clearance on plasma drug concentrations.

Changes in drug clearance affect steady-state plasma drug concentrations. If the dose, dosing interval, and the volume of distribution are all unchanged but clearance increases, plasma drug concentrations will decrease because the drug is being removed at a faster rate. Conversely, if clearance decreases, plasma concentrations will increase because the drug is being removed at a slower rate (**Figure 5-6**).

This can also be demonstrated by the modification of the equation presented above:

$$C_{ss} = K_0 / Cl_t$$

$$Cl_t = KV$$

where K_0 = the rate of drug infusion and Cl_t = total body clearance. (Note: This equation is also derived in the section Continuous Infusion.)

As with volume of distribution, the effect of changes in clearance on plasma drug concentrations can be easily estimated for most drugs. For example, if drug clearance increases by a factor of two, the average steady-state plasma drug concentration decreases by half. Conversely, if drug clearance decreases by half, the average steady-state plasma drug concentration would increase by a factor of two.

Clinical Correlate

Two conditions that may substantially alter the volume of distribution are severe traumatic or burn injuries. Severely traumatized or burned patients often have a cytokine-induced, systemic inflammatory response syndrome (SIRS), which results in decreased plasma proteins (i.e., albumin) and thus an accumulation of fluid in tissues. An average-weight person (70 kg) may gain as much as 20 kg in fluid over a few days. In comparison to the extra fluid, the body has decreased albumin for binding, and with the accumulation of fluid due to this SIRS, free drug shifts from the plasma into the extravascular fluid, causing drugs that are primarily distributed into body water to have an increased volume of distribution.

Continuous Infusion

The remainder of this lesson describes the continuous infusion model and then shows how it can be combined with the IV bolus model, previously described, to yield the commonly used IV intermittent infusion model (i.e., IV piggyback). As stated earlier, repeated doses of a drug (i.e., intermittent infusions) result in fluctuations in the plasma concentration over time. For some drugs, maintenance of a consistent plasma concentration is advantageous because of a desire to achieve a consistent effect. To maintain consistent plasma drug concentrations, continuous IV infusions are often used. Continuous IV infusion can be thought of as the administration of small amounts of drug at infinitely small dosing intervals. If administration is begun and maintained at a constant rate, the plasma drug concentration versus time curve in **Figure 5-7** will result.

The plasma concentrations resulting from the continuous IV infusion of drug are determined by the rate of drug input (rate of drug infusion, K_0), volume of distribution (V), and drug clearance (Cl_t). The relationship among these parameters is:

$$C_t = \frac{K_0}{VK}(1 - e^{-Kt})$$

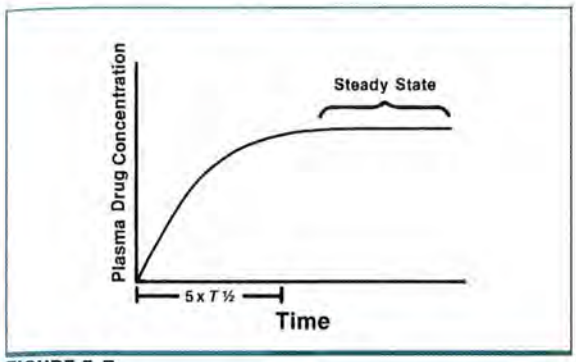

FIGURE 5-7.
Plasma drug concentrations over time with a continuous intravenous infusion.

where t is the time since the beginning of the drug infusion. This equation shows that the plasma concentration is determined by the rate of drug infusion (K_0) and the clearance of drug from the body (remember, $VK = Cl_t$). The equation is used to find a concentration at a time before steady state is reached.

The term $(1 - e^{-Kt})$ gives the fraction of steady-state concentration achieved by time t after the infusion is begun. For example, when t is a very low number just after an infusion is begun, $K_0(1 - e^{-Kt})$ is also very small. When t is very large, $(1 - e^{-Kt})$ approaches 1, so $K_0(1 - e^{-Kt})$ approaches K_0 and plasma concentration approaches steady state.

Suppose that a drug has a half-life of 8 hours (then $K = 0.087\ hr^{-1}$). **Table 5-1** shows how the factor $(1 - e^{-Kt})$ changes with time. When $(1 - e^{-Kt})$ approaches 1 (at approximately five half-lives), steady-state concentrations are approximately achieved.

In Figure 5-7, steady state is attained where the horizontal portion of the curve begins. With a drug such as theophylline given by continuous IV infusion, the average half-life in adults is approximately 7 hours. Therefore, it will take 35 hours (5 × 7 hours) to reach approximate steady-state plasma concentrations.

TABLE 5-1. Changes in Factor $(1 - e^{-Kt})$ Over Time

Time after Starting Infusion (hours)	Value of $(1 - e^{-Kt})$	Drug Half-Lives Elapsed
4	0.29	0.5
8	0.50	1.0
16	0.75	2.0
24	0.88	3.0
40	0.97	5.0
60	0.99	7.5

When steady state is achieved, the factor e^{-nKt} (see Lesson 4) approaches zero, and thus the factor $(1 - e^{-Kt})$ equals 1, and then:

$$C_{ss} = \frac{K_0}{Cl_t}(1 - e^{-\infty}) = \frac{K_0}{Cl_t}(1 - 0) - \frac{K_0}{Cl_t}$$

At steady state, the plasma concentration of drug is directly proportional to the rate of administration (assuming clearance is unchanged). If the infusion is increased, the steady-state plasma concentration (C_{ss}) will increase proportionally. Clearance is the pharmacokinetic parameter that relates the rate of drug input (dosing or infusion rate) to plasma concentration. The actual plasma concentration attained with a continuous IV infusion of drug depends on the following two factors:

1. rate of drug infusion (K_0) and
2. clearance of the drug (Cl_t).

If we know from previous data that a patient receives IV theophylline (or aminophylline), which has a half-life of 6 hours ($K = 0.116\ hr^{-1}$) and a volume of distribution of 30 L (clearance then equals 3.48 L/hour), we can predict the steady-state plasma concentration for a continuous IV theophylline infusion of 40 mg/hour:

$$C_{ss} = \frac{K_0}{Cl_t}(1 - e^{-\infty}) = \frac{K_0}{Cl_t}(1 - 0) - \frac{40\ mg/hr}{3.48\ L/hr} = 11.5\ mg/L$$

If we wish to increase the steady-state theophylline plasma concentration to 14 mg/L, we would use the same equation to determine K_0:

$$14\ mg/L = \frac{K_0}{30\ L \times 0.116\ hr^{-1}}$$

$$K_0 = (14\ mg/L)(30\ L \times 0.116\ hr^{-1}) = 48.7\ mg/hr$$

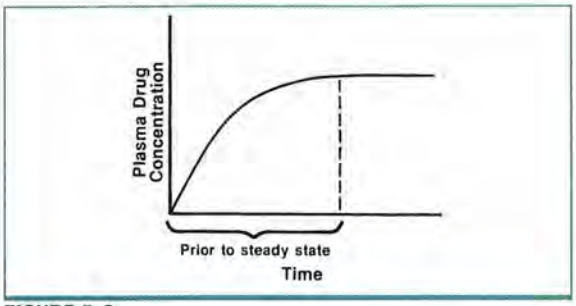

FIGURE 5-8.
Plasma drug concentrations over time with a continuous intravenous infusion.

Or, as concentration and infusion rate are directly proportional, the following equation may be used to find a new infusion rate to obtain a desired steady-state concentration:

$$K_{0(new)} = \frac{C_{ss\ (desired)}}{C_{ss\ (measured)}} \times K_{0(original)}$$

$$= \frac{14\ mg/L}{11.5\ mg/L} \times 40\ mg/hr$$

$$= 48.7\ mg/hr$$

With the continuous IV infusion method of drug administration, it is sometimes necessary to predict drug plasma concentrations at times other than at steady state. In the following section, we examine some of these situations (**Figure 5-8**).

The equation predicting plasma concentrations with continuous IV infusion can be used to estimate plasma drug concentrations at times before steady state, as stated previously in the lesson:

$$C_t = \frac{K_0}{VK}(1 - e^{-Kt})$$

(Remember, $VK = Cl_t$)

For example, if Cl_t for a drug is known to be 4.5 L/hour (with $K = 0.15\ hr^{-1}$) and this drug is given at a rate of 50 mg/hour, then the plasma concentration 8 hours after starting the infusion would be:

$$C_{8\ hr} = \frac{50\ mg/hr}{4.5\ L/hr}(1 - e^{-(0.15\ hr^{-1})(8\ hr)})$$

$$= \frac{50\ mg/hr}{4.5\ L/hr}(0.70)$$

$$= 7.8\ mg/L$$

If this infusion is continued, the steady-state concentration would be:

$$C_{ss} = \frac{K_0}{Cl_t} = \frac{50\ mg/hr}{4.5\ L/hr} = 11.1\ mg/L$$

Remember that with a continuous infusion, the steady-state plasma concentration is determined by the rate of drug going into the body (K_0) and drug clearance from the body (Cl_t). At steady state, the amount of drug going into the body per hour equals the amount of drug being removed per hour.

You have learned that it takes approximately five drug half-lives to reach steady state. Each time the infusion rate is changed, five half-lives will be required to attain a new steady-state concentration. For example, for a patient receiving IV theophylline at 20 mg/hour, the steady-state plasma concentration is 7.5 mg/L, and 25 hours is required to reach steady state ($T½$ = 5 hours, $K = 0.139\ hr^{-1}$). If the infusion rate is increased to 40 mg/hour, an additional 25 hours will be required to attain the new steady-state concentration of 15 mg/L (**Figure 5-9**). If a dosing rate is changed, it takes one half-life to reach 50% of the difference between the old concentration and the new, two half-lives to reach 75% of the difference, three half-lives to reach 87.5%, etc.

If we wish to calculate the plasma concentration before the new steady state is achieved, we can use the factor given before: $(1 - e^{-Kt})$, where t is the time after beginning the new infusion rate and the resulting fraction is the relative "distance" between the old and new steady-state concentrations. For

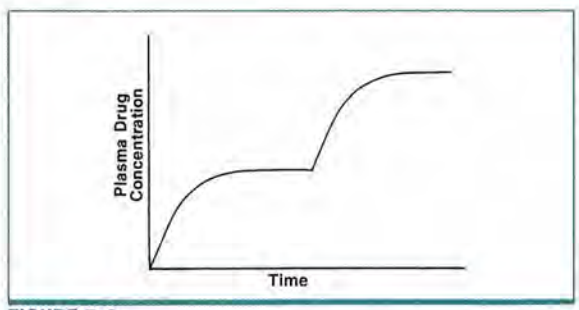

FIGURE 5-9.
Changing plasma drug concentrations with increased drug infusion rate.

the example above (where $K = 0.139\ hr^{-1}$), 8 hours after the infusion rate is increased:

$$(1-e^{-Kt}) = 1-e^{(-0.139\ hr^{-1})(8\ hr)}$$

$$= 0.67$$

So at 8 hours, the concentration would be approximately two-thirds (67%) of the way between 7.5 and 15.0 mg/L (about 12.5 mg/L).

If an infusion is stopped before steady state is reached, the concentration can be determined as follows:

$$C_t = (K_0/Cl_t)(1-e^{-Kt})$$

where t = the duration of the infusion.

Another important situation occurs when a continuous infusion is stopped after steady state is achieved. To predict plasma drug concentrations at some time after the infusion is stopped (**Figure 5-10**), the concentration at steady state (C_{ss}) is treated as if it were a peak concentration after an IV injection (C_0). In this situation, plasma concentrations after C_0 are predicted by:

$$C_t = (C_0 e^{-Kt}) \quad \text{(See } \textbf{Equation 3-2.}\text{)}$$

where t in this case is time after C_0, which is the time after the infusion is stopped.

In the case of continuous infusions:

$$C_t = (C_{ss} e^{-Kt})$$

where t = time after the infusion is stopped.

If, as in the previous example, $K = 0.139\ hr^{-1}$ and C_{ss} = 15 mg/L, the plasma concentration 12 hours after discontinuing the infusion would be:

$$C_{12\ hr} = (15\ mg/L)e^{(-0.139\ hr^{-1})(12\ hr)}$$

$$= 15\ mg/L\ (0.19)$$

$$= 2.9\ mg/L$$

Loading Dose

As stated previously, after a continuous IV infusion of drug is begun, five drug half-lives are needed to achieve steady state. In many clinical situations, an immediate effect of a drug is desired in a patient. In these situations, a *loading dose* is often administered at the initiation of the infusion to achieve an immediate therapeutic plasma concentration of the drug. By doing so, a serum concentration within therapeutic range of the drug is maintained from the outset of therapy. This loading dose is usually relatively large and may produce immediate therapeutic plasma concentrations (**Figure 5-11**). Note that a loading dose should not be used if substantial side effects occur with large doses of the drug. Also, sometimes clinicians prefer that drugs accumulate slowly rather than achieve therapeutic concentrations immediately so that the patient may have adequate time to develop tolerance to the initial side effects (e.g., tricyclic antidepressants).

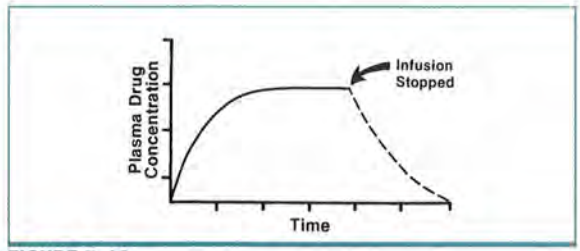

FIGURE 5-10.
Plasma drug concentrations after discontinuation of an intravenous infusion.

The desired loading dose for many drugs can be derived from the definition of the volume of distribution. As shown previously, $V = X_0/C_0$ (see Equation 1-1) for a drug described by a one-compartment model. Rearranging this equation, we see that the loading dose equals the desired concentration multiplied by the volume of distribution:

$$X_0 = C_{0(desired)}V \quad \text{(See } \textbf{Equation 1-1.}\text{)}$$

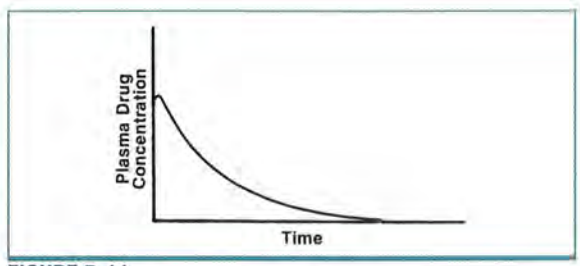

FIGURE 5-11.
Plasma drug concentrations resulting from an intravenous loading dose.

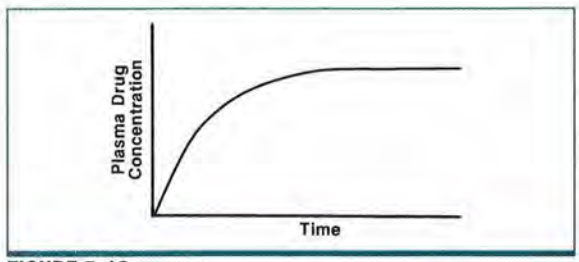

FIGURE 5-12.
Plasma drug concentrations over time resulting from a continuous intravenous infusion.

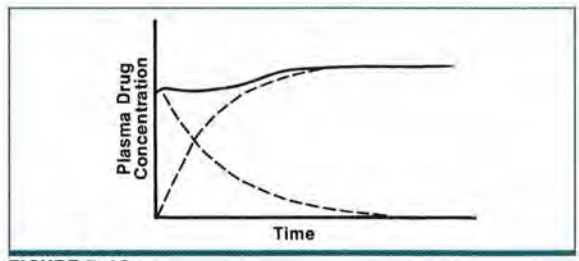

FIGURE 5-13.
Plasma drug concentrations resulting from an intravenous loading dose given with a continuous infusion.

Note that C_0 in this case is equivalent to the desired steady-state concentration.

We know that an IV loading dose produces plasma concentrations as shown in Figure 5-11, and the continuous infusion produces plasma concentrations as shown in **Figure 5-12**. If both the loading dose and the continuous IV infusion are given, the net effect should be a fairly steady plasma concentration, as depicted by the bold line in **Figure 5-13**. Before the constant IV infusion has reached steady state, the bolus loading dose has produced a nearly steady-state drug concentration, and when the drug from the loading dose is almost eliminated, the constant IV infusion should be approximately at steady state. With lidocaine, heparin, and theophylline, loading doses usually precede their continuous IV infusions, providing immediate as well as sustained effects that combine to produce a steady therapeutic plasma concentration.

Previously used equations can be combined to describe the plasma concentration resulting from a bolus injection with continuous infusion. With an IV injection, the equation describing the plasma concentration after a dose is:

$$C_t = \frac{X_0}{V} e^{-Kt}$$

where:

- t = time after dose,
- X_0 = initial loading dose,
- V = volume of distribution, and
- K = elimination rate constant.

With a continuous infusion, the plasma concentrations are described by:

$$C_t = \frac{K_0}{VK}(1 - e^{-Kt'})$$

where:

- t' = time after beginning infusion,
- K_0 = rate of drug infusion,
- V = volume of distribution, and
- K = elimination rate constant.

When both the injection and infusion are administered together, the plasma concentration after beginning the regimen is calculated by adding the two equations:

$$C_t = \frac{X_0}{V} e^{-Kt} + \frac{K_0}{VK}(1 - e^{-Kt'})$$

For example, an adult patient is estimated to have a theophylline half-life of 8 hours ($K = 0.087\ hr^{-1}$) and a V of 30 L. These estimates are obtained from known information about this patient or from published reports of similar patients. If the patient is given a loading dose of 400 mg of theophylline, and a continuous infusion of 35 mg/hour is begun at the same time, what will the plasma concentration be 24 hours later?

$$C_t = \frac{X_0}{V}e^{-Kt} + \frac{K_0}{VK}(1-e^{-Kt})$$

$$= \frac{400\text{ mg}}{30\text{ L}}e^{-0.087\text{ hr}^{-1}(24\text{ hr})} + \frac{35\text{ mg/hr}}{30\text{ L}\times 0.087\text{ hr}^{-1}}(1-e^{-0.087\text{ hr}^{-1}(24\text{ hr})})$$

$$= \frac{400\text{ mg}}{30\text{ L}}(0.124) + \frac{35\text{ mg/hr}}{30\text{ L}\times 0.087\text{ hr}^{-1}}(0.876)$$

$$= 1.6\text{ mg/L} + 11.7\text{ mg/L} = 13.3\text{ mg/L}$$

In clinical practice, drugs such as theophylline usually are not given by IV bolus injection, not even loading doses. Loading doses usually are given as short infusions (often 30–60 minutes). Taking this procedure into account, we can further modify the above equations to predict plasma concentrations.

For the loading dose:

$$C_{peak\ ss} = \frac{X_0/t}{VK}(1-e^{-Kt})$$

where:

X_0 = dose (in this case, the loading dose),
t = infusion period (e.g., 0.5 hour),
K = elimination rate constant, and
V = volume of distribution.

Multiple Intravenous Infusions (Intermittent Infusions)

In Lesson 4, we discussed multiple-dose IV bolus drug administration. With multiple-dose IV bolus administration, we assumed that the drug was administered by rapid IV injection. However, rapid IV injections are often associated with increased risks of adverse effects.

Therefore, many drugs administered intravenously are infused over a 30- to 60-minute time period; some drugs may require a longer infusion time. This method of giving multiple doses by infusion at specified intervals (τ), called *intermittent IV infusion*, changes the plasma concentration profile from what would be seen with multiple rapid IV injections. Therefore, a new model must be created to predict plasma drug concentrations after multiple-dose intermittent IV infusions. This model combines the approaches just presented for multiple-dose injections and continuous infusions.

Let's assume that a drug is given intravenously over 1 hour every 8 hours. For the first in a series of IV infusions lasting 60 minutes each, the plasma concentrations will be similar to those observed during the first 60 minutes of a continuous infusion. Then, when the infusion is stopped, plasma concentrations will decline in a first-order process, just as after IV injections (**Figure 5-14**).

The peak (or maximum) plasma concentration after the first infusion (C_{max1}) is estimated by:

$$C_{max\,1} = \frac{K_0}{VK}(1-e^{-Kt})$$

where:

C = concentration in plasma,
K_0 = rate of drug infusion (dose/time of infusion),
V = volume of distribution,
K = elimination rate constant, and
t = time (duration) of infusion.

This equation was used above to describe plasma drug concentrations with continuous infusion before steady state.

The trough concentration after the first dose (C_{min1}) occurs at the end of the dosing interval (τ) directly before the next dose.

$C_{min\,1}$ is calculated by multiplying $C_{max\,1}$ by $e^{-K(\tau-t)}$ or $C_{min\,1} = C_{max\,1}\,e^{-K(\tau-t)}$.

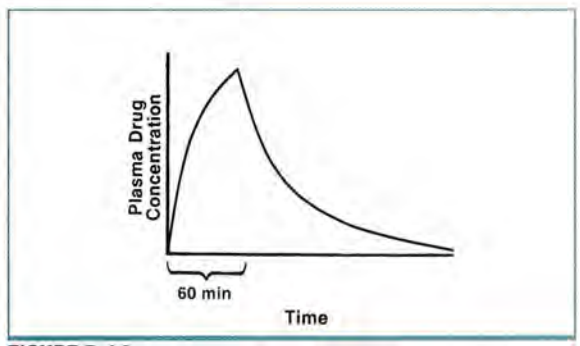

FIGURE 5-14.
Plasma drug concentrations resulting from a short intravenous infusion.

This equation can be rewritten as follows:

$$C_{\min 1} = (K_0 / VK)(1 - e^{-Kt})(e^{-K(\tau - t)})$$

By the principle of superposition (see Lesson 4), C_{max2} can be estimated:

$$C_{\max 2} = C_{\max 1} + C_{\min 1}$$

$$= \frac{K_0}{VK}(1 - e^{-Kt}) + \frac{K_0}{VK}(1 - e^{-Kt})(e^{-K(\tau - t)})$$

$$= \frac{K_0}{VK}(1 - e^{-Kt})(1 + e^{-K(\tau - t)})$$

$C_{\min 2}$ can be calculated:

$$C_{\min 2} = C_{\max 1} \times e^{-K(\tau - t)}$$

$$= \frac{K_0}{VK}(1 - e^{-Kt})(1 + e^{-K(\tau - t)})(e^{-K\tau})$$

$$= \frac{K_0}{VK}(1 - e^{-Kt})(e^{-K\tau} + e^{-2K\tau})$$

This expansion of the equation can continue as in Lesson 4 until n number of infusions have been given:

$$C_{\max n} = \frac{K_0}{VK}\left[\frac{(1 - e^{-Kt})(1 - e^{-nK\tau})}{(1 - e^{-K\tau})}\right]$$

As n becomes very large, $(1 - e^{-nK\tau})$ approaches 1, and the equation becomes:

5-1 $$C_{\max ss} = \frac{K_0}{VK}\left[\frac{(1 - e^{-Kt})}{(1 - e^{-K\tau})}\right]$$

Then, to determine the concentration at any time (t') after the peak, the following multiple IV infusion at steady state equation can be used:

$$C = \frac{K_0}{VK}\left[\frac{(1 - e^{-Kt})}{(1 - e^{-K\tau})}\right]e^{-Kt'}$$

where t' = total hours drug was allowed to be eliminated.

A practical example for this equation is shown below to determine the C_{pmin} or trough concentration of a drug given by intermittent infusion.

5-2 $$C_{\min (\text{steady state})} = \frac{K_0}{VK}\left[\frac{(1 - e^{-Kt})}{(1 - e^{-K\tau})}\right]e^{-Kt'}$$

where $t' = \tau - t$.

The equation for $C_{\min(\text{steady state})}$ is very important in clinical practice. It can be used to predict plasma concentrations for multiple intermittent IV infusions of any drug that follows first-order elimination (assuming a one-compartment model). It also can be used to predict plasma concentrations at any time between C_{max} and C_{min}, where t' equals the time between the end of the infusion and the determination of the plasma concentration. For application of this method, refer to cases that include IV intermittent infusions, which will show a step-by-step process for dose calculations.

Clinical Correlate

Here is one way we can illustrate the relationship of the equations described in this section: Suppose a patient with severe renal dysfunction receives a 100-mg dose of gentamicin, and a peak concentration, drawn at the end of the infusion, is reported by the laboratory as 8.0 mg/L. No additional doses are administered, and a repeat serum concentration drawn 24 hours later is reported as 3.0 mg/L. Before we can administer a second dose of gentamicin in this patient, we want to wait until the serum concentration is 1.0 mg/L. How much longer must we wait until this occurs?

The first step in solving this question is to determine the patient's K. K can be calculated using the equation below. Instead of using the variable C_{min}, we will use the variable C_t, which in this case represents the concentration 24 hours after the first level is drawn:

$$C_t = C_{peak}e^{-Kt}$$

$$3\ \text{mg/L} = (8\ \text{mg/L})e^{-K(24\ \text{hr})}$$

$$\frac{3\ \text{mg/L}}{8\ \text{mg/L}} = e^{-K(24\ \text{hr})}$$

$$0.375 = e^{-K(24\ \text{hr})}$$

$$\ln 0.375 = -K(24\ \text{hr})$$

$$-0.981 = -K(24\ \text{hr})$$

$$\frac{0.981}{24\ \text{hr}} = K$$

$$K = 0.041\ \text{hr}^{-1}$$

Knowing K, we can calculate the time (t) required for the concentration to decrease to 1.0 mg/L. C_t will now be our desired concentration of 1.0 mg/L:

$$C_t = C_{peak}e^{-Kt}$$

$$1.0\ \text{mg/L} = (8\ \text{mg/L})e^{(-0.041\ \text{hr}^{-1})t}$$

$$\frac{1.0\ \text{mg/L}}{8\ \text{mg/L}} = e^{(-0.041\ \text{hr}^{-1})t}$$

$$0.125 = e^{(-0.041\ \text{hr}^{-1})t}$$

$$\ln 0.125 = (-0.041\ \text{hr}^{-1})t$$

$$-2.08 = (-0.041\ \text{hr}^{-1})t$$

$$\frac{-2.08}{-0.041\ \text{hr}^{-1}} = t$$

$$t = 50.7\ \text{hours}$$

Therefore, it will take slightly longer than 2 days after the peak concentration for the serum concentration to decrease to 1.0 mg/L.

Clinically Important Equations Identified in This Chapter

1. $X_0 = C_{0(desired)}V$

   This is **Equation 1-1** rearranged

   X_0 is the Loading Dose, sometimes abbreviated as LD

2. $$C_{max\ ss} = \frac{K_0}{VK}\left[\frac{(1-e^{-Kt})}{(1-e^{-K\tau})}\right]$$ **Equation 5-1**

3. $$C_{min\ ss} = \frac{K_0}{VK}\left[\frac{(1-e^{-Kt})}{(1-e^{-K\tau})}\right]e^{-Kt'}$$ **Equation 5-2**

   where $t' = \tau - t$

   This equation may be rewritten as

   $$C_{trough\ ss} = C_{peak\ ss} \times e^{-K(\tau - t)}$$

   or

   $$C_{min\ ss} = C_{max\ ss} \times e^{-K(\tau - t)}$$

REVIEW QUESTIONS

5-1. For a drug regimen, if the elimination rate (K) of a drug is reduced while V, X_0, and τ remain constant, the peak and trough concentrations will:

A. increase.

B. decrease.

5-2. A decrease in drug dose will result in lower plasma concentrations at steady state but will not change the time to reach steady state.

A. True

B. False

5-3. Which of the following dosing techniques results in smaller fluctuations between peak and trough plasma levels?

A. small doses very frequently

B. large doses relatively less frequently

5-4. When the volume of distribution increases (and clearance remains the same), steady-state plasma concentrations will have more peak-to-trough variation.

A. True

B. False

5-5. When drug clearance decreases (while volume of distribution remains unchanged), steady-state plasma concentrations will:

A. increase.

B. decrease.

5-6. Steady-state plasma concentration is approximately reached when the continuous infusion has been given for at least how many half-lives of the drug?

A. two

B. three

C. five

D. ten

5-7. If you double the infusion rate of a drug, you should expect to see a twofold increase in the drug's steady-state concentration. Assume that clearance remains constant.

A. True

B. False

5-8. Theophylline is administered to a patient at 35 mg/hour via a constant IV infusion. If the patient has a total body clearance for theophylline of 40 mL/minute, what should this patient's steady-state plasma concentration be?

A. 14.6 mg/L

B. 0.875 mg/L

C. 0.1 mg/L

5-9. With a continuous IV infusion of drug, the steady-state plasma concentration is directly proportional to:

A. clearance.

B. volume of distribution.

C. drug infusion rate.

D. K.

5-10. If a drug is given by continuous IV infusion at a rate of 20 mg/hour and produces a steady-state plasma concentration of 10 mg/L, what infusion rate will result in a new C_{ss} of 15 mg/L?

A. 30 mg/hour

B. 35 mg/hour

C. 50 mg/hour

D. 75 mg/hour

5-11. For a continuous infusion, given the equation $C = K_0(1 - e^{-Kt})/Cl_t$, at steady state the value for t approaches infinity and e^{-Kt} approaches infinity.

A. True

B. False

This case applies to **Questions 5-12 and 5-13**. A patient is to be started on a continuous infusion of a drug. To achieve an immediate effect, a loading dose is administered over 30 minutes and then the continuous infusion will begin. From a previous regimen of the same drug, you estimate that the patient's K = 0.04 hr^{-1} and V = 28 L. Assume that none of this drug has been administered in the last month, so the plasma concentration before therapy is 0 mg/L.

5-12. If the $C_{ss(desired)}$ is 12 mg/L, what should the loading dose be?

A. 13 mg
B. 42 mg
C. 336 mg
D. 1200 mg

5-13. What rate of infusion (K_0) should result in a C_{ss} of 12 mg/L?

A. 0.2 mg/hour
B. 13.4 mg/hour
C. 600 mg/hour

Refer to this equation when working **Questions 5-14 through 5-16**:

$$C = \frac{K_0}{VK}\left[\frac{(1-e^{-nKt})}{(1-e^{-K\tau})}\right]e^{-Kt'}$$

5-14. A patient is to be given 100 mg of gentamicin IV over 1 hour every 12 hours. If the patient is assumed to have a K of 0.15 hr^{-1} and a V of 15 L, how long will it take to reach steady state?

A. 3.5 hours
B. 5 hours
C. 17 hours
D. 23 hours

5-15. For the patient in the question above, what will the peak plasma concentration be at steady state?

A. 4.6 mg/L
B. 7.4 mg/L
C. 12.8 mg/L
D. 22 mg/L

5-16. For the patient in the previous question, calculate the trough plasma concentration at steady state.

A. 0.54 mg/L
B. 1.42 mg/L
C. 1.92 mg/L
D. 2.25 mg/L

ANSWERS

5-1. A. CORRECT ANSWER. This can be determined by examination of the equation from Lesson 4:

$$C_{peak(steady\ state)} = \frac{X_0}{V}\left[\frac{1}{(1-e^{-K\tau})}\right]$$

B. *Incorrect answer*

5-2. A. CORRECT ANSWER. The time to reach steady state is determined by K.

B. *Incorrect answer*

5-3. A. CORRECT ANSWER. Because the time interval would be relatively short, there would not be as much time for plasma concentrations to decline.

B. *Incorrect answer*

5-4. A. *Incorrect answer*

B. CORRECT ANSWER. A larger volume of distribution will result in the same amount of drug distributing in a greater volume, which would result in a lower peak-to-trough variation.

5-5. A. CORRECT ANSWER. When clearance decreases, plasma concentrations will increase because drug is administered at the same rate (dose and dosing interval) but is being removed at a lower rate.

B. *Incorrect answer*

5-6. A. *Incorrect answer*. Only 75% of the steady-state concentration would be reached by two half-lives.

B. *Incorrect answer*. Only 87.5% of the steady-state concentration would be reached by three half-lives.

C. CORRECT ANSWER. At five half-lives, approximately 97% of the steady-state concentration has been reached.

D. *Incorrect answer*. This is much longer than necessary.

5-7. A. CORRECT ANSWER. The changes in the infusion rate will directly affect plasma concentrations, if other factors remain constant.

B. *Incorrect answer*

5-8. A. CORRECT ANSWER. The equation $C_{ss} = K_0/Cl_t$ should be used. The value for K_0 is 35 mg/hour. The value for Cl_t must be converted from 40 mL/minute to 2.4 L/hour.

B, C. *Incorrect answers*

5-9. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. The steady-state concentration is directly proportional to the drug infusion rate.

5-10. A. CORRECT ANSWER

B, C, D. *Incorrect answers*

5-11. A. *Incorrect answer*. As t becomes larger, the term e^{-Kt} becomes smaller, and the term $1 - e^{-Kt}$ approaches 1.

B. CORRECT ANSWER

5-12. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. The loading dose is determined by multiplying the desired concentration (12 mg/L) by the volume of distribution:

$C_{ss(desired)} \times V = 12 \text{ mg/L} \times 28 \text{ L} = 336 \text{ mg}.$

Note that the units cancel out to yield milligrams.

5-13. A, C. *Incorrect answers*

B. CORRECT ANSWER. The infusion rate is related to Cl_t and C_{ss} as follows:

$C_{ss} = K_0/Cl_t.$

Cl_t can be determined by multiplying

$V \times K = 1.12$ L/hour.

So, rearranging,

$K_0 = C_{ss} \times Cl_t = 12 \text{ mg/L} \times 1.12 \text{ L/hour} = 13.4 \text{ mg/hour}.$

5-14. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. One half-life is calculated as follows:

$T½ = 0.693/K.$

Steady state is reached by five half-lives, or 23 hours.

5-15. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. At steady state, the equation below would be used:

$$C_{max(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-Kt})}$$

$$= \frac{(100\ mg/hr)(0.139)}{(2.25\ L/hr)(0.835)}$$

$$= 7.4\ mg/L$$

5-16. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The trough concentration is calculated from the peak value as follows:

$$C_{trough} = C_{peak} \times e^{-K(\tau - t)}$$

$$= 7.4\ mg/L \times e^{-0.15\ hr^{-1}(12\ hr - 1\ hr)}$$

$$= 7.4\ mg/L \times 0.192 = 1.42\ mg/L$$

Discussion Points

D-1. With the continuous IV infusion model of drug administration, what two factors determine the steady-state plasma concentration?

D-2. What is the purpose of administering a loading dose of a drug?

D-3. What is the following portion of the multiple-dose equation called, and why is it called that?

$$1/(1 - e^{-K\tau})$$

D-4. Given the equation below for a drug given by intermittent infusion, what does t' represent?

$$C_{\min(\text{steady state})} = \frac{K_0}{VK}\left[\frac{(1-e^{-Kt})}{(1-e^{-K\tau})}\right]e^{-Kt'}$$

D-5. Explain how changing the dosing interval (τ) influences the time to reach steady state when multiple doses are administered.

D-6. If clearance is reduced to 25% of the initial rate and all other factors (such as dose, dosing interval, and volume of distribution) remain constant, how will steady-state plasma concentrations change?

D-7. Explain why, for most drugs, the increase in drug plasma concentrations resulting from a single dose will be the same magnitude whether it is the first or the tenth dose.

LESSON 6

Two-Compartment Models

OBJECTIVES

After completing Lesson 6, you should be able to:

1. Describe when to use back-extrapolation versus method of residuals.
2. Calculate a residual line.
3. Calculate alpha (α), beta (β), and intercepts A and B for a drug conforming to a two-compartment model.
4. Describe when to use a monoexponential versus a biexponential equation.
5. Calculate Vc, V_{area} (also known as V_{β}), and V_{ss} (using both methods) for a two-compartment model.

Prior lessons focused on one-compartment models, but many drugs are better characterized by multicompartment models. In this lesson, we briefly discuss multicompartment models and present a few applications. Multicompartment models are not used as frequently as the one-compartment model in therapeutic drug monitoring, partly because they are more difficult to construct and apply.

Generally, multicompartment models are applied when the natural log of plasma drug concentration versus time curve is not a straight line after an intravenous dose or when the plasma concentration versus time profile cannot be characterized by a single exponential function (i.e., $C_t = C_0e^{-Kt}$). When the natural log of plasma drug concentration versus time curve is not a straight line, a multicompartment model must be constructed to describe the change in concentration over time (**Figure 6-1**).

Of the multicompartment models, the two-compartment model is most frequently used. This model usually consists of a central compartment of the well-perfused tissues and a peripheral compartment of less well-perfused tissues (such as muscle and fat). **Figure 6-2** shows a diagram of the two-compartment model after an intravenous bolus dose, where:

X_0 = dose of drug administered

X_c = amount of drug in central compartment

X_p = amount of drug in peripheral compartment

K_{12} = rate constant for transfer of drug from the central compartment to the peripheral compartment. (The subscript 12 indicates transfer from the first [central] to the second [peripheral] compartment.)

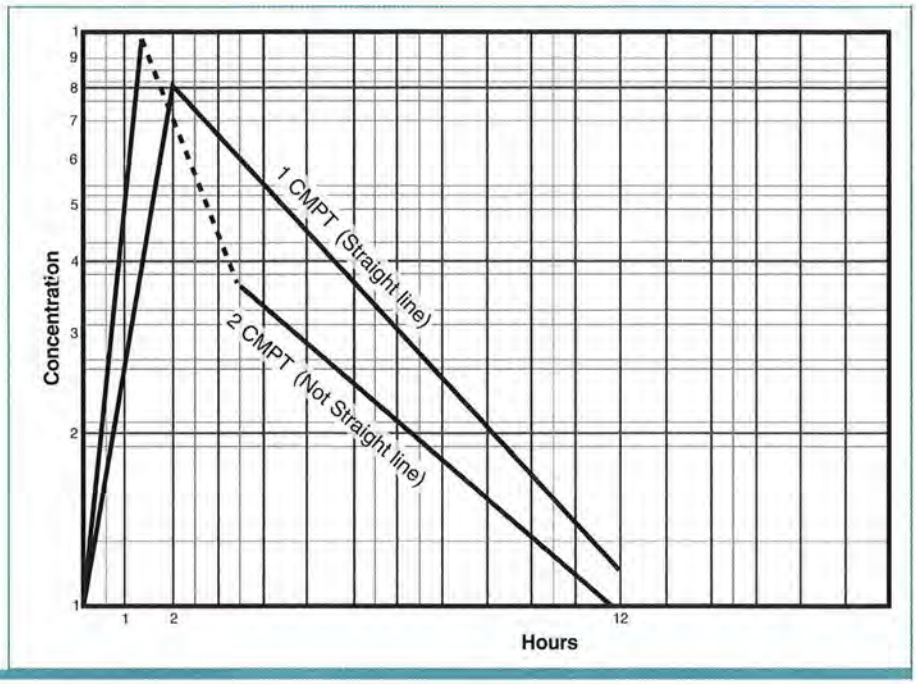

FIGURE 6-1.
Concentration versus time plot for one- versus two-compartment (CMPT) model.

K_{21} = rate constant for transfer of drug from the peripheral compartment to the central compartment. (The subscript 21 indicates transfer from the second [peripheral] to the first [central] compartment. *Note*: Both K_{12} and K_{21} are called *microconstants*.)

K_{10} = first-order elimination rate constant (similar to the K used previously), indicating elimination of drug out of the central compartment into urine, feces, etc.

A natural log of plasma drug concentration versus time curve for a two-compartment model shows a curvilinear profile—a curved portion followed by a straight line. This biexponential curve can be described by two exponential terms (**Figure 6-3**). The phases of the curve may represent rapid distribution to organs with high blood flow (central compartment) and slower distribution to organs with less blood flow (peripheral compartment).

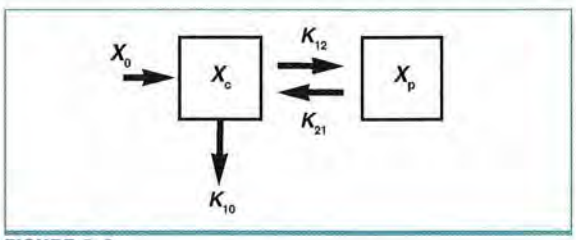

FIGURE 6-2.
Graphic representation of a two-compartment model.

After the intravenous injection of a drug that follows a two-compartment model, the drug concentrations in all fluids and tissues associated with the central compartment decline more rapidly in the distribution phase than during the post-distribution phase. After some time, a pseudo-equilibrium is attained between the central compartment and the tissues and fluids of the peripheral compartment; the plasma drug concentration versus time profile is then characterized as a linear process when plotted on semilog paper (i.e., terminal or linear elimination phase). For many drugs (e.g., aminoglycosides), the distribution phase is very short (e.g., minutes). If plasma concentrations are measured after this phase is completed, the central compartment can be ignored and a one-compartment model adequately represents the plasma concentrations observed. Other drugs (e.g., vancomycin, digoxin) have a longer distribution phase (hours). If plasma concentrations of these drugs are determined within the first few hours after a dose is given, the nonlinear (multiexponential) decline of drug concentrations must be considered when calculating half-life and other parameters.

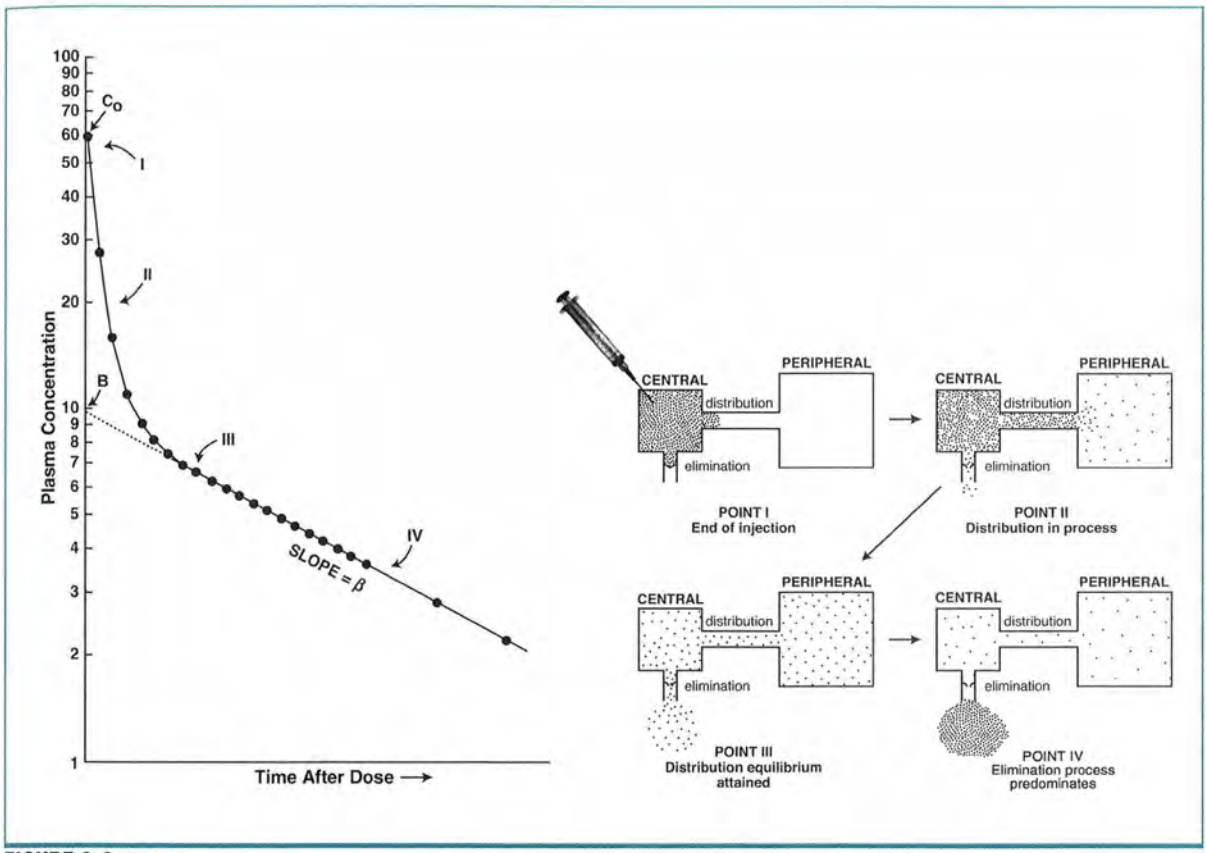

FIGURE 6-3.

Four stages of drug distribution and elimination after rapid intravenous injection. Points I, II, III, and IV (*right*) correspond to the points on the plasma concentration curve (*left*). **Point I:** The injection has just been completed, and drug density in the central compartment is highest. Drug distribution and elimination have just begun. **Point II:** Midway through the distribution process, the drug density in the central compartment is falling rapidly, mainly because of rapid drug distribution out of the central compartment into the peripheral compartment. The density of drug in the peripheral compartment has not yet reached that of the central compartment. **Point III:** Distribution equilibrium has been attained, and drug densities in the central and peripheral compartments are approximately equal. Drug distribution in both directions continues to take place, but the ratio of drug quantities in the central and peripheral compartments remains constant. At this point, the major determinant of drug disappearance from the central compartment becomes the elimination process; previously, drug disappearance was determined mainly by distribution. **Point IV:** During this elimination phase, the drug is being "drained" from both compartments out of the body (via the central compartment) at approximately the same rate.

Source: Reprinted with permission from Greenblatt DJ and Shrader RI. *Pharmacokinetics in Clinical Practice*. Philadelphia, PA: Saunders; 1985.

Clinical Correlate

Digoxin is a drug that, when administered as a short intravenous infusion, is best described by a two-compartment model. After the drug is infused, the distribution phase is apparent for 4–6 hours (**Figure 6-4**). Digoxin distributes out of plasma (the central compartment) and extensively into muscle tissue (the peripheral compartment). After the initial distribution phase, a pseudoequilibrium in distribution is achieved between the central and peripheral compartments. Because the site of digoxin effect is in muscle (specifically, the myocardium), the plasma concentrations observed after completion of the distribution phase more accurately reflect concentrations in the tissue and pharmacodynamic response. For patients receiving digoxin, blood should be drawn for plasma concentration determination after completion of the distribution phase; thus, trough digoxin concentrations are usually used clinically when monitoring digoxin therapy.

Vancomycin is another drug that follows a two-compartment model with an initial 2- to 4-hour α-distribution phase followed by a linear terminal elimination phase. As described later in the vancomycin cases (see Lesson 13), peak vancomycin concentrations must be drawn approximately 2 hours after the end of a vancomycin infusion to avoid obtaining a peak concentration during the initial distribution phase (see Figure 13-3).

Calculating Two-Compartment Parameters

In this section, we apply mathematical principles to the two-compartment model to calculate useful pharmacokinetic parameters.

From discussion of the one-compartment model, we know that the elimination rate constant (K) is estimated from the slope of the natural log of plasma drug concentration versus time curve. However, in a two-compartment model, in which that plot is curvilinear, the slope varies, depending on which portion of the curve is examined (**Figure 6-5**). The slope of the initial portion is determined primarily by the distribution rate, whereas the slope of the terminal portion is determined primarily by the elimination rate.

The linear (or post-distributive) terminal portion of this curve may be back-extrapolated to time zero (t_0). The negative slope of this line is referred to as *beta* (β), and like K in the one-compartment model, β is an elimination rate constant. β is the terminal elimination rate constant, which means it applies after distribution has reached pseudoequilibrium. The y-intercept of this line (B) is used in various equations for two-compartment parameters.

As in the one-compartment model, a half-life (the beta half-life) can be calculated from β:

$$T\frac{1}{2} = \frac{0.693}{\beta} \quad T\frac{1}{2} = \frac{0.693}{K}$$

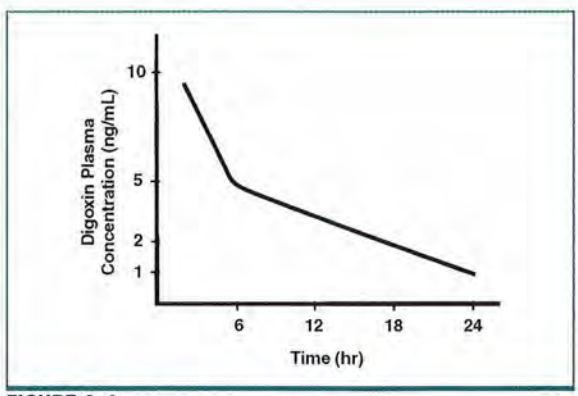

FIGURE 6-4.
Digoxin plasma concentration versus time.

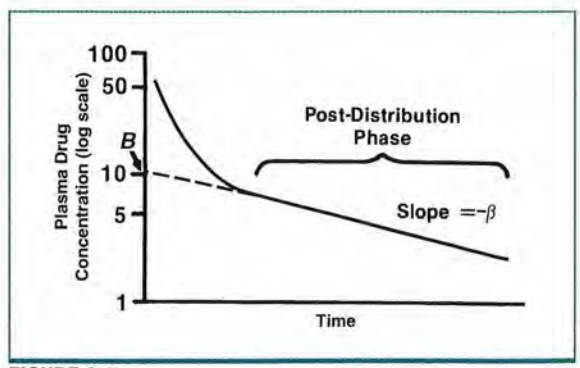

FIGURE 6-5.
Plasma drug concentrations with a two-compartment model after an intravenous bolus dose.

Throughout the time that drug is present in the body, distribution takes place between the central and peripheral compartments. We can calculate a rate of distribution using the method of residuals, which separates the effects of distribution and elimination. This method estimates the effect of distribution on the overall plasma concentration curve and uses the difference between the effect of elimination and the actual plasma concentrations to determine the distribution rate.

To apply the method of residuals, we use the back-extrapolated line used to determine β and *B* (**Figure 6-6**). If *w*, *x*, *y*, and *z* are actual, determined concentration time points, let *w*′, *x*′, *y*′, and *z*′ represent points on the new (extrapolated) line at the same times that the actual concentrations were observed. These newly generated points represent the effect of elimination alone, as if distribution had been instantaneous. Subtraction of the extrapolated points from the corresponding actual points (*w* – *w*′, *x* – *x*′, etc.) yields a new set of plasma concentration points for each time point. If we plot these new points, we generate a new line, the residual line (**Figure 6-7**). The negative slope of the residual line is referred to as *alpha* (α), and α is the distribution rate constant for the two-compartment system. The *y*-intercept of the residual line is *A*.

Let's proceed through an example, applying the method of residuals. Draw the plot for the following example on semilog graph paper. A dose of drug is administered by rapid intravenous injection, and the concentrations shown in **Table 6-1** result.

The last four points form a straight line (similar to Figure 6-5) so back-extrapolate a line that connects

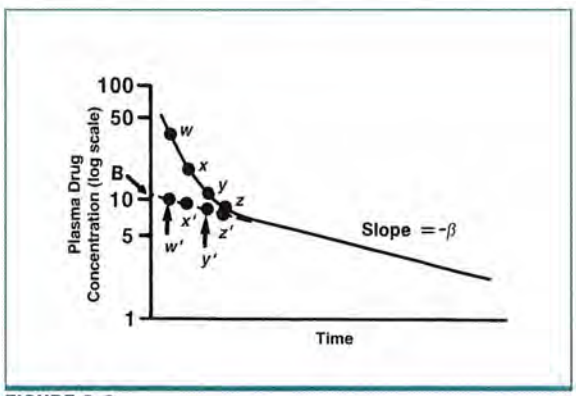

FIGURE 6-6.
Method of residuals.

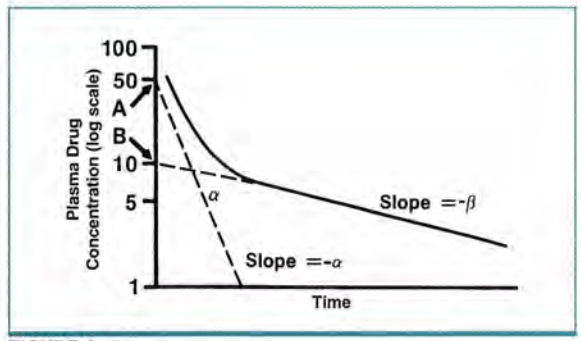

FIGURE 6-7.
Determination of the residual line.

them to the *y*-axis. Then, for the first five points, extrapolated values can be estimated at each time (0.25, 0.5, 1.0, 1.5, and 2.0 hours) where the time intersects the new line (similar to Figure 6-6). Subtracting the extrapolated values from the actual plasma concentrations yields a new set of residual concentration points, similar to those values shown in **Table 6-2**.

Plot the residual concentrations (on the same semilog paper) versus time and draw a straight line connecting all of your new points (similar to Figure 6-7). Determine that the slope of that plot equals –1.8 hours^{-1}.

$$\text{Slope } (\alpha) = \frac{\ln C_1 - \ln C_0}{t_1 - t_0} = \frac{(\ln 3 - \ln 18.5)}{(1.5 \text{ hr} - 0.5 \text{ hr})} = -1.8 \text{ hr}^{-1}$$

(distribution rate)

(See **Equation 3-1**.)

TABLE 6-1. Plasma Drug Concentrations after Rapid Intravenous Injection

Time after Dose (hours)	Plasma Concentration (mg/L)
0.25	43.0
0.5	32.0
1.0	20.0
1.5	14.0
2.0	11.0
4.0	6.5
8.0	2.8
12.0	1.2
16.0	0.52

TABLE 6-2. Residual Concentration Points

Time after Dose (hours)	Plasma Concentration (mg/L)		
	Actual	Extrapolated	Residual
0.25	43	14.5	28.5
0.5	32	13.5	18.5
1.0	20	12.3	7.7
1.5	14	11.0	3.0
2.0	11	10.0	1.0

When the negative is dropped, this slope equals α; we observe from the plot that the intercept (A) of the residual line is 45 mg/L. We also can estimate β (0.21 hour^{-1}) from the slope of the terminal straight-line portion.

$$\text{Slope } (\beta) = \frac{\ln C_1 - \ln C_0}{t_1 - t_0} = \frac{(\ln 2.8 - \ln 6.5)}{(8\text{ hr} - 4\text{ hr})} = -0.21\text{ hr}^{-1}$$

(elimination rate)

Inspection of the extrapolated portion yields a value for B (15 mg/L).

Note that α must be greater than β, indicating that drug removal from plasma by distribution into tissues proceeds at a greater rate than does drug removal from plasma by eliminating organs (e.g., kidneys and liver). The initial portion of the plot is steeper than the terminal portion.

Biexponential Equation and Volumes of Distribution

The estimations of A, B, α, and β performed above are useful for predicting plasma concentrations of drugs characterized by a two-compartment model. For a one-compartment model (**Figure 6-8**), we know that the plasma concentration (C) at any time (t) can be described by:

$$C_t = C_0 e^{-Kt} \quad \text{(See Equation 3-2.)}$$

where C_0 is the initial concentration and K is the elimination rate. The equation is called a *monoexponential equation* because the line is described by one exponent.

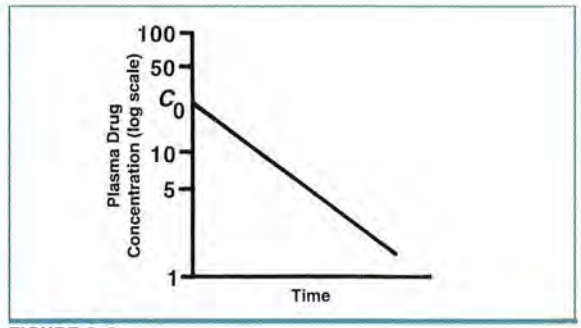

FIGURE 6-8.
Plasma drug concentrations with a one-compartment model after an intravenous bolus dose (first-order elimination).

The two-compartment model (**Figure 6-9**) is the sum of two linear components, representing distribution and elimination (**Figure 6-10**), so we can determine drug concentration (C) at any time (t) by adding those two components. In each case, A or B is used for C_0, and α or β is used for K. Therefore:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t}$$

This equation is called a *biexponential equation* because two exponents are incorporated.

For the two-compartment model, different volume of distribution parameters exist: the central compartment volume (V_c), the volume by area (V_{area}, also known as V_β), and the steady-state volume of distribution (V_{ss}). Each of these volumes relates to different underlying assumptions.

As in the one-compartment model, a volume can be calculated by:

$$V_c = \frac{\text{dose}}{A+B} = \frac{\text{dose}}{C_0}$$

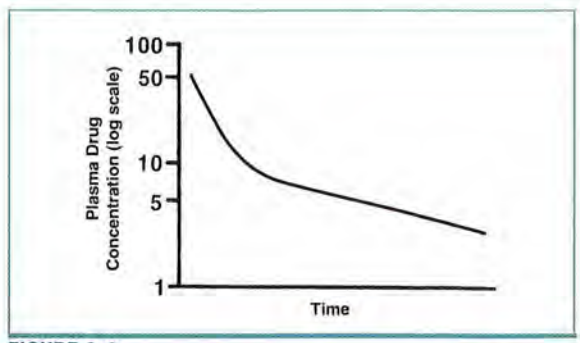

FIGURE 6-9.
Plasma drug concentrations with a two-compartment model after an intravenous bolus dose (first-order elimination).

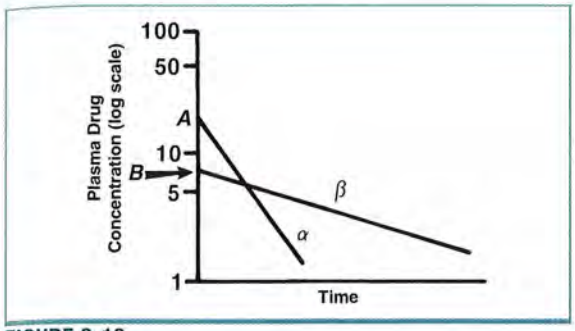

FIGURE 6-10.
Linear components of a two-exponential (two-compartment) model.

For the two-compartment model, this volume would be equivalent to the volume of the central compartment (V_c). The V_c relates the amount of drug in the central compartment to the concentration in the central compartment. In the two-compartment model, C_0 is equal to the sum of intercepts A and B.

If another volume (V_{area} or V_β) is determined from the area under the plasma concentration versus time curve and the terminal elimination rate constant (β), this volume is related as follows:

$$V_{area} = V_\beta = \frac{\text{dose}}{\beta \times \text{AUC}} = \frac{\text{Cl}}{\beta}$$

This calculation is affected by changes in clearance (Cl). The V_{area} relates the amount of drug in the body to the concentration of drug in plasma in the post-absorption and post-distribution phase.

A *final volume* is the volume of distribution at steady state (V_{ss}). Although it is not affected by changes in drug elimination or clearance, it is more difficult to calculate. One way to estimate V_{ss} is to use the two-compartment microconstants:

$$V_{ss} = V_c + \frac{K_{12}}{K_{21}} V_c$$

or it may be estimated by:

$$V_{ss} = \frac{\text{dose}\left(\frac{A}{\alpha^2} + \frac{B}{\beta^2}\right)}{\left(\frac{A}{\alpha} + \frac{B}{\beta}\right)^2}$$

using A, B, α, and β.

Because different methods can be used to calculate the various volumes of distribution of a two-compartment model, you should always specify the method used. When reading a pharmacokinetic study, pay particular attention to the method for calculating the volume of distribution.

Clinical Correlate

Here is an example of one potential problem when dealing with drugs exhibiting biexponential elimination: If plasma concentrations are determined soon after an intravenous dose is administered (during the distribution phase) and a one-compartment model is assumed, then the patient's drug half-life would be underestimated and β would be overestimated (**Figure 6-11**). Recall that:

$$\text{Slope } (\beta \text{ or } K) = \frac{\ln C_1 - \ln C_0}{t_1 - t_0}$$

A steeper slope equals a faster rate of elimination resulting in a shorter half-life.

If a terminal half-life is being calculated for drugs such as vancomycin, you must be sure that the distribution phase is completed (approximately 3–4 hours after the dose) before drawing plasma levels.

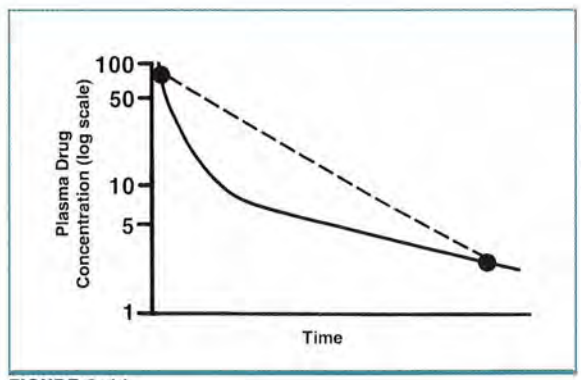

FIGURE 6-11.
Biexponential elimination.

REVIEW QUESTIONS

6-1. In the two-compartment model, X_p represents the:

A. amount of drug in the body.
B. amount of drug in the peripheral compartment.
C. fraction of the dose distributing to the peripheral compartment.
D. parenteral drug dose.

6-2. The plasma drug concentration versus time curve for a two-compartment model is represented by what type of curve?

A. biexponential
B. monoexponential

6-3. With a two-compartment model, K_{12} represents the:

A. first portion of the natural log of plasma drug concentration versus time curve, where the log concentration rapidly declines.
B. elimination rate constant.
C. rate constant for drug transfer from compartment 1 (central) to compartment 2 (peripheral).
D. rate constant for drug transfer from compartment 2 (peripheral) to compartment 1 (central).

6-4. Which of the following is the best definition of beta (β)?

A. initial rate constant of elimination
B. terminal half-life
C. average elimination rate constant
D. terminal elimination rate constant

6-5. For a two-compartment model, which of the following is the term for the residual *y*-intercept for the terminal portion of the natural-log plasma concentration versus time line?

A. A
B. B
C. α (alpha)
D. β (beta)

6-6. The method of back-extrapolation is used to calculate:

A. the rate constant of drug elimination from the body.
B. the area under the plasma concentration versus time curve.
C. the amount of drug present in specific organs.

6-7. Which equation below correctly represents the two-compartment model?

A. $C_t = A + B(e^{-Kt})$
B. $C_t = Ae^{-\beta t} + Be^{-\alpha t}$
C. $C_t = Ae^{-\alpha t} + Be^{-\beta t}$

6-8. The equation describing elimination after an intravenous bolus dose of a drug characterized by a two-compartment model requires two exponential terms.

A. True

B. False

6-9. A patient is given a 500-mg dose of drug by intravenous injection and the following plasma concentrations result:

Plasma Concentration (mg/L)	Time after Dose (hours)
72.0	0.25
46.0	0.5
33.0	0.75
26.3	1.0
20.0	1.5
16.6	2.0
12.2	3.0
9.9	4.0
5.0	6.0
2.7	8.0
0.82	12.0

Which answer below is the best estimate for α and β?

A. 0.30 hr^{-1}, 3.17 hr^{-1}

B. 3.17 hr^{-1}, 0.3 hr^{-1}

C. 2.1 hr^{-1}, 0.6 hr^{-1}

D. 0.6 hr^{-1}, 2.1 hr^{-1}

ANSWERS

6-1. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. X represents amount of drug and p represents the peripheral compartment.

6-2. A. CORRECT ANSWER. A two-compartment model is best represented by a biexponential curve.

B. *Incorrect answer*

6-3. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. K_{12} represents the rate constant for drug transfer from compartment 1 (central) to compartment 2 (peripheral).

6-4. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. β is the terminal elimination rate constant.

6-5. A. CORRECT ANSWER. The y-intercept associated with the residual portion of the curve (which has a slope of $-\alpha$) is A.

B, C, D. *Incorrect answers*

6-6. A. CORRECT ANSWER. It can be used to calculate rate of drug elimination.

B, C. *Incorrect answers*

6-7. A, B. *Incorrect answers*

C. CORRECT ANSWER. The correct equation is: $C_t = Ae^{-\alpha t} + Be^{-\beta t}$

6-8. A. CORRECT ANSWER. One exponent is needed for distribution phase and the other for elimination or post-distribution phase.

B. *Incorrect answer*

6-9. A. *Incorrect answer*

B. CORRECT ANSWER. See table below for result (your numbers may vary slightly).

Time (hours)	Actual – (mg/L)	Extrapolated = (mg/L)	Residual (mg/L)
0.25	72.0	27.8	44.2
0.5	46.0	25.5	20.5
0.75	33.0	24.8	8.2
1.0	26.3	22.2	4.1
1.5	20.0	18.9	1.1

The slope of the residual line is determined to calculate α. Two residual points are selected, such as 0.25 and 1.0 hour:

$$\text{slope} = \frac{\Delta x}{\Delta y} = \frac{\ln C_2 - \ln C_1}{t_2 - t_1}$$

$$= \frac{\ln 4.1 - \ln 44.2}{1.0\ \text{hr} - 0.25\ \text{hr}}$$

$$= \frac{1.41 - 3.79}{0.75\ \text{hr}}$$

$$= -3.17\ \text{hr}^{-1}$$

$$\alpha = -\text{slope} = 3.17\ \text{hr}^{-1}$$

β can be determined from the slope of the terminal straight-line portion of the plot. For example, the points at 3 and 12 hours may be selected:

$$\text{slope} = \frac{\Delta x}{\Delta y} = \frac{\ln C_2 - \ln C_1}{t_2 - t_1}$$

$$= \frac{\ln 0.82 - \ln 12.2}{12\ \text{hr} - 3\ \text{hr}}$$

$$= \frac{-0.198 - 2.5}{9\ \text{hr}} = \frac{-2.698}{9\ \text{hr}}$$

$$= -0.30\ \text{hr}^{-1}$$

$$\beta = -\text{slope} = 0.30\ \text{hr}^{-1}$$

C, D. *Incorrect answers*

Discussion Points

D-1. Describe situations for which it would be better to use a two-compartment model rather than a one-compartment model.

D-2. What is the minimum number of plasma-concentration data points needed to calculate parameters for a two-compartment model?

D-3. Discuss the clinical implications of obtaining a vancomycin peak concentration during the distribution phase on the resultant pharmacokinetic values of K and V.

D-4. Discuss the effect that a two-compartment drug (such as digoxin) with an extensive peripheral compartment has on the value for that drug's apparent volume of distribution (V).

Practice Set 2

The following problems are for your review. Definitions of symbols and key equations are provided here:

- K = elimination rate constant
- C_0 = plasma drug concentration just after a single intravenous injection
- e = base for the natural log function = 2.718
- τ = dosing interval
- K_0 = rate of dose administration (may be expressed as milligrams per hour in the sense of a continuous infusion or as drug dose divided by infusion time for intermittent infusions)
- V = volume of distribution
- C_{peak} = peak plasma drug concentration at steady state
- C_{trough} = trough plasma drug concentration at steady state
- t = duration of intravenous infusion

For multiple-dose, intermittent, intravenous bolus injection at steady state:

$$C_{peak} = \frac{X_0}{V}\left(\frac{1}{1-e^{-K\tau}}\right)$$

$$C_{trough} = C_{peak}e^{-K\tau}$$

For multiple-dose, intermittent, intravenous infusion:

$$C_{peak} = \frac{K_0}{VK}\left(\frac{1-e^{-Kt}}{1-e^{-K\tau}}\right)$$

$$C_{trough} = C_{peak}e^{-K(\tau-t)}$$

For continuous infusion before steady state is reached:

$$C = \frac{K_0}{VK}(1-e^{-Kt})$$

For continuous infusion at steady state:

$$C_{SS} = \frac{K_0}{VK} = \frac{K_0}{Cl_t}$$

QUESTIONS

The following applies to **Questions PS2-1 to PS2-6** below: A 60-kg patient is begun on a continuous intravenous infusion of theophylline at 40 mg/hour. Forty-eight hours after beginning the infusion, the plasma concentration is 12 mg/L.

PS2-1. If we assume that this concentration is at steady state, what is the theophylline clearance?

A. 3.3 L/hour
B. 0.3 L/hour
C. 33 L/hour
D. 198 L/hour

PS2-2. If the volume of distribution is estimated to be 30 L, what is the half-life?

A. 1.7 hours
B. 6.3 hours
C. 13.3 hours
D. 22.1 hours

PS2-3. As we know V and K, what would the plasma concentration be 10 hours after beginning the infusion?

A. 3.2 mg/L
B. 4.8 mg/L
C. 8.1 mg/L
D. 11.0 mg/L

PS2-4. If the infusion is continued for 3 days and then discontinued, what would the plasma concentration be 12 hours after stopping the infusion?

A. 1.2 mg/L
B. 3.2 mg/L
C. 7.6 mg/L
D. 8.1 mg/L

PS2-5. If the infusion is continued for 3 days at 40 mg/hour and the steady-state plasma concentration is 12 mg/L, what rate of drug infusion would likely result in a concentration of 15 mg/L?

A. 46 mg/hour
B. 50 mg/hour
C. 60 mg/hour
D. 80 mg/hour

PS2-6. After the increased infusion rate above is begun, how long would it take to reach a plasma concentration of 15 mg/L?

A. 6.3 hours
B. 12.6 hours
C. 18.9 hours
D. 31.5 hours

The following pertains to **Questions PS2-7 to PS2-10**: A 60-kg patient is started on 80 mg of gentamicin every 6 hours given as 1-hour infusions.

PS2-7. If this patient is assumed to have an average V of 15 L and a normal gentamicin half-life of 3 hours, what will be the peak plasma concentration at steady state?

A. 6.3 mg/L
B. 8.9 mg/L
C. 12.2 mg/L
D. 15.4 mg/L

PS2-8. After the fifth dose, a peak plasma concentration (drawn at the end of the infusion) is 5 mg/L and the trough concentration (drawn right before the sixth dose) is 0.9 mg/L. What is the patient's actual gentamicin half-life?

A. 1 hour
B. 2 hours
C. 4 hours
D. 8 hours

PS2-9. What would be the volume of distribution? [hint, rearrange Equation 5-1]

A. 7.6 L
B. 10.2 L
C. 15.5 L
D. 22.0 L

PS2-10. For this patient, what dose should be administered to reach a new steady-state peak gentamicin concentration of 8 mg/L?

A. 64 mg
B. 82 mg
C. 95 mg
D. 128 mg

ANSWERS

PS2-1. A. CORRECT ANSWER. $Cl_t = K_0/C_{ss}$ = 40 mg/hour/12 mg/L = 3.3 L/hour

B. *Incorrect answer*. You may have inverted the formula.

C, D. *Incorrect answers*

PS2-2. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. First, K can be calculated from the equation $Cl_t = KV$.

Rearranged:

$K = Cl_t/V = 3.3$ L/hour/30 L = 0.11 hr^{-1}

Then:

$T½ = 0.693/K = 6.3$ hours

PS2-3. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. To calculate the plasma concentration with a continuous infusion before steady state is reached, the following equation can be used:

$$C = \frac{K_0}{VK}(1 - e^{-Kt})$$

where t = 10 hr. Then:

$$C = \frac{40 \text{ mg/hr}}{30 \text{ L} \times 0.11 \text{ hr}^{-1}}(1 - e^{-0.11 \text{ hr}^{-1}(10 \text{ hr})})$$

$$= \frac{40 \text{ mg/hr}}{30 \text{ L} \times 0.11 \text{ hr}^{-1}}(0.667)$$

$$= 8.1 \text{ mg/L}$$

PS2-4. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. If the continuous intravenous infusion is continued for 3 days, steady state would have been reached, so the plasma concentration would be 12 mg/L. When the infusion is stopped, the declining drug concentration can be described just as after an intravenous injection:

$$C_t = C_{ss}e^{-Kt}$$

where:

C_t = plasma concentration after infusion has been stopped for t hour,

C_{ss} = steady-state plasma concentrations from continuous infusion, and K = elimination rate constant.

So, when t = 12 hours:

$$C_{12 \text{ hr}} = (12 \text{ mg/L})(e^{-0.11 \text{ hr}^{-1}(12 \text{ hr})})$$

$$= (12 \text{ mg/L})(0.267)$$

$$= 3.2 \text{ mg/L}$$

PS2-5. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The patient's theophylline clearance equals 3.3 L/hour. Then remember that at steady state:

$C_{ss} = K_0/Cl_t$

or, rearranged:

$C_{ss} \times Cl_t = K_0$

If the desired C_{ss} equals 15 mg/L, then:

K_0 = 15 mg/L × 3.3 L/hour

= 49.5 mg/hour (round to 50)

PS2-6. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. Whenever the infusion rate is changed to a new rate (increased or decreased), it will take approximately five half-lives to achieve a new steady state. So it will take 5 × 6.3 hours = 31.5 hours.

PS2-7. A. CORRECT ANSWER. First, recall that the multiple-dose infusion equation should be used:

$$C_{peak} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

where: K_0 = 80 mg/1 hour (because the dose is given over 1 hour). As given, V = 15 L, τ = 6 hours, and $T½$ = 3 hours. So:

$$K = \frac{0.693}{3\ \text{hr}} = 0.231\ \text{hr}^{-1}$$

Then:

$$C_{peak} = \frac{(80\ \text{mg/hr})(1-e^{-0.231\ \text{hr}^{-1}(1\ \text{hr})})}{(15\ \text{L} \times 0.231\ \text{hr}^{-1})(1-e^{-0.231\ \text{hr}^{-1}(6\ \text{hr})})}$$

$$= \frac{(80\ \text{mg/hr})(0.206)}{(15\ \text{L} \times 0.231\ \text{hr}^{-1})(0.75)}$$

$$= 6.34\ \text{mg/L}$$

B, C, D. *Incorrect answers*

PS2-8. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The half-life can be calculated from the concentrations given. Recall that there are two concentrations on a straight line, where K is the slope of the line. The slope equals the change in the y-axis divided by the change in the x-axis. The time between the end of one infusion and the start of the next is 5 hours. Therefore:

$$K = -\text{slope} = -\frac{\Delta y}{\Delta x}$$

$$= -\frac{(\ln 5\ \text{mg/L} - \ln 0.9\ \text{mg/L})}{0 - 5\ \text{hr}}$$

$$= \frac{-[1.61-(-0.11)]}{-5\ \text{hr}} = \frac{1.72}{5\ \text{hr}}$$

$$= 0.344\ \text{hr}^{-1}$$

Then:

$$T½ = \frac{0.693}{K} = \frac{0.693}{0.344\ \text{hr}^{-1}} = 2.01\ \text{hr}$$

PS2-9. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. To calculate V, the multiple-dose infusion equation (**Equation 5-1**) can be used, where:

$$C_{peak} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

and:

C_{peak} = 5 mg/L
K_0 = 80 mg/hour
K = 0.344 hr^{-1}
t = 1 hour
τ = 6 hours

By substituting, we get:

$$5 \text{ mg/L} = \frac{(80 \text{ mg/hr})(1-e^{-0.344 \text{ hr}^{-1}(1 \text{ hr})})}{(V \times 0.344 \text{ hr}^{-1})(1-e^{-0.344 \text{ hr}^{-1}(6 \text{ hr})})}$$

Rearranging gives:

$$V = \frac{(80 \text{ mg/hr})(1-e^{-0.344 \text{ hr}^{-1}(1 \text{ hr})})}{(5 \text{ mg/L} \times 0.344 \text{ hr}^{-1})(1-e^{-0.344 \text{ hr}^{-1}(6 \text{ hr})})}$$

$$= \frac{(80 \text{ mg/hr})(0.291)}{(5 \text{ mg/L} \times 0.344 \text{ hr}^{-1})(0.873)}$$

$$= 15.5 \text{ L}$$

PS2-10. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. To calculate a new dose, we would use the same equation as above but would now include the known V and desired C_{peak} and then solve for K_0:

$$K_0 = \frac{C_{peak}VK(1-e^{-K\tau})}{(1-e^{-Kt})}$$

$$= \frac{(8 \text{ mg/L})(15.5 \text{ L})(0.344 \text{ hr}^{-1})(0.873)}{(0.291)}$$

$$= 128 \text{ mg over 1 hr}$$

So, in practical terms, a 125-mg dose would be infused over 1 hour to attain a peak of approximately 8 mg/L.

LESSON 7

Biopharmaceutics: Absorption

OBJECTIVES

After completing Lesson 7, you should be able to:

1. Define and understand the factors that comprise the term *biopharmaceutics.*
2. Describe the effects of the extent and rate of absorption of a drug on plasma concentrations and area under the curve (AUC).
3. Name factors that can affect a drug's oral bioavailability and explain the relationship of bioavailability to drug absorption and AUC.
4. Calculate an *F* factor for a drug given its intravenous (IV) and oral absorption time versus concentration AUCs.
5. Use the oral absorption model to calculate pharmacokinetic parameters.
6. Describe the pharmacokinetic differences and clinical utility of controlled-release products and the several techniques used in formulating controlled-release drugs.
7. Calculate dose and clearance of controlled-release products given plasma concentration, volume of distribution, and elimination rate constant.

Introduction to Biopharmaceutics

The effect of a drug depends not only on the drug's characteristics but also on the nature of the body's systems. The drug enters the body by some route of administration and is subjected to processes such as absorption, distribution, metabolism, and excretion (**Figure 7-1**).

The concepts used in pharmacokinetics enable us to understand what happens to a drug when it enters the body. Unless a drug is given intravenously or is absorbed cutaneously, it must be absorbed into the systemic circulation to exert its effect. After entering the systemic circulation, the drug is distributed to various tissues and fluids. While the drug is distributing into tissues and producing an effect, the body is working to eliminate the drug and terminate its effect.

A term often used in conjunction with pharmacokinetics is *biopharmaceutics,* which is the study of the relationship between the nature and intensity of a drug's effects and various drug formulations or administration factors. These factors include the drug's chemical nature, inert formulation substances, pharmaceutical processes used to manufacture the dosage form, and routes of administration.

For an orally administered drug, the absorption process depends on the drug dissociating from its dosage form, dissolving in body fluids, and then diffusing

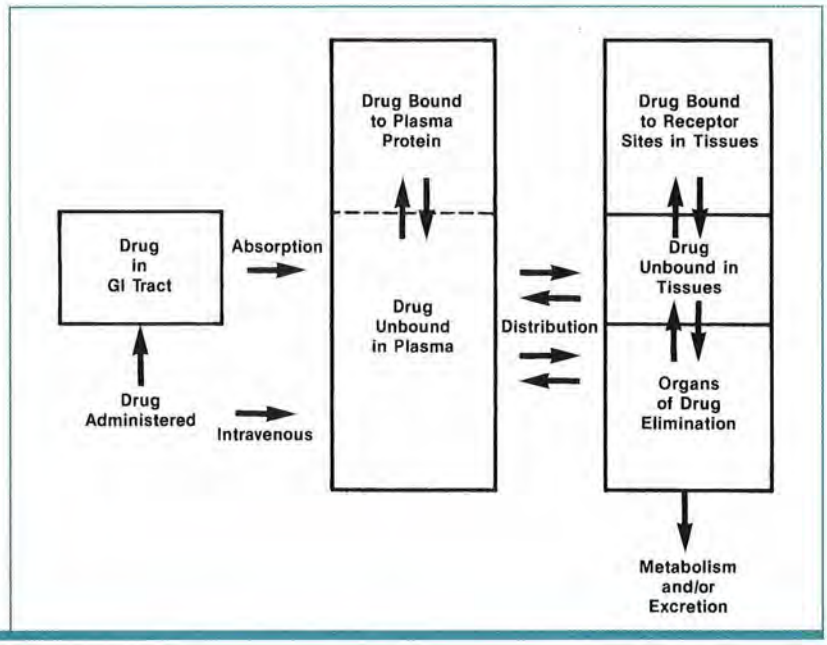

FIGURE 7-1.
Disposition of drug in the body.

across the biologic membrane barriers of the gut wall into the systemic circulation (**Figure 7-2**). Different drugs or different formulations of the same drug can vary considerably in both the rate and extent of absorption. The extent of absorption depends on the nature of the drug itself (e.g., its solubility and pKa) as well as the physiologic environment (pH, gastrointestinal [GI] motility, and muscle vascularity). Most drugs given orally are not fully absorbed into the systemic circulation. The difference in absorption rates of drugs has important therapeutic implications. Assuming that concentration correlates with effect, if one drug is absorbed at a faster rate than another similar drug, the first drug may produce a higher peak concentration, which may lead to a clinical effect sooner than the second drug (**Figure 7-3**).

When drug absorption is delayed (usually through manipulation of the rate of drug release from the formulation), a prolonged or sustained effect can be produced. For certain drugs (e.g., select oral analgesics and hypnotics), rapid absorption is preferable. For other agents (e.g., antiarrhythmics and bronchodilators), a slower rate of absorption with a stable effect over a longer time may be desirable.

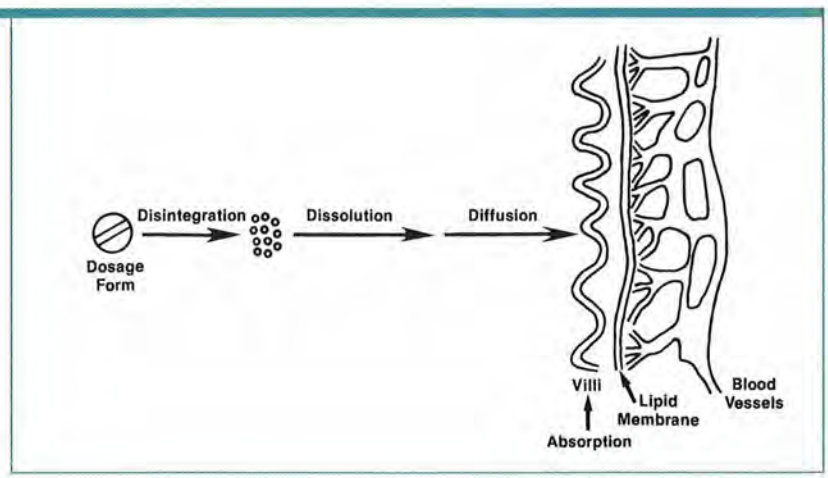

FIGURE 7-2.
Processes involved in drug absorption after oral administration.

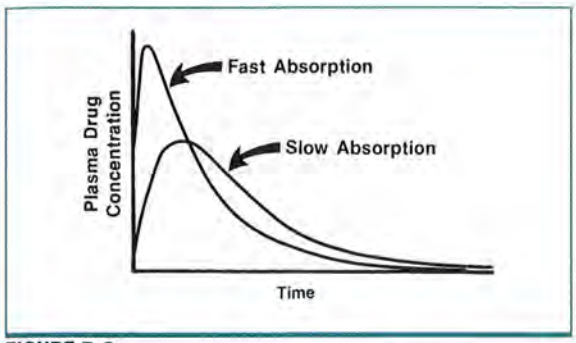

FIGURE 7-3.
Typical effect of absorption rate on plasma drug concentrations.

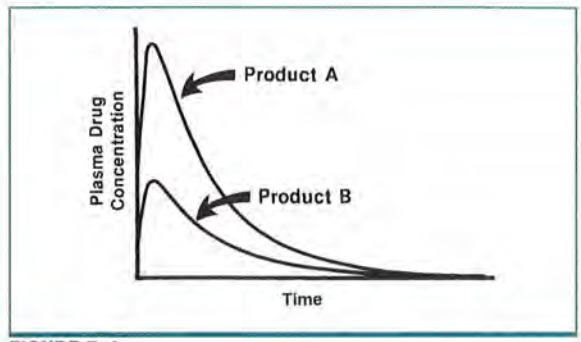

FIGURE 7-4.
Typical effect of different extents of absorption on plasma drug concentrations.

The amount of the drug dose that reaches the systemic circulation determines its bioavailability. Factors that can affect a drug's oral bioavailability include the drug's absorption characteristics, drug metabolism within the intestinal wall, and hepatic first-pass metabolism of a drug. Therefore, overall oral bioavailability can be described by the following equation, which shows the combination of all these factors:

$$F_{oral} = F_{abs} \times F_{gut} \times F_{hepatic}$$

where F is a fraction.

A product with poor bioavailability is not completely absorbed into the systemic circulation or is eliminated by the liver before it reaches the systemic circulation. Differences in bioavailability may be evident between two products (A and B) containing the same drug but producing different plasma concentrations (**Figure 7-4**). Although these products may contain the same amount of drug, their formulations are different (e.g., tablet and capsule). Different formulations may have different absorption characteristics and result in different plasma concentrations. Because product B is not absorbed to the same extent as product A, lower plasma concentrations result for product B.

The AUC of a plasma drug concentration versus time plot reflects the total amount of drug reaching the systemic circulation. Because bioavailability describes the extent of drug eventually reaching the systemic circulation, comparison of the AUCs of various dosage forms of a drug would compare their bioavailabilities.

In Figure 7-4, a drug is given in a similar dose (e.g., 100 mg) in two different oral dosage products (A and B). The AUC for product A is greater than that for product B, indicating that the bioavailability of product A is greater than that of product B. When comparing AUCs to assess bioavailability, we assume that the clearance of drug with each dosage form is the same, so differences in the AUC are directly related to the amount of drug that enters the systemic circulation. For a specific drug, the AUC is determined by the amount of drug that enters the systemic circulation and its clearance from circulation.

In discussing drug absorption and bioavailability, we should recognize that absorption from the GI tract is not always desirable. For some agents, the intended effects are limited to the lumen of the GI tract, so absorption may be undesirable. Examples would be anthelmintics and antibiotics, such as neomycin, given to decrease gut bacterial counts.

A term used to express bioavailability is F. It is a number less than or equal to 1 that indicates the fraction of drug reaching the systemic circulation. F is often erroneously referred to as the fraction of a drug absorbed—it actually represents the *fraction of a drug that reaches the systemic circulation* and can be affected by not only absorption, but that fraction of drug that escapes both presystemic (i.e., intestinal wall) and systemic first-pass metabolism. For instance, for oral formulations of a drug:

$$F = \frac{\text{amount of drug reaching systemic circulation}}{\text{total amount of drug}}$$

Usually, F is determined by comparing the AUC for the oral dosage form with the AUC for IV administration of the same dose. The AUC for IV administration is used because when a drug is given intravenously, it bypasses absorption. The total amount of drug goes into the systemic circulation. A typical value for F is 0.70 for digoxin tablets and 0.80 for digoxin elixir. This indicates that more of the drug reaches systemic circulation when administered as the elixir. The F term gives no indication of how fast a drug is absorbed. Proper studies of drug product bioavailability examine both the rate and extent of absorption.

Clinical Correlate

Absorption of a drug whose bioavailability is low due to a low F factor is erratic and is more likely to be affected by disease-related changes in absorption (e.g., rapid GI transit times, short bowel syndromes).

Bioavailability

We next examine a one-compartment model in which the drug is given orally and absorbed from the GI tract. This example would also apply to intramuscular administration as the drug must undergo absorption from the muscle to produce a therapeutic effect.

Let us assume that:

- The drug is 100% absorbed ($F = 1$).
- The absorption rate is much greater than the elimination rate.
- Distribution to all tissues and fluids is instantaneous (a one-compartment model).
- The drug follows first-order elimination (**Figure 7-5**).

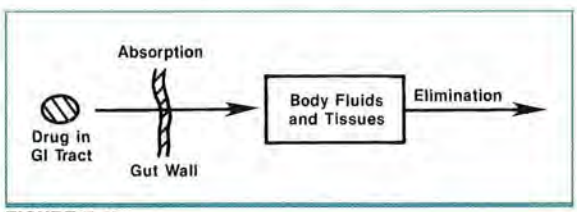

FIGURE 7-5.
First-order elimination.

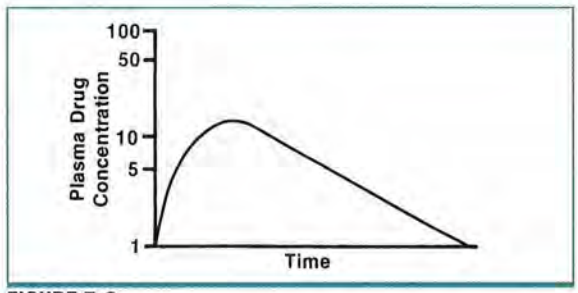

FIGURE 7-6.
Typical plasma drug concentration versus time curve resulting from an oral formulation.

Continuous measurement of plasma drug concentrations would probably produce a plot similar to that shown in **Figure 7-6** when plotted using semilog graph paper. By knowing F to be 1 in this example and the drug concentrations over time, we can calculate the pharmacokinetic parameters of elimination rate (K), volume of distribution (V), half-life ($T\frac{1}{2}$), and total clearance (Cl_t). In many cases, the actual F is not known, so these parameters can be calculated only in terms of their relationship to F (e.g., Cl_t/F, V/F). But first, let's examine the plot more closely. The initial uphill portion of the graph indicates drug absorption. Of course, elimination of drug also begins as soon as some drug is in the body. But in the initial portion of the curve (A), the rate of drug absorption is greater than the rate of elimination so there is an increase in the plasma drug concentration (**Figure 7-7**). As the amount of drug in the GI tract (or in the muscle with intramuscular administration) decreases, the rate of absorption begins to taper off; at point B, the rate of absorption equals the rate of elimination. On the downhill portion of the curve (C), elimination predominates and absorption is nearly complete.

If the drug follows first-order elimination, the terminal portion of the plasma drug concentration

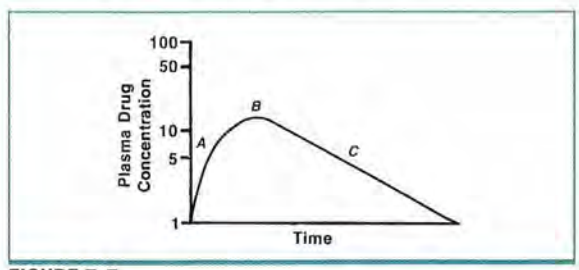

FIGURE 7-7.
Effects of both absorption and elimination on concentration versus time curve.

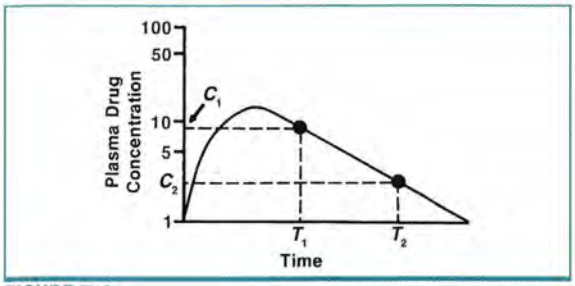

FIGURE 7-8.
Determination of slope (and *K*) from terminal portion of plasma drug concentration curve.

versus time curve should theoretically be a straight line on semilog graph paper (**Figure 7-8**). The slope of the straight-line portion of the curve is related to the elimination rate constant (K). To calculate K or $T½$, we use the techniques described previously, but the calculations are made from the terminal portion (straight-line portion) of the curve.

$$\text{slope} = \frac{\ln C_2 - \ln C_1}{t_2 - t_1} = -K$$

(See **Equation 3-1.**)

$$T½ = \frac{0.693}{K}$$

(See **Equation 3-3.**)

For most drugs, absorption after oral administration is usually nearly complete by 1–2 hours. After that time, plasma concentrations should reflect the effect of elimination. For sustained-release products, however, significant drug absorption can continue for considerably longer than 2 hours.

Let's calculate the volume of distribution after oral or intramuscular administration. This calculation can be performed as follows:

$$V = \frac{\text{amount of drug administered}}{K \times \text{AUC}}$$

(assuming $F = 1$), using the trapezoidal rule to calculate the AUC.

Terms in the equation

$$\frac{\text{mg}}{\text{hr}^{-1} \times (\text{mg/L}) \times \text{hr}}$$

can be canceled, leaving us with a unit for volume of distribution—liters. It is referred to as the V_{area}. Once we have the values of volume of distribution (V) and elimination rate constant (K), the total body clearance (Cl_t) can be calculated as follows:

$$Cl_t = V \times K \quad \text{(See Equation 3-4.)}$$

When drug is absorbed from outside the systemic circulation, as with oral and intramuscular doses, the peak plasma drug concentration occurs sometime after time zero rather than at time zero, as with an IV drug injection. The peak plasma concentration occurs at the point at which the amount eliminated and the amount absorbed are equal (**Figure 7-9**).

Clinical Correlate

When a drug is absorbed more slowly, such as after an intramuscular injection, it will have a smaller peak concentration and a slightly longer duration of action than the IV administration of the same drug. Because of the slower absorption of intramuscularly administered drugs, it will take longer to reach peak concentrations than with IV administration. Consequently, a therapeutic peak concentration may not be attained. To obtain a correct peak concentration time for intramuscularly administered drugs, the measurement must be made in the appropriate time frame. For example, a drug that reaches its peak concentration after 1 hour should not be sampled after 20 minutes; otherwise, a false value will be obtained because absorption is not complete. In addition, because intramuscular absorption occurs more slowly, allowing significant drug elimination to occur before absorption is complete, peak concentrations after an intramuscular injection can yield a lower value than that seen with IV administration. The time to peak is the time corresponding with that peak concentration. The time required to reach the peak plasma concentration depends on the relative rates of absorption and elimination. A rapidly absorbed drug has a short time to peak concentration.

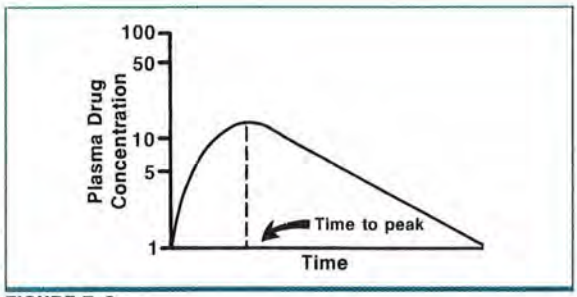

FIGURE 7-9.
Time to peak for oral or intramuscular concentration versus time curve.

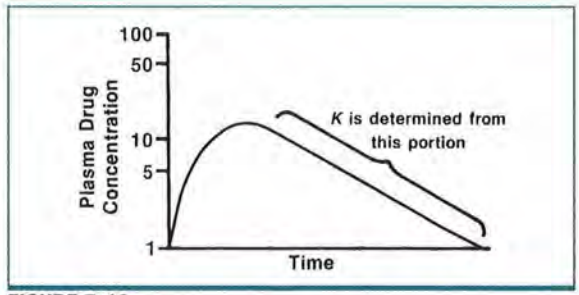

FIGURE 7-10.
Plasma drug concentration versus time for a typical oral formulation.

Oral Absorption Model

The elimination rate constant has been denoted by the symbol K. The absorption rate constant will be represented by K_a. This value indicates the fraction of drug present at the absorption site (usually the GI tract) that is absorbed per unit of time. The usual measurement of K_a is the percentage of drug absorbed per unit of time. If K_a is greater than one in a time unit, almost all of the drug would be absorbed over that time interval.

A high K_a (over 1.0 hr^{-1}) indicates rapid absorption. For this explanation, we will assume that first-order absorption or elimination rates do not change with time. Although the rates do not change, the amount of drug absorbed or eliminated changes.

Clinical Correlate

Some drug absorption rates (K_a) change when large doses are administered as a single oral dose—the percentage of the total dose absorbed is smaller with a large dose than with a smaller dose of the same drug. Gabapentin (Neurontin), which is actively absorbed via the gut's L-amino acid transport system, is a common example of this absorption phenomenon. Consequently, the daily dose must sometimes be given in divided doses, depending on the total daily dose desired.

With an orally administered drug, K is measured by the slope of the terminal portion of the plasma drug concentration versus time curve, the time when absorption no longer has an appreciable effect (**Figure 7-10**). In the first part of the curve (the uphill portion), absorption is occurring, but K_a cannot be measured directly because the curve demonstrates the effects of both absorption and elimination.

Elimination processes begin immediately after the drug is given. A steeper uphill portion indicates a K_a much greater than K, but visual inspection does not provide an accurate assessment of K_a.

One way to calculate K_a is to use the *method of residuals*, which estimates the plasma drug concentration plot if absorption were instantaneous and then uses the difference between the actual and estimated concentrations to determine K_a. We first estimate (by back-extrapolation) the straight-line portion of the curve (**Figure 7-11**). The extrapolated portion represents the effect of elimination alone—as if absorption had been instantaneous.

Let us suppose that A, B, and C are actual measured concentrations and that A', B', and C' are extrapolated concentrations for the same times (**Figure 7-12**). Points on the extrapolated line can be determined visually from the graph or with the following equation:

$$C = (y\text{-intercept}) \times e^{-Kt}$$

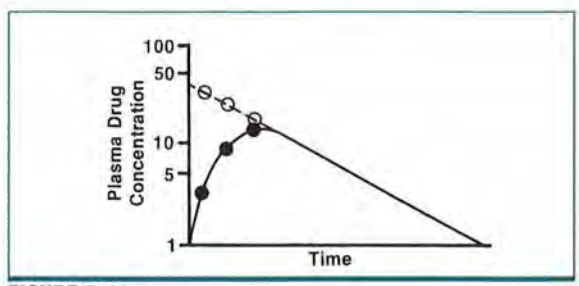

FIGURE 7-11.
Back-extrapolation.

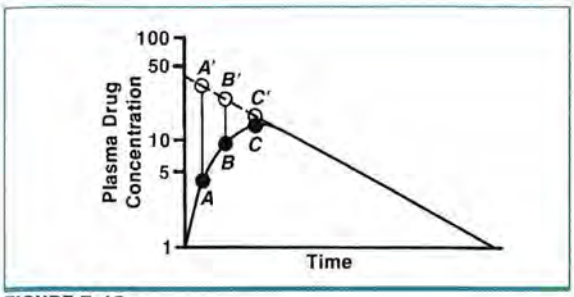

FIGURE 7-12.
Back-extrapolated concentrations.

Subtraction of the actual points on the uphill portion from the corresponding points on the extrapolated line (e.g., $A' - A$, $B' - B$, and $C' - C$) will yield a new set of plasma drug concentrations for each time point. These values can be plotted with the appropriate times, and a line is then drawn that best fits the new points. This new line is called the *residual* (**Figure 7-13**).

The slope of the line for these new points gives an estimate of the absorption rate. Just as the negative slope of the terminal portion of the plasma concentration curve equals K, the negative slope of the residual line equals K_a.

The technique of residuals attempts to separate the two processes of absorption and elimination. These concepts become important when different dosage forms of a drug are evaluated. They can also be used to evaluate the absorption of different brands of the same drug in the same dosage form. A higher K_a indicates a faster absorption rate. This factor is only one component of such evaluations, but it is often important to know how rapidly a drug is made available to the systemic circulation. An overriding assumption of this technique for calculating K_a is that $K_a >>> K$.

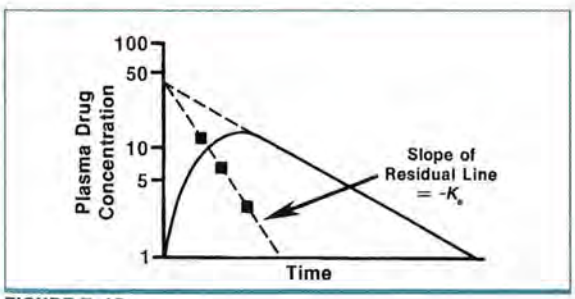

FIGURE 7-13.
Residual line.

Determination of K and K_a can also be used to predict the resulting plasma drug concentrations after an oral drug dose. If K, K_a, and the intercepts of the back-extrapolated line from the drug elimination phase (B) and the residual line (A) are known, the plasma drug concentration (C), which represents the y-intercept, at any time after a single dose (t) can be calculated:

$$C = Be^{-Kt} - Ae^{-K_a t}$$

Although this equation is similar to the one for a single IV injection in a one-compartment model described previously, it accounts for drug yet to be absorbed ($-Ae^{-K_a t}$).

Plasma drug concentration can also be calculated for any given single dose (X_0) when K and K_a are known and estimates of the bioavailability (F) and volume of distribution (V) are available:

$$C_t = \frac{FX_0K_a}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

C_t = concentration at time t,
F = bioavailability,
X_0 = amount of drug given orally,
K_a = absorption rate constant,
V = volume of distribution,
K = elimination rate constant,
t = time after dose has been given.

Just as with multiple IV doses, multiple oral doses result in increasing drug concentrations until steady state is reached (**Figure 7-14**). If K, K_a, V, and F are known, the steady-state plasma drug concentration at any time (t) after a dose (X_0) is given can also be calculated:

$$C_t = \frac{FX_0K_a}{V(K_a - K)}\left[\frac{1}{1-e^{-K\tau}}e^{-Kt} - \frac{1}{1-e^{-K_a\tau}}e^{-K_a t}\right]$$

These equations are presented to demonstrate that plasma drug concentrations after oral doses can be predicted, but they are infrequently applied in clinical practice.

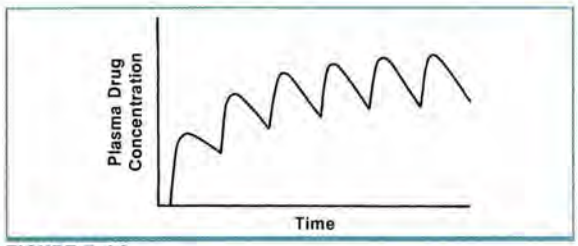

FIGURE 7-14.
Plasma drug concentration versus time for a typical oral formulation given in multiple doses.

Controlled-Release Products

In our discussions of drug absorption so far, it was assumed that the drug formulations used were relatively rapidly absorbed from the GI tract into the systemic circulation. In fact, many drugs are absorbed relatively rapidly from the GI tract. With rapid drug absorption, a peak plasma concentration of drug is evident soon after drug administration (often within 1 hour) and plasma concentrations may decline relatively soon after dose administration, particularly with drugs having short elimination half-lives. When drugs are eliminated rapidly from the plasma, a short dosing interval (e.g., every 6 hours) may be required to maintain plasma concentrations within the therapeutic range.

To overcome the problem of frequent dosage administration with drugs having short elimination half-lives, products have been devised that release drugs into the GI tract at a controlled rate. These controlled-release products (or sustained-release products) usually allow for less frequent dosage administration. As opposed to the first-order absorption that occurs with most rapidly absorbed oral drug products, some controlled-release drug products approximate zero-order drug absorption. With zero-order absorption, the amount of drug absorbed in a given time remains constant for much of the dosing interval. The result of zero-order absorption is a more consistent plasma concentration (**Figure 7-15**).

Many types of controlled-release drug products have been produced. Products from different manufacturers (e.g., theophylline products) that contain the same drug entity may have quite different absorption properties, resulting in different plasma concentration versus time curves.

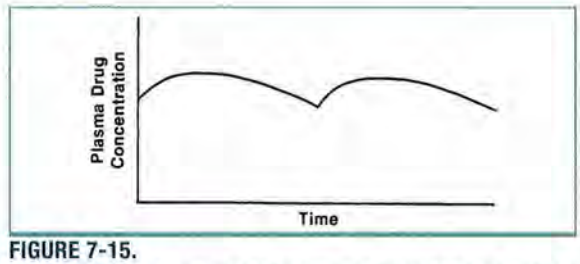

FIGURE 7-15.
Typical plasma drug concentration versus time curve at steady state for a controlled-release oral formulation.

Controlled-release formulations incorporate various techniques to slow drug absorption. These techniques include the application of coatings that delay absorption, the use of slowly dissolving salts or esters of the parent drug, the use of ion-exchange resins that release drug in either acidic or alkaline environments, and the use of gel, wax, or polymeric matrices. Examples of available drugs in controlled-release formulations are shown in **Table 7-1**.

Two features of controlled-release products must be considered in therapeutic drug monitoring:

1. When multiple doses of a controlled-release drug product are administered, before reaching steady state, the difference between peak and trough plasma concentrations is not as great as would be evident after multiple doses of rapidly absorbed drug products (**Figure 7-16**).
2. Because the drug may be absorbed for most of a dosing interval, an elimination phase may not be as apparent—that is, the log of plasma drug concentration versus time curve may not be linear for any part of the dosing interval.

Because, with controlled-release formulations, the drug may be absorbed continuously from the GI tract over the dosing interval, it may not be possible to calculate a drug's half-life.

TABLE 7-1. Examples of Controlled-Release Formulations

Drug	Formulation
Potassium chloride	Wax matrix tablet
Theophylline	Coated pellets in tablet
Decongestants	Coated pellets in capsule
Aspirin	Microencapsulation
Nifedipine	Osmotic pump

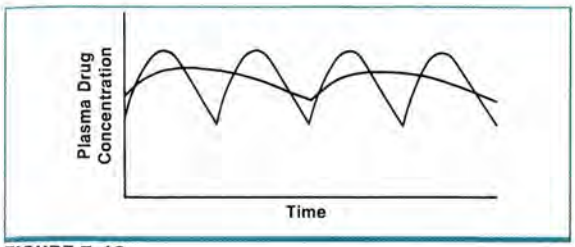

FIGURE 7-16.
Plasma drug concentrations over time with controlled-release and rapid-release products.

Clinical Correlate

The peak and trough concentrations of controlled-release products generally differ very little, so plasma drug concentration sampling is generally done at the approximate midpoint of any dosing interval to approximate the average steady-state concentration.

Some predictions can be made about plasma drug concentrations with controlled-release preparations. For preparations that result in continued release of small drug doses, the plasma drug concentration can be estimated as follows:

$$\text{average steady-state plasma concentration} = \frac{\text{dose} \times \text{fraction reaching systemic circulation}}{\text{dosing interval} \times \text{clearance}}$$

or:

$$\bar{C} = \frac{X_0 \times F}{\tau \times Cl_t}$$

(See **Equation 4-3.**)

Given this equation, the dose, the amount entering the systemic circulation, dosing interval, and clearance can be used to predict the average steady-state plasma drug concentration. Also, if the average plasma drug concentration is estimated (determined approximately halfway through a dosing interval), drug clearance can be determined using the same formula. Finally, the effect of changing the dose or dosing interval on plasma drug concentration can be estimated.

For example, if it is known from previous regimens that a patient has a theophylline half-life of 7 hours (K = 0.1 hr^{-1}) and a volume of distribution of 30 L, what dose of a sustained-release preparation given every 12 hours will be required to achieve an average plasma concentration of 12 mg/L? Assume that the product is 90% absorbed.

First, theophylline clearance must be estimated as follows:

$$\begin{aligned} Cl_t &= K \times V \\ &= 0.1\ hr^{-1} \times 30\ L \\ &= 3.0\ L/hr \end{aligned}$$

Then the known variables can be applied:

$$\bar{C} = \frac{X_0 \times F}{\tau \times Cl_t}$$

$$12\ mg/L = \frac{X_0 \times 0.9}{12\ hr \times 3\ L/hr}$$

Rearranging gives:

$$\begin{aligned} X_0 &= \frac{3\ L/hr \times 12\ hr \times 12\ mg/L}{0.9} \\ &= 480\ mg \text{ given every } 12\ hr \\ &\quad (\text{may be rounded to } 500\ mg) \end{aligned}$$

This same equation could be used to estimate drug clearance if a steady-state plasma drug concentration at the midpoint of a dosing interval is known.

Another feature of sustained-release dosage products is that the drug dose is directly related to the AUC, just as for rapidly absorbed products. If rapid- and sustained-release products of the same drug are absorbed to the same extent, then the resulting AUC at steady state for a similar time will be equivalent for each product if the same daily dosages are given. For example, if 500 mg of a sustained-release drug product is given every 12 hours and 250 mg of a rapidly absorbed formulation of the same drug is given every 6 hours, the AUC over 12 hours (two dosing intervals for the rapidly absorbed product) should be the same. Again, the

assumption is that the bioavailability (F) is the same for each product.

The AUC after administration of a controlled-release dosage formulation is related to drug dosage; the relating factor is drug clearance, as discussed previously:

$$\text{AUC} = \frac{\text{dose} \times F}{\text{clearance}}$$

(See **Equation 3-5.**)

or:

$$\text{clearance} = \frac{\text{dose} \times F}{\text{AUC}}$$

So if the AUC, dose administered, and fraction reaching the systemic circulation are known, drug clearance can be estimated.

The considerations for controlled-release dosage forms will become increasingly important as more drugs are being formulated into preparations that can be administered at convenient intervals (daily or even less frequently).

Clinical Correlate

The importance of the absorption rate depends to some extent on the type of illness being treated. For example, when treating pain, it is usually desirable to use an analgesic that is rapidly absorbed (i.e., has a high absorption rate constant) so that drug effect may begin as soon as possible. For chronic diseases, such as hypertension, it is more desirable to have a product that results in a lower absorption rate and more consistent drug absorption over time so that blood pressure does not change over the dosing interval.

Clinically Important Equation Identified in This Chapter

$$\bar{C} = \frac{X_0 \times F}{\tau \times Cl_t}$$

This is a revision of **Equation 4-3** in which F is incorporated into the equation.

REVIEW QUESTIONS

7-1. Absorption of a drug from a tablet form involves dissolution of the solid dosage form into GI fluids and diffusion through body fluids and membranes.

A. True
B. False

7-2. The extent to which a drug is absorbed partially determines its:

A. elimination rate.
B. bioavailability.
C. half-life.
D. volume of distribution.

7-3. Which of the following statements best describes *F*?

A. rate of absorption of the administered drug into the systemic circulation
B. amount of administered drug that reaches the systemic circulation
C. speed at which the administered drug reaches the systemic circulation
D. fraction of the administered drug that reaches the systemic circulation

7-4. If 500 mg of a drug is given orally and 125 mg is absorbed into the systemic circulation, what is *F*?

A. 0.6
B. 0.5
C. 3
D. 0.25

7-5. A drug given intravenously results in an AUC of 400 (mg/L) × hour. If the same dose of drug is given orally and the resulting AUC is 300 (mg/L) × hour, what percentage of the oral dose reaches the systemic circulation and what is the *F* value?

A. 75%, $F = 0.75$
B. 33%, $F = 0.33$
C. 50%, $F = 0.5$
D. 0.5%, $F = 0.005$

7-6. Two generic brands of equal strength of a drug (as a tablet) are given orally. Tablet A results in an AUC of 300 (mg/L) × hour, whereas tablet B results in an AUC of 500 (mg/L) × hour. Which product has the better bioavailability?

A. tablet A
B. tablet B

7-7. For Figure 7-7, match the sequence of parts of the plasma concentration curve (i.e., *A*, *B*, or *C*) with the following description sequences: (1) The rate of drug absorption is less than the rate of excretion. (2) The rate of drug excretion is less than the rate of absorption. (3) The rate of drug excretion equals the rate of absorption.

A. *A, C, B*
B. *C, A, B*
C. *C, B, A*
D. *A, B, C*

Use the following information for **Questions 7-8 through 7-10**: A 500-mg oral dose of drug X is given, and the following plasma concentrations result:

Plasma Concentration (mg/L)	Time after Dose (hours)
0	0
4.0	0.5
7.3	1.0
9.0	1.5
8.4	2.0
4.6	4.0
2.5	6.0

7-8. Calculate the elimination rate constant (K) and the half-life ($T\frac{1}{2}$).

A. $K = 0.30\ hr^{-1}$; $T\frac{1}{2} = 2.31$ hours
B. $K = 0.03\ hr^{-1}$; $T\frac{1}{2} = 23.1$ hours
C. $K = 0.50\ hr^{-1}$; $T\frac{1}{2} = 1.41$ hour
D. $K = 0.20\ hr^{-1}$; $T\frac{1}{2} = 3.4$ hours

7-9. Calculate the AUC (from $t = 0 \rightarrow \infty$).

A. 8.33 (mg/L) × hour
B. 32.33 (mg/L) × hour
C. 40.71 (mg/L) × hour
D. 7.1 (mg/L) × hour

7-10. Calculate the V_{area} given the above AUC, K, and dose.

A. 24.5 L
B. 51.5 L
C. 409 L
D. 40.9 L

7-11. If two formulations of the same drug are tested and product A has a faster absorption rate than product B, product A will take a shorter amount of time to reach peak concentration.

A. True
B. False

7-12. Refer to **Figure 7-17**. The plasma concentrations and times observed for several points are as follows:

Observed Plasma Concentration (mg/L)	Time after Dose (hours)
3.8	0.25
7.3	0.5
9.1	0.75
9.7	1.0

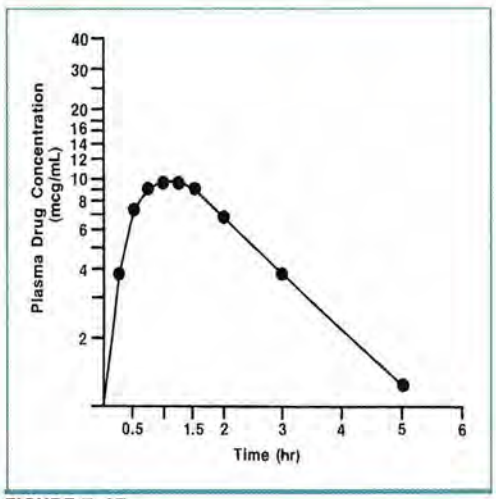

FIGURE 7-17.
Oral absorption plot.

On semilog graph paper, draw the back-extrapolated line from the terminal portion of the curve. Next, using a ruler, draw a line directly upward from the times of 0.25, 0.5, 0.75, and 1.0 hour; then estimate, on the concentration scale (y-axis), the concentrations from the extrapolated line at the following times after drug administration: 0.25, 0.5, 0.75, and 1.0 hour. Which choice below represents these extrapolated values from each time point?

A. 16.0, 14.0, 12.0, and 10.0 mg/L
B. 20.4, 18.0, 16.0, and 14.1 mg/L
C. 18.4, 17.0, 15.0, and 13.1 mg/L
D. 18.4, 16.0, 14.0, and 12.1 mg/L

For each of the four times used in the previous question, calculate the corresponding concentrations for the residual line in **Questions 7-13 through 7-16**.

7-13. Time = 0.25 hour

A. 14.6 mg/L
B. 8.7 mg/L
C. 4.9 mg/L
D. 2.4 mg/L

7-14. Time = 0.5 hour

A. 14.6 mg/L
B. 8.7 mg/L
C. 4.9 mg/L
D. 2.4 mg/L

7-15. Time = 0.75 hour

A. 14.6 mg/L
B. 8.7 mg/L
C. 4.9 mg/L
D. 2.4 mg/L

7-16. Time = 1.0 hour

A. 14.6 mg/L
B. 8.7 mg/L
C. 4.9 mg/L
D. 2.4 mg/L

The following applies to **Questions 7-17 through 7-20**. You wish to begin a patient on a sustained-release preparation of drug Y and to maintain an average plasma drug concentration of 15 mg/L. From published data, you estimate V and K for this drug to be 12 L and 0.21 hr^{-1} in this patient, respectively.

7-17. If the fraction of drug absorbed is assumed to be 1.0 and the drug is to be given every 8 hours, what dose should be administered?

A. 302 mg
B. 720 mg
C. 2400 mg
D. 360 mg

7-18. After 5 days (assume steady state has been reached), the mid-dose (average) plasma drug concentration is 12 mg/L. What is the patient's actual drug clearance?

A. 780 L
B. 3.15 L
C. 6.42 L
D. 20 L

7-19. What should the new daily dose be to result in an average plasma drug concentration of 15 mg/L?

A. 720 mg
B. 552 mg
C. 378 mg
D. 2772 mg

7-20. Finally, due to potential compliance problems with a three-times-a-day dosing interval, the physician wishes to prescribe this drug every 12 hours. What dose administered every 12 hours would be necessary to achieve a steady-state serum level of 15 mg/L?

A. 125 mg
B. 227 mg
C. 468 mg
D. 567 mg

ANSWERS

7-1. A. CORRECT ANSWER. Drug must disintegrate before dissolution.
B. *Incorrect answer*

7-2. A. *Incorrect answer.* Elimination only occurs after drug is absorbed.
B. CORRECT ANSWER
C. *Incorrect answer.* Half-life is related to elimination rate and occurs only after drug is absorbed.
D. *Incorrect answer.* Distribution occurs only after drug is absorbed.

7-3. A, B, C. *Incorrect answers*
D. CORRECT ANSWER

7-4. A, B, C. *Incorrect answers*
D. CORRECT ANSWER.
F = mg absorbed/total dose,
F = 125 mg/500 mg = 0.25.

7-5. A. CORRECT ANSWER. Percentage of dose reaching blood stream =
$AUC_{po\ dose}/AUC_{IV\ dose}$
% = (300 mg/L × hr)/(400 mg/L × hr)
= 75%
B, C, D. *Incorrect answers*

7-6. A. *Incorrect answer*
B. CORRECT ANSWER

7-7. A, C, D. *Incorrect answers*
B. CORRECT ANSWER

7-8. A. CORRECT ANSWER.

$$K = \frac{\ln 8.4\ \text{mg/L} - \ln 2.5\ \text{mg/L}}{6\ \text{hr} - 2\ \text{hr}}$$

$$= \frac{1.21}{4\ \text{hr}} = 0.30\ \text{hr}^{-1}$$

$$T_{1/2} = \frac{0.693}{0.30\ \text{hr}^{-1}} = 2.31\ \text{hr}$$

B, C, D. *Incorrect answers*

7-9. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. Remember that the AUC equals the area under the curve from time zero to 6 hours plus the area under the curve from 6 hours to infinity. The AUC (6 hours to infinity) is obtained by dividing the 6-hour concentration by the elimination rate constant (K) from above.

AUC from 0 to 6 hours is:

$$\frac{0+4}{2}\times 0.5 = 1$$

$$\frac{4+7.3}{2}\times 0.5 = 2.83$$

$$\frac{7.3+9}{2}\times 0.5 = 4.10$$

$$\frac{9+8.4}{2}\times 0.5 = 4.35$$

$$\frac{8.4+4.6}{2}\times 2 = 13.0$$

$$\frac{4.6+2.5}{2}\times 2 = 7.1$$

$$AUC_{0\rightarrow 6\ hr} = 1+2.83+4.10+4.35+13.0+7.1 = 32.38\ (mg/L)\times hr$$

To this value is added $AUC_{6\ hr\rightarrow\infty}$, which is calculated:

$$\frac{C_{6\ hr}}{K} = \frac{2.5\ mg/L}{0.30\ hr^{-1}} = 8.33\ (mg/L)\times hr$$

$$AUC_{0\rightarrow\infty} = AUC_{0\rightarrow 6\ hr} + AUC_{6\ hr\rightarrow\infty}$$

$$= 32.38 + 8.33\ (mg/L)\times hr$$

$$= 40.71\ (mg/L)\times hr$$

7-10. A, C. *Incorrect answers.* Did you use $K = 0.3\ hr^{-1}$?

B. *Incorrect answer.* Did you use AUC = 40.71 (mg/L) × hour?

D. CORRECT ANSWER.

$$V_{area} = \frac{dose}{AUC\times K}$$

$$= \frac{500\ mg}{40.71\ (mg/L\times hr)\times 0.30\ hr^{-1}} = 40.93\ L$$

You can see that this value differs considerably from V_{extrap}; V_{area} is usually a better estimate.

7-11. A. CORRECT ANSWER. Drugs that are absorbed more quickly also reach a higher peak concentration.

B. *Incorrect answer*

7-12. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. Residual concentration = back-extrapolated concentration minus actual concentration.

7-13. A. CORRECT ANSWER. Residual concentration = back-extrapolated concentration minus actual concentration.

B, C, D. *Incorrect answers*

7-14. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. Residual concentration = back-extrapolated concentration minus actual concentration.

7-15. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. Residual concentration = back-extrapolated concentration minus actual concentration.

7-16. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. Residual concentration = back-extrapolated concentration minus actual concentration.

7-17. A. CORRECT ANSWER

B, C, D. *Incorrect answers.*

$$\text{clearance} = VK$$

$$= 12\ \text{L} \times 0.21\ \text{hr}^{-1} = 2.52\ \text{L/hr}$$

Then, the equations below can be used to estimate the dose:

$$\bar{C} = \frac{X_0 \times F}{\text{Cl}_t \times \tau}$$

$$15\ \text{mg/L} = \frac{X_0 \times 1.0}{2.52\ \text{L/hr} \times 8\ \text{hr}}$$

Rearranging gives:

$$X_0 = \frac{15\ \text{mg/L} \times 2.52\ \text{L/hr} \times 8\ \text{hr}}{1.0} = 302.4\ \text{mg}$$

(given every 8 hr)

7-18. A, C, D. *Incorrect answers*

B. CORRECT ANSWER.

We know the following:

τ = 8 hours

X_0 = 302 mg

F = 1.0

$\bar{C}$ = 12 mg/L

And since:

$$\bar{C} = \frac{X_0 \times F}{\text{Cl}_t \times \tau}$$

$$12\ \text{mg/L} = \frac{302\ \text{mg} \times 1.0}{\text{Cl}_t \times 8\ \text{hr}}$$

Rearranging gives:

$$\text{Cl}_t = \frac{302\ \text{mg} \times 1.0}{12\ \text{mg/L} \times 8\ \text{hr}} = 3.15\ \text{L/hr}$$

7-19. A, B, D. *Incorrect answers*

C. CORRECT ANSWER.

$$\bar{C} = \frac{X_0 \times F}{\text{Cl}_t \times \tau}$$

$$15\ \text{mg/L} = \frac{X_0 \times 1.0}{3.15\ \text{L/hr} \times 8\ \text{hr}}$$

Rearranging gives:

$$X_0 = \frac{3.15\ \text{L/hr} \times 8\ \text{hr} \times 15\ \text{mg/L}}{1.0} = 378\ \text{mg}$$

(given every 8 hr)

7-20. A, B, C. *Incorrect answers*

D. CORRECT ANSWER.

$$X_0 = \frac{3.15\ \text{L/hr} \times 12\ \text{hr} \times 15\ \text{mg/L}}{1.0} = 567\ \text{mg}$$

(given every 12 hr)

Discussion Points

D-1. 500 mg of Drug X is administered by continuous infusion every 24 hours. A steady-state serum level is reported as 22 mg/L. Assuming $F = 1$, calculate the clearance for this drug.

D-2. Using the clearance value from discussion point D-1, calculate a new dose administered by continuous infusion every 24 hours that would result in a steady-state serum level of 30 mg/L.

D-3. Look up the bioavailability for the tablet and elixir dosage forms of Lanoxin. Plot representation concentration versus time curves for these two products at the same dose. Discuss all pharmacokinetic differences observed from these plots.

D-4. For the example above (D-3), discuss potential advantages and disadvantages of these two dosage forms. Also, list specific situations in which one dosage form might be preferred or not preferred in a clinical dosing situation.

D-5. Find bioavailability data for at least two different brands of the same drug (brand versus generic, if possible) and describe the bioavailability comparisons made for each product.

D-6. For the drug products researched in discussion point D-5 above, research the U.S. Food and Drug Administration's bioequivalence statement. Can these drugs be generically substituted and, if so, what data are used to support this claim?

D-7. Plot (not to scale) the concentration versus time curves for 100 mg of the following four oral formulations of a drug and then rank (from highest to lowest) their relative peak concentrations and AUCs. Describe the effects of variation in these two factors (K_a and F) on the concentration versus time curves.

A. $F = 1, K_a = 1\ hr^{-1}$
B. $F = 0.7, K_a = 1\ hr^{-1}$
C. $F = 1, K_a = 0.4\ hr^{-1}$
D. $F = 0.7, K_a = 0.4\ hr^{-1}$

LESSON 8

Drug Distribution and Protein Binding

OBJECTIVES

After completing Lesson 8, you should be able to:

1. Describe the major factors that affect drug distribution.
2. Explain the relative perfusion (i.e., high or low) characteristics of various body compartments (e.g., kidneys, fat tissue, lungs).
3. Describe the three main proteins that bind various drugs.
4. List the major factors that affect drug protein binding.
5. Describe the dynamic processes involved in drug protein binding.
6. Compare perfusion-limited distribution and permeability-limited distribution.
7. Calculate the volume of distribution based on drug protein binding data.

Once a drug begins to be absorbed, it undergoes various transport processes, which deliver it to body areas away from the absorption site. These transport processes are collectively referred to as *drug distribution* and are evidenced by the changing concentrations of drug in various body tissues and fluids.

Information concerning the concentration of a drug in body tissues and fluids is limited to a few instances in time (i.e., we know the precise plasma drug concentration only at the few times that blood samples are drawn). Usually, we measure only plasma concentrations of drug, recognizing that the drug can be present in many body tissues.

For most drugs, distribution throughout the body occurs mainly by blood flow through organs and tissues. However, many factors can affect distribution, including:

- differing characteristics of body tissues,
- disease states that alter physiology,
- lipid solubility of the drug,
- regional differences in physiologic pH (e.g., stomach and urine), and
- extent of protein binding of the drug.

Body Tissue Characteristics

To understand the distribution of a drug, the characteristics of different tissues must be considered. Certain organs, such as the heart, lungs, and kidneys, are highly perfused with blood; fat tissue and bone (not the marrow) are much less

perfused. Skeletal muscle is intermediate in blood perfusion. The importance of these differences in perfusion is that for most drugs the rate of delivery from the circulation to a particular tissue depends greatly on the blood flow to that tissue. This is called *perfusion-limited distribution*. Drugs apparently distribute more rapidly to areas with higher blood flow. If the blood flow rate increases, the distribution of the drug to the tissue increases.

Highly perfused organs rapidly attain drug concentrations approaching those in the plasma; less well-perfused tissues take more time to attain such concentrations. Furthermore, certain anatomic barriers inhibit distribution, a concept referred to as *permeability-limited distribution*. This situation occurs for polar drugs diffusing across tightly knit lipoidal membranes. It is also influenced by the oil/water partition coefficient and degree of ionization of a drug. For example, the blood–brain barrier limits the amount of drug entering the central nervous system from the bloodstream. This limitation is especially great for highly ionized drugs and for those with large molecular weights.

After a drug begins to distribute to tissue, the concentration in tissue increases until it reaches an equilibrium at which the amounts of drug entering and leaving the tissue are the same. The drug concentration in a tissue at equilibrium depends on the plasma drug concentration and the rate at which drug distributes into that tissue. In highly perfused organs, such as the liver, the distribution rate is relatively high; for most agents, the drug in that tissue rapidly equilibrates with the drug in plasma. For tissues in which the distribution rate is lower (e.g., fat), reaching equilibrium may take much longer (**Figure 8-1**).

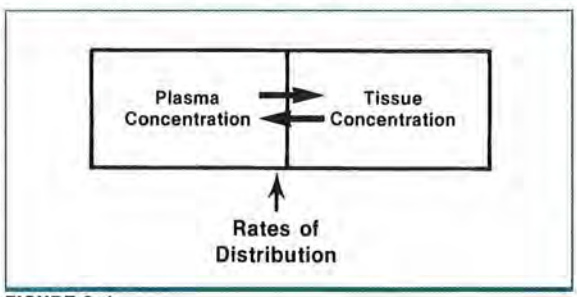

FIGURE 8-1.
Distribution rates.

Disease States Affecting Distribution

Another major factor affecting drug distribution is the effect of various disease states on body physiology. In several disease states, such as liver, heart, and renal failure, the cardiac output and/or perfusion of blood to various tissues is altered. A decrease in perfusion to the tissues results in a lower rate of distribution and, therefore, a lower drug concentration in the affected tissues relative to the plasma drug concentration. When the tissue that receives poor perfusion is the primary eliminating organ, a lower rate of drug elimination results, which then may cause drug accumulation in the body.

Lipid Solubility of the Drug

The extent of drug distribution in tissues also depends on the physiochemical properties of the drug as well as the physiologic functions of the body. A drug that is highly lipid soluble easily penetrates most membrane barriers, which are mainly lipid based, and distributes extensively to fat tissues. Drugs that are very polar and therefore hydrophilic (e.g., aminoglycosides) do not distribute well into fat tissues. This difference becomes important when determining loading dosage requirements of drugs in overweight patients. If total body weight is used to estimate dosage requirements and the drug does not distribute to adipose tissue, the dose can be overestimated.

Clinical Correlate

In general, volume of distribution is based on ideal body weight for drugs that do not distribute well into adipose tissue and on total body weight for drugs that do. If a drug distributes partially into fat, an adjusted body weight between the patient's actual and ideal body weights is often used. Vancomycin is one notable exception to this rule; the patient's total body weight is usually used to calculate volume of distribution for vancomycin.

Regional Differences in Physiologic pH

Another factor affecting drug distribution is the different physiologic pHs of various areas of the body. The difference in pH can lead to localization of drug in tissues and fluids. A drug that is predominantly in its ionized state at physiologic pH (7.4) does not readily cross membrane barriers and probably has a limited distribution. An example of this phenomenon is excretion of drugs in breast milk. Only un-ionized drug can pass through lipid membrane barriers into breast milk. Alkaline drugs, which would be mostly un-ionized at pH 7.4, pass into breast tissue. Once in breast tissue, the alkaline drugs ionize because breast tissue has an acidic pH; therefore, the drugs become trapped in this tissue. This same phenomenon can occur in the urine.

Due to the nature of biologic membranes, drugs that are un-ionized (uncharged) and have lipophilic (fat-soluble) properties are more likely to cross most membrane barriers. Several drugs (e.g., amphotericin) are formulated in a lipid emulsion to deliver the active drug to its intended site while decreasing toxicity to other tissues.

Physiologic Model

It is difficult to conceptualize the effect that the factors discussed above have on the volume of distribution of a drug. Many of these factors can be incorporated into a relatively simple physiologic model. This model describes the critical components that influence a drug's volume of distribution. The equation below represents this physiologic model and provides a conceptual perspective of the volume of distribution:

$$V = V_p + V_t(F_p/F_t)$$

where:

- V = volume of distribution,
- V_p = plasma volume,
- V_t = tissue volume,
- F_p = fraction of unbound drug in the plasma, and
- F_t = fraction of unbound drug in the tissue.

From this model, it is evident that the volume of distribution is dependent on the volume of the plasma (3–5 L), the volume of the tissue, the fraction of unbound drug in the plasma, and the fraction of unbound drug in the tissue. Changes in any of these parameters can influence a drug's volume of distribution. We use this equation to help us understand why the volume of distribution of a drug may have changed as a consequence of drug interactions or disease states. Usually, changes in the volume of distribution of a drug can be attributed to alterations in the plasma or tissue protein binding of the drug. This topic is discussed in the next section, Protein Binding.

The clinical consequence of changes in the volume of distribution of a drug in an individual patient is obvious. An example of this would be the use of drug loading doses. Because the initial plasma concentration of the drug (C_0) is primarily dependent on the size of the loading dose and the volume of distribution (C_0 = loading dose/V), changes in either of these parameters could significantly alter the C_0 achieved. Therefore, one must carefully consider the loading dose of a drug for a patient whose volume of distribution is believed to be unusual.

Phenytoin is an example of a drug that can be used to illustrate the effects of changes in the factors that determine volume of distribution. For a typical 70-kg person, the volume of distribution for phenytoin is approximately 45 L. Generally, the unbound fraction of this drug in plasma is approximately 0.1 (90% bound to albumin). If we assume that the plasma volume is 5 L, the tissue volume is 80 L, and the fraction unbound in tissue is 0.2, we can estimate how changes in plasma unbound fraction affect volume of distribution.

$$V = V_p + V_t(F_p/F_t)$$

$$= 5\text{ L} + 80\text{ L}\ (0.1/0.2)$$

$$= 45\text{ L}$$

If the plasma fraction unbound increases to 0.2, which is possible for patients with hypoalbuminemia, the volume of distribution would change as shown:

$$V = V_p + V_t(F_p/F_t)$$

$$= 5\ \text{L} + 80\ \text{L}\ (0.2/0.2)$$

$$= 85\ \text{L}$$

So, by changing protein binding in the plasma, the volume of distribution has almost doubled.

Protein Binding

Another factor that influences the distribution of drugs is binding to tissues (nucleic acids, ligands, calcified tissues, and adenosine triphosphatase) or proteins (albumins, globulins, alpha-1-acid glycoprotein, and lipoproteins). It is the unbound or free portion of a drug that diffuses out of plasma. Protein binding in plasma can range from 0 to 99% of the total drug in the plasma and varies with different drugs. The extent of protein binding may depend on the presence of other protein-bound drugs and the concentrations of drug and proteins in the plasma.

The usual percentages of binding to plasma proteins for some commonly used agents are shown in **Table 8-1**.

TABLE 8-1. Protein Binding

Drug	Binding (%)
Ampicillin	18
Chloramphenicol	53
Digoxin	25
Gentamicin	< 10
Lidocaine	70
Phenytoin	89
Vancomycin	30

Source: Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 3rd ed. Norwalk, CT: Appleton & Lange; 1993. pp. 594–95.

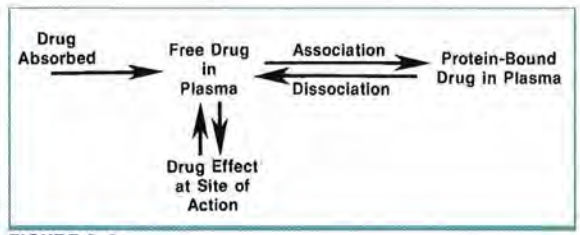

FIGURE 8-2.
Free drug is available to interact with receptor sites and exert effects.

Theoretically, drugs bound to plasma proteins are usually not pharmacologically active. To exert an effect, the drug must dissociate from protein (**Figure 8-2**).

Although only unbound drug distributes freely, drug binding is rapidly reversible (with few exceptions), so some portion is always available as free drug for distribution. The association and dissociation process between the bound and unbound states is very rapid and, we assume, continuous (**Figure 8-3**).

A drug's protein-binding characteristics depend on its physical and chemical properties. Hydrophobic drugs usually associate with plasma proteins. The binding of a drug to plasma proteins will primarily be a function of the affinity of the protein for the drug. The percentage of protein binding of a drug in plasma can be determined experimentally as follows:

$$\%\ \text{protein binding} = \frac{[\text{total}] - [\text{unbound}] \times 100}{[\text{total}]}$$

where [*total*] is the total plasma drug concentration (unbound drug + bound drug) and [*unbound*] refers to the unbound or free plasma drug concentration.

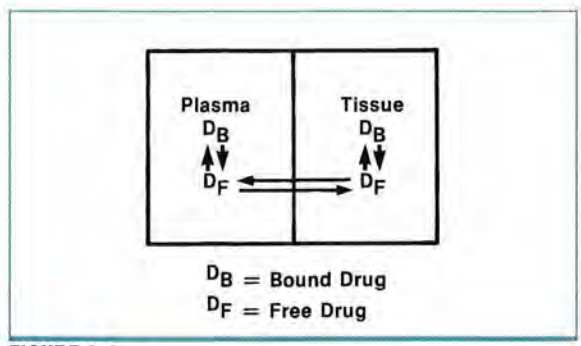

FIGURE 8-3.
Association and dissociation process.

Another way of thinking about the relationship between free and total drug concentration in the plasma is to consider the fraction of unbound drug in the plasma (F_p). F_p is determined by the following relationship:

$$F_p = \frac{[\text{unbound}]}{[\text{total}]}$$

Although the protein binding of a drug will be determined by the affinity of the protein for the drug, it will also be affected by the concentration of the binding protein. Two frequently used methods for determining the percentage of protein binding of a drug are equilibrium dialysis and ultrafiltration.

Three plasma proteins are primarily responsible for the protein binding of most drugs. They are shown in **Table 8-2** with their normal plasma concentration ranges.

Although only the unbound portion of drug exerts its pharmacologic effect, most drug assays measure total drug concentration—both bound and unbound drug. Therefore, changes in the binding characteristics of a drug could affect pharmacologic response to the drug. For example, the anticonvulsant and toxic effects of phenytoin are more closely related to the concentration of free drug in plasma than to the concentration of total drug in plasma. In most patients, the free phenytoin concentration is approximately 10% of the total concentration. However, in patients with low serum albumin concentrations, a lower fraction of phenytoin is bound to protein, and the free portion is up to 20% of the total concentration (**Table 8-3**). With hypoalbuminemia, therefore, a patient with a total phenytoin concentration of 15 mg/L may experience side effects (nystagmus and ataxia) usually seen at a total concentration of 30 mg/L. In these patients, a lower total phenytoin concentration may be effective in controlling seizures.

TABLE 8-3. Phenytoin Concentration with Regard to Serum Albumin Concentration

Phenytoin	Concentration (mg/L)
Total	15.0
Free (normal)	1.5
Free (hypoalbuminemia)	3.0

Clinical Correlate

For certain drugs that are highly protein bound and have a narrow therapeutic index, it may be useful to obtain an unbound plasma drug concentration rather than a total plasma drug concentration. This will more accurately reflect the true concentration of active drug. An example of this is phenytoin.

The implications of protein binding are not fully understood. The extent of protein binding does not consistently predict tissue distribution or half-life of highly bound drugs. In other words, because an agent has a high fraction bound to protein does not mean it achieves poor tissue penetration.

Protein binding must be considered in the interpretation of plasma drug concentration data. A considerable amount of intra- and interpatient variability exists in the plasma concentration of binding proteins (albumin and alpha-1-acid glycoprotein) as well as their affinity for a specific drug. A major contributor to this variability is the presence of a disease or altered physiologic state, which can affect the plasma concentration or affinity of the binding protein. For example, albumin concentrations are decreased with

TABLE 8-2. Plasma Protein Plasma Concentrations

Protein	Normal Concentration	Type of Drugs Bound	Example
Albumin	3.5–4.5 g/L	Anionic, cationic	Phenytoin
Alpha-1-acid glycoprotein	0.4–1.0 g/L	Cationic	Lidocaine
Lipoproteins	Variable	Lipophilic	Cyclosporine

Source: Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 3rd ed. Norwalk, CT: Appleton & Lange; 1993. p. 93.

hepatic failure, renal dysfunction, burns, stress/trauma, and in pregnancy. Alpha-1-acid glycoprotein concentrations are increased with myocardial infarction, renal failure, arthritis, surgery, or stress/trauma. In addition, concomitant administration of a displacer drug (i.e., an agent that competes with the drug of interest for common protein binding sites) can alter the protein binding of a drug. Examples of displacer drugs include salicylic acid and valproic acid.

Changes in plasma protein binding of drugs can have considerable influence on therapeutic or toxic effects that result from a drug regimen. Provided below are practical considerations regarding plasma protein binding, with examples of specific agents for which these considerations are important to therapeutics.

The following questions should be considered when assessing the clinical importance of protein binding for a given drug:

- Does the drug possess a narrow therapeutic index?
- Is a high fraction of the drug bound to plasma protein?
- Which plasma protein is primarily responsible for binding, and does it account for the majority of the drug's binding variability?

Answers to these questions will help you establish a basis on which to evaluate the clinical significance of changes in plasma protein binding due to drug–drug or drug–disease state interactions.

In addition to having an impact on the interpretation of a drug's steady-state plasma concentration data, changes in plasma and tissue protein binding can have a major influence on clearance and volume of distribution. The remainder of this lesson discusses the effect that changes in a drug's protein binding will have on the apparent volume of distribution of a drug. The ramifications of altered protein binding on drug clearance are discussed in Lesson 9.

The consequence of protein binding changes on volume of drug distribution was implied in this equation shown earlier in this lesson:

$$V = V_p + V_t(F_p/F_t)$$

where:

V = volume of distribution,
V_p = plasma volume,
V_t = tissue volume,
F_p = fraction of unbound drug in the plasma, and
F_t = fraction of unbound drug in the tissue.

How can a drug's volume of distribution be altered by the administration of other drugs, diseases, or an altered physiologic state? The unbound fraction in the plasma and tissue is dependent on both the quantity (concentration) and quality (affinity) of the binding proteins; therefore, changes in these parameters can alter the volume of distribution. Four examples are briefly discussed to demonstrate the potential consequences of altered protein binding on a drug's volume of distribution.

EXAMPLE 1.

Plasma Protein Binding Drug Interaction: Effect of Valproic Acid Administration on Volume of Distribution of Phenytoin

Assuming that V_p and V_t are unchanged as a consequence of valproic acid administration, let's consider the effect of valproic acid on the protein binding of phenytoin. Both phenytoin and valproic acid are highly protein bound (approximately 90%) to the same site on the plasma albumin molecule. When these drugs are administered concomitantly, the protein binding of phenytoin is reduced (e.g., from 90% to 80%). This is an example of displacement, or reduction in the protein binding of a drug due to competition from another drug (i.e., the displacer). In this case, valproic acid has a higher affinity for the plasma protein binding site on the albumin molecule and competitively displaces phenytoin, resulting in a higher fraction of unbound phenytoin.

What is the consequence of phenytoin having a higher unbound fraction due to plasma protein binding displacement by valproic acid? The equation above would predict that an increase in the unbound fraction in the plasma would result in an increase in pheny-

toin's volume of distribution and result in a lower plasma drug concentration:

$$V_p(\leftrightarrow)+V_t(\leftrightarrow)\frac{F_p(\uparrow)}{F_t(\leftrightarrow)}=V(\uparrow)$$

EXAMPLE 2.

Tissue Binding Drug Interaction: Effect of Quinidine Administration on Volume of Distribution of Digoxin

As in Example 1, we will assume that V_p and V_t are unchanged as a result of quinidine administration. Digoxin is negligibly bound to plasma proteins (approximately 25%), whereas 70–90% of quinidine is bound to plasma albumin and alpha-1-acid glycoprotein. Digoxin normally has a very large apparent volume of distribution (4–9 L/kg), which suggests extensive tissue distribution. Digoxin is significantly associated with cardiac muscle tissue, as demonstrated by a 70:1 cardiac muscle to plasma digoxin concentration ratio, which explains why its volume of distribution exceeds any normal physiologic space.

When these drugs are administered concomitantly, the tissue binding of digoxin is reduced. This is also an example of displacement but, in this case, quinidine has a higher affinity for the tissue protein binding site and displaces digoxin, resulting in a high unbound fraction in the tissue. What are the consequences of digoxin having a higher unbound fraction in the tissue due to quinidine displacement? The equation given previously predicts that an increase in the unbound fraction in the tissue would result in a decrease in the volume of distribution of digoxin, thus increasing digoxin's plasma drug concentration:

$$V_p(\leftrightarrow)+V_t(\leftrightarrow)\frac{F_p(\leftrightarrow)}{F_t(\uparrow)}=V(\downarrow)$$

Drug–drug interactions are not the only way a drug's apparent volume of distribution can be altered. In Example 3, we next consider the effect of a disease state (chronic renal failure) on the volume of distribution of phenytoin and digoxin.

EXAMPLE 3.

Effect of Disease State on Volume of Distribution: Renal Failure and Volume of Distribution of Phenytoin

Assuming that V_p and V_t are unchanged as a consequence of renal failure, let's consider the consequences of this disease state on the protein binding of phenytoin. Phenytoin's plasma protein binding is dependent on both the quantity and quality of albumin. Because chronic renal failure reduces albumin concentrations as well as albumin's affinity for phenytoin, it is not surprising that the plasma protein binding of phenytoin could be reduced from approximately 90% to 80%. What is the consequence of phenytoin's higher unbound fraction (0.2 [renal failure] versus 0.1 [normal]) due to renal failure?

The equation below predicts that an increase in the unbound fraction in the plasma would result in an increase in the volume of distribution of phenytoin, which would increase the concentration of the active unbound phenytoin able to cross the blood–brain barrier. This increase could result in supratherapeutic unbound concentrations, even when the total concentration is within normal limits:

$$V_p(\leftrightarrow)+V_t(\leftrightarrow)\frac{F_p(\uparrow)}{F_t(\leftrightarrow)}=V(\uparrow)$$

EXAMPLE 4.

Effect of Disease State on Volume of Distribution: Renal Failure and Volume of Distribution of Digoxin

As in Example 3, we will assume that V_p and V_t are unchanged as a consequence of renal failure. Because digoxin is negligibly bound to plasma proteins, changes in its concentration should not be of clinical significance. However, renal failure does reduce the cardiac muscle-to-plasma digoxin concentration ratio to 30:1. What is the consequence of digoxin's higher unbound fraction in the tissue due to renal failure? The equation below predicts that an increase in the unbound fraction in the tissue would result in a decrease in the volume of distribution of digoxin and may cause an increased plasma digoxin drug concentration:

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{F_p(\leftrightarrow)}{F_t(\uparrow)} = V(\downarrow)$$

In all of these examples, the volume of distribution of the drug in question was altered as a consequence of a drug–drug or drug–disease state interaction. Consequently, the calculation of their loading dose ($X_0 = C_0V$) is influenced by changes in a drug's plasma or tissue protein binding. This must be considered in the development of a patient's drug dosing regimen.

REVIEW QUESTIONS

8-1. Drugs that are very lipid soluble tend to distribute poorly into body tissues.

A. True
B. False

8-2. Drugs that are predominantly un-ionized at physiologic pH (7.4) have a limited distribution when compared to drugs that are primarily ionized.

A. True
B. False

8-3. Drugs are generally less well distributed to highly perfused tissues (compared with poorly perfused tissues).

A. True
B. False

8-4. Estimate the volume of distribution for a drug when the volume of plasma and tissue are 5 and 20 L, respectively, and the fraction of drug unbound in plasma and tissue are both 0.7.

A. 18.5 L
B. 100 L
C. 30 L
D. 25 L

8-5. The portion of drug that is bound to plasma protein is pharmacologically active.

A. True
B. False

8-6. Penetration of drug into tissues is not related to the extent bound to plasma proteins.

A. True
B. False

8-7. Cationic drugs and weak bases are more likely to bind to:

A. globulin.
B. alpha-1-acid glycoprotein.
C. lipoprotein.
D. A and C.

8-8. Anionic drugs and weak acids are more likely to bind to:

A. albumin.
B. globulin.
C. alpha-1-acid glycoprotein.
D. lipoprotein.

8-9. Predict how the volume of distribution (V) would change if the unbound fraction of phenytoin in plasma decreased from 90% to 85%. Assume that unbound fraction in tissues (F_t) and volumes of plasma (V_p) and tissues (V_t) are unchanged.

A. increase
B. no change
C. decrease
D. cannot be predicted with the information provided

8-10. A new drug has a tissue volume (V_t) of 15 L, an unbound fraction in plasma (F_p) of 5%, and an unbound fraction in tissues (F_t) of 5%. What will be the resulting volume of distribution if the plasma volume (V_p) is reduced from 5 to 4 L?

A. 13 L
B. 19 L
C. 18 L
D. 5 L

8-11. How is the volume of distribution (V) of digoxin likely to change if a patient has been taking both digoxin and quinidine and the quinidine is discontinued? Assume that plasma volume (V_p), tissue volume (V_t), and unbound fraction of drug in plasma (F_p) are unchanged.

A. increase
B. no change
C. decrease
D. cannot be predicted with the information provided

ANSWERS

8-1. A. *Incorrect answer*
B. CORRECT ANSWER

8-2. A. *Incorrect answer*
B. CORRECT ANSWER

8-3. A. *Incorrect answer*
B. CORRECT ANSWER

8-4. A, B, C. *Incorrect answers*
D. CORRECT ANSWER.

$$V = V_p + V_t\left(\frac{F_p}{F_t}\right)$$

$$= 5\text{ L} + 20\text{ L}\left(\frac{0.7}{0.7}\right) = 25\text{ L}$$

8-5. A. *Incorrect answer*
B. CORRECT ANSWER

8-6. A. *Incorrect answer*
B. CORRECT ANSWER

8-7. A, C, D. *Incorrect answers*
B. CORRECT ANSWER

8-8. A. CORRECT ANSWER
B, C, D. *Incorrect answers*

8-9. A, B, D. *Incorrect answers*
C. CORRECT ANSWER. If fraction bound decreases, then V will also decrease:

$$V = V_p + V_t\left(\frac{F_p}{F_t}\right)$$

If F_p is decreased,

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{F_p(\downarrow)}{F_t(\leftrightarrow)} = V(\downarrow)$$

8-10. A, C, D. *Incorrect answers*
B. CORRECT ANSWER. Solve the equation using V_p = 5 L, then re-solve using 4 L and compare:

$$V = V_p + V_t\left(\frac{F_p}{F_t}\right)$$

$$= 5\text{ L} + 15\text{ L}\left(\frac{0.05}{0.05}\right) = 20\text{ L}$$

If V_p is decreased to 4 L,

$$V = 4\text{ L} + 15\text{ L}\left(\frac{0.05}{0.05}\right) = 19\text{ L}$$

8-11. A. CORRECT ANSWER. Remember, when quinidine is administered concomitantly with digoxin, quinidine competes with digoxin for tissue binding sites and increases the unbound fraction of digoxin in the tissues (F_t). Therefore, assuming V_p and V_t remain unchanged, the effect of quinidine is shown below:

$$V_p(\leftrightarrow)+V_t(\leftrightarrow)\frac{F_p(\leftrightarrow)}{F_t(\uparrow)}=V(\downarrow)$$

When quinidine is discontinued, the unbound fraction of digoxin in the tissues (F_t) decreases as the tissue binding sites formerly occupied by quinidine become available.

$$V_p(\leftrightarrow)+V_t(\leftrightarrow)\frac{F_p(\leftrightarrow)}{F_t(\downarrow)}=V(\uparrow)$$

Therefore, the volume of distribution will increase.

B, C, D. *Incorrect answers*

Discussion Points

D-1. Describe how knowledge of a drug's distribution and lipid solubility affect the calculation of a drug's loading dose. Clinically, what type of loading dose adjustments can be made to account for these factors?

D-2. A patient has a total plasma phenytoin concentration of 19 mcg/mL with a serum albumin concentration of only 2.5 g/dL. Estimate this patient's bound and unbound phenytoin concentration.

D-3. In the same patient as described in discussion point D-2, calculate a new total phenytoin concentration that would yield a therapeutic unbound phenytoin concentration.

D-4. Draw representative concentration versus time curves for: (*a*) a drug that diffuses into highly vascularized tissue before equilibrating in all body compartments, and (*b*) a drug that distributes equally well into all body compartments. Describe how these curves differ and discuss potential clinical implications.

D-5. Discuss major physiologic and physiochemical factors that affect a drug's distribution and comment on how these factors can affect the pharmacokinetic variable *apparent volume of distribution*.

LESSON 9

Drug Elimination Processes

OBJECTIVES

After completing Lesson 9, you should be able to:

1. Describe the impact of disease and altered physiologic states on the clearance and dosing of drugs.
2. Identify the various routes of drug metabolism and excretion.
3. Explain the two general types (Phase I and II) of drug metabolism.
4. Define the methods of hepatic drug metabolism and the approaches used to quantitate and characterize this metabolism.
5. Describe the effects of a drug's hepatic extraction ratio on that drug's removal via the liver's first-pass metabolism.
6. Explain the various processes involved in renal elimination (i.e., filtration, secretion, and reabsorption).
7. Define both the physiologic and mathematical relationship of drug clearance to glomerular filtration.

Drug Elimination

The liver and kidneys are the two major organs responsible for eliminating drugs from the body. Although both organs share metabolic and excretory functions, the liver is principally responsible for metabolism and the kidneys for elimination. The importance of these organs cannot be overestimated in determining the magnitude and frequency of drug dosing. Additionally, an appreciation of the anatomy and physiology of these organs will provide insight into the impact of disease and altered physiologic states, as well as concomitant drug administration, on the clearance and dosing of drugs.

The physical and chemical properties of a drug are important in determining drug disposition. For example, *lipophilic drugs* (compared with hydrophilic drugs) tend to be:

- bound to a greater extent to plasma proteins,
- distributed to a greater extent throughout the body, and
- metabolized to a greater extent in the liver.

Hydrophilic drugs, particularly ionized species, tend to have more limited distribution and more rapid elimination (often by renal excretion).

Drug elimination from the body can be very complex. *Metabolism* (also known as *biotransformation*) involves conversion of the administered drug into another substance. Metabolism can result in the formation of either an active or inactive metabolite, which may then be excreted either faster or slower than the parent compound. The various consequences of hepatic biotransformation include active drug to inactive metabolite, active drug to active metabolite, and inactive drug to active metabolite.

Two examples of drugs with active metabolites are carbamazepine and its active metabolite carbamazepine-10, 11-epoxide and prednisone and its active metabolite prednisolone. For both drugs, the metabolites formed are active and may contribute significantly to the patient's pharmacologic response. Consequently, the plasma concentration of an active metabolite must be considered in addition to that of the parent compound when predicting overall pharmacologic response. In addition, many drugs are actually *pro-drugs*, which require activation to their active forms. An example of a pro-drug is sulfasalazine, which is a pro-drug that is cleaved by colonic bacterial reductases to the antibacterial agent sulfapyridine and the anti-inflammatory agent 5-aminosalicylic acid.

Let's next explore two introductory concepts with regard to metabolite pharmacokinetics. Consider the following situation:

$$\text{drug X} \xrightarrow[K_m]{\text{liver}} \text{metabolite Y} \xrightarrow[K_r]{\text{kidney}} \text{excreted Y}$$

where drug X represents the intravenous bolus administration of the compound and K_m and K_r represent the elimination rate constants for hepatic metabolism of drug X and renal excretion of metabolite Y, respectively.

Figure 9-1 shows the decline in plasma concentration of parent drug X (assuming a one-compartment model after intravenous administration). Now consider the profile of metabolite Y after the same dose of drug X (**Figure 9-2**). If the excretion rate constant of metabolite Y (K_r) is much greater than the elimination rate constant of drug X (K_m), the terminal slope of the natural log of concentration of metabolite Y versus time plot will

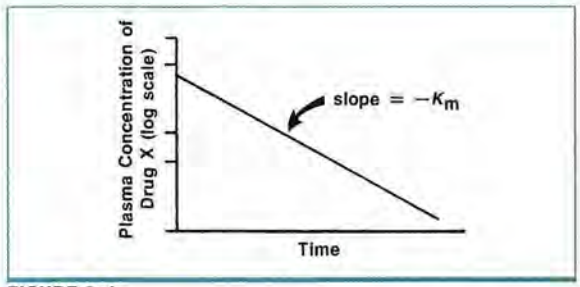

FIGURE 9-1.
Plasma concentration versus time curve for drug X, primarily metabolized by the liver.

be K_m and not K_r. This result occurs because the plasma concentration of metabolite Y is determined by the rate of formation from drug X (the slower rate constant).

On the other hand, if K_r is much less than K_m, the terminal slope of the plasma metabolite Y concentration versus time plot will be K_r (**Figure 9-3**). In this case, the relatively slow renal elimination of metabolite Y determines the resulting plasma concentrations. Although the liver is the major organ of drug biotransformation, the intestines, kidneys, and lungs may also metabolize some drugs. Before we can develop the concepts of drug metabolism, we must first examine the anatomy, physiology, and fundamental functions of the liver. The adult liver weighs 1400–1600 g and is uniquely situated between the gastrointestinal (GI) tract and the systemic circulation (**Figure 9-4**).

The basic functional unit of the liver is the liver lobule (**Figure 9-5**). The human liver contains approximately 50,000–100,000 such lobules. The liver lobule is constructed around a central vein,

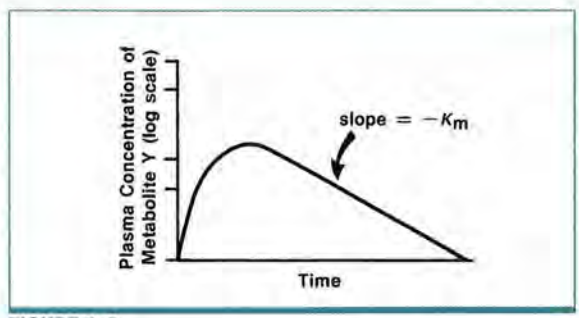

FIGURE 9-2.
Plasma concentrations of metabolite Y (from drug X) when the elimination rate constant (K_r) of metabolite Y is greater than the rate constant for metabolism (K_m) of drug X.

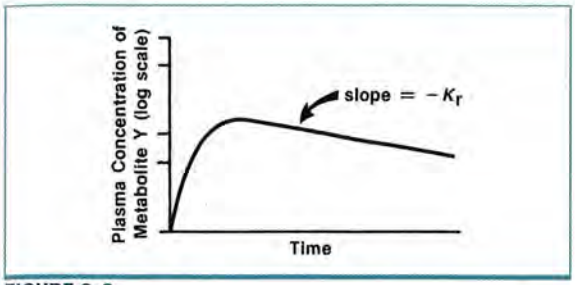

FIGURE 9-3.
Plasma concentrations of metabolite Y (from drug X) when the elimination rate constant (K_r) of metabolite Y is less than the rate constant for metabolism (K_m) of drug X.

which empties into the hepatic veins and the vena cava. Therefore, the hepatic cells (hepatocytes), which are principally responsible for metabolic functions (including drug metabolism), are exposed to portal blood.

The liver (ultimately the liver lobule) receives its blood supply from two separate sources: the portal vein and the hepatic artery. The liver receives approximately 1100 mL/minute of blood from the portal vein and 350 mL/minute of blood from the hepatic artery. Consequently, blood flow in a normal 70-kg adult is approximately 1450 mL/minute.

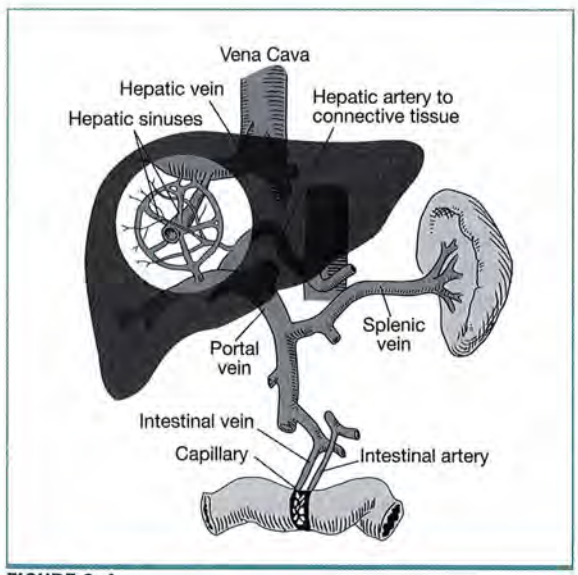

FIGURE 9-4.
Portal and hepatic circulations.

Source: Reproduced with permission from Guyton AC. *Textbook of Medical Physiology.* 7th ed. Philadelphia, PA: WB Saunders; 1986.

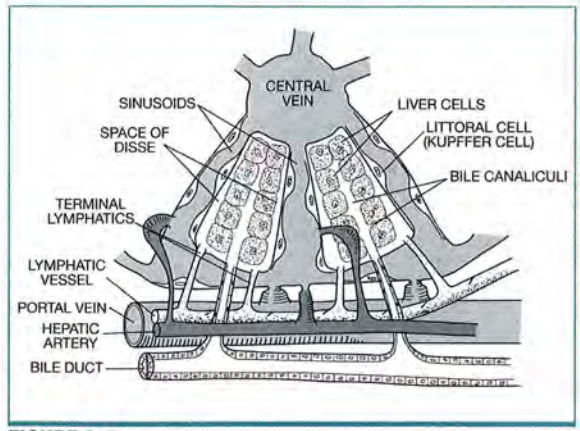

FIGURE 9-5.
Basic structure of a liver lobule showing the hepatic cellular plates, blood vessels, bile-collecting system, and lymph flow system composed of the spaces of Disse and interlobular lymphatics.

Source: Reproduced with permission from Guyton AC. *Textbook of Medical Physiology.* 7th ed. Philadelphia, PA: WB Saunders; 1986.

After entering the liver, blood flows in the veins and arteries of the portal triads, enters the sinusoidal spaces of the liver, and exits via the central hepatic vein. In the sinusoids, the drug is transferred from the blood to the hepatocytes, where it is metabolized or excreted unchanged into the biliary system (**Figure 9-6**).

The liver is involved in numerous functions, including storage and filtration of blood, secretion and excretion processes, and metabolism. In clinical pharmacokinetics, we are primarily interested in the last role, drug metabolism, and the factors that influence it. It is generally recognized that wide interpatient and intrapatient variability exists in the biotransformation of most drugs. It is also accepted that changes in liver function may greatly alter the extent of drug elimination from the body. To appreciate the importance of these functions and patient factors in the metabolism of a specific drug, it is necessary to understand the mechanisms involved in hepatic drug metabolism and the relative ability of the liver to extract that particular drug from the blood into the hepatocyte.

Hepatic metabolism occurs in two phases called *biotransformation* and *conjugation*. During Phase I, biotransformation, drugs undergo oxidation, reduction, or hydrolysis to become more hydro-

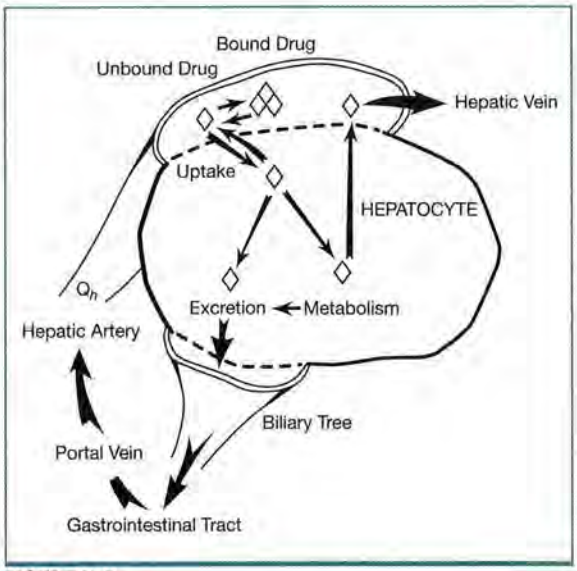

FIGURE 9-6.
Representation of drug metabolism and excretion by the hepatocyte. Q_h = hepatic blood flow.

philic. During Phase II, conjugation, drugs receive a molecular attachment (i.e., glucuronate) that facilitates transport within the body. Drugs may be subjected to either type of reaction, but commonly drugs undergo Phase I (i.e., preparatory) reactions followed by Phase II reactions. The majority of drug–drug or drug–nutrient interactions occurs during Phase I (biotransformation) and involves either the inhibition or induction of the CYP isoenzyme involved in the drug's metabolism.

The major hepatic enzyme system responsible for Phase I metabolism is called the *cytochrome P450 enzyme* system, which contains many isoenzyme subclasses with varying activity and specificity in Phase I drug metabolism processes. Cytochrome P450 isoenzymes are grouped into families according to their genetic similarities. Enzymes with greater than 40% of their genes in common are considered to be from the same family and are designated by an Arabic number (e.g., 1, 2, 3), and those enzymes within each family that contain greater than 55% common genes are given a subfamily designation using a capital letter (e.g., A, B, C). Finally, those enzymes with greater than 97% common genes are further classified with another Arabic number and often represent a very specific drug-metabolizing enzyme. The cytochrome P450 enzymes most important in human drug metabolism are CYP1, CYP2, and CYP3. In addition to the action on specific drug substrates, these isoenzymes can also be either induced or inhibited by other drugs, thus increasing or decreasing the plasma concentration of the drug they metabolize. This can have clinical significance for drugs whose concentration-dependent effects are significantly affected by enzyme inhibition or induction. **Table 9-1** lists common drug-metabolizing isoenzymes and the drugs most commonly affected, as well as other drugs that can either inhibit or induce the drug's metabolism by this enzyme.

Another point regarding Phase I biotransformation reactions is that select drugs may be metabolized by more than one cytochrome P450 isoenzyme. An example is tricyclic antidepressants. Most of these agents are hydroxylated by CYP2D6; however, *N*-demethylation is probably mediated by a combination of CYP2C19, CYP1A2, and CYP3A4. Acetaminophen, another example, appears to be metabolized by both CYP1A2 and CYP2E1.

Phase II reactions, also called *synthetic* (or *conjugation*) *reactions*, result in very polar compounds that are easily excreted in the urine. Examples of drugs that undergo Phase I or Phase II reactions are shown in **Table 9-2**.

Understanding whether a drug undergoes Phase I or Phase II biotransformation may be helpful in predicting how it will be affected by a certain disease state. For example, liver disease and the aging process appear to reduce the elimination of drugs that undergo Phase I metabolism more than those dependent on conjugation (Phase II) reactions. This fact raises a significant question: at what point does liver disease significantly alter Phase I metabolic processes? No single test can accurately estimate liver drug-metabolism capacity. High values for alkaline phosphatase, aspartate aminotransferase (AST), and alanin aminotransferase (ALT) usually indicate acute cellular damage and not poor liver drug-metabolism capacity. On the other hand, abnormal values that may suggest this are elevated serum bilirubin concentrations, low serum albumin concentrations, and a prolonged prothrombin time. The *Child-Pugh Score*, a widely utilized clinical assessment tool for liver disease, may also be used to evaluate a patient's

TABLE 9-1. Drug-Metabolizing Enzymes and Selected Inhibitors and Inducers

Isozyme	Drug	Inhibitors	Inducers
CYP1A2	Caffeine, tacrine, theophylline, lidocaine, R-warfarin	Cimetidine, ciprofloxacin, erythromycin, fluvoxamine, tacrine, zafirlukast	Omeprazole, tobacco, carbamazepine, nafcillin, broccoli
CYP2B6	Cocaine, ifosfamide, cyclophosphamide	Chloramphenicol	Phenobarbital, rifampin
CYP2C9	S-warfarin, phenytoin, diclofenac, piroxicam	Amiodarone, fluconazole, lovastatin, clopidogrel, leflunomide	Rifampin, phenobarbital, secobarbital
CYP2C19	Diazepam, omeprazole, mephenytoin	Fluvoxamine, fluoxetine, omeprazole, oxcarbazepine	Carbamazepine, prednisone, rifampin, phenobarbital
CYP2D6	Codeine, haloperidol, dextromethorphan, tricyclic antidepressants, phenothiazines, metoprolol, propranolol, risperidone, paroxetine, sertraline, venlafaxine	Bupropion, cinacalcet, quinidine, fluoxetine, sertraline, amiodarone, propoxyphene	Rifampin, dexamethasone
CYP2E1	Acetaminophen, alcohol	Disulfiram	Isoniazid, alcohol
CYP3A3/4/5/7	Nifedipine, verapamil, cyclosporine, carbamazepine, astemizole, tacrolimus, midazolam, alfentanil, diazepam, loratadine, ifosfamide, cyclophosphamide	Erythromycin, cimetidine, clarithromycin, fluvoxamine, fluoxetine, ketoconazole, itraconazole, isoniazid, grapefruit juice, metronidazole, ritonavir, indinavir	Carbamazepine, rifampin, phenytoin, phenobarbital, St. John's wort

ability to metabolize drugs eliminated by the liver. A score of 8 to 9 indicates the need to initiate therapy at moderately decreased initial doses (~25%) for drugs primarily (≥ 60%) metabolized hepatically, while a score of ≥ 10 suggests a significant decrease (~50%) in initial doses of drugs primarily metabolized by the liver.

Membrane transport proteins are membrane-spanning substances that facilitate drug transport across the intestinal tract, excretion into the bile and urine, distribution across the blood–brain barrier and drug uptake into target cells. A major transport protein is P-glycoprotein. Commonly utilized agents that are affected by this protein include clopidogrel, digoxin, diltiazem, glyburide, and morphine. Increased or decreased expression of this substance can alter absorption, elimination, and serum concentrations of relevant drugs. Other membrane-transporter families include organic anion transporters (OAT family), the organic anion transporting polypeptides (OATP family), and the organic cation transporters (OCT family).

Biotransformation

Biotransformation processes are affected by many factors. The functioning of metabolic enzyme systems may be quite different at the extremes of age. Historically, neonates were at risk of toxicity from chloramphenicol because they do not conjugate this drug efficiently. Also, the social habits of a patient may affect drug elimination. Alcohol use and smoking may increase hepatic clearance of some drugs by inducing metabolic enzymes. Obviously, disease states such as cirrhosis and conditions that decrease liver blood flow (e.g., heart failure) significantly affect drug metabolism. Finally, concomitant drug use may affect drug metabolism. Certain drugs, such as phenytoin and phenobarbital, may induce hepatic enzymes, whereas other drugs, such as cimetidine and valproic acid, may inhibit them.

Even in healthy individuals, in the absence of hepatic enzyme inducers or inhibitors, the ability to metabolize drugs may vary considerably due to individual genetic makeup. Genetic *polymorphism*

TABLE 9-2. Drugs Undergoing Phase I or II Metabolizing Reactions

Phase I Reactions	Examples
Oxidation:	
Hydroxylation	Cyclosporine, ibuprofen, phenytoin, acetaminophen (also Phase II)
Dealkylation	Diazepam, imipramine, tamoxifen
Deamination	Amphetamine, diazepam
Sulfoxidation	Chlorpromazine, cimetidine, omeprazole
Reduction	Sulfasalazine, chloramphenicol
Hydrolysis	Aspirin, carbamazepine, enalapril
Phase II Reactions	**Examples**
Glucuronidation	Acetaminophen (also Phase I), lorazepam, morphine, chloramphenicol
Methylation	Captopril, levodopa, methyldopa
Acetylation	Clonazepam, corticosteroids, dapsone, isoniazid, sulfonamides

can affect the individual response to a drug. For example, approximately one-third of Caucasians carry at least one variant allele for the gene that encodes CYP2C9 involved in the metabolism of warfarin. Presence of this polymorphism increases the anticoagulant effect of warfarin, thus requiring lower warfarin doses. Investigators have also shown that two distinct subpopulations have varying capacities for drug acetylation (Phase II reaction) as a result of genetic polymorphism. *Fast acetylators* have a greater rate of elimination for drugs such as isoniazid and hydralazine. For *slow acetylators*, the usual doses of these agents may result in excessive plasma concentrations and, therefore, increased drug toxicities. Further discussions regarding genetic alteration of drug metabolism can be found in Lesson 11.

Hepatic Clearance

Now let's focus on hepatic drug metabolism and the approaches used to quantitate and characterize this process. Depending on physical and chemical properties, each drug is taken up or extracted by the liver to different degrees. Knowledge of the affinity of a drug for extraction by the liver is important in anticipating the influence of various factors on drug metabolism. Generally, drugs are characterized as possessing a low to high affinity for extraction by the liver. Briefly, drugs with a low hepatic extraction (< 20%) tend to be more available to the systemic circulation and have a low systemic clearance. Drugs with a high hepatic extraction (> 80%) tend to be less available to the systemic circulation and have a high systemic clearance. Drugs with extraction ratios between 20 and 80 are termed *intermediate-extraction drugs*. These points will become more apparent as we develop a mathematical model to relate a drug's hepatic clearance to hepatic physiology.

The efficiency of the liver in removing drug from the bloodstream is referred to as the *extraction ratio* (E), the fraction of drug removed during one pass through the liver. The value of E theoretically ranges from 0 to 1. With high-extraction drugs, E is closer to 1, and with low-extraction drugs, E is closer to zero. The reader may wish to refer to the discussion of E in Lesson 2.

In Lesson 1, we learned that the concentration of drug in the body was dependent on the dose of the drug administered and the volume into which the agent was distributed. This was represented by the equation:

$$C = \frac{X}{V}$$

(See **Equation 1-1.**)

In Lesson 2, we further discovered that steady-state plasma drug concentrations are affected by several variables, including the rate at which a drug is administered and the drug's clearance. This relationship is demonstrated in the following equation:

$$C_{ss} = \frac{K_0}{Cl_t}$$

where:

Cl_t = the total body clearance of the drug,

K_0 = the drug infusion rate, and

C_{ss} = the steady-state plasma drug concentration.

The factors that determine the extraction ratio and its relationship to overall hepatic clearance can be shown mathematically as:

$$E = \frac{Cl_i}{Q_h + Cl_i}$$

(See **Equation 2-2.**)

where:

Cl_i = intrinsic clearance and

Q_h = hepatic blood flow.

Because $Cl_h = Q_h \times E$, then:

$$Cl_h = \frac{Q_h \times Cl_i}{Q_h + Cl_i}$$

The systemic clearance of a drug relates dosing rate to a steady-state plasma drug concentration. The systemic clearance of a drug equals the hepatic clearance when the liver is the sole organ responsible for elimination. Another way of looking at this relationship is to remember that clearance terms are additive. Therefore:

$$Cl_t = Cl_h + Cl_r + Cl_{\text{other organs}}$$ (See **Equation 2-1.**)

and Cl_t is equal to Cl_h when Cl_r and $Cl_{\text{other organs}}$ are minimal.

For a drug that is totally dependent on the liver for its elimination, a number of useful mathematical models show critical relationships between systemic drug clearance and various physiologic functions. These models consider three factors:

1. the liver's innate ability to remove unbound drug from plasma irreversibly,
2. the fraction of drug unbound in the blood, and
3. hepatic blood flow.

One practical and useful model is called the *jar, venous equilibrium*, or *well-stirred model*:

$$Cl_h = \frac{Q_h F_p Cl_i}{Q_h + F_p Cl_i}$$

where:

Cl_h = hepatic drug clearance,

F_p = fraction of free drug in plasma,

Cl_i = intrinsic clearance, and

Q_h = hepatic blood flow.

Recall that Cl_h equals Cl_t for drugs eliminated only by the liver. Therefore, changes in any of the parameters defined in the previous equation will have a considerable impact on Cl_t and, consequently, the steady-state drug plasma concentration produced by a given dosing regimen. In a normal 70-kg individual, Q_h (portal vein plus hepatic artery blood flows) should approach 1500 mL/minute. Obviously, changes in Q_h would change the rate of drug delivery to the liver and have an impact on Cl_h. However, the magnitude of that impact would depend on the liver's ability to extract the drug. F_p is incorporated into the relationship because only free or unbound drug is available to be metabolized by the hepatocytes. Finally, intrinsic clearance (Cl_i) represents the liver's innate ability to clear unbound drug from intracellular water via metabolism or biliary excretion. Changes in Cl_i should have a profound effect on hepatic clearance. However, as with Q_h, the extent and magnitude of such an effect would depend on the extraction characteristics of the drug.

Examination of the equation for the venous equilibrium model at the extremes of intrinsic clearance values provides insight into the influences of hepatic blood flow and intrinsic clearance on drug dosing. For high intrinsic clearance drugs, Cl_i is much greater than Q_h; Q_h becomes insignificant when compared to

Cl_i. Hepatic clearance of drugs with high extraction ratios (> 0.8) is dependent on hepatic blood flow only. It is not influenced by protein binding or enzymes.

Therefore, when Cl_i is large, Cl_h equals Q_h, or hepatic clearance equals hepatic blood flow. Hepatic clearance is essentially a reflection of the delivery rate (Q_h) of the drug to the liver; changes in blood flow will produce similar changes in clearance. Consequently, after intravenous administration, the hepatic clearance of highly extracted compounds (e.g., lidocaine and propranolol) is principally dependent on liver blood flow and independent of both free fraction and intrinsic clearance. This particular commonly used model is best applied to intravenously administered drugs, as orally absorbed drugs with high extraction ratios may act more like low-extraction drugs. Other models may work better in these cases.

For low intrinsic clearance drugs, Q_h is much greater than Cl_i. Therefore, the hepatic clearance of compounds with a low extraction ratio (e.g., phenytoin) is virtually independent of hepatic blood flow. Hepatic clearance for these drugs becomes a reflection of the drug's intrinsic clearance and the free fraction of drug in the plasma.

Some examples of individual intrinsic clearances are given in **Table 9-3**. However, there is no clear-cut division between the classes described; additional factors may need to be considered when predicting drug disposition.

Clinical Correlate

If the liver's ability to metabolize a drug is increased, possibly due to enzyme induction, then the extraction ratio (E) is also increased. However, the magnitude of change in E depends on the initial value of the intrinsic clearance of the drug.

If Cl_i is small (low intrinsic clearance drug), then E is initially small. Increasing Cl_i causes an almost proportional increase in extraction and hepatic clearance. However, if Cl_i and E are already high, a further increase in intrinsic clearance does not greatly affect the extraction ratio or hepatic drug clearance.

TABLE 9-3. High-, Intermediate-, and Low-Extraction Drugs

High Intrinsic Clearance ($Cl_i >> Q_h$)	Intermediate Intrinsic Clearance	Low Intrinsic Clearance ($Cl_i << Q_h$)
Propranolol	Aspirin	Warfarin
Lidocaine	Quinidine	Phenytoin
Propoxyphene	Desipramine	Isoniazid
Morphine		Theophylline
Meperidine		Diazepam
Nitroglycerin		Procainamide
Isoproterenol		Antipyrine
Pentazocine		Phenobarbital
Verapamil		Erythromycin

First-Pass Effect

An important characteristic of drugs having a high extraction ratio (e.g., propranolol) is that, with oral administration, a significant amount of drug is metabolized before reaching the systemic circulation (**Figure 9-7**). Drug removal by the liver after absorption is called the *first-pass effect*. The result can be that the amount of drug reaching the systemic circulation is considerably less than the dose given.

The first-pass effect becomes obvious when we examine comparable intravenous and oral doses of a drug with a high extraction ratio. For propranolol, plasma concentrations achieved after oral doses of 40–80 mg are equivalent to those achieved after intravenous doses of 1–2 mg. The difference in required dosage is not explained by low oral absorption but by liver first-pass metabolism. Anatomically, the liver receives the blood supply from the GI tract via the portal vein before its entrance into the general circulation via the hepatic vein. Therefore, the liver can metabolize or extract a certain portion of the drug before it reaches the systemic circulation. Also, enzymes in the gut wall can metabolize the drug before it reaches the liver.

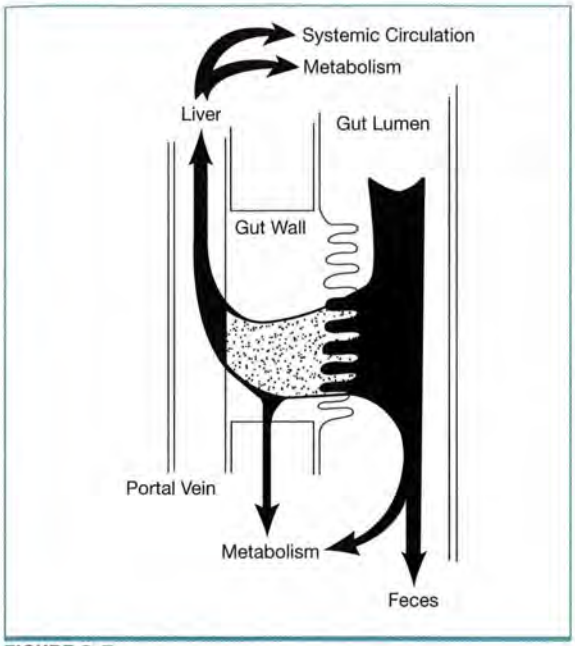

FIGURE 9-7.
Routes of drug disposition with oral drug administration.

Because the blood supply draining the GI tract passes through the liver first, the fraction of an oral dose (F) that reaches the general circulation (assuming the dose is 100% absorbed across the gut wall) is given by:

$$F = 1 - E$$

Remember, E is the extraction ratio that indicates the efficiency of the organ eliminating a drug. For example, if the drug is 100% absorbed across the gut wall and the liver extracts 70% before it reaches the systemic circulation, 30% of the dose finally reaches the bloodstream. Therefore:

$$E = 0.7$$
$$F = 1 - E$$
$$= 0.3$$

Again, F is the fraction of drug reaching the systemic circulation.

Effects of Disease States and Drug Interactions on Hepatically Metabolized Drugs

It is important to appreciate the effect that a potential drug or disease state interaction may have on the pharmacologic response of a drug that is principally eliminated by the liver. Therefore, we will consider the potential impact that changes in Q_h, F_p, and Cl_i will have on the steady-state concentration of both total and free drug concentration. Remember, we will assume that Cl_t (total body clearance) equals Cl_h (hepatic clearance) and that steady-state free drug concentration is the major determinant of pharmacologic response.

When trying to assess clinical implications, always consider the following:

- route of administration (intravenous versus oral),
- extraction ratio (high [> 0.8] versus low [< 0.2]), and
- protein binding (high [> 80%] versus low [< 50%]).

$$Cl_h = \frac{Q_h F_p Cl_i}{Q_h + F_p Cl_i}$$

And

$$C_{ss(total)} = \frac{K_0}{Cl_t} \text{ or } \frac{K_0}{Cl_h}$$

Then, substituting for $C_{ss(total)}$

$$C_{ss(free)} = F_p \times C_{ss(total)} = F_p \times \frac{K_0}{Cl_h}$$

where:

Cl_h = hepatic drug clearance,
F_p = fraction of drug unbound in plasma, and
K_0 = the drug infusion rate.

In the following three examples, we apply the previously described hepatic extraction equation to several cases involving a specific disease state effect on drug interaction.

EXAMPLE 1.

Effect of Addition of Enzyme Inhibitor on Pharmacologic Response of Theophylline

Theophylline (which is metabolized primarily by CYP1A2 of the hepatic cytochrome P450 system) was administered to a patient via a constant intravenous infusion and produced a steady-state total plasma concentration of 15 mg/L (therapeutic range, 5–15 mg/L). Ciprofloxacin, a known inhibitor of the hepatic cytochrome P450 enzyme system, was later added to this patient's drug dosing regimen. Ciprofloxacin reduces the intrinsic clearance of theophylline by 25 to 30%. What impact should ciprofloxacin administration have on this patient's pharmacologic response (assume a 30% reduction in clearance)?

Considerations

- Theophylline (in this example) is administered via a constant intravenous infusion (K_0).
- Theophylline has a low extraction ratio.
- Theophylline possesses low protein binding.

Because theophylline has a low extraction ratio and is not extensively bound to proteins,

$$Cl_h = F_p \times Cl_i$$

and

$$C_{ss(total)} = \frac{K_0}{Cl_h} \text{ or } \frac{K_0}{F_p Cl_i}$$

Then substituting for $C_{ss(total)}$

$$C_{ss(free)} = F_p \times C_{ss(total)} \; F_p \times \frac{K_0}{F_p Cl_i} = \frac{K_0}{Cl_i}$$

Impact on $C_{ss(total)}$

Because K_0 and F_p are unchanged and Cl_i is reduced by 30%, $C_{ss(total)}$ should increase by 30%.

Impact on $C_{ss(free)}$

Because K_0 is unchanged and Cl_i is reduced by 30%, $C_{ss(free)}$ should increase by 30%.

Consequence

You should anticipate significant side effects as a consequence of a higher free steady-state concentration of theophylline (**Figure 9-8**). The dosing rate of theophylline should be reduced by 30% in this example.

EXAMPLE 2.

Effect of Decreased Protein Binding of Phenytoin Due to Renal Failure

Phenytoin (which is metabolized primarily by CYP2C9/10 of the hepatic cytochrome P450 mixed function oxidase system) was administered to a patient by intermittent intravenous administration and produced a steady-state total plasma concentration of 15 mg/L (therapeutic range: 10–20 mg/L). The patient unexpectedly experienced acute renal failure. Renal failure is known to reduce the plasma protein binding of phenytoin from approximately 90% to about 80% but has minimal effect on phenytoin's intrinsic clearance. What impact should renal failure have on this patient's pharmacologic response?

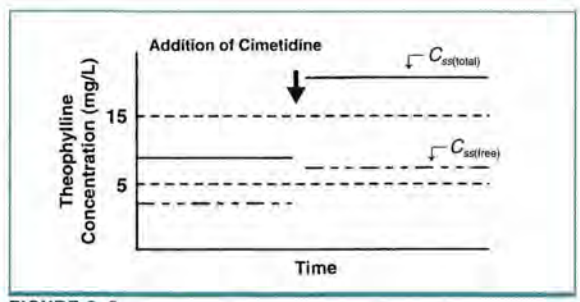

FIGURE 9-8.
Changes in free and total steady-state plasma theophylline concentrations with the addition of cimetidine.

Considerations

- Phenytoin is administered by intermittent intravenous administration.
- Phenytoin has a low extraction ratio.
- Phenytoin possesses high protein binding.
- Because phenytoin has a low extraction ratio and is extensively bound to proteins, $Cl_h = F_p \times Cl_i$

$$C_{ss(total)} = \frac{K_0}{Cl_h} \text{ or } \frac{K_0}{F_p Cl_i}$$

Substituting for $C_{ss(total)}$

$$C_{ss(free)} = F_p \times C_{ss(total)} = F_p \times \frac{K_0}{F_p Cl_i} = \frac{K_0}{Cl_i}$$

Impact on $C_{ss(total)}$

Because K_0 and Cl_i are unchanged and F_p is doubled, $C_{ss(total)}$ should decrease by half.

Impact on $C_{ss(free)}$

Because K_0 and Cl_i are unchanged, $C_{ss(free)}$ should remain unchanged.

Consequence

You should anticipate no significant change in this patient's pharmacologic response (despite a significant drop in phenytoin's steady-state total concentration) because steady-state free drug concentrations remain unchanged (**Figure 9-9**). However, the total concentration necessary to achieve this therapeutic unbound concentration will be less than the normal reference range for phenytoin.

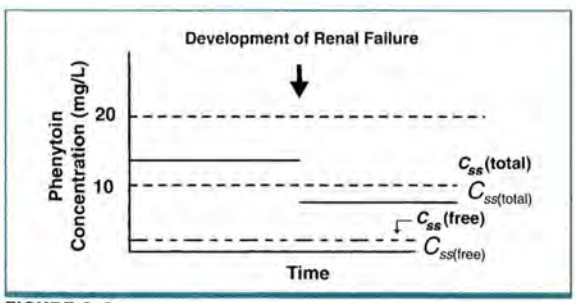

FIGURE 9-9.
Change in total steady-state plasma phenytoin concentration due to renal failure.

EXAMPLE 3.

Effects of Increased Protein Binding of Lidocaine Due to Myocardial Infarction

Lidocaine (which is metabolized primarily by CYP1A2 of the hepatic cytochrome P450 mixed function oxidase system) was administered to a patient for a life-threatening ventricular arrhythmia via a constant intravenous infusion, producing a steady-state total plasma concentration of 4 mg/L (therapeutic range: 2–6 mg/L). The next day, the patient had a myocardial infarction. Myocardial infarctions are known to significantly increase the concentration of alpha-1-acid glycoprotein (a serum globulin) and the protein binding of drugs associated with it. The protein binding of lidocaine is known to be high and primarily dependent on alpha-1-acid glycoprotein. What impact should a myocardial infarction have on this patient's pharmacologic response (assuming that the myocardial infarction had no effect on hepatic blood flow)?

Considerations

- Lidocaine is administered via a constant intravenous infusion.
- Lidocaine has a high extraction ratio.
- Lidocaine possesses high protein binding to alpha-1-acid glycoprotein.

Because lidocaine has a high extraction ratio and binds extensively to alpha-1-acid glycoprotein, $Cl_h = Q_h$.

$$C_{ss(total)} = \frac{K_0}{Cl_h} \text{ or } \frac{K_0}{Q_h}$$

Substituting for $C_{ss(total)}$

$$C_{ss(free)} = F_p \times C_{ss(total)} = F_p \times \frac{K_0}{Q_h}$$

Impact on $C_{ss(total)}$

Because K_0 and Q_h are unchanged, $C_{ss(total)}$ should remain unchanged.

Impact on $C_{ss(free)}$

Because K_0 and Q_h are unchanged and F_p is decreased, $C_{ss(free)}$ should decrease, which could result in a reduced pharmacologic response (**Figure 9-10**).

Consequence

Because only total (bound and unbound) lidocaine concentrations can be measured clinically, you should anticipate a reduced pharmacologic response despite similar steady-state total lidocaine concentrations. This reduced response may necessitate high total lidocaine concentrations and a higher dose to achieve the desired response.

Clinical Correlate

This reduced response is why lidocaine's dose is generally titrated to a clinical response based on electrocardiogram readings (i.e., decrease in arrhythmias) rather than dosed to a therapeutic concentration.

These three examples represent how the well-stirred model and knowledge of the pharmacokinetic characteristics of a drug can be used to predict the effect of changes in hepatic blood flow, protein binding, and intrinsic clearance. These same principles can be used to assess a wide variety of clinically relevant situations.

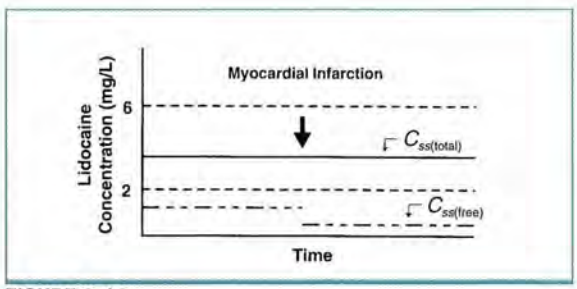

FIGURE 9-10.
Change in free steady-state plasma lidocaine concentrations due to myocardial infarction.

Renal Elimination

As stated previously, *drug elimination* refers to metabolism and excretion (**Figure 9-11**). Some drugs are primarily excreted unchanged; others are extensively metabolized before excretion. The fraction of drug metabolized is different for various agents. The overall elimination rate is the sum of all metabolism and excretion processes and is referred to as *total body elimination*:

total body elimination = drug excreted unchanged + drug metabolized

Excretion is the process that removes a drug from tissues and the circulation. A drug can be excreted through urine, bile, sweat, expired air, breast milk, or seminal fluid. The most important routes of excretion for many drugs and their metabolites are the urine and bile. For anesthetic gases, pulmonary excretion can play a significant role.

Excretion may occur for a biotransformed drug or for a drug that remains unchanged in the body. For example, penicillin G is primarily excreted unchanged in the urine. Elimination of this drug is thus dependent on renal function. Renal excretion is the net effect of three distinct mechanisms within the kidneys:

1. glomerular filtration,
2. tubular secretion, and
3. tubular reabsorption.

With glomerular filtration, blood flows into the capsule of the glomerulus, and there is a passive diffusion of fluids and solutes across the porous glomerular membrane (**Figure 9-12**). In a healthy

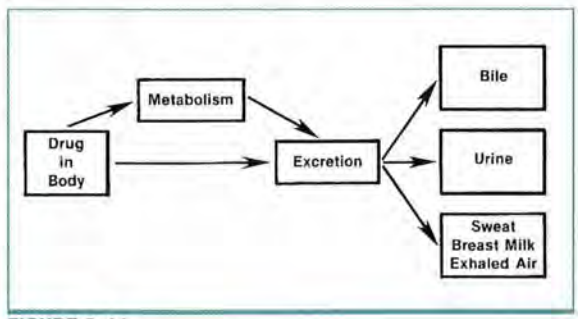

FIGURE 9-11.
Drug elimination.

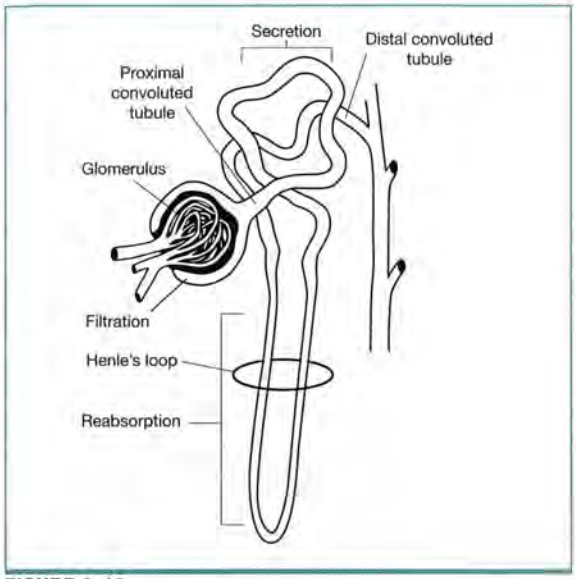

FIGURE 9-12.
Renal nephron.

adult, up to 130 mL of fluid may cross the glomeruli per minute (total of both kidneys). Three factors influence glomerular filtration:

1. molecular size,
2. protein binding, and
3. glomerular integrity and total number of functioning nephrons.

Drugs dissolved in the plasma may be filtered across the glomerulus; drugs that are protein bound or have a molecular weight greater than 60,000 are not filtered. Pathophysiologic changes in the kidneys may also alter glomerular filtration.

Some drugs are actively secreted from the blood into the proximal tubule, which contains urine. These drugs (primarily weak organic acids and some bases) are excreted by carrier-mediated active processes that may be subject to competition from other substances in the body due to broad specificity of the carriers. For example, probenecid and penicillin are both actively secreted. If given together, probenecid competes with penicillin for secretion, so penicillin is secreted less rapidly (it has a longer half-life). This particular relationship can be used in therapeutic situations to extend the duration of penicillin action.

Most drugs also undergo tubular reabsorption back into the blood. This process occurs passively in the distal tubules for drugs that are lipid soluble or not highly ionized. For other agents, it can occur as an active process and (as with tubular secretion) is subject to competition from other agents. An example of reabsorption is glucose, which normally undergoes 100% reabsorption in the distal tubules of the kidneys. With renal dysfunction, glucose often is not reabsorbed and may appear in the urine. Other examples of agents that are actively reabsorbed include endogenous substances such as vitamins, electrolytes, and amino acids.

Tubular reabsorption is dependent on the physical and chemical properties of the drug and the pH of the urine. Drugs that are highly ionized in the urine have less tubular reabsorption; they tend to stay in the urine and are excreted. Drugs must be uncharged to pass easily through biologic membranes. Tubular reabsorption of some compounds may also be dependent on urine flow rate. Urea, for example, has a high tubular reabsorption at low urine flow rates and a low tubular reabsorption at high urine flow rates.

Because renal clearance is determined by filtration, active secretion, and reabsorption, it is fairly complicated. Total renal clearance, Cl_r, can be determined from the following equation:

$$Cl_r = \text{amount excreted in urine}_{(t_1 \to t_2)} / AUC_{(t \to t_2)}$$

where AUC is the area under the plasma concentration curve.

However, because it is not easy to differentiate these processes when measuring the amount of drug in the urine, renal clearance is calculated from the ratio of the urine excretion rate to the drug concentration in plasma:

$$Cl_r = \frac{\text{drug excretion rate}}{\text{drug plasma concentration}}$$

There are several different methods to calculate renal drug clearance. In one method, the excretion rate of the drug is estimated by determining the drug concentration in a volume of urine collected over short time periods after drug administration. This excretion rate is then divided by the plasma

concentration of drug entering the kidneys at the midpoint of the urine collection period. To express this as an equation:

$$Cl_r = \frac{\text{amount of drug in urine from } t_1 \text{ to } t_2/(t_2 - t_1)}{C_{\text{midpoint}}}$$

where t_1 and t_2 are the times of starting and stopping the collection, respectively, and C is the plasma concentration at the midpoint of t_1 and t_2. Therefore, overall renal clearance is calculated usually without differentiating among filtration, secretion, and reabsorption. This method is commonly used to calculate creatinine clearance when the "amount of drug" is the amount of creatinine that appears in the urine over 24 hours, $t_2 - t_1 = 24$ hours, and C_{midpoint} is the serum creatinine determined at the midpoint of the urine collection period.

Relationship Between Renal Clearance and Glomerular Filtration Rate

If a drug is exclusively eliminated renally and the only renal process involved is glomerular filtration, the relationship between total body clearance and glomerular filtration rate (GFR) is as shown in **Figure 9-13**. Creatinine clearance is commonly used as a measure of GFR. Remember that creatinine undergoes some tubular secretion; therefore, GFR can sometimes be slightly overestimated. As GFR increases, clearance of drug increases. When GFR is zero, clearance is zero. Recall that the equation for the line is $Y = mX + b$. Then, the line in Figure 9-13 can be defined as:

$$\text{clearance} = (\text{slope})\ (\text{GFR}) + 0$$

or:

$$\text{clearance} = (\text{slope})\ (\text{GFR})$$

However, if a drug is excreted by glomerular filtration as well as some other route (e.g., biliary excretion), the relationship illustrated in **Figure 9-14** could exist. As GFR increases, the clearance of drug increases; but when GFR is zero, clearance is still greater than zero. In this example, the equation for the line is:

$$\text{clearance} = \text{slope}\ (\text{GFR}) + y\text{-intercept}$$

$$Y = mX + b$$

and we see that when GFR is zero, clearance is the value of the y-intercept, which is nonrenal clearance.

This approach has been used to relate the aminoglycoside elimination rate constant (K) to creatinine clearance. When dosing these agents, we must consider the individual's GFR, as reflected by creatinine clearance. The relationship observed between K and creatinine clearance is shown in **Figure 9-15**.[1] Therefore, K can be predicted for aminoglycosides (such as gentamicin) based on an individual's creatinine clearance.

With the equation for a line, $Y = mX + b$:

$$K = 0.00293\ \text{hr}^{-1} \times \text{creatinine clearance (in mL/minute)} + 0.014$$

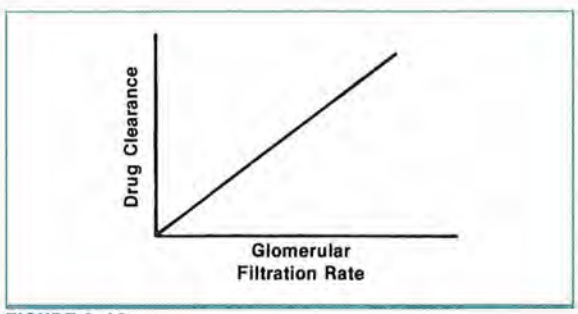

FIGURE 9-13.
Relationship between drug clearance and glomerular filtration rate for a drug that is exclusively eliminated by glomerular filtration.

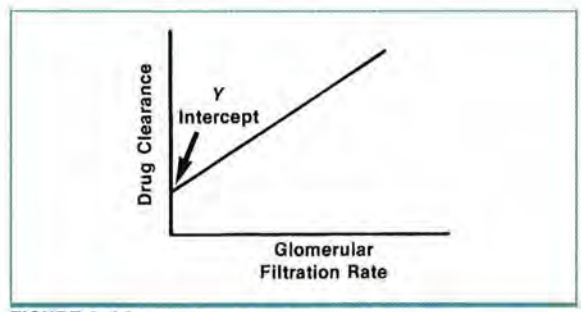

FIGURE 9-14.
Relationship between drug clearance and glomerular filtration rate for a drug that is eliminated by renal and nonrenal processes.

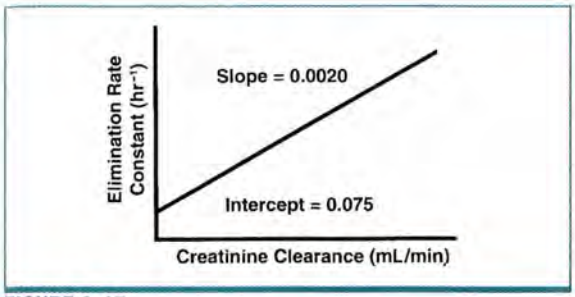

FIGURE 9-15.
Relationship between elimination rate constant and creatinine clearance for aminoglycosides.

Clinical Correlate

Note that drugs that are cleared almost solely by renal mechanisms will have a *y*-intercept of zero or very close to zero. Drugs that have extrarenal routes of elimination will have larger *y*-intercepts.

Determining patient-specific creatinine clearance can be accomplished by either direct measurement of the amount of creatinine contained in a 24-hour urine sample or by estimating this parameter using standard mathematical equations. Direct measurement is the most accurate of these. When using this method, creatinine clearance (CrCl) is determined as follows:

$$\text{CrCl} = \frac{UV}{P \times 1440}$$

where:

- U = urinary creatinine concentration,
- V = volume of urine collected,
- P = plasma creatinine concentration (taken at midpoint of urine collection), and
- 1440 = number of minutes in 24 hours.

Although there are several formulas for estimating creatinine clearance, the Cockcroft–Gault equation is commonly used:

9-1 $$\text{CrCl}_{\text{male}} = \frac{(140 - \text{age})\text{IBW}}{72 \times \text{SCr}}$$

or

$$\text{CrCl}_{\text{female}} = 0.85\frac{(140 - \text{age})\text{IBW}}{72 \times \text{SCr}}$$

where:

- CrCl = creatinine clearance (milliliters per minute),
- age = patient's age (years),
- IBW = ideal body weight (kilograms), and
- SCr = serum creatinine concentration (milligrams per deciliter).

Adjusting this equation for a patient's body surface area is not necessary clinically.

This formula also requires the following patient data:

- ideal body weight (lean body weight) or adjusted body weight (AdjBW),
- age,
- sex, and
- steady-state serum creatinine concentration.

IBW may be estimated as follows:

9-2 $$\text{IBW}_{\text{males}} = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet in height}$$

$$\text{IBW}_{\text{females}} = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet in height}$$

In obese patients, the use of total body weight (TBW) overestimates whereas the use of IBW underestimates creatinine clearance. In patients whose TBW is more than 35% over their IBW, adjusted body weight (AdjBW) should be used to estimate creatinine clearance:

9-3 $$\text{AdjBW} = \text{IBW} + 0.4(\text{TBW} - \text{IBW})$$

For a patient who weighs less than IBW, the actual body weight would be used.

It is important to note that the use of serum creatinine values less than 1 mg/dL will greatly elevate the calculated creatinine clearance value when using **Equation 9-1**. This is especially true in the elderly. In

patients with serum creatinine values of less than 1 mg/dL, it has been recommended to either round the low serum creatinine value up to 1 mg/dL before calculating creatinine clearance, or round the final calculated creatinine clearance value down.

Creatinine clearance, estimated creatinine clearance, and other GFR estimations, such as the modification of diet in renal disease (MDRD) equations, are more fully discussed in Lesson 12.

Reference

1. Matzke GR, Jameson JJ, Halstenson CE. Gentamicin distribution in young and elderly patients with various degrees of renal function. *J Clin Pharmacol* 1987;27:216–20.

REVIEW QUESTIONS

9-1. The body converts a drug to a less active substance by a process called:
- A. phosphorylation.
- B. hydrogenation.
- C. biotransformation.
- D. distransformation.

9-2. Biotransformation is also known as:
- A. hepatic clearance.
- B. elimination.
- C. renal excretion.
- D. metabolism.

9-3. In total, hepatic elimination encompasses both the processes of:
- A. biotransformation and excretion.
- B. oxidation and glucuronidation.
- C. hydroxylation and oxidation.
- D. absorption and demethylation.

9-4. Glucuronidation is a Phase II biotransformation process.
- A. True
- B. False

9-5. Biotransformation may be dependent on factors such as age,
- A. height, and gender.
- B. gender, and weight.
- C. disease, and genetics.
- D. disease, and gender.

9-6. Which of the following is not a Phase I reaction?
- A. oxidation
- B. glucuronidation
- C. reduction
- D. hydrolysis

9-7. The basic functional unit of the liver is the:
- A. renal lobule.
- B. hepatocyte.
- C. liver cell.
- D. liver lobule.

9-8. The liver receives its blood from the:
- A. portal artery and hepatic vein.
- B. portal vein and hepatic artery.
- C. vena cava and aorta.
- D. portal artery and hepatic artery.

9-9. A drug administered orally must go through the liver before it is available to the systemic circulation.
- A. True
- B. False

9-10. Because the extraction ratio can maximally be 1, the maximum value that hepatic clearance can approach is that of:
- A. creatinine clearance.
- B. glomerular filtration.
- C. renal blood filtration.
- D. hepatic blood flow.

9-11. Intrinsic clearance is the maximal ability of the liver to eliminate drug in the absence of any blood flow limitations.
- A. True
- B. False

9-12. Smoking is known to increase the enzymes responsible for theophylline metabolism (a drug with a low hepatic extraction). Would a patient with a history of smoking likely require a higher, lower, or equivalent theophylline total daily dose compared to a nonsmoking patient?
- A. lower
- B. higher
- C. equivalent

9-13. Heart failure reduces cardiac output and hepatic blood flow. Consequently, the total daily dose of lidocaine may need to be decreased in a patient with heart failure who has a myocardial infarction.

A. True
B. False

9-14. Which of the following types of metabolism do drugs with a high extraction ratio undergo to a significant extent?

A. first-pass
B. zero-order
C. intraluminal
D. nonlinear

9-15. Significant first-pass metabolism means that much of the drug's metabolism occurs before its arrival at the:

A. hepatocyte.
B. systemic circulation.
C. portal blood.
D. liver lobule.

9-16. The liver receives blood supply from the GI tract via the:

A. portal vein.
B. hepatic artery.
C. hepatic vein.
D. portal artery.

9-17. For a drug that is totally absorbed without any presystemic metabolism and then undergoes hepatic extraction, which of the following is the correct equation for F?

A. $F = 1 - K_a$
B. $F = 1 - F_p$
C. $F = 1 - E$
D. F = 1 – the fraction of the drug absorbed

9-18. Route of administration, extraction ratio, and protein binding are all factors that should be considered when trying to assess the effect of disease states on plasma concentrations of drugs eliminated by the liver.

A. True
B. False

9-19. Will drugs that inhibit the hepatic cytochrome P450 system likely increase or decrease the plasma clearance of theophylline?

A. increase
B. decrease

9-20. Disease states may increase or decrease drug protein binding.

A. True
B. False

9-21. Drug elimination encompasses both:

A. metabolism and excretion.
B. metabolism and biotransformation.
C. absorption and metabolism.
D. metabolism and distribution.

9-22. Two important routes of drug excretion are:

A. hepatic and tubular secretion.
B. biliary and metabolic.
C. renal and biliary.
D. renal and metabolic.

9-23. Fluid is filtered across the glomerulus through active transport.

A. True
B. False

9-24. Tubular secretion most often occurs with weak organic acids.

A. True
B. False

9-25. Which of the following statements about tubular reabsorption is *false*?

A. Tubular reabsorption depends on the pH of the urine.

B. Highly ionized drugs tend to remain in the urine.

C. Tubular reabsorption can only be an active transport process.

D. A and C.

9-26. Renal clearance can be calculated from the ratio of which of the following rates to the drug's concentration in plasma?

A. tubular reabsorption rate

B. tubular secretion rate

C. glomerular filtration rate

D. excretion rate

9-27. For aminoglycoside doses, which of the following must be calculated to estimate an individual patient's drug elimination rate? An individual patient's:

A. pulmonary clearance.

B. biliary clearance.

C. creatinine clearance.

D. A and C.

9-28. For aminoglycosides, the terminal elimination rate constant can be estimated from the creatinine clearance using which of the following equations?

A. $K = 0.00293\ hr^{-1} \times$ (creatinine clearance in mL/minute) + 1.4

B. $K = 0.00293\ hr^{-1} \times$ (creatinine clearance in mL/minute) + 0.014

C. $K = 2.93\ hr^{-1} \times$ (creatinine clearance in mL/minute)

D. $K = 0.00293\ hr^{-1}$ + (creatinine clearance in mL/minute)

ANSWERS

9-1. A, B, D. *Incorrect answers*

C. CORRECT ANSWER

9-2. A, B, C. *Incorrect answers*

D. CORRECT ANSWER

9-3. A. CORRECT ANSWER

B, C, D. *Incorrect answers*

9-4. A. CORRECT ANSWER

B. *Incorrect answer.* Oxidation, reduction, and hydrolysis are examples of Phase I reactions.

9-5. A, B, D. *Incorrect answers*

C. CORRECT ANSWER

9-6. A, C, D. *Incorrect answers*

B. CORRECT ANSWER

9-7. A, B, C. *Incorrect answers*

D. CORRECT ANSWER

9-8. A, C, D. *Incorrect answers*

B. CORRECT ANSWER

9-9. A. CORRECT ANSWER

B. *Incorrect answer*

9-10. A, B, C. *Incorrect answers*

D. CORRECT ANSWER

9-11. A. CORRECT ANSWER

B. *Incorrect answer*

9-12. A, C. *Incorrect answers*

B. CORRECT ANSWER. Smoking raises the concentrations of enzymes that also metabolize theophylline, so more theophylline would be metabolized, requiring a higher theophylline dose.

9-13. A. CORRECT ANSWER
B. *Incorrect answer*

9-14. A. CORRECT ANSWER
B. *Incorrect answer*. Zero-order processes are not determined by amount of hepatic extraction.
C. *Incorrect answer*. Intraluminal metabolism is independent of hepatic extraction.
D. *Incorrect answer*. Nonlinear metabolism involves only saturation of hepatic enzymes.

9-15. A, C, D. *Incorrect answers*
B. CORRECT ANSWER

9-16. A. CORRECT ANSWER
B, C, D. *Incorrect answers*

9-17. A, B, D. *Incorrect answers*
C. CORRECT ANSWER. F represents the fraction of drug that reaches the systemic circulation; E is the extraction ratio.

9-18. A. CORRECT ANSWER
B. *Incorrect answer*

9-19. A. *Incorrect answer*
B. CORRECT ANSWER. Theophylline is a low-extraction drug and its clearance is roughly equal to intrinsic hepatic clearance (Cl_i), so the effect of cytochrome P450 enzyme induction is likely to decrease intrinsic and overall clearance.

9-20. A. CORRECT ANSWER
B. *Incorrect answer*

9-21. A. CORRECT ANSWER
B. *Incorrect answer*. Biotransformation is a type of metabolism.
C. *Incorrect answer*. Absorption is not an elimination process.
D. *Incorrect answer*. Distribution is not an elimination process.

9-22. A, B, D. *Incorrect answers*
C. CORRECT ANSWER

9-23. A. *Incorrect answer*
B. CORRECT ANSWER

9-24. A. CORRECT ANSWER
B. *Incorrect answer*

9-25. A. *Incorrect answer*. Urine pH does affect tubular reabsorption.
B. *Incorrect answer*. Highly ionized drugs do remain in the urine because ionized forms of drugs do not cross membranes well.
C. CORRECT ANSWER
D. *Incorrect answer*

9-26. A. *Incorrect answer*. Tubular reabsorption rate cannot be directly measured.
B. *Incorrect answer*. Tubular secretion rate cannot be directly measured.
C. *Incorrect answer*. Glomerular filtration rate does not account for tubular secretion or reabsorption.
D. CORRECT ANSWER

9-27. A, B, D. *Incorrect answers*. Aminoglycosides do not undergo hepatic or pulmonary clearance.
C. CORRECT ANSWER

9-28. A. *Incorrect answer*. The y-intercept is wrong. Aminoglycosides undergo little if any extrarenal elimination and, therefore, the y-intercept value should be close to zero.
B. CORRECT ANSWER
C. *Incorrect answer*. The answer should represent the approximate fraction of drug excreted per hour, and this value should be less than one.
D. *Incorrect answer*. The correct answer should be expressed as a product, not a sum (i.e., $A \times B$, not $A + B$).

Discussion Points

D-1. Research the metabolism of primidone and discuss the clinical significance of its metabolites. Discuss the proper method to monitor a patient receiving primidone.

D-2. Select several drugs whose prescribing information indicates that the dose should be decreased with hepatic impairment. Describe the pharmacokinetics of these drugs and discuss why this drug's dose should be decreased. Finally, indicate specifically how you would go about decreasing this dose.

D-3. Research the pharmacokinetics of carbamazepine and discuss its metabolism when given alone and when given with other enzyme inhibitors or inducers. Specifically, how would you begin a patient on carbamazepine and how would you monitor and adjust its dose?

D-4. Research the various oral fluoroquinolones to determine which can affect the metabolism of theophylline and to what extent. Discuss why some of these drugs affect theophylline and others do not.

D-5. Describe several clinical situations in which a drug's ability to compete for renal secretion with another drug can be either useful or harmful.

D-6. Describe situations in which alteration of urine pH with urine acidifier or alkalinizing agents can be used to enhance the clinical response of other drugs.

D-7. Look up and compare the various equations that can be used to calculate the elimination rate constant for gentamicin, tobramycin, and amikacin. Are these equations the same or different? Try to explain why they are either the same or different.