

Chapter 8. Clinical Pharmacokinetics and Pharmacodynamics

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Key Concepts

- 1 Clinical pharmacokinetics is the discipline that describes the absorption, distribution, metabolism, and elimination of drugs in patients requiring drug therapy.
- 2 Clearance is the most important pharmacokinetic parameter because it determines the steady-state concentration for a given dosage rate. Physiologically, clearance is determined by blood flow to the organ that metabolizes or eliminates the drug and the efficiency of the organ in extracting the drug from the bloodstream.
- 3 The volume of distribution is a proportionality constant that relates the amount of drug in the body to the serum concentration. The volume of distribution is used to calculate the loading dose of a drug that will immediately achieve a desired steady-state concentration. The value of the volume of distribution is determined by the physiologic volume of blood and tissues and how the drug binds in blood and tissues.
- 4 Half-life is the time required for serum concentrations to decrease by one-half after absorption and distribution are complete. It is important because it determines the time required to reach steady state and the dosage interval. Half-life is a dependent kinetic variable because its value depends on the values of clearance and volume of distribution.
- 5 The fraction of drug absorbed into the systemic circulation after extravascular administration is defined as its bioavailability.
- 6 Most drugs follow linear pharmacokinetics, whereby steady-state serum drug concentrations change proportionally with long-term daily dosing.
- 7 Some drugs do not follow the rules of linear pharmacokinetics. Instead of steady-state drug concentration changing proportionally with the dose, serum concentration changes more or less than expected. These drugs follow nonlinear pharmacokinetics.
- 8 Pharmacokinetic models are useful to describe data sets, to predict serum concentrations after several doses or different routes of administration, and to calculate pharmacokinetic constants such as clearance, volume of distribution, and half-life. The simplest case uses a

single compartment to represent the entire body.

- 9 Factors to be taken into consideration when deciding on the best drug dose for a patient include age, gender, weight, ethnic background, other concurrent disease states, and other drug therapy.
- 10 Cytochrome P450 is a generic name for the group of enzymes that are responsible for most drug metabolism oxidation reactions. Several P450 isozymes have been identified, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.
- 11 The importance of transport proteins in drug bioavailability and elimination is now better understood. The principal transport protein involved in the movement of drugs across biologic membranes is P-glycoprotein. P-glycoprotein is present in many organs, including the GI tract, liver, and kidney.
- 12 When deciding on initial doses for drugs that are renally eliminated, the patient's renal function should be assessed. A common, useful way to do this is to measure the patient's serum creatinine concentration and convert this value into an estimated creatinine clearance ($CrCl_{est}$). For drugs that are eliminated primarily by the kidney ($\geq 60\%$ of the administered dose), some agents will need minor dosage adjustments for $CrCl_{est}$ between 30 and 60 mL/min (0.50 and 1.00 mL/s), moderate dosage adjustments for $CrCl_{est}$ between 15 and 30 mL/min (0.25 and 0.50 mL/s), and major dosage adjustments for $CrCl_{est}$ less than 15 mL/min (0.25 mL/s). Supplemental doses of some medications also may be needed for patients receiving hemodialysis if the drug is removed by the artificial kidney or for patients receiving hemoperfusion if the drug is removed by the hemofilter.
- 13 When deciding on initial doses for drugs that are hepatically eliminated, the patient's liver function should be assessed. The Child-Pugh score can be used as an indicator of a patient's ability to metabolize drugs that are eliminated by the liver. In the absence of specific pharmacokinetic dosing guidelines for a medication, a Child-Pugh score equal to 8 or 9 is grounds for a moderate decrease ($\sim 25\%$) in the initial daily drug dose for agents that are metabolized primarily hepatically ($\geq 60\%$), and a score of 10 or greater indicates that a significant decrease in the initial daily dose ($\sim 50\%$) is required for drugs that are metabolized mostly hepatically.
- 14 For drugs that exhibit linear pharmacokinetics, steady-state drug concentration (C_{SS}) changes proportionally with dose (D). To adjust a patient's drug therapy, a reasonable starting dose is administered for an estimated three to five half-lives. A serum concentration is obtained, assuming that it will reflect C_{SS} . Independent of the route of administration, the new dose (D_{new}) needed to attain the desired $C_{SS}(C_{SS,new})$ is calculated as $D_{new} = D_{old}(C_{SS,new} / C_{SS,old})$, where D_{old} and $C_{SS,old}$ are the old dose and old C_{SS} , respectively.
- 15 If it is necessary to determine the pharmacokinetic constants for a patient to individualize his or her dose, a small pharmacokinetic evaluation is conducted in the individual. Additionally, Bayesian computer programs that aid in the individualization of therapy are available for many different drugs.

16 Pharmacodynamics is the study of the relationship between the concentration of a drug and the response obtained in a patient. If pharmacologic effect is plotted against concentration for most drugs, a hyperbola results with an asymptote equal to the maximum attainable effect.

Learning Objectives

Upon completion of the chapter, the reader will be able to:

1. Define the following terms: clinical pharmacokinetics, pharmacodynamics, and clearance, volume of distribution, half-life, bioavailability, linear pharmacokinetics, and nonlinear pharmacokinetics.
2. Calculate a maintenance dose, loading dose, and dosage interval for a patient given values of clearance, volume of distribution, and half-life.
3. Compare the attributes of linear pharmacokinetics and nonlinear pharmacokinetics.
4. List patient characteristics needed to decide upon the best drug dose for an individual.
5. Discuss the various drug metabolism enzymes and drug transport proteins and their importance in drug bioavailability and elimination.
6. Calculate the estimated creatinine clearance and Child-Pugh score for a patient.
7. Recommend when drug doses should be modified for patients with renal or hepatic dysfunction.
8. Calculate a modified drug dosage regimen for an agent that follows linear pharmacokinetics given a steady-state drug concentration and current drug dose.
9. Identify when a patient would benefit from the determination of pharmacokinetic constants for the use of dosage adjustment using drug-specific techniques or bayesian computer dosing programs.
10. Calculate an initial dose for a patient for the following medications: aminoglycoside antibiotics, [vancomycin](#), [digoxin](#), [theophylline](#), phenytoin, and [cyclosporine](#).

Clinical Pharmacokinetics and Pharmacodynamics: Introduction

Pharmacokinetic concepts have been used successfully by pharmacists to individualize patient drug therapy for about a quarter century. Pharmacokinetic consultant services and individual clinicians routinely provide patient-specific drug-dosing recommendations that increase the efficacy and decrease the toxicity of many medications. Laboratories routinely measure patient serum or plasma samples for many drugs, including antibiotics (e.g., aminoglycosides and [vancomycin](#)), [theophylline](#), antiepileptics (e.g., phenytoin, [carbamazepine](#), valproic acid, phenobarbital, and ethosuximide), [methotrexate](#), [lithium](#), antiarrhythmics (e.g., [lidocaine](#) and [digoxin](#)), and immunosuppressants (e.g., [cyclosporine](#) and [tacrolimus](#)). Combined with a knowledge of the disease states and conditions that influence the disposition of a particular drug,

kinetic concepts can be used to modify doses to produce serum drug concentrations that result in desirable pharmacologic effects without unwanted side effects. This narrow range of concentrations within which the pharmacologic response is produced and adverse effects prevented in most patients is defined as the *therapeutic range* of the drug. [Table 8–1](#) lists the therapeutic ranges for commonly used medications.

TABLE 8-1 Selected Therapeutic Ranges

Drug	Therapeutic Range
Digoxin	0.5–2 ng/mL or mg/L
	0.6–2.6 nmol/L
Lidocaine	1.5–5 mcg/mL or mg/L
	6.4–21 μ mol/L
Procainamide/ <i>N</i> -acetylprocainamide (total)	10–30 mcg/mL or mg/L (total)
	42–127 μ mol/L
Quinidine	2–5 mcg/mL or mg/L
	6–15 μ mol/L
Amikacin ^a	20–30 mcg/mL or mg/L (peak)
	34–51 μ mol/L (peak)
	<5 mcg/mL or mg/L (trough)
	<9 μ mol/L (trough)
Gentamicin ^a	5–10 mcg/mL or mg/L (peak)
	10–21 μ mol/L (peak)

Drug	Therapeutic Range
	<2 mcg/mL or mg/L (trough)
	<4 µmol/L (trough)
Tobramycin, Netilmicin ^a	5–10 mcg/mL or mg/L (peak)
	11–21 µmol/L (peak)
	<2 mcg/mL or mg/L (trough)
	<4 µmol/L (trough)
Vancomycin	20–40 mcg/mL or mg/L (peak)
	14–28 µmol/L (peak)
	5–15 mcg/mL or mg/L (trough) ^b
	3–10 µmol/L (trough) ^b
Chloramphenicol	10–20 mcg/mL or mg/L
	31–62 µmol/L
Lithium	0.6–1.4 mEq/L
	0.6–1.4 mmol/L
Carbamazepine	4–12 mcg/mL or mg/L

Drug	Therapeutic Range
	17–51 $\mu\text{mol/L}$
Ethosuximide	40–100 mcg/mL or mg/L
	283–708 $\mu\text{mol/L}$
Phenobarbital	15–40 mcg/mL or mg/L
	65–172 $\mu\text{mol/L}$
Phenytoin	10–20 mcg/mL or mg/L
	40–79 $\mu\text{mol/L}$
Primidone	5–12 mcg/mL or mg/L
	23–55 $\mu\text{mol/L}$
Valproic acid	50–100 mcg/mL or mg/L
	347–693 $\mu\text{mol/L}$
Theophylline	10–20 mcg/mL or mg/L
	56–111 $\mu\text{mol/L}$
Cyclosporine (blood)	150–400 ng/mL or mcg/L
	125–333 nmol/L

^aUsing a multiple dose per day conventional dosage schedule.

^bFor patients with pneumonia or other life-threatening infections, trough concentrations as high as 20 mcg/mL or mg/L (14 μ mol/L) have been suggested.

Although most individuals experience favorable effects with serum drug concentrations in the therapeutic range, the effects of a given serum concentration can vary widely among individuals. Clinicians should never assume that a serum concentration within the therapeutic range will be safe and effective for every patient. The response to the drug, such as the number of seizures a patient experiences while taking an antiepileptic agent, should always be assessed when serum concentrations are measured.

Throughout this chapter, abbreviations for various pharmacokinetic parameters are used frequently. [Table 8-2](#) lists commonly used abbreviations.

TABLE 8-2 Pharmacokinetic Abbreviations

Abbreviation	Definition
CL	Clearance
k_0	IV infusion rate
C_{SS}	Steady-state concentration
D	Dose
τ	Dosage interval
F	Fraction of drug absorbed into the systemic circulation
Q	Blood flow
E	Extraction ratio
f_b	Fraction of drug in the blood that is unbound
Cl_{int}	Intrinsic clearance
$C_{SS, u}$	Steady-state concentration of unbound drug
V_D	Volume of distribution
LD	Loading dose
MD	Maintenance dose

Abbreviation	Definition
$t_{1/2}$	Half-life
k	Elimination rate constant
k_a	Absorption rate constant
α	Distribution rate constant
β	Terminal rate constant
t'	Postinfusion time
T	Duration of infusion
AUC	Area under serum or blood concentration-versus-time curve
V_{\max}	Maximum rate of drug metabolism
K_m	Serum concentration at which the rate of metabolism equals $V_{\max} / 2$
C_{\max}	Maximum serum or blood concentration
C_{\min}	Minimum serum or blood concentration
DR	Dosage rate
P-gp	P-glycoprotein

Clinical Pharmacokinetic Concepts

1 Clinical pharmacokinetics is the discipline that describes the absorption, distribution, metabolism, and elimination of drugs in patients requiring drug therapy. When a drug is administered extravascularly to patients, it must be absorbed across biologic membranes to reach the systemic circulation. If the drug is given orally, the drug molecules must pass through the GI tract wall into capillaries. For transdermal patches, the drug must penetrate the skin to enter the vascular system. In general, the pharmacologic effect of the drug is delayed when it is given extravascularly because time is required for the drug to be absorbed into the vascular system.

The vascular system generally provides the “transportation” for the drug molecule to its site of activity. After the drug reaches the systemic circulation, it can leave the vasculature and penetrate the various tissues or remain in the blood. If the drug remains in the blood, it may bind to endogenous protein, such as albumin and α_1 -acid glycoprotein. This binding usually is reversible, and an equilibrium is created between protein-bound drug and unbound drug. Unbound drug in the blood provides the driving force for distribution of the agent to body tissues. If unbound drug leaves the bloodstream and distributes to tissue, it may become tissue-bound, it may remain unbound in the tissue, or if the tissue can metabolize or eliminate the drug, it may be rendered inactive and/or eliminated from the body. If the drug becomes tissue-bound, it may bind to the receptor that causes its pharmacologic or toxic effect or to a nonspecific binding site that causes no effect. Again, tissue binding is usually reversible, so that the tissue-bound drug is in equilibrium with the unbound drug in the tissue.

Certain organs—such as the liver, GI tract wall, and lung—possess enzymes that metabolize drugs. The resulting metabolite may be inactive or have a pharmacologic effect of its own. The blood also contains esterases, which cleave ester bonds in drug molecules and generally render them inactive.

Drug metabolism usually occurs in the liver through one or both of two types of reactions. Phase I reactions generally make the drug molecule more polar and water soluble so that it is prone to elimination by the kidney. Phase I modifications include oxidation, hydrolysis, and reduction. Phase II reactions involve conjugation to form glucuronides, acetates, or sulfates. These reactions generally inactivate the pharmacologic activity of the drug and may make it more prone to elimination by the kidney.

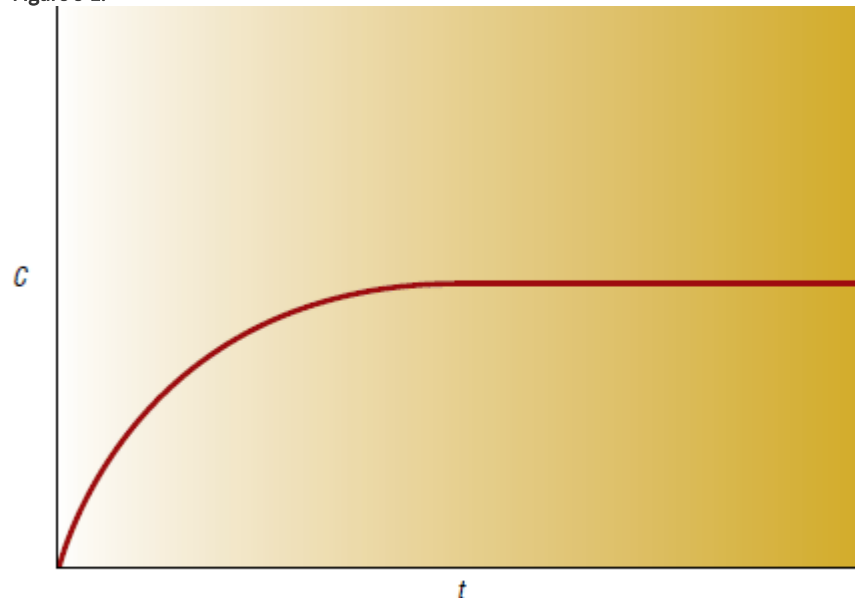
Other organs have the ability to eliminate drugs or metabolites from the body. The kidney can excrete drugs by glomerular filtration or by such active processes as proximal tubular secretion. Drugs also can be eliminated via bile produced by the liver or air expired by the lungs.

Linear Pharmacokinetics

6 Most drugs follow linear pharmacokinetics; serum drug concentrations change proportionally with long-term daily dosing. For example, if a drug dose were doubled from 300 to 600 mg daily, the patient's serum drug concentration would double.

When a drug is given by continuous IV infusion, serum concentrations increase until an equilibrium is established between the drug dosage rate and the rate of drug elimination. At that point, the rate of drug administration equals the rate of drug elimination, and the serum concentrations remain constant (Fig. 8-1). For example, if a patient were receiving a continuous IV infusion of **theophylline** at 40 mg/h, the **theophylline** serum concentration would increase until the patient's body was eliminating **theophylline** at 40 mg/h. When serum drug concentrations reach a constant value, steady state is achieved.

Figure 8-1.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

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Normal serum concentration-time curve following a continuous IV infusion.

If the drug is given at intermittent dosage intervals, such as 250 mg every 6 hours, steady state is achieved when the serum-concentration-versus-time curves for each dosage interval are superimposable. The amount of drug eliminated during the dosage interval equals the dose.

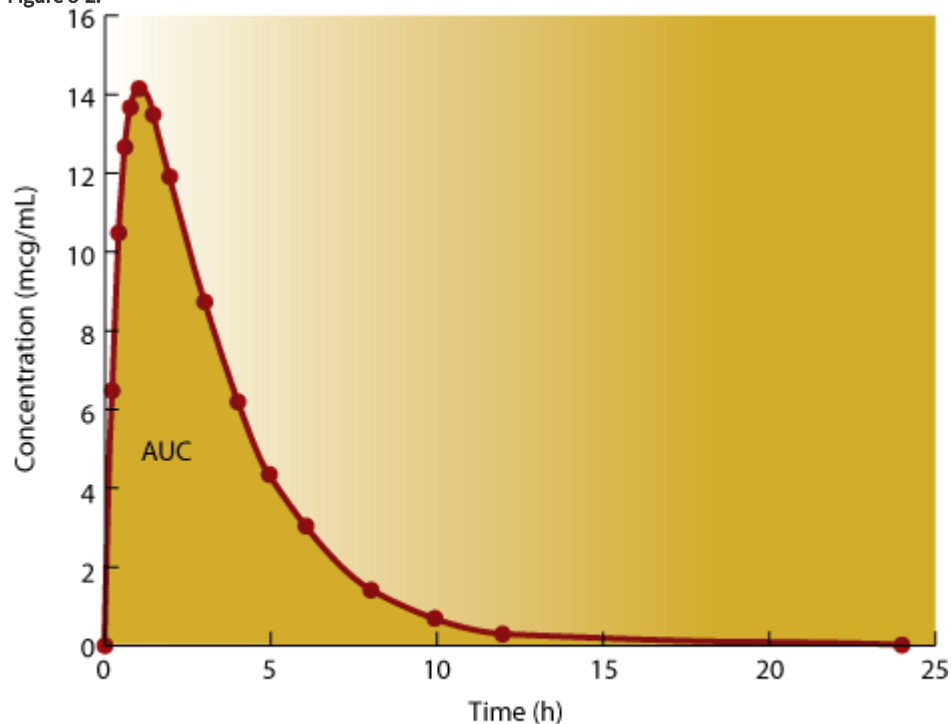
Bioavailability and Bioequivalence

When drugs are administered extravascularly, drug molecules must be released from the dosage form (dissolution) and pass through several biologic barriers before reaching the vascular system (absorption). The fraction of drug absorbed into the systemic circulation (F) after extravascular administration is defined as its *bioavailability* and can be calculated after single IV and extravascular doses as¹

$$F = \frac{D_{iv}(AUC_{0-\infty})}{D(AUC_{iv,0-\infty})}$$

where D and D_{iv} are the extravascular and IV doses, respectively, and $AUC_{iv,0-\infty}$ and $AUC_{0-\infty}$ are the IV and extravascular areas under the serum- or blood-concentration-versus-time curves, respectively, from time zero to infinity. The AUC represents the body's total exposure to the drug and is a function of the fraction of the drug dose that enters the systemic circulation via the administered route and clearance (Fig. 8-2). When F less than 1 for a drug administered extravascularly, either the dosage form did not release all the drug contained in it, or some of the drug was eliminated or destroyed (by stomach acid or other means) before it reached the systemic circulation.

Figure 8-2.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

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Area under the concentration-versus-time curve (AUC) after the administration of an extravascular dose. The AUC is a function of the fraction of drug dose that enters the systemic circulation and clearance. AUCs measured after IV and extravascular doses can be used to determine bioavailability for the extravascular dose.

When the extravascular dose is administered orally, part of the dose may be metabolized by enzymes or removed by transport proteins contained in the GI tract wall or liver before it reaches the systemic circulation.^{2,3} This occurs commonly when drugs have a high liver extraction ratio or are subject to GI tract wall metabolism because, after oral administration, the drug must pass through the GI tract wall and into the portal circulation of the liver. Transport proteins are also present in the GI tract wall that can actively pump drug molecules that already have been absorbed back into the lumen of the GI tract. P-glycoprotein (P-gp) is the primary transport protein that interferes with drug absorption by this mechanism. For example, if an orally administered drug is 100% absorbed from the GI tract but has a hepatic extraction ratio of 0.75, only 25% of the original dose enters the systemic circulation. This first-pass effect through the liver and/or GI tract wall is avoided when the drug is given by other routes of administration. The computation of F does not separate loss of oral drug metabolized by the first-pass effect and drug not absorbed by the GI tract. Special techniques are needed to determine the fraction of drug absorbed orally for drugs with high liver extraction ratios or substantial gut wall metabolism.

Two different dosage forms of the same drug are considered to be bioequivalent when the $AUC_{0-\infty}$, maximum serum or blood concentrations (C_{max}), and the times that C_{max} occurs (t_{max}) are neither clinically nor statistically different. When this occurs, the serum-concentration-versus-time curves for the two dosage forms should be superimposable and identical. Bioequivalence studies have become very important as expensive drugs become available in less costly generic form. Most bioequivalence studies involve 18 to 25 healthy adults who are given the brand-name product and the generic product in a randomized, crossover study design.

Clearance

2 Clearance (CL) is the most important pharmacokinetic parameter because it determines the steady-state concentration for a given dosage rate. When a drug is given at a continuous IV infusion rate equal to k_0 , the steady-state concentration (C_{ss}) is determined by the quotient of k_0 and CL ($C_{ss} = k_0/CL$). If the drug is administered as individual doses (D) at a given dosage interval (τ), the average steady-state concentration (C_{ss}) over the dosage interval is given by the equation⁴

$$C_{ss} = \frac{F(D/\tau)}{CL}$$

where F is the fraction of dose absorbed into the systemic vascular system. The average steady-state concentration over the dosage interval is the steady-state concentration that would have occurred had the same dose been given as a continuous IV infusion (e.g., 300 mg every 6 hours would produce an average C_{SS} equivalent to the actual C_{SS} produced by a continuous infusion administered at a rate of 50 mg/h).

Physiologically, clearance is determined by (a) blood flow (Q) to the organ that metabolizes (liver) or eliminates (kidney) the drug and (b) the efficiency of the organ in extracting the drug from the bloodstream.⁵ Efficiency is measured using an extraction ratio (E), calculated by subtracting the concentration in the blood leaving the extracting organ (C_{out}) from the concentration in the blood entering the organ (C_{in}) and then dividing the result by C_{in} :

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

Clearance for that organ is calculated by taking the product of Q and E ($CL = QE$). For example, if liver blood flow equals 1.5 L/min, and the drug's extraction ratio is 0.33, hepatic clearance equals 0.5 L/min. Total clearance is computed by summing all the individual organ clearance values. Clearance changes occur in patients when the blood flow to extracting organs changes or when the extraction ratio changes. Vasodilators such as hydralazine and nifedipine increase liver blood flow, whereas congestive heart failure (CHF) and hypotension can decrease hepatic blood flow. Extraction ratios can increase when enzyme inducers increase the amount of drug-metabolizing enzyme. Extraction ratios may decrease if enzyme inhibitors inhibit drug-metabolizing enzymes or necrosis causes loss of parenchyma.

Intrinsic Clearance

The extraction ratio also can be thought of in terms of the unbound fraction of drug in the blood (f_b), the intrinsic ability of the extracting organ to clear unbound drug from the blood (CL_{int}), and blood flow to the organ (Q):^{6,7}

$$E = \frac{f_b(CL_{int})}{Q + f_b(CL_{int})}$$

By substituting this equation for E , the clearance equation becomes

$$CL = \frac{Q[f_b(CL_{int})]}{Q + f_b(CL_{int})}$$

Clearance changes will occur when blood flow to the clearing organ changes (in conditions where blood flow is reduced, e.g., shock and CHF, or where blood flow is increased, e.g., administration of medications, such as vasodilators, and resolution of shock or CHF), binding in the blood

changes (e.g., if the concentration of binding proteins is low or highly protein-bound drugs are displaced), or intrinsic clearance of unbound drug changes (e.g., when metabolizing enzymes are induced or inhibited by other drug therapy or functional organ tissue is destroyed by disease processes).

If CL_{int} is large (enzymes have a high capacity to metabolize the drug), the product of f_b and CL_{int} is much larger than Q . When $f_b(CL_{int})$ is much greater than Q , the sum of Q and $f_b(CL_{int})$ in the denominator of the clearance equation almost equals $f_b(CL_{int})$:

$$f_b(CL_{int}) \approx Q + f_b(CL_{int})$$

Substituting this expression in the denominator of the clearance equation and canceling common terms leads to the following expression for drugs with a large CL_{int} : $CL \approx Q$. In this case, clearance of the drug is equal to blood flow to the organ; such drugs are called *high-clearance drugs* and have large extraction ratios. [Propranolol](#), [verapamil](#), [morphine](#), and [lidocaine](#) are examples of high-clearance drugs. High-clearance drugs such as these typically exhibit high first-pass effects when administered orally.

If CL_{int} is small (enzymes have a limited capacity to metabolize the drug), Q is much larger than the product of f_b and CL_{int} . When Q is much greater than $f_b(CL_{int})$, the sum of Q and $f_b(CL_{int})$ in the denominator of the clearance equation becomes almost equal to Q : $Q \approx Q + f_b(CL_{int})$. Substituting this expression in the denominator of the clearance equation and canceling common terms leads to the following expression for drugs with a small CL_{int} : $CL \approx f_b(CL_{int})$. In this case, clearance of the drug is equal to the product of the fraction unbound in the blood and the intrinsic ability of the organ to clear unbound drug from the blood; such drugs are known as *low-clearance drugs* and have small extraction ratios. [Warfarin](#), [theophylline](#), diazepam, and phenobarbital are examples of low-clearance drugs.

As mentioned previously, the concentration of unbound drug in the blood is probably more important pharmacologically than the total (bound plus unbound) concentration. The unbound drug in the blood is in equilibrium with the unbound drug in the tissues and reflects the concentration of drug at its site of action. Therefore, the pharmacologic effect of a drug is thought to be a function of the concentration of unbound drug in the blood. The unbound steady-state concentration ($C_{ss,u}$) can be calculated by multiplying C_{ss} and f_b : $C_{ss,u} = C_{ss}f_b$. The effect that changes in Q , f_b , and CL_{int} have on $C_{ss,u}$ and therefore on the pharmacologic response of a drug depends on whether a high- or low-clearance drug is involved. Because $CL = Q$ for high-clearance drugs, a change in f_b or CL_{int} does not change CL or C_{ss} ($C_{ss} = k_0/CL$). However, a change in unbound drug fraction does alter $C_{ss,u}$ ($C_{ss,u} = f_b C_{ss}$), thereby affecting the pharmacologic response. Plasma protein-binding displacement drug interactions can be very important clinically, but they are also dangerous because the changes in $C_{ss,u}$ are not reflected in changes in C_{ss} for high-clearance drugs. Because laboratories usually measure only total concentrations (concentrations of unbound drug are

difficult to determine), the interaction is hard to detect. If CL_{int} changes for high-clearance drugs, CL , C_{ss} , $C_{ss,u}$, and pharmacologic response do not change. Changes in Q cause a change in CL ; changes in C_{ss} , $C_{ss,u}$, and drug response are indirectly proportional to changes in CL .

For low-clearance drugs, total clearance is determined by unbound drug fraction and intrinsic clearance: $CL = f_b(CL_{int})$. A change in Q does not change CL , C_{ss} , $C_{ss,u}$, or pharmacologic response. However, a change in f_b or CL_{int} does alter CL and C_{ss} ($C_{ss} = k_0/CL$). Changes in CL_{int} will cause a proportional change in CL .

Changes in C_{ss} , $C_{ss,u}$, and drug response are indirectly proportional to changes in CL . Altering f_b for low-clearance drugs produces interesting results. A change in f_b alters CL and C_{ss} ($C_{ss} = k_0/CL$). Because CL and C_{ss} change in opposite directions with changes in f_b , $C_{ss,u}$ ($C_{ss,u} = f_b C_{ss}$) and pharmacologic response do not change with alterations in the fraction of unbound drug in the blood. For example, a low-clearance drug is administered to a patient until steady-state is achieved:

$$CL = f_b(CL_{int})$$

$$C_{ss} = \frac{k_0}{CL}$$

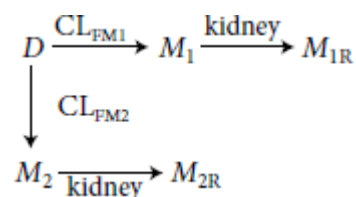
Suppose that another drug is administered to the patient that displaces the first drug from plasma-protein-binding sites and doubles f_b (f_b now equals $2f_b$). CL doubles because of the protein-binding displacement [$2CL = 2f_b(CL_{int})$], and C_{ss} decreases by one-half because of the change in clearance [$\frac{1}{2}(C_{ss}) = k_0/(2CL)$]. $C_{ss,u}$ does not change because even though f_b is doubled, C_{ss} decreased by one-half ($C_{ss,u} = f_b C_{ss}$). The potential for error in this situation is that clinicians may increase the dose of a low-clearance drug after a protein-binding displacement interaction because C_{ss} decreased. Because $C_{ss,u}$ and the pharmacologic effect do not change, the dose should remain unaltered. Plasma protein binding decreases occur commonly in patients taking phenytoin. Low albumin concentrations (as in trauma or pregnant patients), high concentrations of endogenous plasma protein-binding displacers (as with high concentrations of bilirubin), or plasma protein-binding drug interactions (as with concomitant therapy with valproic acid) can result in subtherapeutic total phenytoin concentrations. Despite this fact, unbound phenytoin concentrations usually are within the therapeutic range, and often the patient is responding appropriately to treatment. Thus, in these situations, unbound rather than total phenytoin serum concentrations should be monitored and used to guide future therapeutic decisions.

Clearances for Different Routes of Elimination and Metabolic Pathways

Clearances for individual organs can be computed if the excretion the organ produces can be obtained. For example, renal clearance can be calculated if urine is collected during a pharmacokinetic experiment. The patient empties his or her bladder immediately before the dose is

given. Subsequent urine production is collected until the last serum concentration (C_{last}) is obtained. Renal clearance (CL_R) is computed by dividing the amount of drug excreted in the urine by $AUC_{0-t, last}$. Biliary and other clearance values are computed in a similar fashion.

Clearances also can be calculated for each metabolite that is formed from the parent drug. This computation is particularly useful in drug-interaction studies to determine which metabolic pathway is stimulated or inhibited. In the following metabolic scheme, the parent drug (D) is metabolized into two different metabolites (M_1 , M_2) that subsequently are eliminated by the kidney (M_{1R} , M_{2R}):



To compute the formation clearance of M_1 and M_2 (CL_{FM1} , CL_{FM2}), urine would be collected for five or more half-lives after a single dose or during a dosage interval at steady state. The amount of metabolite eliminated in the urine is then determined. The fraction of the dose (in moles, because the molecular weights of the parent drug and metabolites are not equal) eliminated by each metabolic pathway ($f_{M1} = M_{1R}/D$ and $f_{M2} = M_{2R}/D$) can then be computed. Formation clearance for each pathway can be calculated using the following equations: $CL_{FM1} = f_{M1}CL_M$ and $CL_{FM2} = f_{M2}CL_M$, where CL_M is the metabolic clearance for the parent drug.

Volume of Distribution

3 The volume of distribution (V_D) is a proportionality constant that relates the amount of drug in the body to the serum concentration (amount in body = CV_D). V_D is used to calculate the loading dose (LD) of a drug that will immediately achieve a desired C_{SS} ($LD = C_{SS} V_D$). However, in practice, the patient's own V_D is not known at the time the loading dose is administered. In this case, an average V_D is assumed and used to calculate a loading dose. Because the patient's V_D is almost always different from the average V_D for the drug, a loading dose does not attain the calculated C_{SS} , but it hopefully achieves a therapeutic concentration. As usual, steady-state conditions are achieved in three to five half-lives for the drug.

The numeric value for the volume of distribution is determined by the physiologic volume of blood and tissues and how the drug binds in blood and tissues:⁸

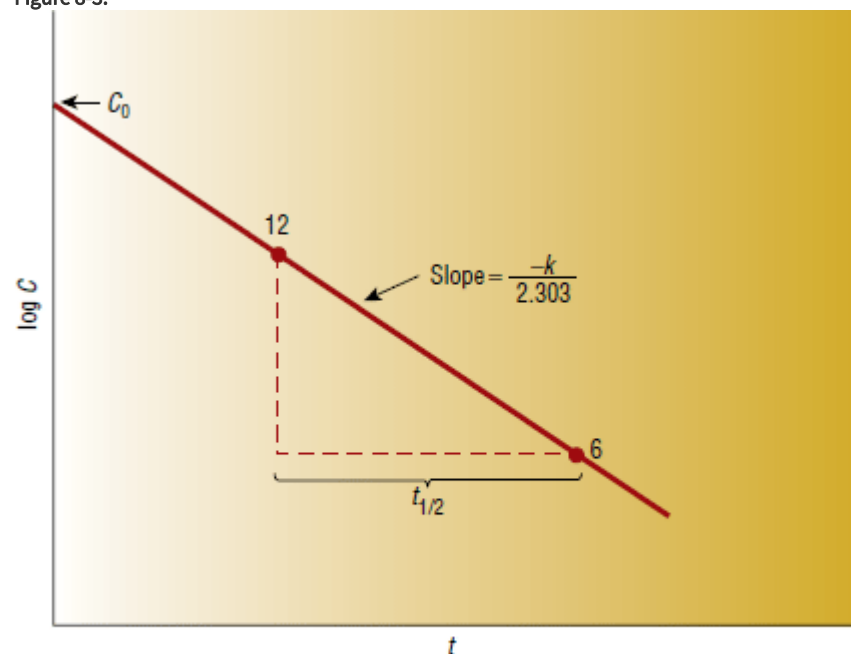
$$V_D = V_b + (f_b/f_t) V_t$$

where V_b and V_t are the volumes of blood and tissues, respectively, and f_b and f_t are the fractions of unbound drug in blood and tissues, respectively.

Half-Life

4 Half-life ($t_{1/2}$) is the time required for serum concentrations to decrease by one-half after absorption and distribution are complete. It takes the same amount of time for serum concentrations to drop from 200 to 100 mg/L as it does for concentrations to decline from 2 to 1 mg/L (Fig. 8-3).

Figure 8-3.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Calculation of the half-life of a drug following IV bolus dosing.

Half-life is important because it determines the time required to reach steady state and the dosage interval. It takes approximately three to five half-lives to reach steady-state concentrations during continuous dosing. In three half-lives, serum concentrations are at ~90% of their ultimate steady-state values. Because most serum drug assays have an ~10% error, it is difficult to differentiate concentrations that are within 10% of each other. For this reason, many clinicians consider concentrations obtained after three half-lives to be C_{ss} .

Half-life is also used to determine the dosage interval for a drug. For instance, it may be desirable to maintain maximum steady-state concentrations at 20 mg/L and minimum steady-state concentrations at 10 mg/L. In this case, it would be necessary to administer the drug every half-life because the minimum desirable concentration is one-half the maximum desirable concentration.

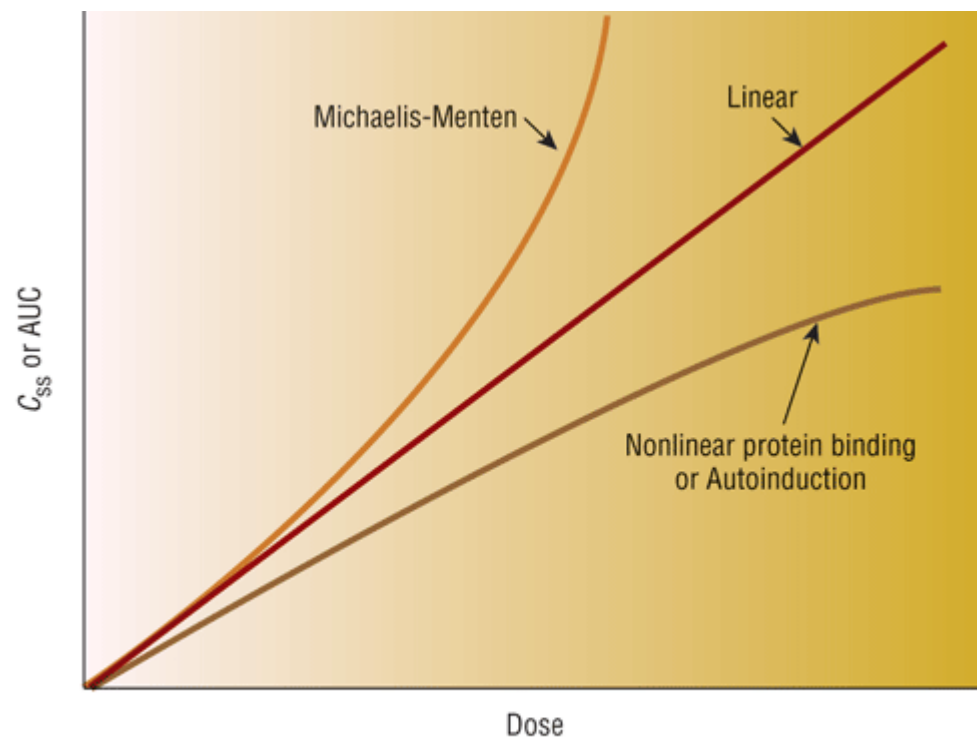
Half-life is a dependent kinetic variable because its value depends on the values of CL and V_D .⁸ The equation that describes the relationship among the three variables is $t_{1/2} = 0.693 V_D / CL$. Changes in $t_{1/2}$ can result from a change in either V_D or CL; a change in $t_{1/2}$ does not necessarily indicate that CL has changed. Half-life can change solely because of changes in V_D . The elimination rate constant (k) is related to the half-life by the following equation: $k = 0.693 / t_{1/2}$. Both the half-life and elimination rate constant describe how quickly serum concentrations decrease in the serum or blood.

Nonlinear Pharmacokinetics

Michaelis-Menten Kinetics

7 Some drugs do not follow the rules of linear pharmacokinetics. Instead of C_{SS} and AUC increasing proportionally with dose, serum concentrations change more or less than expected (Fig. 8-4). One explanation for the greater-than-expected increase in C_{SS} and AUC after an increase in dose is that the enzymes responsible for the metabolism or elimination of the drug may start to become saturated. When this occurs, the maximum rate of metabolism (V_{max}) for the drug is approached. This is called *Michaelis-Menten kinetics*. The serum concentration at which the rate of metabolism equals $V_{max}/2$ is K_m . Practically speaking, K_m is the serum concentration at which nonproportional changes in C_{SS} and AUC start to occur when the dose is increased. The Michaelis-Menten constants (V_{max} and K_m) determine the dosage rate (DR) needed to maintain a given C_{SS} : $DR = V_{max} C_{SS} / (K_m + C_{SS})$. Most drugs eliminated by the liver are metabolized by enzymes but still appear to follow linear kinetics. The reason for this disparity is that the therapeutic range for most drugs is well below the K_m of the enzyme system that metabolizes the agent. The therapeutic range is higher than K_m for some commonly used drugs. The average K_m for phenytoin is about 4 mg/L (16 μ mol/L). The therapeutic range for phenytoin is usually 10 to 20 mg/L (40 to 79 μ mol/L). Most patients experience Michaelis-Menten kinetics while taking phenytoin.

Figure 8-4.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Relationship of dose and steady-state drug concentration (C_{ss}) or area under the concentration-versus-time curve (AUC) under linear and nonlinear conditions.

Nonlinear Protein Binding

Another type of nonlinear kinetics can occur if C_{ss} and AUC increase less than expected after an increase in dose of a low-clearance drug. This usually indicates that plasma protein-binding sites are starting to become saturated, so that f_b increases with increases in the dose (see Fig. 8-4). For a low-clearance drug, CL depends on the values of f_b and CL_{int} ($CL = f_b CL_{int}$). When a dosage increase takes place, f_b increases because nearly all plasma protein-binding sites are occupied, and no binding sites are available. If f_b increases, CL increases, and C_{ss} increases less than expected with the dosage change ($C_{ss} = k_0/CL$). However, $C_{ss,u}$ increases proportionally with the dose because $C_{ss,u}$ depends on CL_{int} for low-clearance drugs ($C_{ss,u} = k_0/CL_{int}$). Valproic acid⁹ and disopyramide¹⁰ both follow saturable protein-binding pharmacokinetics.

Autoinduction

For some drugs, clearance increases as the dose or concentration of the drug increases. In this situation, increasing the drug dose or concentration increases the ability of the enzyme system to eliminate the compound and to clear the drug from the body. This is usually accomplished by inducing the enzyme system responsible for the metabolism of the drug, so that the intrinsic clearance of the drug increases.

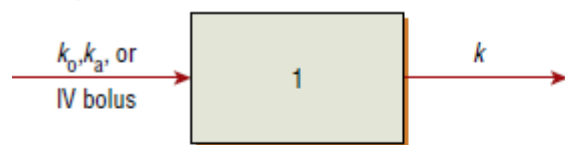
Because the drug itself is causing the induction effect, this process is called *autoinduction*. For some drugs, such as carbamazepine,⁵⁸ the autoinduction effect is continuous within the typical dosage range, which produces a curve for the dose versus C_{SS} or AUC plot similar to nonlinear protein binding (see Fig. 8–4). Detailed pharmacokinetic studies are conducted to differentiate between nonlinear protein binding and autoinduction when dose versus C_{SS} or AUC plots systematically deviate below the linear line.

Pharmacokinetic Models and Equations

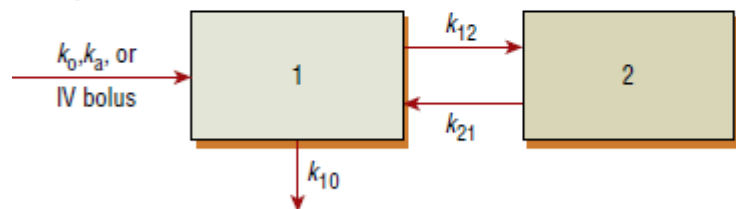
8 Pharmacokinetic models are useful to describe data sets, to predict serum concentrations after several doses or different routes of administration, and to calculate pharmacokinetic constants such as CL, V_D , and $t_{1/2}$.¹¹ Compartmental models depict the body as one or more discrete compartments to which a drug is distributed and/or from which a drug is eliminated. The shape of the serum-concentration-versus-time curve determines the number of compartments in the pharmacokinetic model and the equation used in computations (Fig. 8–5). First-order rate constants, known as *microconstants*, describe the rate of transfer from one compartment to another. Each compartment also has its own V_D . For clinical dosage adjustment purposes using drug concentrations, a one-compartment model is the most commonly used pharmacokinetic model.

Figure 8-5.

1 compartment



2 compartments



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Visual representations of one- and two-compartment drug-distribution models.

One-Compartment Model

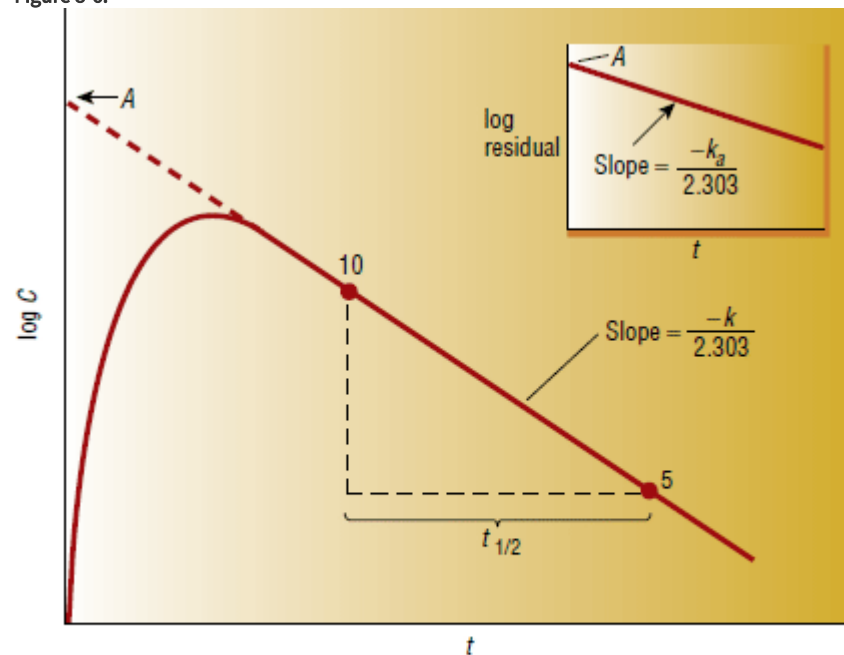
The simplest case uses a single compartment to represent the entire body (see Fig. 8–5). The drug enters the compartment by continuous IV infusion (k_0), absorption from an extravascular site with an absorption rate constant of k_a , or IV bolus (D). After an IV bolus, serum concentrations decline in a straight line when plotted on semilogarithmic coordinates (see Fig. 8–3). The slope of the line is $-k/2.303$; $t_{1/2}$ can be computed by determining the time required for concentrations to decrease by one-half ($t_{1/2} = 0.693/k$). The equation that describes the data is $C = (D/V_D)e^{-kt}$. V_D is calculated by dividing the IV dose by the y intercept (the concentration at time zero, C_0) of the graph. CL is computed by taking the product of k and V_D . Once V_D and k are known, concentrations at any time after the dose can be computed [$C = (D/V_D)e^{-kt}$].

When an extravascular dose is given, one-compartment-model serum concentrations rise during absorption, reach C_{\max} , then decrease in a straight line with a slope equal to $-k/2.303$. The equation that describes the data is $C = \{(FDk_a)/[V_D(k_a - k)]\}(e^{-kt} - e^{-k_a t})$, where F is the fraction of the dose absorbed into the systemic circulation. The absorption rate constant (k_a) is obtained using the method of residuals.

The method of residuals is used to obtain the individual rate constants (Fig. 8–6). A is determined by extrapolating the terminal slope to the y axis; k can be obtained by calculating the slope or $t_{1/2}$ and using the formulas given for the IV bolus case. At each time point in the absorption portion

of the curve, the concentration value from the extrapolated line is noted and called the *extrapolated concentration*. For each point, the actual concentration is subtracted from the extrapolated concentration to compute the *residual concentration*. When the residual concentrations are plotted on semilogarithmic coordinates (see Fig. 8-6, inset), a line with y intercept equal to A and slope equal to $-k_a/2.303$ is obtained. When these values are calculated, they can be placed into the equation ($C = Ae^{-kt} - Ae^{-k_a t}$, where $A = FDk_a/[V_D(k_a - k)]$) and used to compute the serum concentration at any time after the extravascular dose. The intercepts and rate constants also can be used to compute CL and V_D : $CL = FD/(A/k - A/k_a)$ and $V_D = CL/k$, where F is the fraction of the dose absorbed into the systemic circulation.

Figure 8-6.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy:*

A Pathophysiologic Approach, 8th Edition: www.accesspharmacy.com

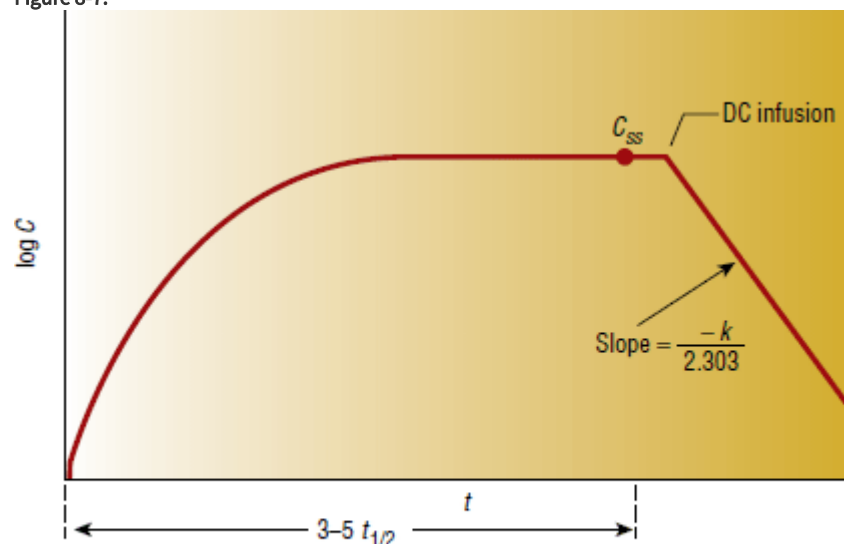
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Calculation of the half-life of a drug following oral, intramuscular, or other extravascular dosing route. Inset shows calculation of the absorption rate constant (k_a) using the method of residuals.

During a continuous IV infusion, the serum concentrations in a one-compartment model change according to the following function: $C = (k_0/CL)(1 - e^{-kt})$. If the infusion has been running for more than three to five half-lives, the patient will be at steady state, and CL can be calculated ($CL =$

k_0/C_{ss}). When the infusion is discontinued, serum concentrations appear to decline in a straight line when plotted on semilogarithmic paper with a slope of $-k/2.303$. V_D is computed by dividing CL by k (Fig. 8-7).

Figure 8-7.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Achievement of steady-state serum concentrations after three to five half-lives of a drug. Note the elimination phase after discontinuance of the infusion.

Multicompartment Model

After an IV bolus dose, serum concentrations often decline in two or more phases. During the early phases, the drug leaves the bloodstream by two mechanisms: (a) distribution into tissues and (b) metabolism and/or elimination. Because the drug is leaving the bloodstream through these two mechanisms, serum concentrations decline rapidly. After tissues and blood are in equilibrium, only metabolism and elimination remove the drug from the blood. During this terminal phase, serum concentrations decline more slowly. The half-life is measured during the terminal phase by determining the time required for concentrations to decline by one-half.

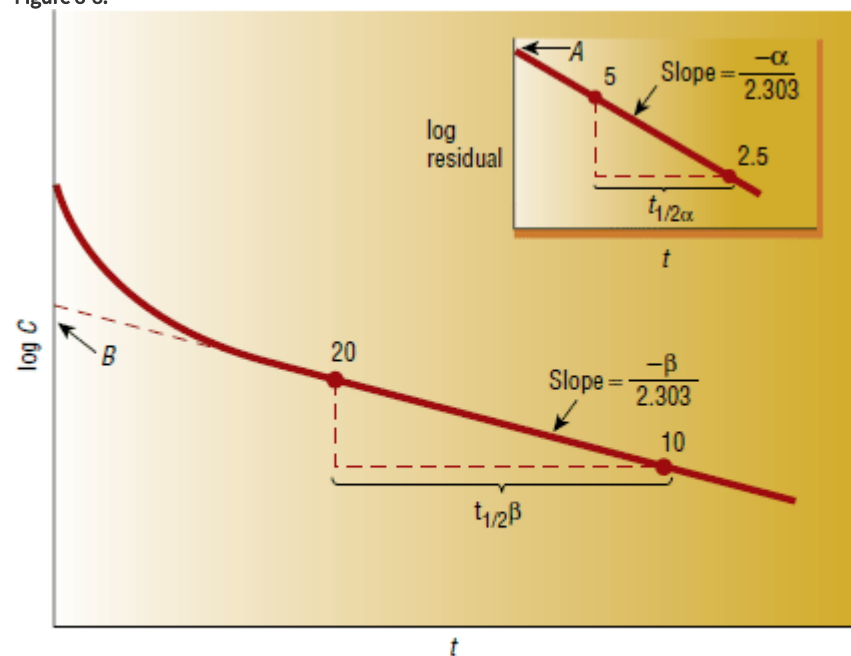
After an IV bolus dose, serum concentrations decrease as if the drug were being injected into a central compartment that not only metabolizes and eliminates the drug but also distributes the drug to one or more other compartments. Of these multicompartment models, the two-

compartment model is encountered most commonly (see Fig. 8-5). After an IV bolus injection, serum concentrations decrease in two distinct phases, described by the equation

$$C = \frac{D(\alpha - k_{21})}{V_{D1}(\alpha - \beta)} e^{-\alpha t} + \frac{D(k_{21} - \beta)}{V_{D1}(\alpha - \beta)} e^{-\beta t}$$

or $C = Ae^{-\alpha t} + Be^{-\beta t}$, where k_{21} is the first-order rate constant that reflects the transfer of the drug from compartment 2 to compartment 1, V_{D1} is the V_D of compartment 1, $A = D(\alpha - k_{21})/[V_{D1}(\alpha - \beta)]$ and $B = D(k_{21} - \beta)/[V_{D1}(\alpha - \beta)]$. The rate constants α and β found in the exponents of the equations describe the distribution and elimination of the drug, respectively (Fig. 8-8). A and B are the y intercepts of the lines that describe drug distribution and elimination, respectively, on the log concentration-versus-time plot.

Figure 8-8.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Calculation of α and β half-lives following IV dosing. Inset shows calculation of the distribution rate constant (α) using the method of residuals.

The residual line is calculated as before using the method of residuals (see Fig. 8-8, inset). The terminal line is extrapolated to the y axis, and extrapolated concentrations are determined for each time point. Because actual concentrations are greater in this case, residual concentrations

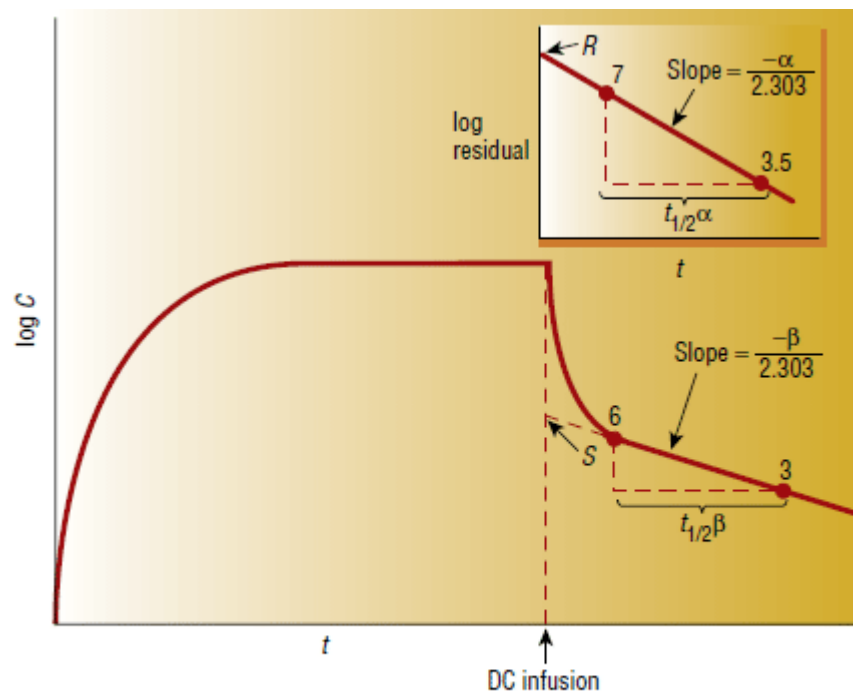
are calculated by subtracting the extrapolated concentrations from the actual concentrations. When plotted on semilogarithmic paper, the residual line has a y intercept equal to A . The slope of the residual line is used to compute α (slope = $-\alpha/2.303$). With the rate constants (α and β) and the intercepts (A and B), concentrations can be calculated for any time after the IV bolus dose ($C = Ae^{-\alpha t} + Be^{-\beta t}$), or pharmacokinetic constants can be computed: $CL = D/[(A/\alpha) + (B/\beta)]$, $V_{D,\beta} = CL/\beta$, $V_{D,ss} = \{D[(A/\alpha^2) + (B/\beta^2)]\}/[(A/\alpha) + (B/\beta)]^2$.

If serum concentrations of a drug given as a continuous IV infusion decline in a biphasic manner after the infusion is discontinued, a two-compartment model describes the data set (Fig. 8-9).^{12,13} In this instance, the postinfusion concentrations decrease according to the equation $C = Re^{-\alpha t'} + Se^{-\beta t'}$, where t' is the postinfusion time ($t' = 0$ when infusion is discontinued), and R , S , α , and β are determined from the postinfusion concentrations using the method of residuals with the y axis set at $t' = 0$. R and S are used to compute A and B . A and B are the y intercepts that would have occurred had the total dose given during the infusion ($D = k_0 T$) been administered as an IV bolus dose:

$$A = \frac{RD\alpha}{k_0(1 - e^{-\alpha T})}$$

$$B = \frac{SD\beta}{k_0(1 - e^{-\beta T})}$$

Figure 8-9.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Calculation of α and β half-lives following a steady-state infusion. Inset shows calculation of the distribution rate constant (α) using the method of residuals.

where T is the duration of infusion. Once A , B , α , and β are known, the equations for an IV bolus are used to compute the pharmacokinetic constants. Often, when a drug is given as an IV bolus or continuous IV infusion, a two-compartment model is used to describe the data, but when the same agent is given extravascularly, a one-compartment model applies.¹⁴ In this case, distribution occurs during the absorption phase, so a distribution phase is not observed.

Volumes of Distribution in Multicompartment Models

Two different V_D values are needed as proportionality constants for drugs that require multicompartment models to describe the serum-concentration-versus-time curve. The V_D that is used to compute the amount of drug in the body during the terminal (β) portion of the curve is called $V_{D, \beta}$ (amount of drug in body = $V_{D, \beta} C$). During a continuous IV infusion at steady state, $V_{D, ss}$ is used to compute the amount of drug in the body (amount of drug in body = $V_{D, ss} C$). $V_{D, ss}$ is also the V_D that can be computed using the physiologic volumes of blood and tissues and

the ratio of unbound drug in blood to that in tissues [$V_{D,ss} = V_b + (f_b/f_t)V_t$]. Because the value of $V_{D,\beta}$ changes when CL changes, $V_{D,ss}$ should be used to indicate if drug distribution changes during pharmacokinetic or drug-interaction experiments.

Multiple Dosing and Steady-State Equations

Any of these compartmental equations can be used to determine serum concentrations after multiple doses. The multiple-dosing factor $(1 - e^{-nK\tau})/(1 - e^{-K\tau})$, where n is the number of doses, K is the appropriate rate constant, and τ is the dosage interval, is simply multiplied by each exponential term in the equation, substituting the rate constant of each exponent for K . Time (t) is set at 0 at the beginning of each dosage interval. For example, a single-dose two-compartment IV bolus is calculated as follows: $C = Ae^{-\alpha t} + Be^{-\beta t}$. Thus, the equation for a multiple-dose two-compartment IV bolus is

$$C = Ae^{-\alpha t} \frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}} + Be^{-\beta t} \frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}$$

A single-dose one-compartment IV bolus is calculated as $C = (D/V_D)e^{-kt}$. For a multiple-dose one-compartment IV bolus, the concentration is $C = (D/V_D)e^{-kt}[(1 - e^{-nk\tau})/(1 - e^{-k\tau})]$.

At steady state, the number of doses becomes large, $e^{-nK\tau}$ approaches zero, and the multiple-dosing factor equals $1/(1 - e^{-K\tau})$. Therefore, the steady-state versions of the equations are simpler than their multiple-dose counterparts:

$$C = \frac{Ae^{-\alpha t}}{1 - e^{-\alpha\tau}} + \frac{Be^{-\beta t}}{1 - e^{-\beta\tau}}$$

and

$$C = \frac{(D/V_D)e^{-kt}}{1 - e^{-k\tau}}$$

for a steady-state two-compartment IV bolus and a steady-state one-compartment IV bolus, respectively.

Use of Pharmacokinetic Concepts for Individualization of Drug Therapy

9 Many factors must be taken into consideration when deciding on the best drug dose for a patient. For example, the age of the patient is important because the dose (in milligrams per kilogram) for pediatric patients may be higher and for geriatric patients may be lower than the

typically prescribed dose for young adults. Gender also can be a factor because male and female patients metabolize and eliminate some drugs differently. Patients who are significantly obese or cachectic also may require different drug doses because of clearance and volume of distribution changes. Other drug therapy that could cause drug interactions needs to be considered. Disease states and conditions may alter the drug-dosage regimen for a patient. Three disease states that deserve special mention are CHF, renal disease, and hepatic disease. Renal and hepatic diseases cause loss of organ function and decreased drug elimination and metabolism. CHF causes decreased blood flow to organs that clear the drug from the body.

Many drug compounds are racemic mixtures of stereoisomers. In most cases, one of the isomers is more pharmacologically active than the other isomer, and each isomer may exhibit different pharmacokinetic properties. [Warfarin](#), [propranolol](#), [verapamil](#), and ibuprofen are all racemic mixtures of stereoisomers. Some drug interactions inhibit or increase the elimination of only one stereoisomer. The importance of the drug interaction depends on which isomer is affected. Other drugs, such as [dextromethorphan](#), [levofloxacin](#), and diltiazem, are composed of just one stereoisomer.

10 Genetics also plays a role in drug metabolism. *Cytochrome P450* is a generic term for the group of enzymes that are responsible for most drug metabolism oxidation reactions. Several cytochrome P450 (CYP) isozymes have been identified that are responsible for the metabolism of many important drugs ([Table 8–3](#)). CYP2C19 is responsible for aromatic hydroxylation of (S)-mephenytoin, and CYP2D6 oxidizes debrisoquine.¹⁵ These subsets of the cytochrome P450 enzyme family are also responsible for the metabolism of several other drugs (CYP2D6: many tricyclic antidepressants, codeine, (S)-metoprolol; CYP2C19: most proton pump inhibitors, [sertraline](#), [voriconazole](#)). CYP2C9, CYP2C19, and CYP2D6 isozymes appear to be under genetic control. As a consequence, there are “poor metabolizers” who have a defective mutant gene for the isozyme, cannot manufacture a fully functional isozyme, and therefore cannot metabolize the drug substrate very well. “Extensive metabolizers” have the standard gene for the isozyme and metabolize the drugs normally. Poor metabolizers usually are a minority of the general population. They may achieve toxic concentrations of a drug when usual doses are prescribed for them or, if the active drug moiety is a metabolite, may fail to have any pharmacologic effect from the drug. The ethnic background of the patient can affect the likelihood that the patient will be a poor metabolizer.¹⁵ For example, the incidence of poor metabolizers for CYP2D6 is ~5% to 10% for whites and ~0% to 1% for Asians, whereas for CYP2C19, poor metabolizers make up ~3% to 6% of the white population and ~20% of the Asian population. Approximately 7% of the whites are poor metabolizers for CYP2C9 substrates.

TABLE 8-3 Cytochrome P450 Enzyme Family and Selected Substrates

CYP1A2 Acetaminophen Caffeine Ondansetron Tacrine Theophylline <i>R</i> -warfarin Zileuton
CYP2C9 Candesartan Diclofenac Ibuprofen Losartin Naproxen Phenytoin Tolbutamide Valsartin <i>S</i> -warfarin
CYP2C19 Diazepam Lansoprazole (S)-mephenytoin Nelfinavir Omeprazole Pantoprazole

[Voriconazole](#)

CYP2D6

Carvedilol

Codeine

Debrisoquine

[Dextromethorphan](#)

Encainide

Fluoxetine

Haloperidol

(S)-metoprolol

[Paroxetine](#)

Propafenone

[Risperidone](#)[Thioridazine](#)[Venlafaxine](#)

CYP2E1

Enflurane

Ethanol

Halothane

[Isoflurane](#)

CYP3A4

Alfentanil

Alprazolam

Astemizole

[Carbamazepine](#)[Cyclosporine](#)

Diltiazem
Erythromycin
Felodipine
Itraconazole
Ketoconazole
Lidocaine
Lovastatin
Midazolam
Nifedipine
Quinidine
Simvastatin
Tacrolimus
Verapamil
Ziprasidone

Other cytochrome P450 isozymes have been isolated.¹⁵ CYP1A2 is the enzyme that is responsible for the demethylation of [caffeine](#) and [theophylline](#); CYP2C9 metabolizes phenytoin, [tolbutamide](#), [losartan](#), and ibuprofen; some antiretroviral protease inhibitors, [cyclosporine](#), [nifedipine](#), [lovastatin](#), [simvastatin](#), and atorvastatin are metabolized by CYP3A4; and ethanol is a substrate for CYP2E1. It is important to recognize that a drug may be metabolized by more than one cytochrome P450 isozyme. Although most tricyclic antidepressants are hydroxylated by CYP2D6, *N*-demethylation probably is mediated by a combination of CYP2C19, CYP1A2, and CYP3A4. [Acetaminophen](#) appears to be metabolized by both CYP1A2 and CYP2E1. The 4-hydroxy metabolite of [propranolol](#) is produced by CYP2D6, but side chain oxidation of [propranolol](#) is probably a product of CYP2C19. The CYP3A enzyme family comprises ~90% of the drug-metabolizing enzyme present in the intestinal wall but only ~30% of the drug-metabolizing enzyme found in the liver. The remainder of hepatic drug-metabolizing enzyme is ~20% for the CYP2C family, ~13% for CYP1A2, ~7% for CYP2E1, and ~2% for CYP2D6.

Understanding which cytochrome P450 isozyme is responsible for the metabolism of a drug is extraordinarily useful in predicting and understanding drug interactions. Some drug-metabolism inhibitors and inducers are highly selective for certain cytochrome P450 isozymes.¹⁵ Quinidine is an extremely potent inhibitor of the CYP2D6 enzyme system;¹⁵ a single 50 mg dose of quinidine can change a rapid metabolizer of debrisoquine into a poor metabolizer. [Ciprofloxacin](#) and [zileuton](#) inhibit, whereas tobacco and marijuana smoke induces, CYP1A2. Some drugs

that are enzyme inhibitors are also substrates for that same enzyme system and appear to cause drug interactions by being a competitive inhibitor. For example, [erythromycin](#) is both a substrate for and an inhibitor of CYP3A4. Obviously, if one knows that a new drug is metabolized by a given cytochrome P450 enzyme system, it is logical to assume that the new drug will exhibit drug interactions with the known inducers and inhibitors of that cytochrome P450 isozyme.

11 The importance of transport proteins in drug bioavailability and elimination is now better understood. A principal transport protein involved in the movement of drugs across biologic membranes is P-gp. P-gp is present in many organs, including the GI tract, liver, and kidney. If a drug is a substrate for P-gp, its oral absorption may be decreased when P-gp transports drug molecules that have been absorbed back into the GI tract lumen. In the liver, some drugs are transported by P-gp from the blood into the bile, where the drug is eliminated by biliary secretion. Similarly, some drugs eliminated by the kidney are transported from the blood into the urine by P-gp. [Digoxin](#) is a substrate of P-gp. Other possible mechanisms for drug interactions are when two drugs that are substrates for P-gp compete for transport by the protein and when a drug is an inhibitor or inducer of P-gp. Drug interactions involving inhibition of P-gp decrease drug transportation in these organs and potentially can increase GI absorption of an orally administered drug, decrease biliary secretion of the drug, or decrease renal elimination of drug molecules. The drug interaction between amiodarone and [digoxin](#) probably involves all three of these mechanisms; this explains why [digoxin](#) concentrations increase so dramatically in patients receiving amiodarone. Many drugs that are metabolized by CYP3A4 are also substrates for P-gp, and some of the drug interactions attributed to inhibition of CYP3A4 may be a result of decreased drug transportation by P-gp. Drug interactions involving induction of P-gp have the opposite effect in these organs and may decrease GI absorption of an orally administered drug, increase biliary secretion of the drug, or increase renal elimination of drug molecules.

Selection of Initial Drug Doses

12 When deciding on initial doses for drugs that are eliminated renally, the patient's renal function should be assessed. A common, useful way to do this is to measure the patient's serum creatinine concentration and convert this value into a $CL_{Cr \text{ est}}$. Serum creatinine values alone should not be used to assess renal function because they do not include the effects of age, body weight, or gender. The Cockcroft-Gault equation¹⁶ is probably the most widely used method to estimate creatinine clearance (in milliliters per minute) in adults (age 18 years or older) who are within ~30% of their ideal body weight and have stable renal function:

$$\text{Men: } CL_{Cr \text{ est}} = \frac{(140 - \text{age})BW}{S_{Cr} \times 72}$$

$$\text{Women: } CL_{Cr \text{ est}} = \frac{0.85(140 - \text{age})BW}{S_{Cr} \times 72}$$

where BW is body weight (in kilograms), age is the patient's age (in years), 0.85 is a correction factor to account for lower muscle mass in women, and S_{Cr} is serum creatinine (in milligrams per deciliter). For children, the following estimation equations are available according to the age of the child:¹⁷ age 0 to 1 year: $CL_{Cr\ est} \text{ (in mL/min/1.73 m}^2\text{)} = (0.45 \times Lt)/S_{Cr}$; age 1 to 20 years: $CL_{Cr\ est} \text{ (in mL/min/1.73 m}^2\text{)} = (0.55 \times Lt)/S_{Cr}$, where Lt is patient length in centimeters. (To use these equations, S_{Cr} expressed in $\mu\text{mol/L}$ must first be divided by 88.4 to obtain conventional units of mg/dL. Conversion of CL_{Cr} to units of mL/s/m² requires multiplication of CL_{Cr} expressed in milliliters per minute per 1.73 m² by 0.00963.) Other methods to determine $CL_{Cr\ est}$ for obese adults¹⁸ and patients with rapidly changing renal function¹⁹ are available. Creatinine is a by-product of muscle breakdown in the body, so none of these estimation methods work well in patients with muscle disease, such as multiple sclerosis, or diseases that alter muscle mass, such as cachexia, malnutrition, cancer, or spinal cord injury. Nomograms that adjust initial doses according to a patient's renal function are available for several drugs, including digoxin,²⁰ vancomycin,²¹ and the aminoglycoside antibiotics.²²

For drugs that are eliminated primarily by the kidney ($\geq 60\%$ of the administered dose), some agents will need minor dosage adjustments for $CL_{Cr\ est}$ between 30 and 60 mL/min (0.50 and 1.00 mL/s), moderate dosage adjustments for $CL_{Cr\ est}$ between 15 and 30 mL/min (0.25 and 0.50 mL/s), and major dosage adjustments for $CL_{Cr\ est}$ less than 15 mL/min (0.25 mL/s). Specific recommendations for dosage adjustments of other drugs for patients with renal disease are available.^{23,24} Supplemental doses of some medications also may be needed for patients receiving hemodialysis if the drug is removed by the artificial kidney or for patients receiving hemoperfusion if the drug is removed by the hemofilter.²⁴

13 A similar assessment of liver function should be made for drugs that are metabolized hepatically. Unfortunately, there is no single test that can estimate liver drug-metabolism capacity accurately, and those that are used do not always prove accurate. High aminotransferase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and alkaline phosphatase concentrations usually indicate acute hepatic cellular damage and do not establish poor liver drug metabolism reliably. Abnormal values for three tests that usually indicate that drugs will be metabolized poorly by the liver are high serum bilirubin concentration, low serum albumin concentration, and a prolonged prothrombin time. Bilirubin is metabolized by the liver, and albumin and clotting factors are manufactured by the liver, so aberrant values for all three of these tests are a more reliable indicator of abnormal liver drug metabolism. The Child-Pugh score,²⁵ a widely used clinical classification for liver disease that incorporates clinical signs and symptoms (ascites and hepatic encephalopathy), in addition to these three laboratory tests, can be used as an indicator of a patient's ability to metabolize drugs that are eliminated by the liver. A score in excess of 10 suggests very poor liver function. As a general rule, patients with cirrhosis have the most severe decreases in liver drug metabolism. Patients with acute or chronic hepatitis often retain relatively normal or slightly decreased hepatic drug-metabolism capacity. In the absence of specific pharmacokinetic dosing guidelines for a medication, a Child-Pugh score equal to 8 to 9 is grounds for a moderate decrease ($\sim 25\%$) in initial daily drug dose for agents that are

metabolized primarily ($\geq 60\%$) hepatically, and a score of 10 or greater indicates that a significant decrease in initial daily dose ($\sim 50\%$) is required for drugs that are metabolized mostly by the liver. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects.

Because there are no good markers of liver function, clinicians have come to rely on pharmacokinetic parameters derived in various patient populations to compute initial doses of drugs that are eliminated hepatically. [Table 8–4](#) contains average pharmacokinetic parameters for [theophylline](#) in several disease states. Initial doses of many liver-metabolized drugs are computed by determining which disease states and/or conditions the patient has that are known to alter the kinetics of the drug and by using these average pharmacokinetic constants to calculate doses. The patient is then monitored for therapeutic and adverse effects, and drug serum concentrations are obtained to ensure that concentrations are appropriate and to adjust doses, if necessary. The following computations illustrate the estimated IV loading dose and the IV continuous infusion necessary to achieve a [theophylline](#) concentration of 10 mg/L (10 mcg/mL; 55.5 $\mu\text{mol/L}$) for a 55-year-old, 70 kg (154 lb) man with liver cirrhosis (mean kinetic parameters obtained from [Table 8–4](#)):

$$\begin{aligned}
 V_D &= (0.5 \text{ L/kg})(70 \text{ kg}) = 35 \text{ L} \\
 LD &= C_{ss}V_D = (10 \text{ mg/L})(35 \text{ L}) \\
 &= 350 \text{ mg theophylline infused over 20 to 30 min} \\
 CL(\text{in L/h}) &= \frac{(0.35 \text{ mL/min/kg})(70 \text{ kg})(60 \text{ min/h})}{1000 \text{ mL/L}} \\
 &= 1.5 \text{ L/h} \\
 k_0 &= C_{ss}CL = (10 \text{ mg/L})(1.5 \text{ L/h}) \\
 &= 15 \text{ mg/h of theophylline to begin after loading dose is given}
 \end{aligned}$$

TABLE 8-4 Theophylline Pharmacokinetic Parameters for Selected Disease States/Conditions

Disease State/Condition	Mean Clearance (mL/min/kg)	Mean Dose (mg/kg/h)
Children 1–9 years old	1.4	0.8
Children 9–12 years old or adult smokers	1.25	0.7
Adolescents 12–16 years old or elderly smokers (> 65 years)	0.9	0.5
Adult nonsmokers	0.7	0.4
Elderly nonsmokers (> 65 years)	0.5	0.3
Decompensated CHF, cor pulmonale, cirrhosis	0.35	0.2

Mean volume of distribution = 0.5 L/kg.

CHF = congestive heart failure

Data from Edwards DJ, Zarowitz BJ, Slaughter RL. *Theophylline*. In: Evans E, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. Vancouver, WA: *Applied Therapeutics*; 1992:13–1-13–38.

If theophylline is to be given as the aminophylline salt form, each dose would need to be changed to reflect the fact that aminophylline contains only 85% theophylline ($LD = 350 \text{ mg of theophylline} / 0.85 = 410 \text{ mg of aminophylline}$ infused over 20 to 30 minutes, $k_0 = 15 \text{ mg/h of theophylline} / 0.85 = 18 \text{ mg/h of aminophylline}$ to begin after loading dose is given).

Heart failure is often overlooked as a disease state that can alter drug disposition. Severe heart failure decreases cardiac output and therefore reduces liver blood flow. Theophylline,²⁶ lidocaine,²⁷ and drugs with high extraction ratios are compounds whose clearance declines with decreased liver blood flow. Initial dosages of these drugs should be reduced in patients with moderate to severe heart failure (New York Heart Association class III or IV) by 25% to 50% until steady-state concentrations and response can be determined.

Use of Steady-State Drug Concentrations

14 Serum drug concentrations are readily available to clinicians to use as guides for the individualization of drug therapy. The therapeutic ranges for several drugs have been identified, and it is likely that new drugs also will be monitored using serum concentrations. Although several individualization methods have been advocated for specific drugs, one simple, reliable method is used commonly. For drugs that exhibit linear pharmacokinetics, C_{SS} changes proportionally with the dose. To adjust a patient's drug therapy, a reasonable starting dose is administered for an estimated three to five half-lives. A serum concentration is obtained, assuming that it will reflect C_{SS} . Independent of the route of administration, the new dose (D_{new}) needed to attain the desired C_{SS} ($C_{SS,new}$) is calculated: $D_{new} = D_{old}(C_{SS,new}/C_{SS,old})$, where D_{old} and $C_{SS,old}$ are the old dose and old C_{SS} , respectively. To use this method, $C_{SS,old}$ must reflect steady-state conditions. Often patients are noncompliant with regard to their drug dosage and therefore are not at steady state. This occurs not only in outpatients but also in hospital inpatients. Inpatients can spit out oral doses or alter the infusion rates on IV pump rates after the nurse leaves the hospital room. Doses also can be missed if the patient is absent from his or her room at the time medications are to be administered. If $C_{SS,old}$ is much larger or smaller than expected for the D_{old} the patient is taking, one should suspect noncompliance and repeat the serum concentration determination after another three to five half-lives or change the patient's dose cautiously and monitor for signs of toxicity or lack of effect.

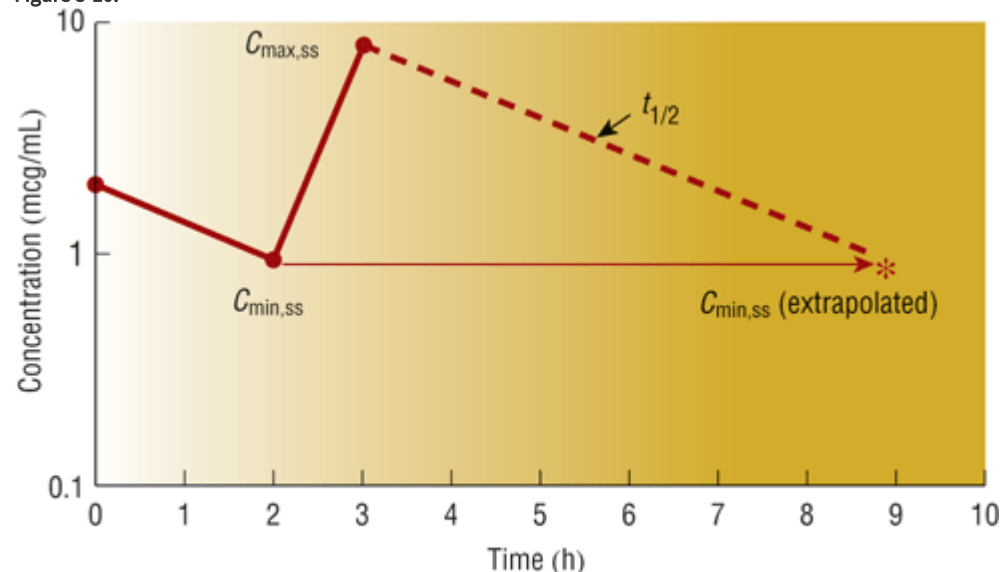
Measurement of Pharmacokinetic Parameters in Patients

15 If it is necessary to determine the kinetic constants for a patient to individualize his or her dose, a small kinetic evaluation is conducted in the individual. In these cases, the number of serum concentrations obtained from the patient is held to the minimum needed to calculate accurate pharmacokinetic parameters and doses. The reason for using fewer serum drug concentration determinations is to be as cost-effective as possible because these laboratory tests generally cost \$20 to \$50 each.

Although many drugs follow two-compartment-model pharmacokinetics (especially after IV administration), a one-compartment model is used to compute kinetic parameters in patients because too many serum concentration determinations would be needed to determine accurately both the distribution and elimination phases found in the two-compartment model. Because of this, serum concentrations usually are not measured in patients during the distribution phase. Another important reason serum concentrations are not measured during the distribution phase for therapeutic drug-monitoring purposes in patients is that drug in the blood and drug in the tissues are not in equilibrium during this time, so that serum concentrations do not reflect tissue concentrations. When drug serum concentrations are obtained in patients for the purpose of assessing efficacy or toxicity, it is important that they be measured in the postdistribution phase when drug in the blood is in equilibrium with drug at the site of action.

In the case where the patient has received enough doses to be at steady state, pharmacokinetic parameters can be computed using a predose minimum concentration and a postdose maximum concentration. Under steady-state conditions, serum concentrations after each dose are identical, so the predose minimum concentration is the same before each dose (Fig. 8-10). This situation allows the predose concentration to be used to compute both the patient's $t_{1/2}$ and V ($V = \text{Dose} / (C_{\max,ss} - C_{\min,ss})$). If the drug was given extravascularly or has a significant distribution phase, the postdose concentration should be determined after absorption or distribution is finished. To ensure that steady-state conditions have been achieved, the patient needs to receive the drug on schedule for at least three to five estimated half-lives. To make sure that this is the case, inpatients should have their medication administration records checked, and the patient's nurse should be consulted regarding missed or late doses. Outpatients should be interviewed about compliance with the prescribed dosage regimen. When compliance with the dosage regimen has been verified, steady-state conditions reasonably can be assumed.

Figure 8-10.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

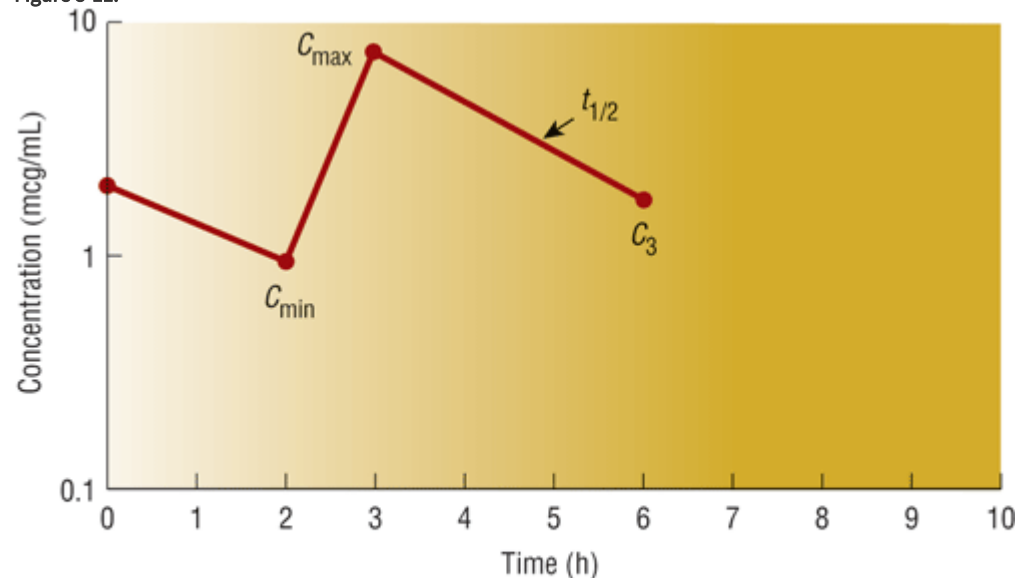
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When a patient has received enough doses to be at steady state, steady-state maximum ($C_{\max,ss}$) and minimum ($C_{\min,ss}$) concentrations can be used to compute clearance, volume of distribution, and half-life. At steady state, consecutive $C_{\min,ss}$ values are equal, so the predose value can be extrapolated to the time before the next dose and used to calculate the half-life (*dashed line*).

If the patient is not at steady state, an additional postdose serum concentration determination should be done to compute the patient's pharmacokinetic parameters. Ideally, the third concentration (C_3) should be acquired approximately one estimated half-life after the postdose

maximum concentration. Determining serum concentrations too close together will hamper the drug assay's ability to measure differences between them, and getting the third sample too late could result in a concentration too low for the assay to detect. In this situation, the predose minimum and postdose maximum concentrations are used to compute V ($V = \text{Dose} / (C_{\max} - C_{\min})$), and both postdose concentrations are used to calculate $t_{1/2}$ (Fig. 8-11).

Figure 8-11.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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If a patient has not received enough doses to be at steady state, or doses have been given on an irregular schedule, the minimum concentration (C_{\min}), maximum concentration (C_{\max}), and an additional postdose concentration (C_3) can be used to compute clearance, volume of distribution, and half-life.

After CL, V , and $t_{1/2}$ have been computed for a patient, the dose and dosage interval necessary to achieve desired steady-state serum concentrations can be calculated using one-compartment-model equations. Specific examples of these methods to calculate initial doses and individualized doses using serum concentrations are discussed later in this chapter for the aminoglycoside antibiotics, [vancomycin](#), [digoxin](#), [theophylline](#), phenytoin, and [cyclosporine](#).

Computer Programs

Computer programs that aid in the individualization of therapy are available for many different drugs. The most sophisticated programs use nonlinear regression to fit CL and V_D to actual serum concentrations obtained in a patient.²⁸ After drug doses and serum concentrations are entered into the computer, nonlinear least-squares regression programs adjust CL and V_D until the sum of the squared error between actual (C_{act}) and computer-estimated concentrations (C_{est}) is at a minimum $[\Sigma(C_{est} - C_{act})^2]$. Once estimates of CL and V_D are available, doses are calculated easily.

Many programs also take into account what the CL and V_D should be on the basis of disease states and conditions present in the patient.²⁹ Incorporation of expected population-based parameters allows the computer to use a limited number of serum concentrations (one or two) to provide estimates of CL and V_D . This type of computer program is called Bayesian because it incorporates portions of Bayes' theorem during the fitting routine.³⁰ Bayesian pharmacokinetic dosing programs are used widely to adjust the dose of a variety of drugs. In the case of renally eliminated drugs (e.g., aminoglycosides, **vancomycin**, and **digoxin**), population estimates for kinetic parameters are generated by entering the patient's age, weight, height, gender, and serum creatinine concentration into the computer program. For hepatically eliminated drugs (e.g., **theophylline** and phenytoin), population estimates for kinetic parameters are computed using the patient's age, weight, and gender, as well as other factors that might change hepatic clearance, such as the presence or absence of disease states (e.g., cirrhosis or CHF) or other drug therapy that might cause a drug interaction. The population-based estimates of the pharmacokinetic parameters are then modified using nonlinear least-squares regression fits of serum concentrations to result in individualized parameters for the patient. The individualized parameters are used to compute doses for the patient that will result in desired steady-state concentrations of the drug.

Aminoglycosides

Although aminoglycoside pharmacokinetics follow multicompartment models,³¹ a one-compartment model appears sufficient to individualize doses in patients.³² Aminoglycosides usually are given as short-term intermittent IV infusions and administered as a single daily dose or multiple doses per day. Initial doses for aminoglycosides can be computed using estimated kinetic parameters derived from population pharmacokinetic data. The elimination rate constant is estimated using the patient's creatinine clearance in the following formula: $k \text{ (in h}^{-1}\text{)} = 0.00293(\text{CL}_{Cr}) + 0.014$, where CL_{Cr} is the measured or estimated creatinine clearance in milliliters per minute. The volume of distribution is estimated using the average population value for normal-weight (within 30% of ideal weight) individuals equal to 0.26 L/kg [$V = 0.26(\text{Wt})$, where Wt is the patient's weight] or for obese individuals (>30% of ideal weight)³³ by taking into account the patient's excess adipose tissue: $V = 0.26[\text{IBW} + 0.4(\text{TBW} - \text{IBW})]$, where TBW is total body weight, IBW is ideal body weight [$\text{IBW}_{\text{males}}$ (in kilograms) = $50 + 2.3(\text{Ht} - 60)$ or $\text{IBW}_{\text{females}}$ (in kilograms) = $45 +$

2.3(Ht – 60), and Ht is the patient's height in inches] (height in cm can be converted to inches by multiplying by 0.394). Additional volume of distribution population estimates are available for other disease states and conditions, such as cystic fibrosis,³⁴ ascites,³⁵ and neonates.³⁶

Appropriate $C_{\max,ss}$ and $C_{\min,ss}$ values are selected for the patient based on the site and severity of the infection and the sensitivity of the known or suspected pathogen, as well as avoidance of adverse effects. For example, $C_{\max,ss}$ values of 8 to 10 mg/L (8 to 10 mcg/mL) generally are selected for gram-negative pneumonia patients, whereas $C_{\min,ss}$ values of less than 2 mg/L (2 mcg/mL; 4 μ mol/L) usually are chosen to avoid aminoglycoside-induced nephrotoxicity when **tobramycin** and **gentamicin** are prescribed using conventional multiple-daily-dosing regimens. Once appropriate steady-state serum concentrations are selected, the dosage interval required to achieve those concentrations is calculated, and τ is rounded to a clinically acceptable value (e.g., 8, 12, 18, 24, 36, or 48 hours): $\tau = [(\ln C_{\max,ss} - \ln C_{\min,ss})/k] + T$. Finally, a dose is computed for the patient using the one-compartment-model intermittent IV infusion equation at steady state, and the dose is rounded off to the nearest 5 to 10 mg:

$$D = TkV_D C_{\max,ss} \frac{1 - e^{-k\tau}}{1 - e^{-kT}}$$

The Hull and Sarrubi aminoglycoside dosage nomogram (Table 8–5) is based on this dosage-calculation method and includes precalculated doses and dosage intervals for a variety of creatinine clearance values.²² The nomogram assumes that $V_D = 0.26$ L/kg and should not be used to compute doses for disease states with altered V_D .

TABLE 8-5 Aminoglycoside Dosage Chart

Percentage of Loading Dose Required for Dosage Interval Selected				
CrCl (mL/min) ^b	Estimated Half-Life (h)	8 h (%)	12 h (%)	24 h (%)
1. Compute the patient's creatinine clearance (CrCl) using the Cockcroft-Gault method: $\text{CrCl} = [(140 - \text{age})\text{BW}] / (\text{Scr} \times 72)$ where Scr is expressed in units of mg/dL. Multiply by 0.85 for women. (Scr expressed in $\mu\text{mol/L}$ must be divided by 88.4 to obtain conventional units of mg/dL.)				
2. Use the patient's weight if within 30% of IBW; otherwise use adjusted dosing weight = $\text{IBW} + [0.40(\text{TBW} - \text{IBW})]$ where IBW and TBW are expressed in kg.				
3. Select the loading dose in mg/kg to provide peak serum concentrations in the range listed below for the desired aminoglycoside antibiotic:				
Aminoglycoside	Usual Loading Doses	Expected Peak Serum Concentrations		
Tobramycin	1.5–2 mg/kg	4–10 mcg/mL or mg/L		
		9 to 21 $\mu\text{mol/L}$		
Gentamicin		4 to 10 mcg/mL or mg/L		
		8 to 21 $\mu\text{mol/L}$		
Netilmicin		4 to 10 mcg/mL or mg/L		
		8 to 21 $\mu\text{mol/L}$		
Amikacin	5–7.5 mg/kg	15–30 mcg/mL or mg/L		
		26 to 51 $\mu\text{mol/L}$		

Percentage of Loading Dose Required for Dosage Interval Selected				
CrCl (mL/min) ^b	Estimated Half-Life (h)	8 h (%)	12 h (%)	24 h (%)
Kanamycin		15 to 30 mcg/mL or mg/L		
		31 to 62 μmol/L		
4. Select the maintenance dose (as a percentage of the loading dose) to continue peak serum concentrations indicated above according to the desired dosage interval and the patient's creatinine clearance. To maintain the usual peak/trough ratio, use dosage intervals in clear areas.				
>90	2–3	90	—	—
90	3.1	84	—	—
80	3.4	80	91	—
70	3.9	76	88	—
60	4.5	71	84	—
50	5.3	65	79	—
40	6.5	57	72	92
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75

Percentage of Loading Dose Required for Dosage Interval Selected				
CrCl (mL/min) ^b	Estimated Half-Life (h)	8 h (%)	12 h (%)	24 h (%)
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10 ^a	20.4	24	34	56
7 ^a	25.9	19	28	47
5 ^a	31.5	16	23	41
2 ^a	46.8	11	16	30
0 ^a	69.3	8	11	21

^aDosing for patients with CrCl ≤10 mL/min should be assisted by measuring serum concentrations.

^bCrCl expressed in mL/min can be converted to units of mL/s by multiplying by 0.0167.

BW = body weight, IBW = ideal body weight, Scr = serum creatinine, TBW = total body weight

Data from Sarubbi FA, Hull JH. *Amikacin* serum concentrations: Predictions of levels and dosage guidelines. *Ann Intern Med* 1978;89:612–618.

An example of this initial dosage scheme for a typical case is provided to illustrate the use of the various equations. Mr. JJ is a 65-year-old, 80 kg (176 lb), 6-ft-tall (72 in. or 183 cm) man with the diagnosis of gram-negative pneumonia. His serum creatinine concentration is 2.1 mg/dL (186

$\mu\text{mol/L}$) and is stable. Compute a conventional **gentamicin** dosage regimen (infused over 1 hour) that would provide approximate peak and trough concentrations of $C_{\text{max,ss}} = 8 \text{ mg/L}$ (8 mcg/mL; 17 $\mu\text{mol/L}$) and $C_{\text{min,ss}} = 1.5 \text{ mg/L}$ (1.5 mcg/mL; 3.1 $\mu\text{mol/L}$), respectively. The patient is within 30% of his ideal body weight [$\text{IBW}_{\text{male}} = 50 + 2.3(72 \text{ in} - 60) = 78 \text{ kg}$] and has stable renal function, so the Cockcroft-Gault creatinine clearance estimation equation can be used: $\text{CL}_{\text{Cr est}} = [(140 - 65 \text{ y})80 \text{ kg}]/[72(2.1 \text{ mg/dL})] = 40 \text{ mL/min}$ (0.67 mL/s). The patient's weight and estimated creatinine clearance are used to compute his V and k , respectively: $V = 0.26 \text{ L/kg}(80 \text{ kg}) = 20.8 \text{ L}$; $k = 0.00293(40 \text{ mL/min}) + 0.014 = 0.131 \text{ h}^{-1}$ or $t_{1/2} = 0.693/0.131 \text{ h}^{-1} = 5.3 \text{ h}$. The dosage interval and dose for the desired serum concentrations would then be calculated: $\tau = [(\ln 8 \text{ mg/L} - \ln 1.5 \text{ mg/L})/0.131 \text{ h}^{-1}] + 1 \text{ h} = 13.7 \text{ h}$ rounded to 12 h; $D = (1 \text{ h})(0.131 \text{ h}^{-1})(20.8 \text{ L})(8 \text{ mg/L}) [1 - e^{-(0.131 \text{ h}^{-1}(12 \text{ h}))}]/[1 - e^{-(0.131 \text{ h}^{-1}(1 \text{ h}))}] = 140 \text{ mg}$. Thus, the prescribed dose would be **gentamicin** 140 mg every 12 hours administered as a 1-hour infusion. If a loading dose were deemed necessary, it would be given as the first dose [$\text{LD} = (20.8 \text{ L})(8 \text{ mg/L}) = 166 \text{ mg}$ rounded to 170 mg infused over 1 hour], and the first maintenance dose would be administered 12 hours (e.g., one dosage interval) later. Using the Hull and Sarrubi nomogram for the same patient, the loading dose is 160 mg (**gentamicin** loading dose for serious gram-negative infection is 2 mg/kg; $2 \text{ mg/kg} \times 80 \text{ kg} = 160 \text{ mg}$), and the maintenance dose is 115 mg every 12 hours (for a 12-hour dosage interval and $\text{CL}_{\text{Cr est}} = 40 \text{ mL/min}$ (0.65 mL/s), maintenance dose is 72% of the loading dose: $0.72 \times 160 \text{ mg} = 115 \text{ mg}$).

For extended-interval therapy, $C_{\text{max,ss}}$ values of 20 to 30 mg/L (20 to 30 mcg/mL; 42 to 63 $\mu\text{mol/L}$) and $C_{\text{min,ss}}$ values less than 1 mg/L (1 mcg/mL; 2 $\mu\text{mol/L}$) generally are accepted as appropriate for gram-negative pneumonia patients. A minimum 24-hour dosage interval is chosen for this dosing technique, and the dosing interval is increased in 12- to 24-hour increments for patients with renal dysfunction.

An example of this initial dosage scheme for the same case is provided to illustrate the use of extended-interval dosing. Mr. JJ is a 65-year-old, 80 kg (176 lbs), 6-ft-tall (72 in. or 183 cm) man with the diagnosis of gram-negative pneumonia. His serum creatinine concentration is 2.1 mg/dL (186 $\mu\text{mol/L}$) and is stable. Compute an extended-interval **gentamicin** dosage regimen (infused over 1 hour) that would provide approximate peak and trough concentrations of $C_{\text{max,ss}} = 25 \text{ mg/L}$ (25 mcg/mL; 52 $\mu\text{mol/L}$) and $C_{\text{min,ss}} = 0.5 \text{ mg/L}$ (0.5 mcg/mL; 1 $\mu\text{mol/L}$), respectively. The patient is within 30% of his ideal body weight [$\text{IBW}_{\text{male}} = 50 + 2.3(72 \text{ in} - 60) = 78 \text{ kg}$] and has stable renal function, so the Cockcroft-Gault creatinine clearance estimation equation can be used: $\text{CL}_{\text{Cr est}} = [(140 - 65 \text{ y})80 \text{ kg}]/[72(2.1 \text{ mg/dL})] = 40 \text{ mL/min}$ (0.67 mL/s). The patient's weight and estimated creatinine clearance are used to compute his V and k , respectively: $V = 0.26 \text{ L/kg}(80 \text{ kg}) = 20.8 \text{ L}$; $k = 0.00293(40 \text{ mL/min}) + 0.014 = 0.131 \text{ h}^{-1}$ or $t_{1/2} = 0.693/0.131 \text{ h}^{-1} = 5.3 \text{ h}$. The dosage interval and dose for the desired serum concentrations would then be calculated: $\tau = [(\ln 25 \text{ mg/L} - \ln 0.5 \text{ mg/L})/0.131 \text{ h}^{-1}] + 1 \text{ h} = 31 \text{ h}$ rounded to 36 h; $D = (1 \text{ h})(0.131 \text{ h}^{-1})(20.8 \text{ L})(25 \text{ mg/L}) [1 - e^{-(0.131 \text{ h}^{-1}(36 \text{ h}))}]/[1 - e^{-(0.131 \text{ h}^{-1}(1 \text{ h}))}] = 550 \text{ mg}$. Thus, the prescribed dose would be **gentamicin** 550 mg every 36 hours administered as a 1-hour infusion.

Sidebar: Clinical Controversy

Some clinicians use conventional dosing or extended-interval dosing exclusively for patients requiring aminoglycosides, whereas others use a mix of both approaches according to the perceived benefit to the patient. Definitive, authoritative recommendations to guide the choice of one method of aminoglycoside dosing over the other are not available.

If appropriate aminoglycoside serum concentrations are available, kinetic parameters can be calculated at any point in therapy. When the patient is not at steady state, serum aminoglycoside concentrations are obtained before a dose (C_{\min}), after a dose administered as an IV infusion of ~1 hour or as a 30-minute infusion followed by a 30-minute waiting period to allow for drug distribution (C_{\max}), and at one additional postdose time (C_3) approximately one estimated half-life after C_{\max} . The $t_{1/2}$ and k values are computed using C_{\max} and C_3 : $k = (\ln C_{\max} - \ln C_3) / \Delta t$ and $t_{1/2} = 0.693 / k$, where Δt is the time that expired between the times C_{\max} and C_3 were obtained. If the patient is at steady state, serum aminoglycoside concentrations are obtained before a dose ($C_{\min,ss}$) and after a dose administered as an IV infusion of ~1 hour or as a 30-minute infusion followed by a 30-minute waiting period to allow for drug distribution ($C_{\max,ss}$). Because the patient is at steady state, it can be assumed that $C_{\min,ss}$ is identical for each dosage interval. The $t_{1/2}$ and k values are computed using $C_{\max,ss}$ and $C_{\min,ss}$: $k = (\ln C_{\max,ss} - \ln C_{\min,ss}) / (\tau - T)$ and $t_{1/2} = 0.693 / k$, where τ is the dosage interval, and T is the dose infusion time or dose infusion time plus waiting time.

Assuming a one-compartment model, the following equation is used to compute V_D :³²

$$V_D = \frac{(D/T)(1 - e^{-kT})}{k(C_{\max} - C_{\min}e^{-kT})}$$

where D is the dose, and T is the duration of infusion. Once these are known, the dose and dosage interval (τ) can be calculated for any desired maximum C_{ss} ($C_{\max,ss}$) and minimum C_{ss} ($C_{\min,ss}$):

$$\tau = \frac{\ln C_{\max,ss} - \ln C_{\min,ss}}{k} + T$$

$$D = TkV_D C_{\max,ss} \frac{1 - e^{-k\tau}}{1 - e^{-kT}}$$

The dose and dosage interval should be rounded to provide clinically accepted values (every 8, 12, 18, 24, 36, and 48 hours for dosage interval, nearest 5 to 10 mg for conventional dosing or every 24, 36, and 48 hours for dosage interval, or nearest 10 to 25 mg for extended interval dosing).

This method also has been used to individualize IV theophylline dosage regimens.³⁷

To provide an example of this technique, the problem given previously for conventional dosing will be extended to include steady-state concentrations. Please note that this method of dosage adjustment using serum concentrations can also be used for extended-interval dosing. Mr. JJ was prescribed [gentamicin](#) 140 mg every 12 hours (infused over 1 hour) for the treatment of gram-negative pneumonia. Steady-state trough ($C_{\min,ss}$) and peak ($C_{\max,ss}$) values were obtained before and after the fourth dose was given (more than three to five estimated half-lives), respectively, and equaled $C_{\min,ss} = 2.8 \text{ mg/L}$ (2.8 mcg/mL; $5.9 \text{ } \mu\text{mol/L}$) and $C_{\max,ss} = 8.5 \text{ mg/L}$ (8.5 mcg/mL; $18 \text{ } \mu\text{mol/L}$). Clinically, the patient was improving with decreased white blood cell counts and body temperatures and a resolving chest radiograph. However, the serum creatinine value had increased to 2.5 mg/dL ($221 \text{ } \mu\text{mol/L}$). Because of this, a new dosage regimen with a similar peak (to maintain high intrapulmonary levels) but lower trough (to decrease the risk of drug-induced nephrotoxicity) concentrations was suggested. The patient's elimination rate constant and half-life can be computed using the following formulas: $k = (\ln 8.5 \text{ mg/L} - \ln 2.8 \text{ mg/L}) / (12 \text{ h} - 1 \text{ h}) = 0.101 \text{ h}^{-1}$ and $t_{1/2} = 0.693 / 0.101 \text{ h}^{-1} = 6.9 \text{ h}$. The patient's volume of distribution can be calculated using the following equation:

$$V = \frac{(140 \text{ mg/1 h}) [1 - e^{-(0.101 \text{ h}^{-1})(1 \text{ h})}]}{(0.101 \text{ h}^{-1}) \{8.5 \text{ mg/L} - [(2.8 \text{ mg/L})e^{-(0.101 \text{ h}^{-1})(1 \text{ h})}]\}} = 22.3 \text{ L}$$

Thus, the patient's volume of distribution was larger and half-life was longer than originally estimated; this led to higher serum concentrations than anticipated. To achieve the desired serum concentrations ($C_{\min,ss} = 1.5 \text{ mg/L}$ [1.5 mcg/mL ; $3.1 \text{ } \mu\text{mol/L}$] and $C_{\max,ss} = 8 \text{ mg/L}$ [8.0 mcg/mL ; $17 \text{ } \mu\text{mol/L}$]), the patient's actual kinetic parameters are used to compute a new dose and dosage interval: $\tau = [(\ln 8 \text{ mg/L} - \ln 1.5 \text{ mg/L}) / 0.101 \text{ h}^{-1}] + 1 \text{ h} = 17.6 \text{ h}$, rounded to 18 h and

$$D = (1 \text{ h})(0.101 \text{ h}^{-1})(8 \text{ mg/L}) \frac{(1 - e^{-(0.101 \text{ h}^{-1})(18 \text{ h})})}{(1 - e^{-(0.101 \text{ h}^{-1})(1 \text{ h})})}$$

= 157 mg, round to 160 mg

Thus, the new dose would be [gentamicin](#) 160 mg every 18 hours and infused over 1 hour; the first dose of the new dosage regimen would be given 18 hours (e.g., the new dosage interval) after the last dose of the old dosage regimen.

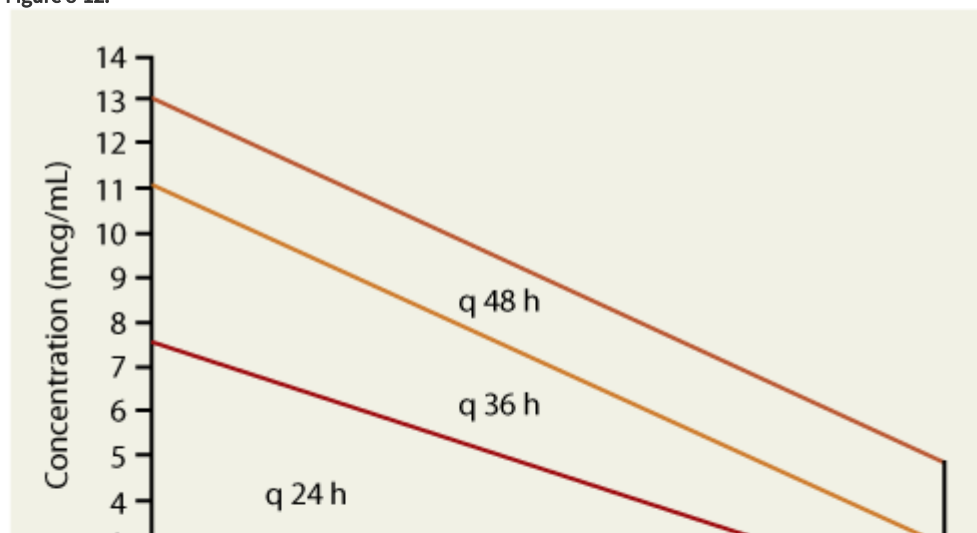
Because aminoglycoside antibiotics exhibit concentration- dependent bacterial killing, and the postantibiotic effect is longer with higher concentrations, investigators studied the possibility of giving a higher dose of aminoglycoside using an extended-dosage interval (24 hours or longer, depending on renal function). Generally, these studies have shown comparable microbiologic and clinical cure rates for many infections and about the same rate of nephrotoxicity (~5–10%) as with conventional dosing. Ototoxicity has not been monitored using audiometry in most

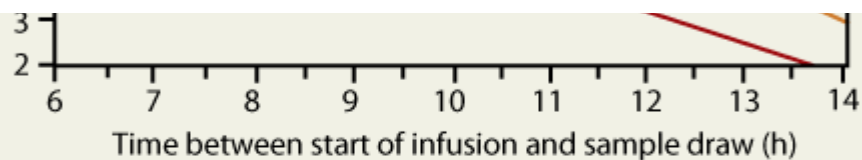
of these investigations, but loss of hearing in the conversational range, as well as signs and symptoms of vestibular toxicity, usually has been assessed and found to be similar to that with aminoglycoside therapy dosed conventionally. Based on these data, clinicians are using extended-interval dosing in selected patients. For *Pseudomonas aeruginosa* infections where the organism has an expected minimum inhibitory concentration (MIC) \approx 2 mg/L, peak concentrations between 20 and 30 mg/L (20 and 30 mcg/mL) and trough concentrations less than 1 mg/L (1 mcg/mL; 2 μ mol/L) for **gentamicin** or **tobramycin** have been suggested.³⁸

At the present time, there is no consensus on how to approach concentration monitoring using this mode of administration. Some clinicians obtain steady-state peak and trough concentrations and use the kinetic equations given earlier to adjust the dose and dosage interval in order to attain appropriate target levels. Other clinicians measure only trough concentrations, trusting that the large doses administered to patients achieve adequate peak concentrations.

Also, a nomogram that adjusts extended-interval doses based on a single postdose concentration to achieve these steady-state concentration goals has been proposed (Fig. 8-12). The dose is 7 mg/kg of **gentamicin** or **tobramycin**. The initial dosage interval is set according to the patient's creatinine clearance. The Hartford nomogram includes a method to adjust doses based on serum concentrations. This portion of the nomogram contains average serum concentration time lines for **gentamicin** or **tobramycin** in patients with creatinine clearances of 60, 40, and 20 mL/min (1, 0.67, 0.33 mL/s). A serum concentration is measured 6 to 14 hours after the first dose is given, and this concentration/time point is plotted on the graph (see Fig. 8-12). The modified dosage interval is indicated by which zone the serum concentration/time point falls. Because cystic fibrosis patients have a different volume of distribution (0.35 L/kg) than assumed by this dosing technique, and extended-interval dosing has not been tested adequately in patients with endocarditis, the Hartford nomogram should not be used in these situations.

Figure 8-12.





1. Administer 7 mg/kg gentamicin with initial dosage interval:

Estimated CL_{cr} (mL/min)	Initial dosage interval
≥ 60 mL/min	q 24 h
40–59 mL/min	q 36 h
20–39 mL/min	q 48 h
< 20 mL/min	Monitor serial concentrations and administer next dose when < 1 mcg/mL.

2. Obtain timed serum concentration 6 to 14 hours after dose (ideally first dose).

3. Alter dosage interval to that indicated by the nomogram zone (above q 48 h zone, monitor serial concentrations and administer next dose when < 1 mcg/mL)

Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Hartford nomogram for extended-interval aminoglycosides. (Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. *Antimicrob Agents Chemother* 1995;39:650–655. Reproduced with permission from American Society for Microbiology.) To determine the corresponding creatinine clearance in units of mL/s multiply the value in mL/min by 0.0167. Gentamicin levels in mcg/mL can be converted to units of $\mu\text{mol/L}$ by multiplying by 2.09.

To illustrate how the Hartford nomogram is used, the same patient example used previously will be repeated for this dosage approach. Mr. JJ is an 80 kg man (176 lb) with a $CL_{cr \text{ est}}$ of 40 mL/min (0.67 mL/s). Using the Hartford nomogram, the patient would receive gentamicin 560 mg every

36 hours ($7 \text{ mg/kg} \times 80 \text{ kg} = 560 \text{ mg}$; the initial dosage interval for $\text{CL}_{\text{Cr est}} = 40 \text{ mL/min}$ [0.67 mL/s] is 36 hours). Ten hours after the first dose was given, the serum **gentamicin** concentration is 8.2 mg/L ($17 \text{ } \mu\text{mol/L}$). According to the graph contained in the nomogram, the dosage interval should be changed to 48 hours. The new dose is 560 mg every 48 hours.

Sidebar: Clinical Controversy

“Trough only” measurement of steady-state **vancomycin** concentrations is a mainstream method to monitor therapy. The exact range for this value is uncertain. Many clinicians recommend 5 to 15 mcg/mL (5 to 15 mg/L ; 3.45 to $10 \text{ } \mu\text{mol/L}$). For some sites of infection with specific organisms, such as hospital-acquired pneumonia due to multidrug-resistant organisms, guidelines suggest **vancomycin** trough concentrations as high as 15 to 20 mcg/mL (15 to 20 mg/L ; 10 to $14 \text{ } \mu\text{mol/L}$) may be necessary. Some clinicians continue to measure both steady-state peak and trough **vancomycin** concentrations.

Vancomycin

Vancomycin requires multicompartment models to completely describe its serum-concentration-versus-time curves. However, if peak serum concentrations are obtained after the distribution phase is completed (usually 30 minutes to 1 hour after a 1-hour IV infusion), a one-compartment model can be used for patient dosage calculations. Also, because **vancomycin** has a relatively long half-life compared with the infusion time, only a small amount of drug is eliminated during infusion, and it is usually unnecessary to use more complex IV infusion equations. Thus, simple IV bolus equations can be used to calculate **vancomycin** doses for most patients. Although a recent review article³⁹ questioned the clinical usefulness of measuring **vancomycin** concentrations on a routine basis, other research articles^{40,41} have shown potential benefits in obtaining **vancomycin** concentrations in select patient populations. Some clinicians advocate monitoring only steady-state trough concentrations of vancomycin.⁴² The decision to conduct **vancomycin** concentration monitoring should be made on a patient-by-patient basis.

Initial doses of **vancomycin** can be computed for adult patients using estimated kinetic parameters derived from population pharmacokinetic data. Clearance is estimated using the patient's creatinine clearance in the following equation:⁴¹ $\text{CL (in mL/min/kg)} = 0.695(\text{CL}_{\text{Cr in mL/min/kg}}) + 0.05$. The volume of distribution is computed assuming the standard value of 0.7 L/kg : $V_D = 0.7(\text{Wt})$, where Wt is the patient's weight. In the case of obese patients, actual or total body weight is used in the calculation of clearance, but ideal body weight is used to compute volume of distribution.⁴⁴ The elimination rate constant is calculated using clearance and volume of distribution estimates, correcting for possible

differences in units for these parameters: $k = CL/V_D$. A nomogram that uses this type of approach for [vancomycin](#) therapy is available to determine initial doses rapidly for patients ([Table 8–6](#)).⁴⁵

TABLE 8-6 **Vancomycin** Dosage Chart

1. Compute patient's creatinine clearance (CL_{Cr}) using the Cockcroft-Gault method: $CL_{Cr} = [(140 - \text{age})BW]/(S_{Cr} \times 72)$ where S_{Cr} is expressed in units of mg/dL. Multiply by 0.85 for women. (S_{Cr} expressed in $\mu\text{mol/L}$ must be divided by 88.4 to obtain conventional units of mg/dL.)	
2. Use the patient's TBW to compute doses.	
3. Dosage chart designed to achieve peak serum concentrations of 30 mcg/mL (30 mg/L; 21 $\mu\text{mol/L}$) and trough concentrations of 7.5 mcg/mL (7.5 mg/L; 5 $\mu\text{mol/L}$).	
4. Compute loading dose of 25 mg/kg.	
5. Compute maintenance dose of 19 mg/kg given at the dosage interval listed in the following chart for the patient's CL_{Cr} :	
CL_{Cr} (mL/min) ^a	Dosage Interval (Days)
≥ 120	0.5
100	0.6
80	0.75
60	1.0
40	1.5
30	2.0
20	2.5
10	4.0

5	6.0
0	12.0

$^a\text{Cl}_{\text{Cr}}$ expressed in mL/min can be converted to units of mL/s by multiplying by 0.0167.

BW = body weight, Scr = serum creatinine, TBW = total body weight

Data from Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of *vancomycin* in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984;25:433–437.

Steady-state peak and trough concentrations are chosen for the patient based on the site and severity of the infection, as well as the known or suspected pathogen and avoidance of potential side effects. $C_{\text{max,ss}}$ values of between 20 and 40 mg/L (20 and 40 mcg/mL; 14 and 28 $\mu\text{mol/L}$) and $C_{\text{min,ss}}$ values of between 5 and 15 mg/L (5 and 15 mcg/mL; 3 and 10 $\mu\text{mol/L}$) typically are used for patients with moderate to severe methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, or penicillin-resistant enterococcal infections. For patients with pneumonia or other life-threatening infections, $C_{\text{min,ss}}$ as high as 20 mg/L (20 mcg/mL; 14 $\mu\text{mol/L}$) have been suggested.⁵⁶ After appropriate steady-state concentrations are chosen, the dosage interval required to attain those concentrations is computed, and τ is rounded to a clinically acceptable value (12, 18, 24, 36, 48, or 72 hours): $\tau = (\ln C_{\text{max,ss}} - \ln C_{\text{min,ss}})/k$. Finally, the maintenance dose is computed for the patient using a one-compartment-model IV bolus equation at steady state, and the dose is rounded off to the nearest 100 to 250 mg:

$$D = C_{\text{max,ss}} V_D (1 - e^{-k\tau})$$

If desired, a loading dose can be computed using the following equation:

$$\text{LD} = V_D C_{\text{max,ss}}$$

The following case will illustrate the use of this dosage methodology. Ms. HJ is a 65-year-old, 68 kg (150 lbs), 5 ft, 4 inch (64 in or 163 cm) patient who has developed a surgical wound infection, with *S. epidermidis* the suspected pathogen. Her serum creatinine concentration is 1.8 mg/dL (159 $\mu\text{mol/L}$) and stable. Compute a *vancomycin* dosage regimen that would provide approximate peak (obtained 1 hour after a 1-hour infusion) and trough concentrations of 30 and 7 mg/L (30 and 7 mcg/mL; 21 and 5 $\mu\text{mol/L}$), respectively. The patient is within 30% of her ideal body weight [$\text{IBW}_{\text{female}} = 45 + 2.3(64 \text{ in} - 60) = 54 \text{ kg}$] and has stable renal function, so the Cockcroft-Gault creatinine clearance estimation formula can be

used: $CL_{Cr\ est} = 0.85[(140 - 65\ y)68\ kg]/[72(1.8\ mg/dL)] = 33\ mL/min\ (0.55\ mL/s)$. The patient's weight and estimated creatinine clearance are used to calculate her estimated CL , V_D , and k , respectively: $CL = 0.695\ (33\ mL/min/68\ kg) + 0.05 = 0.387\ mL/min/kg$; $V_D = 0.7\ L/kg(68\ kg) = 48\ L$; and $k = [(0.387\ mL/min/kg)(68\ kg)(60\ min/h)]/[(48\ L)(1,000\ mL/L)] = 0.033\ h^{-1}$ or $t_{1/2} = 0.693/0.033\ h^{-1} = 21\ h$. The dosage interval, maintenance dose, and loading dose for the desired serum concentrations can be computed: $\tau = (\ln 30\ mg/L - \ln 7\ mg/L)/0.033\ h^{-1} = 44\ h$, rounded to 48 h; $D = (30\ mg/L)(48\ L)(1 - e^{-(0.033\ h^{-1})(48\ h)}) = 1,145\ mg$, rounded to 1,250 mg; $LD = (48\ L)(30\ mg/L) = 1,440\ mg$, rounded to 1,500 mg. Therefore, the prescribed doses would be **vancomycin** 1,250 mg every 48 hours administered as a 1-hour infusion. If a loading dose was used, it would be given as the first dose, and the first maintenance dose would be administered 48 hours (one dosage interval) later. Using the Matzke nomogram for the same patient, the loading dose would be 1,750 mg (**vancomycin** loading dose is 25 mg/kg: $25\ mg/kg \times 68\ kg = 1,700\ mg$, rounded to 1,750 mg), followed by a maintenance dose of 1,250 mg every 48 hours (for $CL_{Cr\ est} = 30\ mL/min\ (0.50\ mL/s)$, the maintenance dose is 19 mg/kg every 2 days: $19\ mg/kg \times 68\ kg = 1,292\ mg$, rounded to 1,250 mg).

If appropriate **vancomycin** serum concentrations are available, kinetic parameters can be computed at any point in therapy. When the patient is not at steady state, serum **vancomycin** concentrations are obtained before a dose (C_{min}), after a dose administered as an IV infusion of 1 hour followed by a 30-minute to 1-hour waiting period to allow for drug distribution (C_{max}), and at one additional postdose time (C_3) approximately one estimated half-life after C_{max} . The $t_{1/2}$ and k values are computed using C_{max} and C_3 : $k = (\ln C_{max} - \ln C_3)/\Delta t$ and $t_{1/2} = 0.693/k$, where Δt is the time that expired between the times C_{max} and C_3 were obtained. If the patient is at steady state, serum **vancomycin** concentrations are obtained before a dose ($C_{min,ss}$) and after a dose administered as an IV infusion of about 1 hour followed by a 30-minute to 1-hour waiting period to allow for drug distribution ($C_{max,ss}$). The $t_{1/2}$ and k values are computed using $C_{max,ss}$ and $C_{min,ss}$: $k = (\ln C_{max,ss} - \ln C_{min,ss})/(\tau - T_{max})$ and $t_{1/2} = 0.693/k$, where τ is the dosage interval, and T_{max} is the dose infusion time plus waiting time.

Assuming a one-compartment model, the following equation is used to compute V_D :

$$V_D = \frac{D}{C_{max} - C_{min}}$$

where D is dose. Once these are known, the dose and dosage interval (τ) can be calculated for any desired maximum $C_{ss}(C_{max,ss})$ and minimum $C_{ss}(C_{min,ss})$:

$$\tau = \frac{\ln C_{max,ss} - \ln C_{min,ss}}{k}$$

$$D = C_{\max,ss} V_D (1 - e^{-k\tau})$$

The dose and dosage interval should be rounded to provide clinically accepted values (every 12, 18, 24, 36, 48, or 72 hours for dosage interval, nearest 100 to 250 mg for dose).

To provide an example for this dosage-calculation method, the preceding problem will be extended to include steady-state concentrations. Ms. HJ was prescribed [vancomycin](#) 1,200 mg every 48 hours (infused over 1 hour) for the treatment of a surgical wound infection. Steady-state trough ($C_{\min,ss}$) and peak ($C_{\max,ss}$) values ($C_{\max,ss}$ obtained 1 hour after the end of the infusion) were obtained before and after the third dose was given (more than three to five estimated half-lives), respectively, and equaled $C_{\min,ss} = 2.5$ mg/L (2.5 mcg/mL; 1.7 μ mol/L) and $C_{\max,ss} = 22.4$ mg/L (22.4 mcg/mL; 15.5 μ mol/L). Clinically, the patient had improved somewhat, but her white blood cell count was still elevated, and the patient was still febrile. Because of this, a modified dosage regimen with a $C_{\max,ss} = 30$ mg/L (30 mcg/mL; 21 μ mol/L) and $C_{\min,ss} = 7$ mg/L (7 mcg/mL; 5 μ mol/L) was suggested to maintain trough concentrations three to five times above the MIC for the suspected pathogen. The patient's actual elimination rate constant and half-life can be calculated using the following formulas: $k = (\ln 22.4 \text{ mg/L} - \ln 2.5 \text{ mg/L}) / (48 \text{ h} - 2 \text{ h}) = 0.048 \text{ h}^{-1}$ and $t_{1/2} = 0.693 / 0.048 \text{ h}^{-1} = 14.4 \text{ h}$. The patient's volume of distribution can be calculated using the following equation:

$$V_D = \frac{1,200 \text{ mg}}{22.4 \text{ mg/L} - 2.5 \text{ mg/L}} = 60 \text{ L}$$

Thus, the patient's volume of distribution was larger and half-life shorter than originally estimated; this led to lower serum concentrations than anticipated. To achieve the desired serum concentrations ($C_{\max,ss} = 30$ mg/L [30 mcg/mL; 21 μ mol/L] and $C_{\min,ss} = 7$ mg/L [7 mcg/mL; 5 μ mol/L]), the patient's actual kinetic parameters are used to calculate a new dose and dosage interval:

$$\begin{aligned} \tau &= \frac{\ln 30 \text{ mg/L} - \ln 7 \text{ mg/L}}{0.048 \text{ h}^{-1}} \\ &= 30 \text{ h, rounded to 36 h} \\ D &= (30 \text{ mg/L})(60 \text{ L})(1 - e^{-(0.048 \text{ h}^{-1})(36 \text{ h})}) \\ &= 1,480 \text{ mg, rounded to 1,500 mg} \end{aligned}$$

The new dose would be [vancomycin](#) 1,500 mg every 36 hours (infused over 1 hour); the first dose of the new dosage regimen would be given 36 hours (the new dosage interval) after the last dose of the old dosage regimen.

For routine monitoring, many clinicians measure only steady-state [vancomycin](#) trough concentrations in patients. The justification for this approach is that because [vancomycin](#) exhibits time-dependent bacterial killing, the minimum concentration is the most important with regard to

therapeutic outcome. **Vancomycin** pharmacokinetics also support this approach because the volume of distribution is relatively stable and is not changed by many disease states or conditions. Because of this important point, it is difficult to attain peak steady-state concentrations in the toxic range when the steady-state **vancomycin** trough is in the therapeutic range if typical doses are used (15 mg/kg or $\approx 1,000$ mg for average-weight individuals). Also, toxic peak concentrations (generally greater than 80–100 mg/L [80 to 100 mcg/mL; 55 to 69 $\mu\text{mol/L}$]) are quite a bit higher than therapeutic peak concentrations, which adds a safety margin between effective concentrations and those yielding adverse drug effects.

Coupled with trough-only **vancomycin** concentration monitoring is a widening of the therapeutic steady-state trough concentration range from 5 to 15 mg/L (5 to 15 mcg/mL; 3 to 10 $\mu\text{mol/L}$). The justification for increasing the top of the range from 10 to 15 mg/L (10 to 15 mcg/mL; 7 to 10 $\mu\text{mol/L}$) comes from limited retrospective⁴¹ and prospective⁴² studies. Trough concentrations in the range of 15 to 20 mg/L (15 to 20 mcg/mL; 10 to 14 $\mu\text{mol/L}$) should be reserved for specific clinical situations, such as hospital-acquired pneumonia caused by multidrug-resistant organisms.⁵⁶

When trough-only monitoring of **vancomycin** concentrations is chosen by a clinician, a simple variant of linear pharmacokinetics can be used to adjust the dose (D) and dosage interval (τ): $(D_{\text{new}}/\tau_{\text{new}}) = (D_{\text{old}}/\tau_{\text{old}})(C_{\text{ss,new}}/C_{\text{ss,old}})$, where *new* and *old* indicate the new target trough concentration and the old measured trough concentration, respectively. In practice, the dose (typically 1,000 mg) is held constant, and only the dosage interval is changed. This equation is an approximation of the actual new steady-state trough concentration that will be attained in the patient because, mathematically, $C_{\text{ss,new}}$ is an exponential function of τ .

An example of this approach is given in the following case. Mr. MK, a 72-year-old, 72 kg [158 lb], 5 ft, 9 inch [69 in. or 175 cm] patient, was prescribed **vancomycin** 1,000 mg every 12 hours (infused over 1 hour) for the treatment of an *S. epidermidis* central venous catheter infection. A steady-state trough ($C_{\text{min,ss}}$) value was obtained before the fifth dose was given (more than three to five estimated half-lives), and $C_{\text{min,ss}} = 19$ mg/L (19 mcg/mL; 13 $\mu\text{mol/L}$). Clinically, the patient was improving, but the trough concentration was judged to be too high. Because of this, a modified dosage regimen with a $C_{\text{min,ss}} = 10$ mg/L (10 mcg/mL; 7 $\mu\text{mol/L}$) was suggested to maintain trough concentrations three to five times above the MIC for the suspected pathogen: $(D_{\text{new}}/\tau_{\text{new}}) = (1,000 \text{ mg}/12 \text{ h})(10 \text{ mg/L}/19 \text{ mg/L}) = 44 \text{ mg/h}$. Because the patient is near his ideal weight, the same dose of 1,000 mg can be used (D_{new}), and the new dosage interval (τ_{new}) can be computed: $\tau = 1,000 \text{ mg}/44 \text{ mg/h} = 23 \text{ h}$, rounded to 24 h. The new prescribed dose for the patient would be 1,000 mg every 24 hours.

Digoxin

Digoxin pharmacokinetics are best described by a two-compartment model. However, because **digoxin** has a long half-life compared with its dosage interval and a very long distribution phase, simple pharmacokinetic equations can be used to individualize dosing when postdistribution serum concentrations are used. **Digoxin** can be given as an IV injection and orally as elixir ($F=0.8$), tablets ($F=0.7$), or capsules ($F=0.9$). When given orally, the appropriate bioavailability fraction must be used to compute the correct dose. Initial doses of **digoxin** can be computed using population pharmacokinetic data obtained from published studies. **Digoxin** clearance is estimated using the patient's creatinine clearance in the following formula:²⁰ CL (in milliliters per minute) = $1.303(CL_{Cr}$ in milliliters per minute) + CL_m , where CL_m is metabolic clearance and equals 40 mL/min for patients with no or mild heart failure or 20 mL/min for patients with moderate to severe heart failure. The volume of distribution decreases with declining renal function and is estimated using the following equation:²⁰ V_D (in liters) = $226 + [298(CL_{Cr}$ in milliliters per minute)]/($29.1 + CL_{Cr}$ in milliliters per minute). The elimination rate constant can be computed by taking the product of CL and V_D : $k = CL/V_D$. For obese individuals, **digoxin** dosing should be based on ideal body weight.⁴⁶

Appropriate C_{SS} values are chosen for the patient based on the disease state being treated, the goal of therapy, and avoidance of adverse effects. The inotropic effects of **digoxin** occur at lower concentrations than do the chronotropic effects. Therefore, initial serum concentrations of **digoxin** for the treatment of heart failure generally are 1 ng/mL (1 mcg/L; 1.3 nmol/L) or less and for the treatment of atrial fibrillation 1 to 1.5 ng/mL (1 to 1.5 mcg/L; 1.3 to 1.9 nmol/L). Once the appropriate C_{SS} is selected, a dose is computed for the patient: $D/\tau = (C_{SS}CL)/F$.

An example of this initial dosage scheme is provided in the following case. Mr. PO is a 72-year-old, 83 kg (183 lbs), 5 ft, 11 inch (71 in. or 180 cm) man admitted to the hospital for the treatment of community-acquired pneumonia. His past medical history is positive for moderate heart failure. While in the hospital, Mr. PO develops atrial fibrillation, and the decision is made to treat him with **digoxin** to provide ventricular rate control. His serum creatinine concentration is 2.5 mg/dL (221 μ mol/L) and stable. Calculate an IV loading dose and oral maintenance dose that will achieve a C_{SS} of 1.5 ng/mL (1.5 mcg/L; 1.9 nmol/L). The Cockcroft-Gault equation can be used to estimate the patient's creatinine clearance because his serum creatinine concentration is stable, and he is within 30% of his ideal body weight [$IBW_{male} = 50 + 2.3(71 \text{ in} - 60) = 75 \text{ kg}$]: $CL_{Cr} = [(140 - 72 \text{ y})83 \text{ kg}]/[72(2.5 \text{ mg/dL})] = 31 \text{ mL/min}$ (0.52 mL/s). Using the estimated CL_{Cr} , both CL and V_D can be computed:

$$CL = 1.303(31 \text{ mL/min}) + 20 = 60 \text{ mL/min}$$

$$V_D = 226 + \frac{298(31 \text{ mL/min})}{29.1 + 31 \text{ mL/min}} = 380 \text{ L}$$

The maintenance dose will be given as **digoxin** tablets, so $F=0.7$ in the dosing equation: $D/\tau = [(1.5 \text{ mcg/L})(60 \text{ mL/min})(60 \text{ min/h})(24 \text{ h/day})]/[0.7(1,000 \text{ mL/L})] = 185 \text{ mcg/day}$, rounded to 187.5 mcg/day (given as 1½ of 125 mcg tablets). The loading dose will be given IV as a

digoxin injection: $LD = (1.5 \text{ mcg/L})(380 \text{ L}) = 570 \text{ mcg}$, rounded to 500 mcg. The loading dose would be given 50% now (250 mcg), 25% (125 mcg) in 4 to 6 hours after monitoring the patient's heart rate and blood pressure and assessing the patient for **digoxin** adverse effects, and the final 25% (125 mcg) 4 to 6 hours later after monitoring the same clinical parameters. The first maintenance dose would be given one dosage interval (in this case, 24 hours) after the first part of the loading dose was given.

Adjustment of **digoxin** doses using steady-state concentrations is accomplished using linear pharmacokinetics and dosage ratios: $D_{\text{new}} = D_{\text{old}}(C_{\text{ss,new}}/C_{\text{ss,old}})$. For example, Mr. PO's atrial fibrillation responded to **digoxin** therapy, and he was discharged after resolution of his pneumonia. A month later, he was followed up in the clinic with moderate nausea, possibly a result of **digoxin** toxicity. His heart rate was 51 beats per minute, and his serum creatinine was unchanged. A steady-state **digoxin** concentration was determined and reported by the clinical laboratory as 2.2 mcg/L (2.8 nmol/L). Compute a new dose for the patient to achieve a C_{ss} of 1.5 mcg/L (1.9 nmol/L). The **digoxin** C_{ss} and old dose would be used to calculate a new dose using the linear pharmacokinetic equation: $D_{\text{new}} = 187.5 \text{ mcg/day}[(1.5 \text{ mcg/L})/(2.2 \text{ mcg/L})] = 128 \text{ mcg/day}$, rounded to 125 mcg/day.

Theophylline

Theophylline disposition is described most accurately by nonlinear kinetics.^{47,48} However, at the usual doses, **theophylline** acts as if it obeys linear kinetics in most patients. Initial **theophylline** doses are computed by taking a detailed medical history of the patient and noting disease states and conditions that are known to change **theophylline** disposition. Age, smoking of tobacco-containing products, heart failure, and liver disease are among the important factors that alter **theophylline** kinetic parameters and dosage requirements. Once the patient has been assessed, average **theophylline** kinetic parameters obtained from the literature for patients similar to the one being currently treated are used to compute either oral or IV doses. Dosage guidelines that take into account most common disease states and conditions that change **theophylline** kinetic parameters are available (see Table 8–4).⁴⁹ Once **theophylline** is administered, the patient is monitored for the therapeutic effect and potential adverse effects. **Theophylline** concentrations then are used to individualize the **theophylline** dose that the patient receives. An example of this approach was given previously for a patient in the section on drug dosing in patients with liver disease (please see Selection of Initial Drug Doses).

Continuous IV infusions of **theophylline** (or its salt, aminophylline) can be individualized rapidly by determining the patient's CL before steady state occurs.⁵⁰ Assuming that the patient receives **theophylline** only by continuous IV infusion (previous doses of sustained-release oral **theophylline** are completely absorbed), two serum **theophylline** concentration determinations are done 4 hours or more apart. The infusion rate

(k_0) cannot be changed between the times the samples are drawn. With one-compartment model equations, the first (C_1) and second (C_2) theophylline concentrations are used to calculate theophylline CL:

$$CL = \frac{2k_0}{C_1 + C_2} + \frac{2V_D(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

V_D is assumed to be 0.5 L/kg, and t_1 and t_2 are the times at which C_1 and C_2 , respectively, are obtained. Once CL is known, k_0 can be computed easily for any desired C_{SS} ($C_{SS} = k_0/CL$). This method probably can be applied to other drugs that are administered as continuous IV infusions, such as IV antiarrhythmics, when rapid individualization of drug dosage is desirable.

An example of this approach can be obtained by continuing the theophylline patient case from the section on drug dosing in liver disease (please see [Selection of Initial Drug Doses](#)). In this example, a 55-year-old, 70 kg (154 lb) man with liver cirrhosis was prescribed a loading dose of theophylline 350 mg IV over 20 to 30 minutes, followed by a maintenance dose of 15 mg/h of theophylline as a continuous infusion. The infusion began at 9 am, blood samples were obtained at 10 am and 4 pm, and the clinical laboratory reported the theophylline serum concentrations as 10.9 and 12.3 mg/L (10.9 and 12.3 mcg/mL; 60.5 and 68.3 μ mol/L), respectively. The patient's theophylline clearance and revised continuous infusion to maintain a C_{SS} of 15 mg/L (15 mcg/mL; 83.3 μ mol/L) can be computed as follows (patient's V_D estimated at 0.5 L/kg):

$$CL = \frac{2(15 \text{ mg/h})}{10.9 \text{ mg/L} + 12.3 \text{ mg/L}} + \frac{2(0.5 \text{ L/kg} \times 70 \text{ kg})(10.9 \text{ mg/L} - 12.3 \text{ mg/L})}{(10.9 \text{ mg/L} + 12.3 \text{ mg/L})(16 - 10 \text{ h})} = 0.59 \text{ L/h}$$

$$k_0 = C_{SS}CL = (15 \text{ mg/L})(0.59 \text{ L/h}) = 9 \text{ mg/h theophylline}$$

If theophylline is to be given as the aminophylline salt form, the doses would need to be changed to reflect the fact that aminophylline contains only 85% theophylline ($k_0 = 9 \text{ mg/h theophylline} / 0.85 = 11 \text{ mg/h aminophylline}$).

If continuous IV infusions or oral dosage regimens are given long enough for steady state to occur (three to five estimated half-lives based on previous studies conducted in similar patients), linear pharmacokinetics can be used to adjust doses for either route of administration: $D_{\text{new}} = D_{\text{old}}(C_{SS,\text{new}}/C_{SS,\text{old}})$. For example, a patient receiving 200 mg of sustained-release oral theophylline every 12 hours with a theophylline steady-state serum concentration of 9.5 mcg/mL (9.5 mg/L; 52.7 μ mol/L) can have the dose required to achieve a new steady-state concentration equal to 15 mcg/mL (15 mg/L; 83.3 μ mol/L) computed by applying linear pharmacokinetics: $D_{\text{new}} = 200 \text{ mg}[(15 \text{ mcg/mL})/(9.5 \text{ mcg/mL})] = 316 \text{ mg}$, rounded to 300 mg. Thus the new theophylline dose would be 300 mg every 12 hours.

Phenytoin

Phenytoin doses are very difficult to individualize because the drug follows Michaelis-Menten kinetics, and there is a large amount of interpatient variability in V_{\max} and K_m . Initial maintenance doses of phenytoin in adults usually range between 4 and 7 mg/kg daily, yielding starting doses of 300 to 400 mg daily in most individuals. If needed, loading doses of phenytoin or fosphenytoin (a prodrug of phenytoin used IV) can be administered in adults at a dose of 15 mg/kg, which is approximately 1,000 mg in many individuals. Loading doses of phenytoin can be given orally but need to be administered in divided doses separated by several hours in order to avoid decreased bioavailability and gastrointestinal intolerance (for total loading dose of 1,000 mg: 400 mg, 300 mg, then 300 mg with each dose separated by 4–6 h). Since phenytoin is metabolized hepatically, decreased doses may be needed in patients with liver disease. Because phenytoin follows dose-dependent pharmacokinetics, the half-life of phenytoin increases for a patient as the maintenance dose increases. Therefore, the time to steady-state phenytoin concentrations increases with dose. On average, at a phenytoin dose of 300 mg daily, it takes approximately 5 to 7 days to achieve steady state; at a dose of 400 mg daily, it takes approximately 10 to 14 days to achieve steady state; and at a dose of 500 mg daily, it takes approximately 21 to 28 days to achieve steady state. It should be noted that the injectable and capsule dosage forms of phenytoin are phenytoin sodium, and the labeled dosage amounts contain 92% of active phenytoin (300 mg phenytoin sodium capsules contain 276 mg [$300 \text{ mg} \times 0.92 = 276 \text{ mg}$] of active phenytoin). Unbound phenytoin concentrations are useful in patients with hypoalbuminemia (e.g., liver disease, nephrotic syndrome, pregnancy, cystic fibrosis, burns, trauma, and malnourishment, as well as in the elderly), in patients in whom displacement with endogenous compounds is possible (e.g., hyperbilirubinemia, liver disease, or end-stage renal disease), and in patients receiving other drugs that may displace phenytoin from plasma protein-binding sites (e.g., valproic acid, [aspirin](#) therapy >2 g daily, [warfarin](#), and nonsteroidal antiinflammatory drugs with high albumin binding).⁵⁷

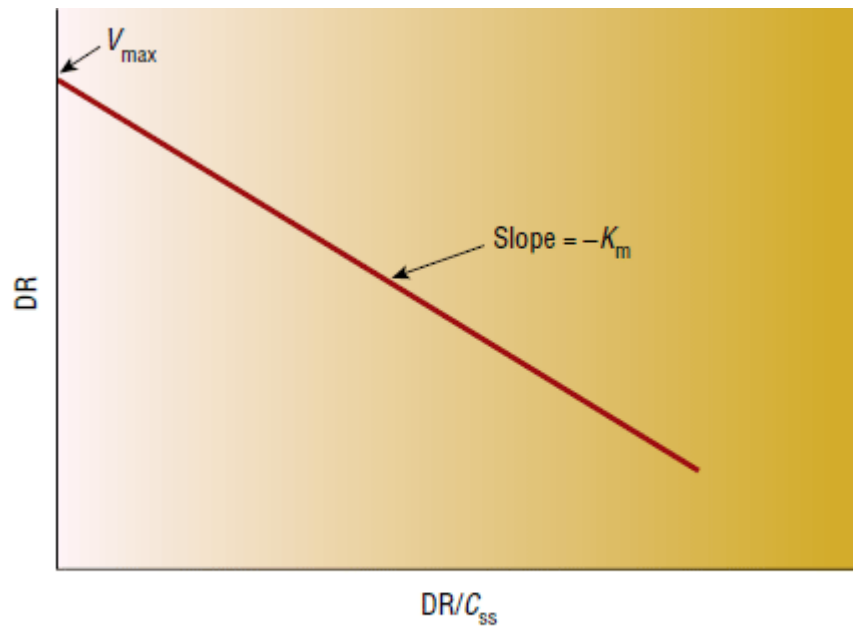
After steady state has occurred, phenytoin serum concentrations can be obtained as an aid to dosage adjustment. A simple, easy way to approximate new serum concentrations after a dosage adjustment with phenytoin is to temporarily assume linear pharmacokinetics and then add 15% to 33% for a dosage increase or subtract 15% to 33% for a dosage decrease to account for Michaelis-Menten kinetics. To avoid large disproportionate changes in phenytoin concentrations when using this empirical method, dosage adjustments should be limited to 50 to 100 mg daily. This technique is intended only to provide a rough approximation of the resulting phenytoin steady-state concentration after an appropriate dosage adjustment has been made.

For example, Ms. PP is a 35-year-old, 65 kg (143 lb) patient with grand mal seizures who is receiving phenytoin capsules 300 mg orally at bedtime. A steady-state concentration of 9.2 mcg/mL (9.2 mg/L; 37 $\mu\text{mol/L}$) is measured. It is observed that her seizure frequency decreased by only ~15%, and that she has had no adverse effects as a consequence of phenytoin treatment. Because of this, her phenytoin dose is increased to 400 mg orally at bedtime. The expected phenytoin steady-state concentration would be estimated using linear pharmacokinetics [$C_{\text{new}} =$

$(D_{\text{new}}/D_{\text{old}})C_{\text{old}} = (400 \text{ mg}/300 \text{ mg})/(9.2 \text{ mcg/mL}) = 12.3 \text{ mcg/mL}$ and then increased by 15% to 33% to account for nonlinear kinetics [$C_{\text{new}} = 1.15(12.3 \text{ mcg/mL}) = 14.1 \text{ mcg/mL}$ or $C_{\text{new}} = 1.33(12.3 \text{ mcg/mL}) = 16.4 \text{ mcg/mL}$]. Thus, the patient would be expected to have a steady-state phenytoin concentration of approximately 14 to 16 mcg/mL (14 to 16 mg/L; 56 to 63 $\mu\text{mol/L}$) as a consequence of the dosage increase. An alternative approach would be to use a graphic Bayesian method that allows an estimate of V_{max} and K_{m} from one steady-state phenytoin concentration and the prediction of new steady-state concentrations when doses are changed.⁵¹

Other methods used to individualize phenytoin doses involve rearrangements of the Michaelis-Menten equation [$\text{DR} = V_{\text{max}}C_{\text{SS}}/(K_{\text{m}} + C_{\text{SS}})$, in which DR is the dosage rate at steady state] so that two or more doses and C_{SS} values can be used to obtain graphic solutions for V_{max} and K_{m} . One rearrangement⁵² is $\text{DR} = -K_{\text{m}}(\text{DR}/C_{\text{SS}}) + V_{\text{max}}$. When DR is plotted on the y axis, and DR/C_{SS} is plotted on the x axis of Cartesian graph paper, a straight line with a y intercept of V_{max} and slope equal to $-K_{\text{m}}$ is found (Fig. 8-13). To use this method, patients are prescribed an initial phenytoin dose, and C_{SS} is obtained. The phenytoin dose is then changed, and a second C_{SS} from the new dose is obtained. Each dose is divided by its respective C_{SS} to derive DR/C_{SS} values. The DR/C_{SS} and C_{SS} values are plotted on the graph to calculate V_{max} (y intercept) and K_{m} (minus slope). The steady-state Michaelis-Menten equation can be used to compute C_{SS} .

Figure 8-13.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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Relationship between dosage rate (DR) and steady-state serum concentrations (C_{ss}).

Cyclosporine

Because of the large amount of variability in **cyclosporine** pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standardized initial **cyclosporine** doses for various situations is warranted. Indeed, most transplant centers use doses that are determined employing a locally derived **cyclosporine** dosage protocol. The original computations of these doses were based on the pharmacokinetic dosing methods described in preceding sections and subsequently modified based on clinical experience. In general, the expected **cyclosporine** steady-state concentration used to compute these doses depends on the type of transplanted tissue and the posttransplantation time line. Generally speaking, initial oral doses of 8 to 18 mg/kg daily or IV doses of 3 to 6 mg/kg daily (one-third the oral dose to account for ~30% oral bioavailability) are used and vary greatly from institution to institution. For obese individuals (>30% over ideal body weight), ideal body weight should be used to compute initial doses.

It is likely that doses computed using patient population characteristics will not always produce **cyclosporine** concentrations that are expected or desirable. Additionally, there is a very high amount of interday variation in **cyclosporine** concentrations. Because of pharmacokinetic variability, the narrow therapeutic index of **cyclosporine**, and the severity of **cyclosporine** adverse side effects, measurement of **cyclosporine** concentrations

is mandatory for patients to ensure that therapeutic, nontoxic levels are present. When [cyclosporine](#) concentrations are measured in patients, and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change [cyclosporine](#) doses using steady-state concentrations and assuming that the drug follows linear pharmacokinetics:

$$D_{\text{new}} = D_{\text{old}} \frac{C_{\text{ss,new}}}{C_{\text{ss,old}}}$$

The C_{ss} can be either a steady-state trough concentration or a steady-state concentration measured 2 hours (+/-15 min) after a dose (C_2). When C_2 levels are used, recommended concentrations vary according to transplant type and posttransplant time (see [Table 8-7](#)).⁵⁹⁻⁶¹

TABLE 8-7 Recommended 2 hour (+/- 15 min) Postdose Steady-state Cyclosporine Concentrations (C2) for Various Solid Organ Transplant Types and Posttransplant Times

<i>Renal transplant</i>	
Posttransplant time (months)	C2 level
1	1,500–2,000 ng/mL or mcg/L
	1,248–1,664 nmol/L
2	1,500 ng/mL or mcg/L
	1,248 nmol/L
3	1,300 ng/mL or mcg/L
	1,082 nmol/L
4–6	1,100 ng/mL or mcg/L
	915 nmol/L
7–12	900 ng/mL or mcg/L
	749 nmol/L
>12	800 ng/mL or mcg/L
	666 nmol/L
<i>Liver Transplant</i>	

<i>Renal transplant</i>	
Posttransplant time (months)	C2 level
Posttransplant time (months)	C2 level
0–3	1,000 ng/mL or mcg/L
	832 nmol/L
4–6	800 ng/mL or mcg/L
	666 nmol/L
>6	600 ng/mL or mcg/L
	499 nmol/L

Data from Cole E, Midtvedt K, Johnston A, et al. Recommendations for the implementation of Neoral C(2) monitoring in clinical practice. *Transplantation* 2002;73(9 suppl):S19–S22; Levy G, Thervet E, Lake J, et al. Patient management by Neoral C(2) monitoring: An international consensus statement. *Transplantation* 2002;73(9 suppl):S12–S18; and Levy GA. C2 monitoring strategy for optimixing [cyclosporine](#) immunosuppression from the Neoral formulation. *Bio Drugs* 2001;15(5):279–290.

For example, LK is a 50-year-old, 75 kg (165 lb), 5 ft, 11 inch (71 in. or 180 cm) male renal transplant recipient who is receiving oral [cyclosporine](#) 400 mg every 12 hours. The current steady-state blood [cyclosporine](#) concentration is 375 ng/mL (375 mcg/L; 312 nmol/L). To compute a [cyclosporine](#) dose that will provide a steady-state concentration of 200 ng/mL (200 mcg/L; 166 nmol/L), linear pharmacokinetic equations can be used. The new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose × 2 doses/d = 800 mg/d):

$$\begin{aligned}
 D_{\text{new}} &= D_{\text{old}} \frac{C_{\text{ss,new}}}{C_{\text{ss,old}}} = 800 \text{ mg/day} \frac{200 \text{ ng/mL}}{375 \text{ ng/mL}} \\
 &= 427 \text{ mg/day, round to 400 mg/day}
 \end{aligned}$$

The new suggested dose would be 400 mg/day or 200 mg every 12 hours of [cyclosporine](#) capsules to be started at the next scheduled dosing time.

Clinical Pharmacodynamics

16 Pharmacodynamics is the study of the relationship between the concentration of a drug and the response obtained in a patient. Originally, investigators examined the dose–response relationship of drugs in humans but found that the same dose of a drug usually resulted in different concentrations in individuals because of pharmacokinetic differences in clearance and volume of distribution. Examples of quantifiable pharmacodynamic measurements include changes in blood pressure during antihypertensive drug therapy, decreases in heart rate during β -blocker treatment, and alterations in prothrombin time or international normalized ratio during [warfarin](#) therapy.

For drugs that exhibit a direct and reversible effect, the following diagram describes what occurs at the level of the drug receptor:

[Drug + receptor](#) \leftrightarrow [drug – receptor complex](#) \leftrightarrow [response](#)

According to this scheme, there is a drug receptor located within the target organ or tissue. When a drug molecule “finds” the receptor, it forms a complex that causes the pharmacologic response to occur. The drug and receptor are in dynamic equilibrium with the drug–receptor complex.

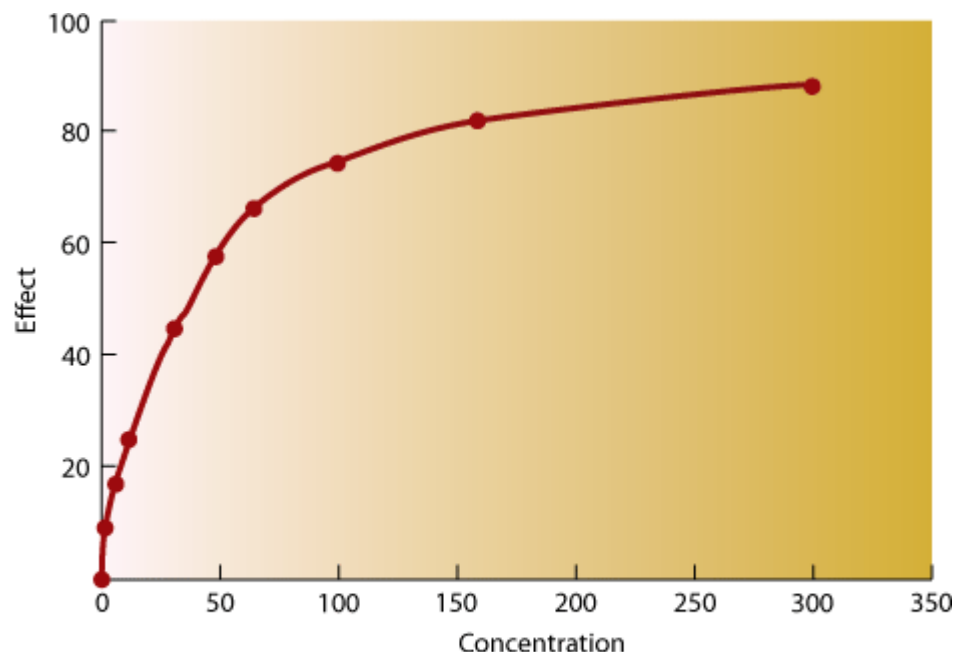
The E_{\max} and Sigmoid E_{\max} Models

The mathematical model that comes from the classic drug receptor theory shown previously is known as the E_{\max} model:

$$E = \frac{E_{\max} \times C}{EC_{50} + C}$$

where E is the pharmacologic effect elicited by the drug, E_{\max} is the maximum effect the drug can cause, EC_{50} is the concentration causing one-half the maximum drug effect ($E_{\max}/2$), and C is the concentration of drug at the receptor site. EC_{50} can be used as a measure of drug potency (a lower EC_{50} , indicating a more potent drug), whereas E_{\max} reflects the intrinsic efficacy of the drug (a higher E_{\max} , indicating greater efficacy). If pharmacologic effect is plotted against concentration in the E_{\max} equation, a hyperbola results with an asymptote equal to E_{\max} ([Fig. 8–14](#)). At a concentration of zero, no measurable effect is present.

Figure 8-14.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

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The E_{\max} model [$E = (E_{\max} \times C) / (EC_{50} + C)$] has the shape of a hyperbola with an asymptote equal to E_{\max} . EC_{50} is the concentration where effect = $E_{\max}/2$.

When dealing with human studies in which a drug is administered to a patient, and pharmacologic effect is measured, it is very difficult to determine the concentration of the drug at the receptor site. Because of this, serum concentrations (total or unbound) usually are used as the concentration parameter in the E_{\max} equation. Therefore, the values of E_{\max} and EC_{50} are much different than if the drug were added to an isolated tissue contained in a laboratory beaker.

The result is that a much more empirical approach is used to describe the relationship between concentration and effect in clinical pharmacology studies. After a pharmacodynamic experiment has been conducted, concentration–effect plots are generated. The shape of the concentration–effect curve is used to determine which pharmacodynamic model will be used to describe the data. Because of this, the pharmacodynamic models used in a clinical pharmacology study are deterministic in the same way that the shape of the serum-concentration-versus-time curve determines which pharmacokinetic model is used in clinical pharmacokinetic studies.

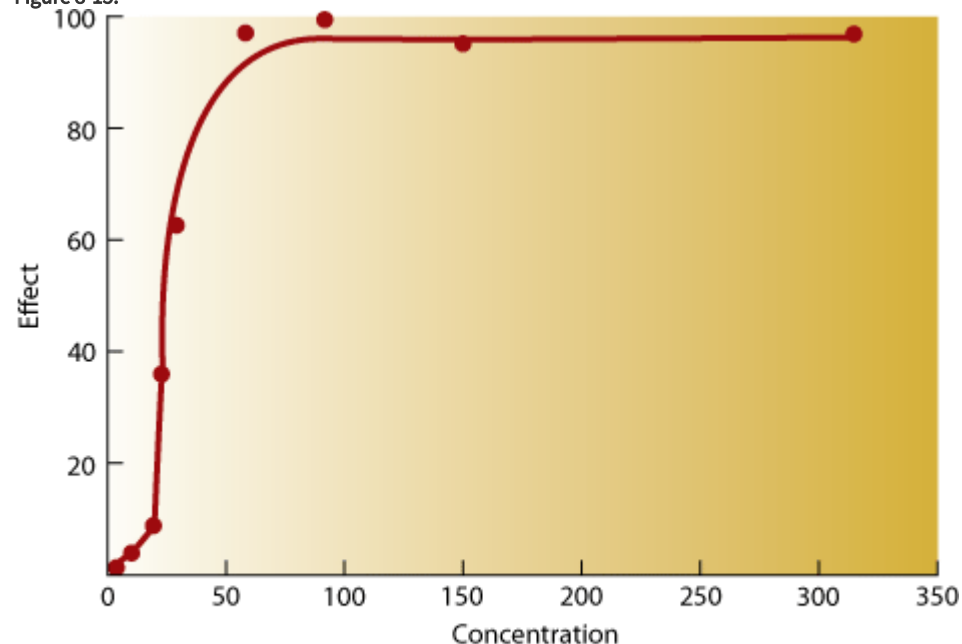
Sometimes a hyperbolic function does not describe the concentration–effect relationship at lower concentrations adequately.

When this is the case, the sigmoid E_{\max} equation may be superior to the E_{\max} model:

$$E = \frac{E_{\max} \times C^n}{EC_{50}^n + C^n}$$

where n is an exponent that changes the shape of the concentration–effect curve. When $n > 1$, the concentration–effect curve is S- or sigmoid-shaped at lower serum concentrations. When $n < 1$, the concentration–effect curve has a steeper slope at lower concentrations (Fig. 8–15).

Figure 8-15.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com
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The sigmoid E_{\max} model [$E = (E_{\max} \times C^n) / (EC_{50}^n + C^n)$] has an S-shaped curve at lower concentrations. In this example, E_{\max} and EC_{50} have the same values as in Fig. 8–14.

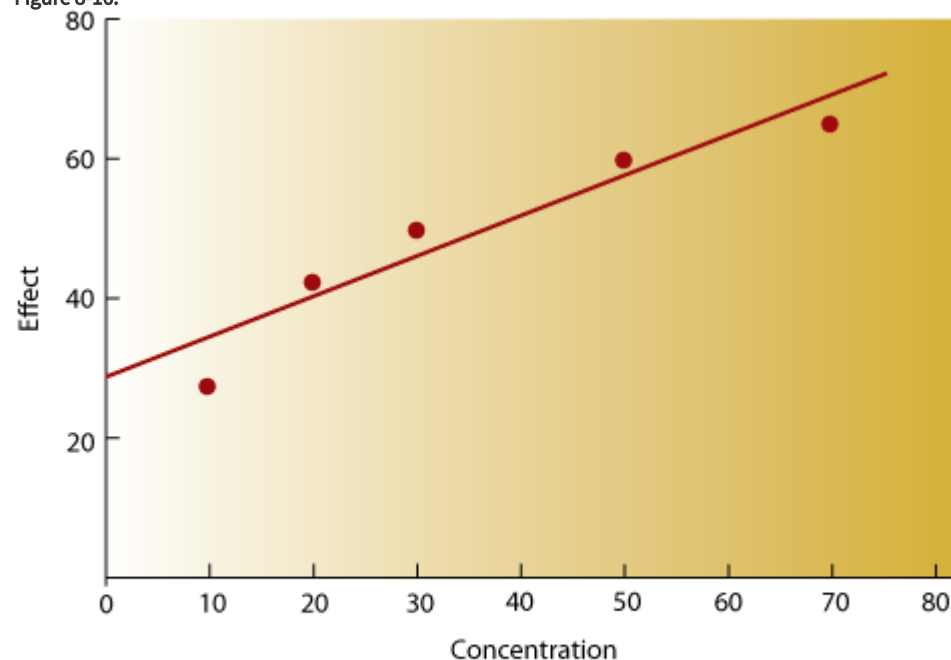
With both the E_{\max} and sigmoid E_{\max} models, the largest changes in drug effect occur at the lower end of the concentration scale. Small changes in low serum concentrations cause large changes in effect. As serum concentrations become larger, further increases in serum concentration result in smaller changes in effect. Using the E_{\max} model as an example and setting $E_{\max} = 100$ units and $EC_{50} = 20$ mg/L, doubling the serum concentration from 5 to 10 mg/L increases the effect from 20 to 33 units (a 67% increase), whereas doubling the serum

concentration from 40 to 80 mg/L only increases the effect from 67 to 80 units (a 19% increase). This is an important concept for clinicians to remember when doses are being titrated in patients.

Linear Models

When serum concentrations obtained during a pharmacodynamic experiment are between 20% and 80% of E_{\max} , the concentration–effect curve may appear to be linear (Fig. 8–16). This occurs often because lower drug concentrations may not be detectable with the analytic technique used to assay serum samples, and higher drug concentrations may be avoided to prevent toxic side effects. The equation used is that of a simple line: $E = S \times C + I$, where E is the drug effect, C is the drug concentration, S is the slope of the line, and I is the y intercept. In this situation, the value of S can be used as a measure of drug potency (the larger the value of S , the more potent the drug). The linear model can be derived from the E_{\max} model. When EC_{50} is much greater than C , $E = (E_{\max}/EC_{50})C = S \times C$, where $S = E_{\max}/EC_{50}$.

Figure 8-16.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach*, 8th Edition: www.accesspharmacy.com

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The linear model ($E = S \times C + I$) is often used as a pharmacodynamic model when the measured pharmacologic effect is 20% to 80% of E_{\max} . In this situation, the determination of E_{\max} and EC_{50} is not possible. To illustrate this, effect measurements from Fig. 8–14 between 20% and 80%

of E_{\max} are graphed using the linear pharmacodynamic model.

The linear model allows a nonzero value for effect when the concentration equals zero. This may be a baseline value for the effect that is present without the drug, the result of measurement error when determining effect, or model misspecification. Also, this model does not allow the prediction of a maximum response.

Some investigators have used a log-linear model in pharmacodynamic experiments: $E = S \times (\log C) + I$, where the symbols have the same meaning as in the linear model. The advantages of this model are that the concentration scale is compressed on concentration–effect plots for experiments where wide concentration ranges were used, and the concentration values are transformed so that linear regression can be used to compute model parameters. The disadvantages are that the model cannot predict a maximum effect or an effect when the concentration equals zero. With the increased availability of nonlinear regression programs that can compute the parameters of nonlinear functions such as the E_{\max} model easily, use of the log-linear model has been discouraged.⁵³

Baseline Effects

At times, the effect measured during a pharmacodynamic study has a value before the drug is administered to the patient. In these cases, the drug changes the patient's baseline value. Examples of these types of measurements are heart rate and blood pressure. In addition, a given drug may increase or decrease the baseline value. Two basic techniques are used to incorporate baseline values into pharmacodynamic data. One way incorporates the baseline value into the pharmacodynamic model; the other transforms the effect data to take baseline values into account.

Incorporation of the baseline value into the pharmacodynamic model involves the addition of a new term to the previous equations. E_0 is the symbol used to denote the baseline value of the effect that will be measured. The form that these equations takes depends on whether the drug increases or decreases the pharmacodynamic effect. When the drug increases the baseline value, E_0 is added to the equations:

$$E = E_0 + \frac{E_{\max} \times C}{EC_{50} + C}$$

$$E = E_0 + \frac{E_{\max} \times C^n}{EC_{50}^n + C^n}$$

$$E = S \times C + E_0$$

When E_0 is not known with any better certainty than any other effect measurement, it should be estimated as a model parameter similar to the way that one would estimate the values of E_{\max} , EC_{50} , S , or n .^{54,55} If the baseline effect is well known and has only a small amount of measurement error, it can be subtracted from the effect determined in the patient during the experiment and not estimated as a model parameter. This approach can lead to better estimates of the remaining model parameters.⁵⁵ Using the linear model as an example, the equation used would be $E - E_0 = S \times C$.

If the drug decreases the baseline value, the drug effect is subtracted from E_0 in the pharmacodynamic models:

$$E = E_0 - \frac{E_{\max} \times C}{IC_{50} + C}$$

$$E = E_0 - \frac{E_{\max} \times C^n}{IC_{50}^n + C^n}$$

$$E = E_0 - S \times C$$

where E_{\max} represents the maximum reduction in effect caused by the drug, and IC_{50} is the concentration that produces a 50% inhibition of E_{\max} . These forms of the equations have been called the *inhibitory E_{\max}* and *inhibitory sigmoidal E_{\max} equations*, respectively. In this arrangement of the pharmacodynamic model, E_0 is a model parameter and can be estimated. If the baseline effect is well known and has little measurement error, the effect in the presence of the drug can be subtracted from the baseline effect and not estimated as a model parameter. Using the inhibitory E_{\max} model as an example, the formula would be $E_0 - E = (E_{\max} \times C)/(IC_{50} + C)$.

When using the inhibitory E_{\max} model, a special situation occurs if the baseline effect can be obliterated completely by the drug (e.g., decreased premature ventricular contractions during antiarrhythmic therapy). In this situation, $E_{\max} = E_0$, and the equation simplifies to a rearrangement known as the *fractional E_{\max} equation*:

$$E = E_0 \left(1 - \frac{C}{IC_{50} + C} \right)$$

This form of the model relates drug concentration to the fraction of the maximum effect.

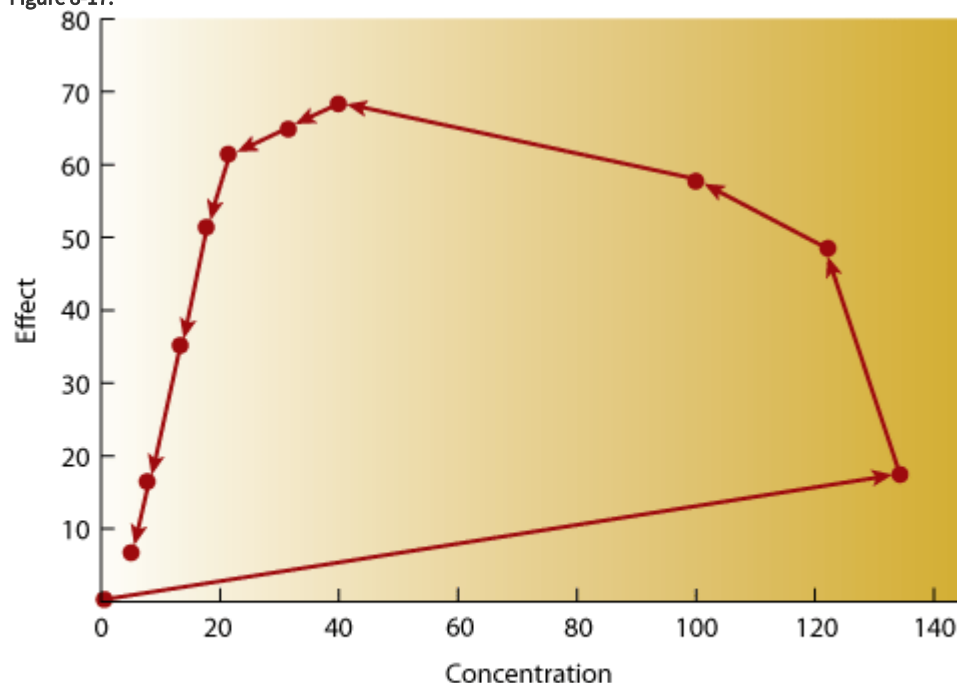
An alternative approach to the pharmacodynamic modeling of drugs that alter baseline effects is to transform the effect data so that they represent a percentage increase or decrease from the baseline value.⁵⁵ For drugs that increase the effect, the following transformation equation

would be used: $\text{percent effect}_t = [(\text{treatment}_t - \text{baseline}) / \text{baseline}] \times 100$. For drugs that decrease the effect, the following formula would be applied to the data: $\text{percent inhibition}_t = [(\text{baseline} - \text{treatment}_t) / \text{baseline}] \times 100$. The subscript indicates the treatment, effect, or inhibition that occurred at time t during the experiment. If the study included a placebo control phase, baseline measurements made at the same time as treatment measurements (i.e., heart rate determined 2 hours after placebo and 2 hours after drug treatment) could be used in the appropriate transformation equation.⁵⁵ The appropriate model (excluding E_0) then would be used.

Hysteresis

Concentration–effect curves do not always follow the same pattern when serum concentrations increase as they do when serum concentrations decrease. In this situation, the concentration–effect curves form a loop that is known as *hysteresis*. With some drugs, the effect is greater when serum concentrations are increasing, whereas with other drugs, the effect is greater while serum concentrations are decreasing (Fig. 8–17). When individual concentration–effect pairs are joined in time sequence, this results in clockwise and counterclockwise hysteresis loops.

Figure 8-17.



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Hysteresis occurs when effect measurements are different at the same concentration. This is commonly seen after short-term IV infusions or extravascular doses where concentrations increase and subsequently decrease. Counterclockwise hysteresis loops are found when concentration–effect points are joined as time increases (*shown by arrows*) and effect is larger at the same concentration but at a later time. Clockwise hysteresis loops are similar, but the concentration–effect points are joined in clockwise order, and the effect is smaller at a later time.

Clockwise hysteresis loops usually are caused by the development of tolerance to the drug. In this situation, the longer the patient is exposed to the drug, the smaller is the pharmacologic effect for a given concentration. Therefore, after an extravascular or short-term infusion dose of the drug, the effect is smaller when serum concentrations are decreasing compared with the time when serum concentrations are increasing during the infusion or absorption phase.

Accumulation of a drug metabolite that acts as an antagonist also can cause clockwise hysteresis.

Counterclockwise hysteresis loops can be caused by the accumulation of an active metabolite, sensitization to the drug, or delay in time in equilibration between serum concentration and concentration of drug at the site of action. Combined pharmacokinetic/pharmacodynamic models have been devised that allow equilibration lag times to be taken into account.

Summary


The availability of inexpensive, rapidly achievable serum drug concentrations has changed the way clinicians monitor drug therapy in patients. The therapeutic range for many drugs is known, and it is likely that more drugs will be monitored using serum concentrations in the future. Clinicians need to remember that the therapeutic range is merely an average guideline and to take into account interindividual pharmacodynamic variability when treating patients. Individual patients may respond to smaller concentrations or require concentrations that are much greater to obtain a therapeutic effect. Conversely, patients may show toxic effects at concentrations within or below the therapeutic range. Serum concentrations should never replace clinical judgment.


Three kinetic constants determine the dosage requirements of patients. Clearance determines the maintenance dose ($MD = CLC_{SS}$), volume of distribution determines the loading dose ($LD = V_D C_{SS}$), and half-life determines the time to steady state and the dosage interval. Several methods are available to compute these parameters.


Methods available to individualize drug therapy range from clinical pharmacokinetic techniques using simple mathematical relationships that hold for all drugs that obey linear pharmacokinetics to very complex computer programs that are specific to one drug.


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
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







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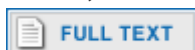
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