Chapter e6: Clinical Pharmacokinetics and Pharmacodynamics

Kristin M. Janzen; Samuel M. Poloyac

KEY CONCEPTS

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1. Clinical pharmacokinetics is the discipline that describes the absorption, distribution, and elimination of medications in patients requiring pharmacotherapy.

2. The pharmacokinetic parameter that describes absorption is the bioavailability. Bioavailability refers to the proportion of the dose of a medication that reaches systemic circulation.

3. The pharmacokinetic parameter that describes distribution is the volume of distribution. The volume of distribution is a proportionality constant that relates the amount of medication in the body to the serum concentration.

4. To characterize differences in drug distribution, we can use compartmental models to describe the different behaviors. Compartmental models are mathematical descriptions of the grouped body spaces that the medication penetrates and the overall time it takes to get into each space.

5. The pharmacokinetic parameter that describes elimination is clearance. Clearance describes the volume of plasma cleared of the given drug over time, and it may be either linear or nonlinear.

6. Most drugs follow linear pharmacokinetics, in which serum drug concentrations change proportionally with changes in dose.

7. Some drugs do not follow the rules of linear pharmacokinetics, which leads to a variety of nonlinear pharmacokinetic profiles. Instead of concentration increasing proportionally with dose, serum concentrations change more or less than expected.

8. The pharmacokinetic parameter that describes the time required for serum concentrations to decrease by one-half is half-life. Half-life is dependent on the values of clearance and volume of distribution.

9. 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.

10. Many factors should be taken into consideration when deciding on the best drug dose for a patient. These include patient-specific factors, including age, sex, weight, race/ethnic background, genetics, other concurrent disease states, kidney function, and hepatic function, as well as drug-specific factors (drug-drug interactions, drug-food interactions).

11. Cytochrome P450 enzymes are responsible for most drug metabolism oxidation reactions.

12. Membrane transporters are protein molecules that actively transport drugs across cell membranes. Transport proteins are important in the processes of drug bioavailability, elimination, and distribution.

13. When deciding on initial doses for drugs that are renally eliminated, the patient's kidney 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 (CL_{cr}).

14 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.

15 For drugs that exhibit linear pharmacokinetics, steady-state drug concentration changes proportionally with dose.

16 Some drugs with narrow therapeutic windows require determination of the pharmacokinetic constants to individualize the patient's dose. In these cases, a small pharmacokinetic evaluation is conducted in the individual.

17 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. The potency of a drug is estimated by the concentration required to achieve 50% of that maximal effect.

BEYOND THE BOOK

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Watch the video titled "Introduction to Pharmacokinetics", available at https://www.youtube.com/watch?v=TwSsMHtfQD4. This video provides a brief overview of basic pharmacokinetic concepts. This website is useful to enhance student understanding of basic pharmacokinetic concepts.

INTRODUCTION

Pharmacokinetic concepts have been used successfully to individualize pharmacotherapy and optimize patient care since the 1970s. Clinical pharmacists provide patient-specific drug-dosing recommendations that increase the efficacy and decrease the toxicity of many medications as a part of routine patient care responsibilities. Laboratories measure patient serum or plasma samples for many drugs, including antibiotics (eg, aminoglycosides and vancomycin), antiepileptics (eg, phenytoin, carbamazepine, valproic acid, and phenobarbital), methotrexate, lithium, antiarrhythmics (eg, lidocaine and digoxin), and immunosuppressants (eg, cyclosporine and tacrolimus). The process of measuring serum concentrations and using the results to optimize dose regimens is called therapeutic drug monitoring.[1] As practice has continued to evolve, the role of pharmacists in a variety of patient care settings has changed to include provision of therapeutic drug monitoring services through collaborative practice agreements and institutional protocols.[2] However, the entire healthcare team is necessary to ensure therapeutic drug monitoring is utilized appropriately.[1] As such, it is more important now than ever for the healthcare practitioner to understand and be able to apply pharmacokinetic and pharmacodynamic principles to practice.

Combined with a knowledge of the disease states and conditions that influence the disposition of a particular medication, kinetic concepts can be used to modify doses to produce serum drug concentrations that result in desirable pharmacologic effects without unwanted side effects. This range of concentrations within which the pharmacologic response is produced and adverse effects prevented in most patients is referred to as the therapeutic range or the therapeutic window of a given medication. Table e6-1 lists the therapeutic ranges for selected medications. 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 medication, such as the number of seizures while taking an antiepileptic agent, should always be assessed as the primary measure of efficacy with serum concentrations used as an additional informative measure.

TABLE e6-1

Selected Therapeutic Ranges

Drug	Therapeutic Range
Digoxin	0.5-2 ng/mL or mcg/L
	0.6-2.6 nmol/L
Gentamicin, tobramycin[a]	5-10 mcg/mL or mg/L (peak)
	10-21 µmol/L (peak)
	<2 mcg/mL or mg/L (trough)
	<4 µmol/L (trough)
Lithium	0.6-1.4 mEq/L
	0.6-1.4 mmol/L
Carbamazepine	4-12 mcg/mL or mg/L
	17-51 µmol/L
Phenobarbital	15-40 mcg/mL or mg/L
	65-172 µmol/L
Phenytoin/Fosphenytoin	10-20 mcg/mL or mg/L
	40-79 µmol/L
Valproic acid	50-100 mcg/mL or mg/L
	347-693 µmol/L
Cyclosporine (blood)	150-400 ng/mL or mcg/L
	125-333 nmol/L

[a]Using a multiple dose per day conventional dosage schedule.

Pharmacokinetic and pharmacodynamic principles are essential for selecting the appropriate dose, route, and frequency of pharmacotherapy in order to maximize efficacy and minimize adverse drug effects for both populations and individual patients.

PHARMACOKINETIC PRINCIPLES

[1] Clinical pharmacokinetics is the discipline that describes the absorption, distribution, and elimination of medications in patients requiring pharmacotherapy. In order to describe how a medication behaves in a patient, one must first define several characteristics of the medication's

concentration-time profile. These characteristics are called pharmacokinetic parameters and are used to determine the optimal dose and interval for a given medication. Each of these concepts will be discussed in turn.

Absorption

When a medication is administered extravascularly to patients, it must be absorbed across biologic membranes to reach the systemic circulation. If the medication is given orally, the drug molecules must pass through the gastrointestinal (GI) tract wall into capillaries. For transdermal patches, the medication must penetrate the skin to enter the vascular system. In general, the pharmacologic effect of the medication is delayed when it is given extravascularly because time is required for the medication to be absorbed from the administration site into the vascular system and distributed to the tissue site of action.

2 The pharmacokinetic parameter that describes the extent of absorption is the bioavailability. Bioavailability (F) refers to the proportion of the dose of a medication that reaches systemic circulation. For medications administered intravascularly, 100% of the dose enters into circulation and F equals 1. For medications administered via different routes (oral, transdermal, etc.), it is common that some of the medication fails to enter circulation, either via incomplete absorption due to low permeability or solubility, metabolism by enzymes in the GI tract or liver before the medication reaches systemic circulation or secretion of the medication back into the GI tract via transport proteins.[3,4] In this case, F would be less than 1, as less than 100% of the medication reaches systemic circulation.

Distribution

The vascular system generally provides the “transportation” for the drug molecule to its site of activity. After the medication reaches the systemic circulation, it can leave the vasculature and penetrate the various tissues or remain in the blood. If the medication remains in the blood, it may bind to endogenous circulating blood proteins, such as albumin and α1-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 eliminate the drug 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.

3 The pharmacokinetic parameter that describes the apparent drug distribution is the volume of distribution. The volume of distribution (V_D) is a proportionality constant that relates the amount of drug in the body to the serum concentration (C). The volume of distribution can be calculated by dividing the amount of medication administered (dose) by the initial concentration achieved (C_0):

$$V_D = \frac{dose}{C_0} \quad VD = doseC0$$

Conversely, if a given concentration is being targeted to achieve an effect, then the dose can be calculated by multiplying the targeted C_0 by the medication’s estimated volume of distribution. This is known as the loading dose (LD) of a medication and can be calculated using the following equation:

$$\text{Loading dose} = C_0 V_D \quad \text{Loading dose} = C0VD$$

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 based on population studies. The estimated V_D can be used to calculate an expected serum concentration after a weight-based loading dose is given or can be used to calculate a loading dose to obtain a desired C_0; however, it should be noted that the patient’s actual V_D is almost always different from the average V_D for the medication. As such, a loading dose does not usually attain the calculated C_0, but it does ideally achieve a therapeutic concentration. Of note, steady-state conditions are achieved in 3 to 5 half-lives for the medication.

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[5]:

$$V_D = V_b + \left(\frac{f_{ub}}{f_{ut}}\right) V_t \quad VD = Vb + (fubfut)Vt$$

where V_b and V_t are the volumes of blood and tissues, respectively, and f_{ub} and f_{ut} are the fractions of unbound drug in blood and tissues, respectively.

This is a useful pharmacokinetic equation in that it related the unbound fraction of the drug to the volume of distribution. For example, if the f_{ub} increases, the V_D increases because more drug is now free to distribute to the tissues. Conversely, if the f_{ut} increases, then V_D decreases because drug is not being bound in the tissues as extensively and is free to distribute back into the central circulation.

4 Another way to characterize a medication's pharmacokinetic behavior is by evaluating the distributional characteristics of the medication after administration. For some medications the distribution into the tissues is very rapid relative to the overall time it takes for elimination. For other medications, there is a lag or delay in the time that it takes for the blood and the body tissues to equilibrate. To characterize differences in drug distribution, we can use compartmental models to describe the different behaviors. Compartmental models are mathematical descriptions of the grouped body spaces that the medication penetrates and the overall time it takes to get into each space. For example, the blood and tissues that are easily perfused will often be grouped into the central compartment because the equilibration happens rapidly after administration. Some medications only enter easily or rapidly perfused tissue; therefore, a single compartment (one compartment model) can be used to describe the drugs distributional behavior. In contrast, some medications may distribute into harder to perfuse tissues as well, such as the brain, muscle, and/or adipose tissue. If a medication has both rapid central compartment with easily perfused tissue and also gets into harder to perfuse tissues, then the medication's distribution may be best characterized by a multiple compartmental model. Overall, compartmental models are used as an oversimplification of the complexity of a medication's pharmacokinetic behavior; however, this oversimplification allows for the use of basic mathematical concepts that can assist in estimating a medication's concentration, dose, and overall pharmacokinetic behavior.

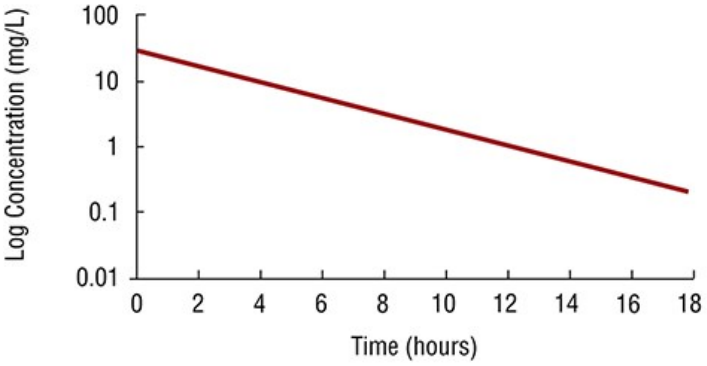
One Compartment Model

For the simplest case, a single compartment can describe the drug's distribution to the entire body (see Fig. e6-1). The medication can be administered and enter the central compartment by intravenous (IV) bolus dosing (D_{iv}), by rate of zero order IV infusion (R_0), or by absorption from an extravascular site with an absorption rate constant of k_a (D) depending on the route of administration. If the medication has one compartment model distribution characteristics, then the medication reaches a very rapid distribution in all of the tissues into which the medication will distribute. In this case, the time from when the medication is administered until the first blood sample is drawn is enough time that the medication has reached equilibration with all of the tissues to which it is distributed. In this case, the medication concentrations will decrease in a monoexponential fashion as long at the medication has first-order, concentration dependent (linear) pharmacokinetic characteristics, which will be described later in this chapter.

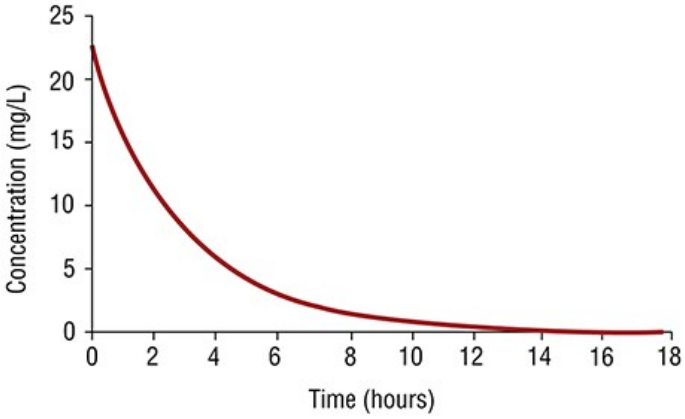
FIGURE e6-1

Representative serum concentration-time curves following intravenous or extravascular dosing.

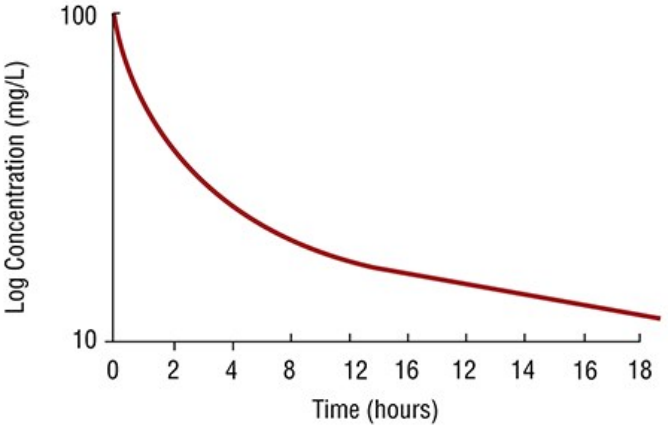
IV bolus, 1 compartment (logarithmic)



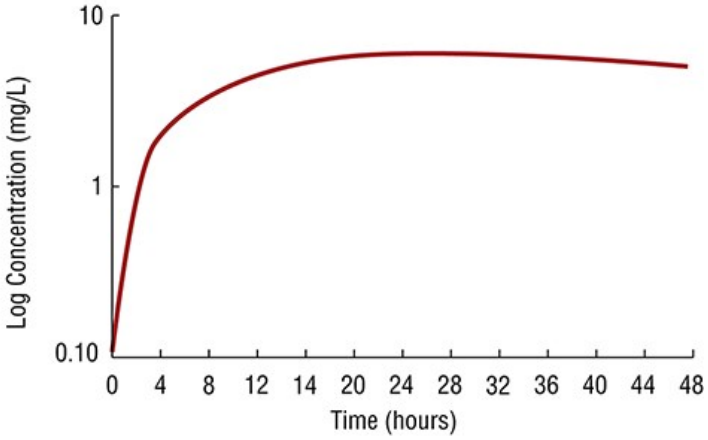
IV bolus, 1 compartment (non-logarithmic)



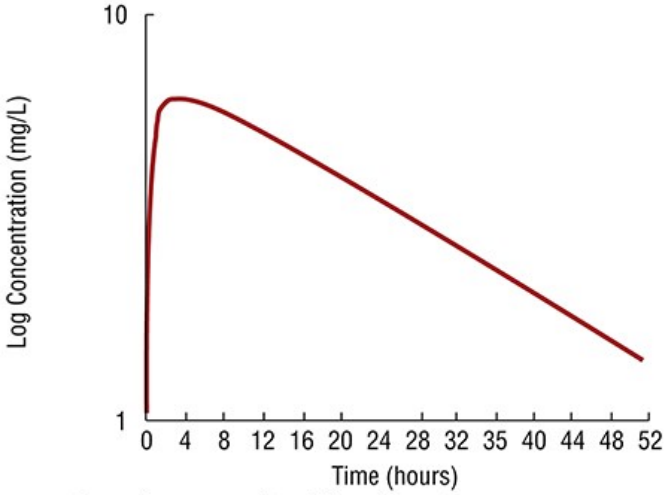
IV bolus, 2 compartments



IV continuous infusion



Extravascular



Multiple Compartment Model

For medications whose pharmacokinetics follow multicompartment distribution, additional time is needed for some of the tissues to reach equilibration, which can be observed in the initial phase of the medication's concentration time profile (Fig. e6-1). Again, the medication can be administered and enter the central compartment by IV bolus dosing (D_{iv}), by continuous IV infusion (R_0), or by absorption from an extravascular site with an absorption rate constant of k_a (D) depending on the route of administration. The systemic blood circulation as well as the highly perfused and rapidly distributed tissues will make up the central compartment as with the one compartment model. However, for multicompartment drugs, there are other body tissues that require additional time to reach equilibration with the blood for distribution. These harder to perfuse tissues are considered in the peripheral compartment. There can be several different peripheral compartments depending on the complexity of a given medication's pharmacokinetic behavior. For a two compartmental model drug, there is a central, easy to perfuse blood/tissue compartment and single, hard to perfuse tissue compartment that describe the medication's behavior. As such, two different V_D values are needed to describe the serum-concentration-versus-time curve, which include the central compartment volume (V_c) and the volume of distribution after tissue distribution (V_{area}).

At the early time points after administration, drug is being both distributed (prior to equilibration in hard to perfuse tissues) and eliminated. This creates a biexponential decrease in the drug concentration over time. If elimination is still the slowest overall rate for this two-compartmental drug, then over time, the hard to perfuse tissues and blood will eventually reach a point of equilibrium, which is known as pseudoequilibrium. At this point, the medication has equilibrated with all tissues and will follow a mono-exponential decline with time.

Elimination

5 Elimination is the process in which the body clears the medication from the body, which may occur through metabolism and/or excretion. The pharmacokinetic parameter that describes elimination is clearance. Clearance describes the volume of plasma cleared of the given medication over time, and it may be either linear or nonlinear. Clearance (CL) is the most important pharmacokinetic parameter because it determines the steady-state drug concentration (C_{ss}) for a given dosage, which is essential in maintaining the targeted therapeutic concentration of a drug in a patient and determining the appropriate maintenance dose (MD).

Clearance includes two main strategies: metabolism and excretion. 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 excretion 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 ultimate 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 can also be excreted via bile produced by the liver or by air expired by the lungs.

Clearance can be described mathematically as follows:

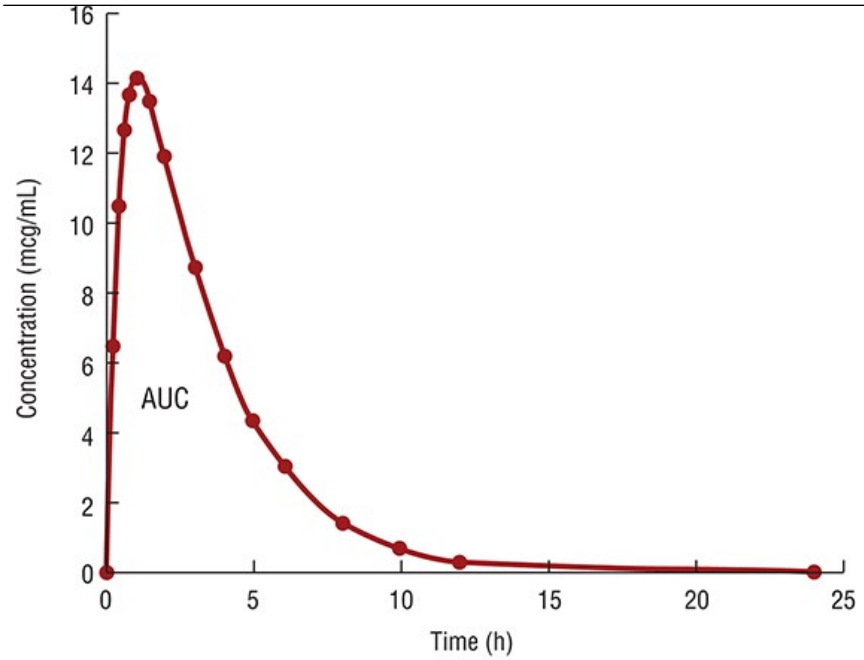
$\mathrm{CL} = \frac{\Delta A}{\Delta t}/C$CL = ΔAΔtC

where clearance is equal to the elimination rate (ΔA/Δt) divided by the plasma concentration. As such, clearance is inversely proportional to concentration—when clearance increases, plasma concentration decreases. Clearance can also be defined in terms of dose and area under the curve (AUC). The AUC represents the body's total exposure to the drug over time (Fig. e6-2). When the rate divided by concentration is integrated from 0 to infinity (∞), the amount from 0 to ∞ is equal to the dose. When the concentration multiplied by change in time is integrated from 0 to ∞, the result is the AUC. This results in the integrated equation:

$\mathrm{CL} = D/\mathrm{AUC}_0^\infty$CL = DAUC0∞

FIGURE e6-2

Area under the concentration-versus-time curve (AUC) after the administration of an extravascular dose in a two-compartment model. The AUC is a function of the fraction of drug dose that enters the systemic circulation and clearance.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

where clearance is equal to the dose divided by AUC. In practice, AUC is rarely measured directly due to the need for intensive blood sampling for accurate calculation. Instead, if the clearance of a given drug is known, the AUC can be calculated using:

$$\text{AUC} = \frac{D}{\text{CL}}$$ AUC = DCL

Clearances for Different Routes of Elimination and Metabolic Pathways

When a medication is given as a continuous IV infusion at a rate equal to R_0, the C_{ss} is determined by the quotient of R_0 and CL ($C_{ss} = R_0/\text{CL}$). If the medication is administered as individual doses (D) at a given dosage interval (τ), then the average C_{ss} over the dosage interval is given by the equation[6]:

$$C_{ss} = \frac{F\left(\frac{D}{\tau}\right)}{\text{CL}}$$ Css = F(Dτ)CL

where F is the fraction of dose absorbed into the systemic vascular system. The average C_{ss} over the dosage interval is the C_{ss} that would have occurred had the same dose been given as a continuous IV infusion (eg, 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/hr).

Physiologically, clearance is determined by (1) blood flow (Q) to the organ that metabolizes (liver) or excretes (kidney) the medication, and (2) the efficiency of the organ in extracting the medication from the bloodstream. 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}:

$$E = \frac{C_{in} - C_{out}}{C_{in}}$$ E = Cin−CoutCin

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 (CL_H) equals 0.5 L/min. Total clearance is computed by summing all the individual organ clearance values.

While many organs have the capability to clear drugs, the liver is the site of the vast majority of drug metabolism; therefore, the clearance provided by the liver is especially important and will be tahe focus of this section.

Clearance is altered when either the blood flow to extracting organs or the extraction ratio changes. Vasodilators such as hydralazine and nifedipine increase liver blood flow, whereas heart failure (HF) and hypotension can decrease hepatic blood flow. Extraction ratios can increase when enzyme

inducers increase the amount of drug-metabolizing enzyme, whereas extraction ratios may decrease if necrosis causes loss of hepatic parenchyma. An understanding of these variables can help the clinician predict the impact on the clearance and, ultimately, the C_{ss} of the drug when changes occur.

The extraction ratio cannot be directly measured because of the inability to clinically measure concentrations of drug coming into and out of the liver. Therefore, an estimation of the extraction ratio must be made. One method of estimating the extraction ratio is through the well-stirred model, which assumes that the liver represents one well-stirred compartment. This model can estimate the extraction ratio by accounting for the unbound fraction of drug in the blood (f_u), the intrinsic ability of the extracting organ to clear unbound drug from the blood (CL_{int}), and blood flow to the organ (Q).[7,8] Mathematically, this can be described as follows:

$$E = \frac{f_u(CL_{int})}{Q + f_u(CL_{int})}$$ E = fu(CLint)Q+fu(CLint)

Extraction ratio can thus be affected by any of these variables. Intrinsic clearance, which refers to the liver's maximum capacity to metabolize the drug in normal conditions (ie, enzymatic activity), is especially important. Drugs that have high intrinsic clearance usually have high extraction ratios, as drugs with low extraction ratios usually have low extraction ratios.

By substituting this equation for E in the formula $CL_H = QE$, the clearance equation becomes

$$CL_H = \frac{Q[f_u(CL_{int})]}{Q + f_u(CL_{int})}$$ CLH = Q[fu(CLint)]Q+fu(CLint)

Understanding the variables in this equation is important for predicting how the clearance of the drug will be altered when either the blood flow to the liver (Q), fraction of unbound drug (f_u), or enzymatic activity (CL_{int}) change. Binding in the blood can change if the concentration of binding proteins is low (as in hypoalbuminemia due to malnutrition, for example) or if highly protein-bound drugs are displaced by a drug interaction. Intrinsic clearance is affected when the maximal enzymatic activity changes, such as when metabolizing enzymes are induced or inhibited by other pharmacotherapy or functional organ tissue is destroyed by disease processes such as cirrhosis. Depending on the properties of the drug, a clinician can use the well-stirred model to predict the clearance and C_{ss} following changes in any of these parameters.

Drugs such as propranolol, verapamil, and morphine have high intrinsic clearance, meaning that the liver is very effective at metabolizing the drug. This leads to a high extraction ratio—a large proportion of the drug that enters the liver is metabolized. If CL_{int} is large (enzymes have a high capacity to metabolize the drug), the product of f_u and CL_{int} is much larger than Q. When f_u (CL_{int}) is much greater than Q, the sum of Q and $f_u(CL_{int})$ in the denominator of the clearance equation almost equals f_u (CL_{int}):

$$f_u(CL_{int}) \approx Q + f_u(CL_{int})$$ fu(CLint)≈Q+fu(CLint)

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}:

$$CL_H \approx Q$$ CLH ≈ 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. This results in clearance being highly affected by the blood flow to the liver. In disease states such as cardiogenic shock, in which blood flow to the liver may be reduced, clearance will also be reduced.

Because they have high extraction ratios, these drugs often exhibit what is called a first-pass effect when administered orally. When drugs are given enterally, they are absorbed into the blood and pass through the liver prior to entering systemic circulation. If a large amount of the drug is extracted prior to reaching systemic circulation, the overall bioavailability of the drug is reduced. In order to reach desired concentrations systemically, larger doses are needed as compared to the IV formulations.

Conversely, drugs such as warfarin, diazepam, and phenobarbital have low extraction ratios. When CL_{int} is small (enzymes have a limited capacity to metabolize the drug), Q is much larger than the product of f_u and CL_{int}. When Q is much greater than $f_u(CL_{int})$, the sum of Q and $f_u(CL_{int})$ in the denominator of the clearance equation becomes almost equal to Q:

$$Q \approx Q + f_u(CL_{int})$$ Q≈Q+fu(CLint)

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}:

$CL \approx f_u(CL_{int})$CL≈fu(CLint)
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. Because the liver is poorly able to metabolize the drug, the clearance is less affected by change in blood flow and is instead much more affected by unbound drug concentration and the intrinsic clearance. For example, if given with an enzyme inducer, the clearance of a low extraction ratio drug would increase and could cause below expected serum concentrations.

As mentioned previously, the concentration of unbound drug in the blood is 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 typically most closely associated with 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_u: $C_{ss,u} = C_{ss}\ f_u$. The effect that changes in Q, f_u, 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 $CL_H = Q$ for high-clearance drugs, a change in f_u or CL_{int} does not change CL_H or C_{ss} (ie, $C_{ss} = R_0/CL$). However, a change in unbound drug fraction does alter $C_{ss,u}$ (ie, $C_{ss,u} = f_u C_{ss}$), 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_H, C_{ss}, $C_{ss,u}$, and pharmacologic response do not change. Changes in Q cause a change in CL_H; changes in C_{ss}, $C_{ss,u}$, and drug response are indirectly proportional to changes in CL_H.

For low-clearance drugs, total clearance is determined by unbound drug fraction and intrinsic clearance: $CL_H = f_u(CL_{int})$. A change in Q does not change CL_H, C_{ss}, $C_{ss,u}$, or pharmacologic response. However, a change in f_u or CL_{int} does alter CL and C_{ss} (ie, $C_{ss} = R_0/CL_H$). Changes in CL_{int} will cause a proportional change in CL_H. Changes in C_{ss}, $C_{ss,u}$, and drug response are indirectly proportional to changes in CL_H. Altering f_u for low-clearance drugs produces interesting results. A change in f_u alters CL_H and C_{ss} (ie, $C_{ss} = R_0/CL_H$) but will not change the steady-state concentration of unbound drug (ie, $C_{ss,u} = f_u C_{ss}$). By substituting the C_{ss} formula in the equation for $C_{ss,u}$

$C_{ss,u} = f_u \cdot \frac{R_0}{f_u \cdot CL_{int}}$Css,u = fu · R0fu · CLint
After canceling common terms, the equation becomes

$C_{ss,u} = \frac{R_0}{CL_{int}}$Css,u = R0CLint
Thus, the $C_{ss,u}$ is related to only the rate of infusion and intrinsic clearance. Therefore, changes in f_u will alter total concentration, but no change in drug dosing is warranted since $C_{ss,u}$ is not expected to be altered by change in protein binding for a low extraction ratio drug.

Suppose that another drug is administered to the patient that displaces the first drug from plasma-protein-binding sites and doubles f_u (f_u now equals $2f_u$). CL_H doubles because of the protein-binding displacement ($2CL = 2f_u[CL_{int}]$), and C_{ss} decreases by one-half because of the change in clearance ($½[C_{ss}] = R_0/[2Cl]$). $C_{ss,u}$ does not change because even though f_u is doubled, C_{ss} decreased by one-half ($C_{ss,u} = f_u C_{ss}$). 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 patients who have experienced trauma or are pregnant), 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 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.

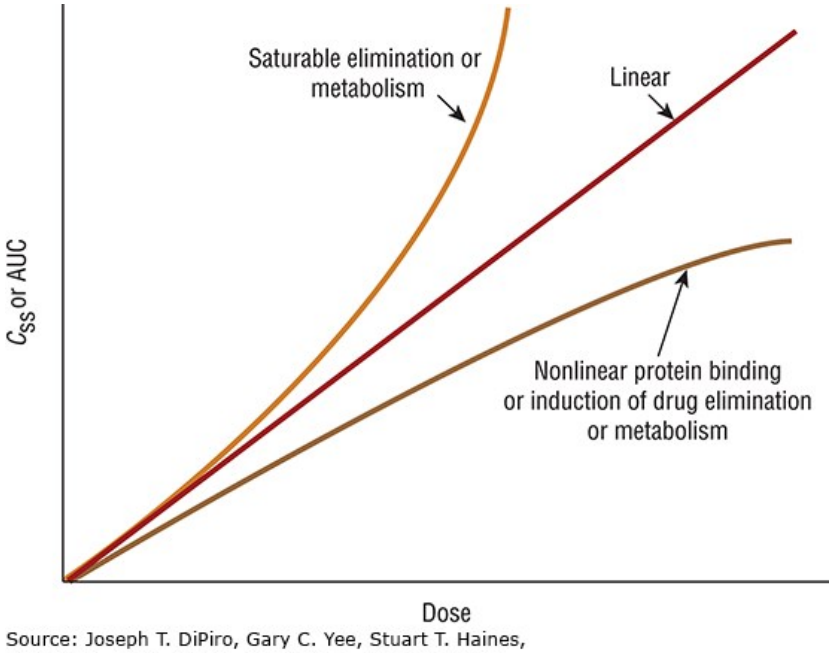
Linear Pharmacokinetics

6 Most drugs follow linear pharmacokinetics, in which serum drug concentrations change proportionally with changes in dose over the clinically administered drug dosing range (Fig. e6-3). For example, if a drug dose were doubled from 300 mg to 600 mg daily, the expected serum concentration would double. Drugs exhibit linear pharmacokinetics when they are dosed over a range of concentrations that does not saturate the enzymes or transporters responsible for their elimination or the proteins or tissues to which they are bound. In other words, the elimination rate for the drug increases proportionately with increases in concentration. This occurs physiologically because as the concentrations increase, the pathways of enzymatic or non-enzymatic elimination can also increase, thereby, proportionately increasing the elimination rate. The elimination rate is the change in concentration per change in time and represents the rate at which the drug can be removed from the bloodstream.

$$\frac{\Delta C}{\Delta t} = -kC \Delta C \Delta t = -kC$$

FIGURE e6-3

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



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Where $\Delta C/\Delta t$ is the change in the concentration per change in time (ie, the elimination rate), C is the plasma concentration, and k is the elimination rate constant. For drugs with first-order, non-saturable (linear) pharmacokinetics, the increases in plasma concentration produce a proportionate increase in the elimination rate over the dosing range of that drug. Consequently, the AUC of drugs that exhibit linear pharmacokinetics also increases proportionally with increase in dose.

Nonlinear Pharmacokinetics

7 Some drugs do not follow the rules of linear pharmacokinetics, which leads to a variety of nonlinear pharmacokinetic profiles. Instead of concentration changing proportionally with dose, serum concentrations change more or less than expected (Fig. e6-3).

Drugs exhibit nonlinear pharmacokinetics when their dosing range produces systemic concentrations that saturate the enzymes responsible for their elimination (Michael-Menten) or binding proteins (nonlinear protein binding), induce their own metabolism (autoinduction), or bind extremely tightly to their receptor target (target-mediated drug distribution). For example, if a drug is required to be dosed at concentrations that saturate the drug metabolizing enzymes responsible for the drug's elimination, then the elimination rate will no longer be able to increase in proportion with increases in drug dose or concentration. Therefore, as concentration rate increases, elimination rate (ΔC/Δt) will not change and become a flat, constant rate of elimination (zero order). In this example, the concentrations will now increase disproportionately with an increase in dose. This is particularly clinically relevant because a doubling in dose would produce a more than doubling of the plasma concentration, which could put the patient are risk of toxicity if the concentrations achieved are outside of the therapeutic range. Nonlinear protein binding can cause the reverse—an increase in f_u will lead to increased CL for low clearance drugs. An increase in dose would then result in a less than anticipated serum concentration, which may fail to reach the intended therapeutic range and/or produce the desired effect of the medication.

Phenytoin is an anti-seizure medication that is well known to have nonlinear pharmacokinetics.[9] The doses of phenytoin commonly administered can produce plasma concentrations that saturate the enzymes responsible for its elimination. It is important that pharmacists recognize drugs like phenytoin with nonlinear pharmacokinetics so that dose changes are not incorrectly assumed to produce equal changes in systemic concentration. Drugs with nonlinear pharmacokinetics should be adjusted cautiously and monitored closely, often with plasma drug concentrations, to ensure both safe and effective dosing.

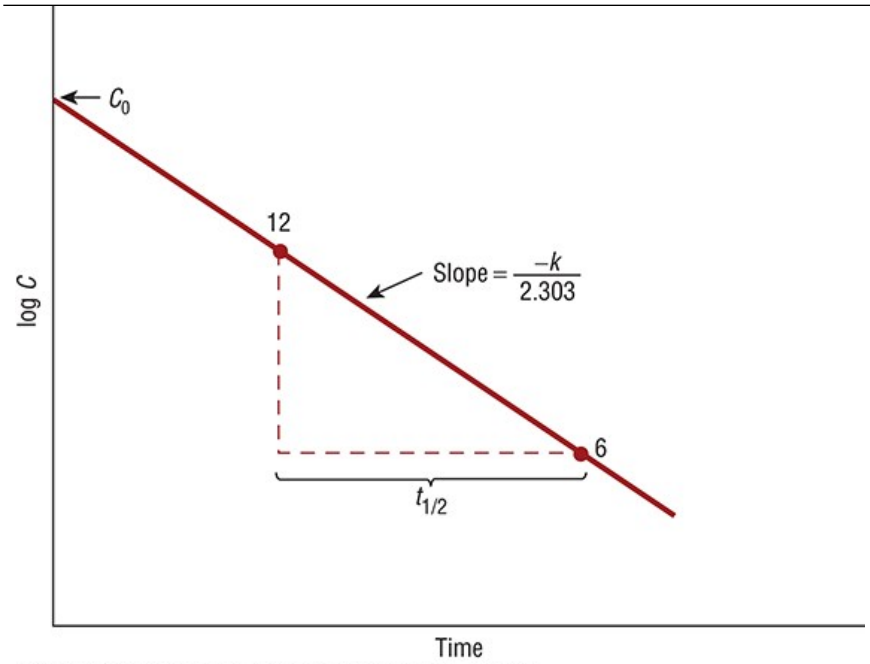
Half-Life

8 The pharmacokinetic parameter that describes the time required for serum concentrations to decrease by one-half is half-life. Half-life is dependent on the values of clearance and volume of distribution. 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. e6-4) due to concentration-dependent elimination. Charted on logarithmic graph paper, the elimination rate constant can be described as the slope of the serum concentration ($-k/2.303$), though this is often changed to a natural log (ln) for presentation purposes, with the slope then equal to $-k$. For the remainder of this chapter, formulas will be presented using natural log. The $t_{1/2}$ can then be calculated using the equation:

$$t_{½} = \frac{\ln 2}{k} = \frac{0.693}{k} \quad t½ = \ln 2k = 0.693k$$

FIGURE e6-4

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



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Half-life is a dependent kinetic variable because its value depends on the values of CL and V_D.[5] 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 only occur when CL has changed. Half-life can also 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.

Half-life is important because it determines the time required to reach steady state, the time to complete drug elimination, and the dosage interval. It takes approximately three to five half-lives to reach steady-state concentrations during continuous dosing. In 3 to 5 half-lives, serum concentrations are at ~90% and 96.9% of their ultimate steady-state values, respectively. 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 within the 3 to 5 half-live range to be C_{ss}.

Half-life is also used to determine the dosage interval for a drug (τ). For example, it may be desirable to maintain peak or maximal steady-state concentrations at 20 mg/L and minimum or trough 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.

Linear Pharmacokinetic Concepts

9 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.[10] Figure e6-1 contains examples of different administration methods and distributions that follow linear pharmacokinetics.

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. e6-1). For clinical dosage adjustment purposes using drug concentrations, a one-compartment model is the most commonly used pharmacokinetic model.

IV Bolus, One Compartment

After an IV bolus in a one compartment linear model, the concentration of the drug will decrease in exponential fashion when plotted on graph paper (Fig e6-1); however, using semilogarithmic coordinates, serum concentrations decline in a straight line. The slope of the line is $-k/2.303$; when using a natural log scale, this means slope is $-k$. Once k is known, the $t_{1/2}$ can be computed by determining the time required for concentrations to decrease by one-half ($t_{1/2} = 0.693/k$) (see Fig. e6-4). The equation that describes the concentration (C_t) at a given time (t) is as follows:

$C_t = C_0 e^{-kt}$ Ct = C0e−kt

The y-intercept is the concentration at time zero (C_0), which can also be described as follows:

$C_0 = \frac{dose}{V_D}$ C0 = doseVD

When substituting this equation for C_0, the resulting equation can be used to compute concentration at any time after the dose once V_D and are known:

$C_t = \frac{\text{dose}}{V_D} e^{-kt}$ Ct = doseVDe−kt

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.

IV Bolus, Two Compartment

After an IV bolus dose, serum concentrations often decline in two or more phases (see Fig e6-1). During the early phases, the drug leaves the bloodstream by two mechanisms: (1) distribution into tissues and (2) metabolism and/or elimination. Both the distribution and elimination processes are often first order, concentration-dependent rate processes; therefore, at early time points after an IV bolus when concentrations are high, these serum concentrations will decline rapidly. 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. 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.

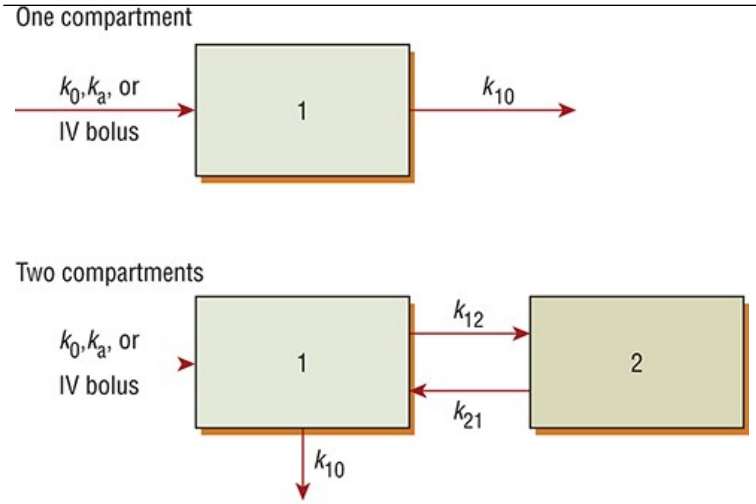
The two-compartment model is encountered most commonly (see Fig. e6-5). After an IV bolus injection, serum concentrations decrease in two distinct phases, described by the equation:

$C_t = \frac{D(\alpha - k_{21})}{V_{D1}(\alpha - \beta)} e^{-\alpha t} + \frac{D(k_{21} - \beta)}{V_{D1}(\alpha - \beta)} e^{-\beta t}$ Ct=D(α−k21)VD1(α−β)e−αt+D(k21−β)VD1(α−β)e−βt

or $C_t = Ae^{-\alpha t} + Be^{-\beta t}$, 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 $B = D(k_{21} - \beta)/(V_{D1}[\alpha -])$. The rate constants α and found in the exponents of the equations describe the distribution and elimination of the drug, respectively (Fig. e6-6). A and B are the y intercepts of the lines that describe drug distribution and elimination, respectively, on the concentration-versus-time plot.

FIGURE e6-5

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



The residual line is calculated as before using the method of residuals (see Fig. e6-6, 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, where

$Actual: C_t = Ae^{-\alpha t} + Be^{-\beta t}$ Actual: Ct = Ae−αt+Be−βt
$Extrapolated: C_{ext,t} = Be^{-\beta t}$ Extrapolated: Cext,t = Be−βt
$Residual: C_{res,t} = Ae^{-\alpha t}$ Residual: Cres,t = Ae−αt

When using a natural log scale, the residual line has a *y* intercept equal to *A*. The slope of the residual line is used to compute α (slope = $-\alpha$). 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 ($C_t = Ae^{-\alpha t} + Be^{-\beta t}$), or pharmacokinetic constants can be computed:

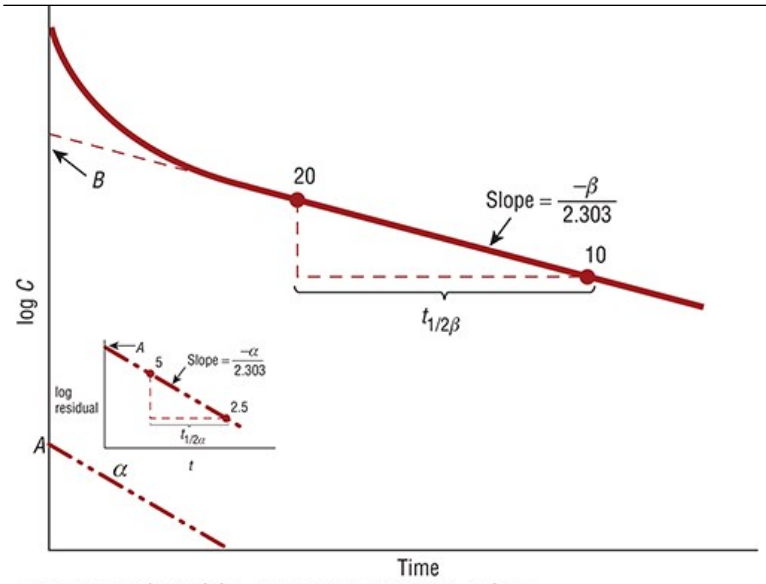
$\mathrm{AUC}_0^\infty = \frac{A}{\alpha} + \frac{B}{\beta}$ AUC0∞=Aα+Bβ
$\mathrm{CL} = \frac{\mathrm{dose}}{\mathrm{AUC}_0^\infty}$ CL=doseAUC0∞

In multicompartment models, multiple V_D parameters are needed to accurately describe the data. $V_{D,\beta}$ describes the volume of distribution after the distribution phase, and $V_{D,ss}$ describes the sum of the volumes of the compartments when at equilibrium. In order to calculate $V_{D,ss}$, an area under the moment (AUMC) curve is used, in which the product of the concentration and time is plotted by time.

$V_{D,\beta} = \frac{\mathrm{dose}}{\mathrm{AUC}_0^\infty \cdot \beta}$ VD,β=doseAUC0∞ · β
$V_{D,ss} = \frac{\mathrm{dose} \cdot \mathrm{AUMC}}{\mathrm{AUC}^2}$ VD,ss=dose · AUMCAUC2

FIGURE e6-6

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



Continuous IV Infusion

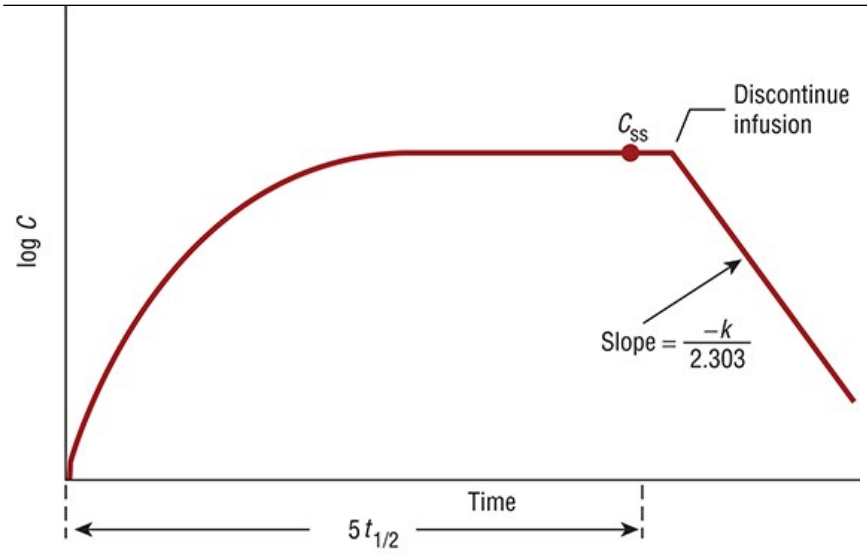
During a continuous IV infusion, the serum concentrations in a one-compartment model change according to the following function:

$C_t = \frac{R_0}{CL}\left(1 - e^{-kt}\right)$ Ct=R0CL(1−e−kt)

Serum concentrations increase until an equilibrium is established between the drug dosage rate and the rate of drug elimination. As time increases and approaches steady state at 3 to 5 half-lives, the ($1-e^{kt}$) function approaches a value of 1. At that point, the rate of drug administration equals the rate of drug elimination, and the serum concentrations remain constant (Fig. e6-1). CL can then be calculated ($CL = R_0/C_{ss}$). When the infusion is discontinued, serum concentrations decline in a straight line on the natural log scale with a slope of $-k$. V_D is computed by dividing CL by k (Fig. e6-7).

FIGURE e6-7

Achievement of steady-state serum concentrations after 3 to 5 half-lives of a drug. Note the elimination phase after discontinuance of the infusion.



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For example, if a patient were receiving a continuous IV infusion of theophylline at 40 mg/hr, the theophylline serum concentration would increase until the patient's body was eliminating theophylline at 40 mg/hr. When serum drug concentrations reach a constant value, steady state is achieved.

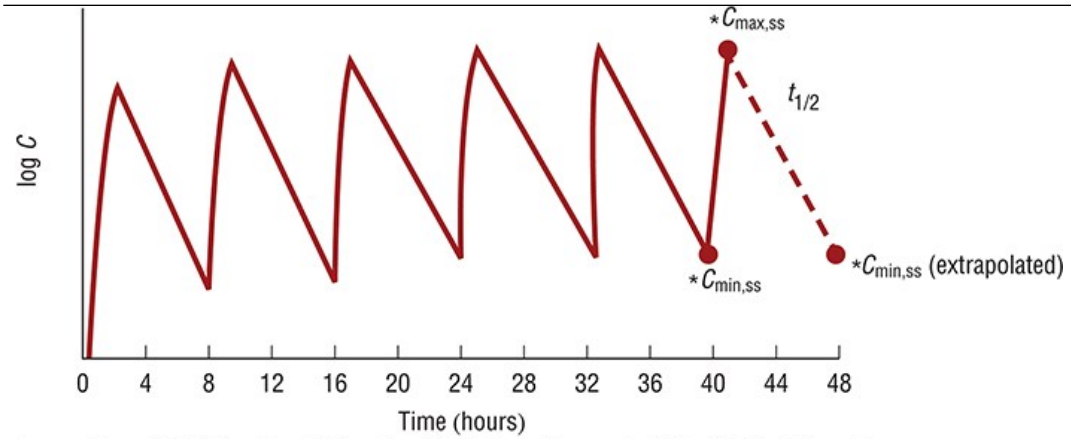
Multiple Dosing and Steady-State Equations

Any of these compartmental equations can be used to determine serum concentrations after multiple doses (Fig. e6-8). The multiple-dosing factor $(1 - e^{-kK\tau})/(1 - e^{-k\tau})$ 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: $C_t = Ae^{-\alpha t} + Be^{-\beta t}$. Thus, the equation for a multiple-dose two-compartment IV bolus is

$$C_t = Ae^{-\alpha t}\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}} + Be^{-\beta t}\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}$$Ct=Ae−αt1−e−nατ1−e−ατ+Be−βt1−e−nβτ1−e−βτ

FIGURE e6-8

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).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

A single-dose one-compartment IV bolus is calculated as $C_t = (D/V_D)e^{-kt}$. For a multiple-dose one-compartment IV bolus, the concentration is C:

$C_t = \left(\frac{D}{V_D}\right) e^{-kt} \times \frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}}$Ct=(DVD) e−kt × 1−e−nkτ1−e−kτ

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:

$C_t = Ae^{-\alpha t}\frac{1}{1 - e^{-\alpha\tau}} + Be^{-\beta t}\frac{1}{1 - e^{-\beta\tau}}$Ct=Ae−αt11−e−ατ+Be−βt11−e−βτ

and

$C_t = C_0 e^{-kt} \times \frac{1}{1 - e^{-k\tau}}$Ct=C0e−kt×11−e−kτ

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

Extravascular Administration

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 as[11]

$F = \frac{D_{iv} * AUC_0^{\infty}}{D * AUC_{iv_0}^{\infty}}$F=Div*AUC0∞D*AUCiv0∞

where D and D_{iv} are the extravascular and IV doses, respectively, and $AUC_{iv,0\text{-}\infty}$ and $AUC_{0\text{-}\infty}$ are the IV and extravascular areas under the serum- or blood-concentration-versus-time curves, respectively, from time zero to infinity. (Fig. e6-2). When is 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.

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.[12,13] 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. This removal/metabolism of the parent drug by the liver prior to reaching the circulation is known as the "first-pass effect." This is so named because the drug must first pass the liver before reaching systemic circulation. 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. 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. 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 and/or substantial gut wall metabolism.

When an extravascular dose is given, one-compartment-model serum concentrations rise during absorption, then decrease in a straight line with a slope equal to $-k$. The equation that describes the data is shown below, 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. e6-9). 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. e6-9, 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:

$C = Ae^{-kt} - Ae^{-kat}$ C=Ae−kt−Ae−kat
where $A = \frac{FDk_a}{V_D(k_a - k)}$ A=FDkaVD(ka−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:

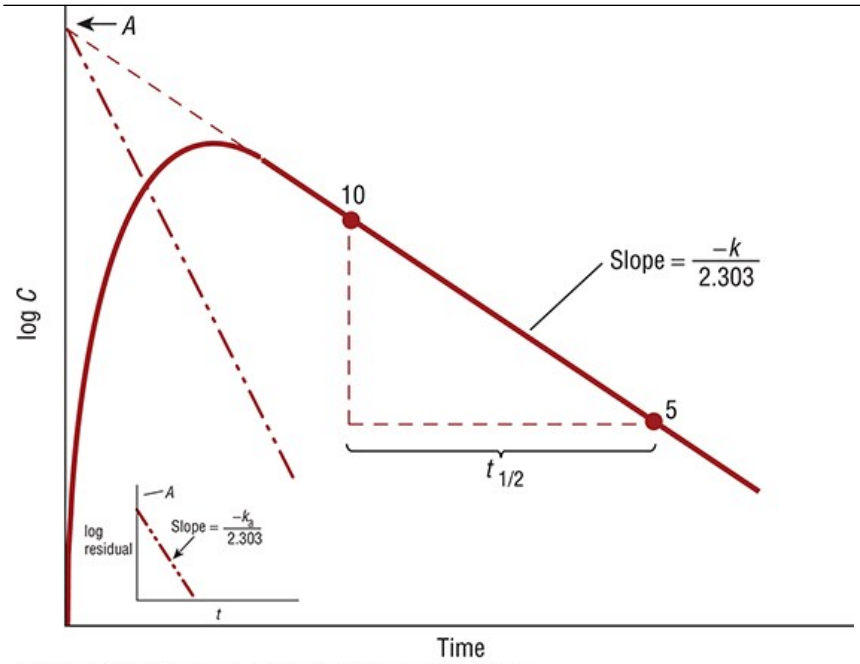
$\mathrm{CL} = \frac{\mathrm{FD}}{(A/k - A/k_a)}$ and $V_D = {}^{\mathrm{CL}}/_{k}$ CL=FD(Ak−Aka) and VD=CLk
where F is the fraction of the dose absorbed into the systemic circulation.

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 in order to statistically compare the two formulations' pharmacokinetic profiles.

Usually, the elimination is the rate limiting step in the drug's pharmacokinetic profile (ie, $k >>> k_a$). However, some oral drugs are prolonged or delayed absorption so that the half-life appears much longer when administered enterally than when given IV. This means that the rate-limiting step is the absorption instead of the elimination (ie, $k_a >>> k$), which leads to "flip flop kinetics." In this case, the slope does not solely represent the elimination process. This may be a coincidental finding, as with acamprosate, or may be a result of sustained release formulation. In these cases, the k_a is important for determining the $t_{½}$ of the drug.[14] Many sustained release products take advantage of slow gastrointestinal transit time to prolong k_a and thus, prolong the $t_{½}$ of the drug.

FIGURE e6-9

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.



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Nonlinear Pharmacokinetic Concepts

Michaelis-Menten Kinetics

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. e6-3). 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 when drug concentrations are high. This is called Michaelis-Menten kinetics. The potency of a given drug is determined by the serum concentration at which the rate of metabolism equals $V_{max}/2$, which is known as the K_m. Practically speaking, K_m is the serum concentration above 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 maintenance dose (mg/day) needed to maintain a given C_{ss}:

$$\text{Maintenance dose} = \frac{V_{max} C_{ss}}{(K_m + C_{ss})}$$ Maintenance dose=VmaxCss(Km+Css)

Most drugs eliminated by the liver are metabolized by enzymes but still 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; however, some drugs are dosed at ranges that are well above the K_m to reach therapeutic concentrations. One example is the antiseizure medication phenytoin. For example, the average K_m for phenytoin is about 5 to 6 mg/L (mcg/mL; 20-24 µmol/L).[15] The therapeutic range for phenytoin is usually 10 to 20 mg/L (mcg/mL; 40-79 µmol/L). Thus, most patients experience saturable Michaelis-Menten kinetics while taking phenytoin and changes in dosing must be cautiously optimized.

Nonlinear Protein Binding

Typical 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_u increases with increases in the dose (Fig. e6-3). For a low-

clearance drug, CL depends on the values of f_u and CL_{int} ($CL = f_u CL_{int}$). When a dosage increase takes place, f_u increases because nearly all plasma protein-binding sites are occupied, and no binding sites are available. If f_u increases, CL increases, and C_{ss} increases less than expected with the dosage change ($C_{ss} = R_0/CL$). However, $C_{ss,u}$ increases proportionally with the dose because $C_{ss,u}$ depends on CL_{int} for low-clearance drugs ($C_{ss,u} = R_0/CL_{int}$). Clinically, the increased f_u will result in increased total concentration but no change in free concentration; thereby, an observed increase in total concentration would not warrant a change in dose since free drug in responsible for the effect. Valproic acid is an example of a commonly used drug that follows saturable protein-binding pharmacokinetics.[9,15,16]

Atypical Nonlinear Protein Binding

Some drugs may also display an atypical nonlinear protein binding, in which the fraction of unbound drug is not linear but does not follow the saturation model as above.[17,18] The most common is the reverse of typical protein binding—the fraction of unbound drug decreases with increasing plasma concentrations. Several of the tetracyclines, including doxycycline and eravacycline, display this effect. Even more complex, some drugs, such as tigecycline, seems to have a U-shaped relationship between serum concentration and free fraction. In both of these instances, increasing doses may achieve lower than expected concentrations of free drug and fail to produce the desired clinical effect. Drugs that display these effects require complex modeling to describe their pharmacokinetics.[17,18]

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 an increase in its own metabolism, this process is called autoinduction. For some drugs, such as carbamazepine,[9,15] 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 (Fig. e6-3). 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.

Target-Mediated Drug Disposition

Nonlinear pharmacokinetics are often seen in both large molecule drugs, such as monoclonal antibodies (eg, denosumab) or recombinant proteins (eg, filgrastim), and in some small molecule drugs, such as linagliptin, a commonly used medication to treat type 2 diabetes mellitus.[19–21] This phenomenon is a result of a pharmacodynamic process (high-affinity binding of the drug to its receptor target) affecting the pharmacokinetics of the drug, which is called target-mediated drug disposition.[21] While target-mediated drug disposition was first described in the 1990s, the rapid increase in large molecule drugs that fit the pharmacokinetic pattern has increased substantially. A number of factors are needed to result in target-mediated drug disposition: the drug must have high binding affinity to its receptor, the binding must be specific (ie, the drug binds with high affinity only to its target, not to other proteins or tissues), and the capacity for binding must be low, which means the process can be easily saturated.[19] When a single, low dose is given, most of the drug binds to its intended target and little is left remaining in systemic circulation. Because the capacity for binding the drug is low, when doses are increased, there are not as many available binding sites for the drug. As such, increasing amounts of the drug will remain in systemic circulation and the serum concentration will increase more than would be expected with linear pharmacokinetics. After all sites are saturated (typically at high doses), the serum concentration will usually increase linearly. The increasing emergence of large molecule and immunotherapeutic novel drug therapies is increasing the importance of understanding nonlinear pharmacokinetic processes as they relate to patient drug dosing.

Use of Pharmacokinetic Concepts for Individualization of Pharmacotherapy

10 Many factors should be taken into consideration when deciding on the best drug dose for a patient. These include patient-specific factors, including age, sex, weight, race/ethnic background, genetics, other concurrent disease states, kidney function, and hepatic function, as well as drug-specific factors (drug-drug interactions, drug-food interactions).

Patient-Specific Factors

The age of the patient is important because developmental stage and aging may result in alterations in drug absorption, distribution, and/or elimination.[22,23] For example, 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. Sex can also 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. Disease states and conditions may alter the drug-dosage regimen for a patient. Three disease states that deserve special mention are heart failure, kidney disease, and hepatic disease. Kidney and hepatic diseases cause loss of organ function and decreased drug elimination and metabolism. Heart failure causes decreased blood flow to organs that clear the drug from the body. Coadministered pharmacotherapy that could cause drug interactions needs to be considered. Additionally, several enzymes responsible for drug metabolism have been found to exhibit significant genetic variations. These pharmacogenetic implications are discussed extensively in Chapter e7.

Drug-Specific Considerations

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. In some cases, drug development has focused on administration of a single isomer to improve drug therapeutic and pharmacokinetic variability. One such drug is escitalopram for the treatment of depression.

11 The cytochrome P450 family of enzymes is 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 e6-2). CYP2C19 metabolizes most proton pump inhibitors, sertraline, and voriconazole; CYP1A2 is the enzyme that is responsible for the demethylation of caffeine and theophylline; CYP2C9 metabolizes phenytoin, losartan, and ibuprofen; CYP3A4 metabolizes some antiretroviral protease inhibitors, cyclosporine, and; 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 metabolizes by both CYP1A2 and CYP2E1. The CYP3A enzyme family comprises ~90% of the drug-metabolizing enzyme present in the intestinal wall but only ~29% of the drug-metabolizing enzyme found in the liver. The remainder of hepatic drug-metabolizing enzyme is ~18% for the CYP2C family, ~13% for CYP1A2, ~7% for CYP2E1, and ~2% for CYP2D6.[24]

TABLE e6-2

Cytochrome P450 Enzyme Family and Selected Substrates

CYP1A2	CYP2E1
Acetaminophen	Enflurane
Caffeine	Ethanol
Ondansetron	Halothane
Tacrine	Isoflurane
Theophylline	CYP3A4
R-warfarin	Alfentanil
Zileuton	Alprazolam
CYP2C9	Astemizole
Candesartan	Carbamazepine
Diclofenac	Cyclosporine
Ibuprofen	Diltiazem
Losartan	Erythromycin
Naproxen	Felodipine
Phenytoin	Itraconazole
Tolbutamide	Ketoconazole
Valsartan	Lidocaine
S-warfarin	Lovastatin
CYP2C19	Midazolam
Diazepam	Nifedipine
Lansoprazole	Quinidine
(S)-mephenytoin	Simvastatin
Nelfinavir	Tacrolimus
Omeprazole	Verapamil
Pantoprazole	Ziprasidone
Voriconazole	
CYP2D6	
Carvedilol	
Codeine	
Debrisoquine	
Dextromethorphan	
Encainide	
Fluoxetine	
Haloperidol	
(S)-metoprolol	
Paroxetine	
Propafenone	
Risperidone	
Thioridazine	
Venlafaxine	

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 CYP isozymes.[25] Clarithromycin is a strong inhibitor of the CYP3A4 enzyme system; when given with simvastatin, which is metabolized by CYP3A4, the hepatic clearance of the simvastatin is reduced,

leading to increased risk of toxicity.[26] Ciprofloxacin and zileuton inhibit, whereas tobacco and marijuana smoke induce, CYP1A2. Some drugs that are enzyme inhibitors are also substrates for that same enzyme system and 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 CYP enzyme system, it is logical to assume that the new drug will exhibit drug interactions with the known inducers and inhibitors of that CYP isozyme.

12 Membrane transporters are protein molecules concerned with the active transport of drugs across cell membranes. Transport proteins are important in the processes of drug bioavailability, elimination, and distribution. The importance of membrane transport proteins is now better understood.[25,27,28] Membrane transporters are protein molecules concerned with the active transport of drugs across cell membranes. This results in the transfer of drug molecules either out of or into cells. Membrane transporters have been found in the intestine, liver, kidney, and the blood-brain barrier (Table e6-3).

TABLE e6-3

Membrane Transport Proteins and Selected Substrates

P-Glycoprotein (P-gp)

Sites: Intestinal enterocytes, kidney proximal tubule, hepatocytes (canalicular), brain endothelia

- Alfentanil
- Aliskiren
- Ambrisentan
- Atorvastatin
- Azithromycin
- Cetirizine
- Citalopram
- Clopidogrel
- Cyclosporine
- Daunorubicin
- Dexamethasone
- Digoxin
- Diltiazem
- Doxorubicin
- Erythromycin
- Etoposide
- Fexofenadine
- Glyburide
- Indinavir
- Imatinib
- Loperamide
- Loratadine
- Lovastatin
- Morphine
- Nelfinavir
- Olanzapine
- Ondansetron
- Paclitaxel
- Quinidine
- Raltegravir
- Ranolazine
- Risperidone
- Rifampin
- Ritonavir
- Saquinavir
- Tacrolimus
- Telaprevir
- Verapamil
- Vinblastine
- Vincristine

OAT1B1

Site: Hepatocytes (sinusoidal)

- Bosentan
- Olmesartan
- Repaglinide
- Statins
- Valsartan

OAT1

Sites: Kidney proximal tubule, placenta

- Acyclovir
- Cephradine
- Ciprofloxacin
- Methotrexate
- Zidovudine

OAT3

Sites: Kidney proximal tubule, choroid plexus, brain endothelia

- Bumetanide
- Cefaclor
- Ceftizoxime
- Furosemide
- NSAIDs

OCT1

Sites: Hepatocytes (sinusoidal), intestinal enterocytes

- Metformin
- Oxaliplatin

OCT2

Sites: Kidney proximal tubule, neurons

- Amantadine
- Amiloride
- Metformin
- Pindolol
- Procainamide
- Ranitidine

OAT, organic anion transporter; OCT, organic cation transporter; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from Reference 4.

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. Other membrane transporter families include the organic cation transporters (OCT family), organic anion transporters (OAT family), and the organic anion transporting polypeptides (OATP family).

Many CYP isozymes and transport proteins have been associated with genetic variations. CYP and other enzymes with more than one form of the give enzymatic functional protein are known as poly- (many) -morphic (form). Genetic differences will produce polymorphic variants of a given enzymatic protein in a population of patients with some patients inheriting a non-functional or poorly metabolizing variant of the enzyme. 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. Occasionally, patients will inherit multiple highly functional copies of the same enzyme and are known as “ultrarapid metabolizers” based on their enhanced ability to metabolize drugs in comparison to the average individual. Poor and ultrarapid metabolizers usually are a minority of the general population. They may achieve supra- or sub-therapeutic concentrations, respectively, of a drug when usual doses are prescribed for them. If the active drug moiety is a metabolite, it may fail to have any pharmacologic effect from the drug in poor metabolizers or lead to toxicity in ultrarapid metabolizers. Detailed discussion of these concepts can be found in Chapter e7.

Kidney Function Considerations

13 When deciding on initial doses for drugs that are eliminated renally, the patient’s kidney 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 CL_{cr} or estimated glomerular filtration rate (eGFR).

Serum creatinine values alone should not be used to assess kidney function because they do not include the effects of age, body weight, or sex. Methods for evaluating kidney function can be found in Chapter e60.

For drugs that are primarily excreted as unchanged drug in the urine, dose adjustments are usually required with declining kidney function due to a decrease in renal clearance. Many drugs have specific renal adjustments included in the FDA-approved labeling. For drugs that are eliminated primarily by the kidney but that do not have specific pharmacokinetic dosing guidelines, clinicians should consider adjustment of dose based on kidney function. In addition to a decrease in renal excretion, other pharmacokinetic parameters can also be altered by kidney disease. Detailed recommendations for adjusting doses in patients with chronic kidney disease are available in Chapter 67. When adjusting the dose for kidney function, careful consideration must be paid to the therapeutic index of the drug, alternate clearance pathways, patient-specific factors (eg, concurrent disease states), and the risk/benefit profile for the drug in question.

Liver Function Considerations

14 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. 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,[29] 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 (~25%) in initial daily drug dose for agents that are metabolized primarily (more than or equal to 60%) hepatically, and a score of 10 or greater indicates that a significant decrease in initial daily dose (~50%) is required for drugs that are metabolized mostly by the liver. It is also important to note that patients with severely impaired liver function often have reduced clearance of renally eliminated drugs as a function of their disease.[30] 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. 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.

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,[31] lidocaine,[32] 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 by 25% to 50% until steady-state concentrations and response can be determined.

Use of Steady-State Drug Concentrations

15 Serum drug concentrations are readily available to clinicians to use as guides for the individualization of pharmacotherapy. 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 pharmacotherapy, 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. An assessment of adherence to the regimen should be conducted prior to ordering serum concentrations and prior to adjusting dose based on the results. For example, a patient may have missed doses due to inability to procure their medications because of lack of transportation to the pharmacy or may routinely ration doses due to the cost of the medication. In the inpatient setting, 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 investigate potential reasons for nonadherence and address them with the patient and the healthcare team. Once addressed, 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

16 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 $50 to $100 each.

Although many drugs follow two-compartment-model pharmacokinetics (especially after IV administration), a one-compartment model can be used to compute kinetic parameters in patients by delaying the first sample until after biphasic distribution has reached pseudoequilibrium with the tissues. Such an approach avoids intensive blood sampling required for characterization of the two-compartment model pharmacokinetic parameter estimates. Because of this, serum concentrations usually are not measured in patients during the distribution phase. Another important reason serum

concentration is 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 post-distribution 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 pre-dose minimum concentration and a post-dose maximum concentration. Under steady-state conditions, serum concentrations after each dose are identical, so the pre-dose minimum concentration is the same before each dose (Fig. e6-8). This situation allows the pre-dose concentration to be used to compute both the patient's $t_{1/2}$ and V, where $V = \text{Dose}/(C_{max,ss} - C_{min,ss})$. If the drug was given extravascularly or has a significant distribution phase, the post-dose 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 adherence to the prescribed dosage regimen. When adherence with the dosage regimen has been verified, steady-state conditions can be reasonably assumed.

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 and vancomycin antibiotics.

Computational Approaches

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.[33] After drug doses and serum concentrations are entered, nonlinear least-squares regression programs adjust CL and V_D until the sum of the squared error between actual (C_{act}) and computer predicted concentrations (C_{pred}) is at a minimum $[\Sigma(C_{pred} - C_{act})^2]$[Σ(Cpred−Cact)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.[34] Incorporation of expected population-based parameters allows the program 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.[35] Several pharmacokinetic dosing programs are available to adjust the dose of a variety of drugs. In the case of renally eliminated drugs (eg, aminoglycosides, vancomycin), 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 (eg, 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 (eg, cirrhosis or heart failure) or other pharmacotherapy 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 are expected to result in desired steady-state concentrations of the drug.

Aminoglycosides

Although aminoglycoside pharmacokinetics follow a multicompartment model,[36] a one-compartment model is sufficient to individualize doses in patients due to the relatively rapid biphasic distribution phase of the drug.[37] Aminoglycosides usually are given as short- term intermittent IV infusions and administered as a single daily dose (extended interval dosing) or multiple doses per day (conventional dosing). Initial doses for aminoglycosides can be computed using estimated kinetic parameters derived from population pharmacokinetic studies. The elimination rate constant is estimated using the patient's creatinine clearance in the following formula:

$k(\text{in hr}^{-1}) = 0.00293(CL_{cr}) + 0.014$k(in hr−1)=0.00293(CLcr)+0.014

where CL_{cr} is the 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

$V_D = 0.26\ L/kg\ (V = 0.26[weight])$VD=0.26 L/kg (V=0.26[weight])

Because aminoglycosides are highly hydrophilic, the V_D approximates the extracellular fluid. As such, the ideal body weight (IBW) is used for patients who are of normal weight. IBW can be calculated with the following formulas:

$IBW_{males}[in\ kilograms] = 50 + 2.3\ [Ht - 60]$
$IBW_{females}[in\ kilograms] = 45 + 2.3[Ht - 60]$IBWmales[in kilograms] = 50+2.3 [Ht – 60]IBWfemales[in kilograms] = 45+2.3[Ht – 60]

where Ht is the patient's height in inches. For patient whose actual or total body weight (TBW) is less than their IBW, the TBW is used. To adjust for excess adipose tissue, an adjusted body weight is used instead of ideal for obese individuals (more than 30% of ideal weight).[38] This weight can be calculated by adding 40% of the difference between actual and ideal body weight to the ideal weight. Adjusted BW = IBW + 0.4(TBW – IBW). Additional volume of distribution population estimates are available for other disease states and conditions that cause alterations in extracellular fluid, such as cystic fibrosis,[39] ascites,[40] and neonates.[41]

Aminoglycoside antibiotics exhibit concentration-dependent bacterial killing and also continue to kill susceptible bacteria even after the concentrations are below the minimum bactericidal range. This phenomenon is known as the post-antibiotic effect. Because the post-antibiotic effect is longer with higher concentrations, multiple investigators studied the possibility of giving a higher dose of aminoglycoside using an extended-dosage interval (24 hours or longer, depending on kidney 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 as the preferred method for most patients. Most clinical guidelines recommend the use of extended-interval dosing, with exceptions notably for combination therapy in Enterococcus spp. catheter-related infections or infective endocarditis.[42–46] Empiric dosing is usually weight-based, with different ranges based on disease state, likely pathogen, local susceptibility rates, and kidney function of the patient. For example, in Pseudomonas aeruginosa infections where the organism has an expected (MIC) ≂ 2 mg/L, peak concentrations between 20 and 30 mg/L (mcg/mL; 40 and 65 µmol/L) and trough concentrations less than 1 mg/L (mcg/mL; 2 µmol/L) for gentamicin or tobramycin have been suggested.[47] However, because of the post-antibiotic effect of aminoglycosides, many institutions target an undetectable trough.

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 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. Emerging evidence has also suggested the AUC monitoring may be the preferred indicator for aminoglycosides; however, no consensus has been reached regarding targets of this dosing method.[48] An international, multiorganization position paper endorsed the use of AUC-based monitoring for patients with critical illness but also provided guidance for more traditional C_{max} and $_{min}$ monitoring with goal $C_{max,ss}$/MIC ratio of ≥ 8-10 and $C_{min,ss}$ of <0.5 mg/L for gentamicin/tobramycin and <2.5 mg/dL for amikacin.[49]

Several nomograms to aid in the dosing of extended interval aminoglycosides have been proposed (Table e6-4).[47,50,51] Weight-based dosing, which is set at either 5 or 7 mg/kg of gentamicin or tobramycin depending on the nomogram, is intended to reach minimum $C_{max,ss}$ values of at least 8 to 10 times the MIC of most organisms, with the initial dosage interval set according to the patient's CL_{cr}. The nomograms also assume patients have a V_D that falls within expected parameters, so these tools are not intended to be used with patients with known alterations in V_D, such as patients with cystic fibrosis or who are pregnant. Many institutions have developed their own nomograms based on one or multiple of the nomograms noted and customized to their patient population, but most have not been validated.

TABLE e6-4

Selected Nomograms for Dosing of Extended Interval Aminoglycosides

Creatinine Clearance	Recommended interval
Hartford[a] and Barnes-Jewish Hospital[b]	
≥60 mL/min	Every 24 hours
40 to 59 mL/min	Every 36 hours
20 to 39 mL/min	Every 48 hours
<20 mL/min	Dosed on levels
University of Rochester[b]	
≥60 mL/min	Every 24 hours
30 to 59 mL/min	Every 36 hours
<30 mL/min	Dosed on levels

Values for creatinine clearance expressed in units of mL/min are converted to mL/s by multiplying by 0.0167.

[a]7mg/kg dosing utilized

[b]5 mg/kg dosing utilized.

Data from References 47, 50, and 51.

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 (eg, 8, 12, 18, 24, 36, or 48 hours). The formula is as follows:

$\tau = \frac{ln\ C_{max,ss} - ln\ C_{min,ss}}{k} + T$τ=ln Cmax,ss−ln Cmin,ssk+T

Finally, a dose is computed for the patient using the one-compartment-model intermittent IV infusion equation at steady state. The dose is rounded, usually to the nearest 20 or 40 mg because the vial is supplied in a concentration of 40 mg/mL:

$D = TkV_D C_{max,ss} \frac{1 - e^{-k\tau}}{1 - e^{-kT}}$D=TkVDCmax,ss1−e−kτ1−e−kT

For example, patient JJ is a 65-year-old male (he/him) who weighs 80 kg (176 lb), 6-ft-tall (72 in. or 183 cm) and has been diagnosed with hospital acquired pneumonia caused by Pseudomonas aeruginosa with an MIC of 2 mg/L to tobramycin. His serum creatinine concentration is 2.1 mg/dL (186 µmol/L) and is stable. Compute an extended interval dosing regimen (infused over 1 hour) for tobramycin this patient that would achieve an approximate $C_{max,ss}$ of 25 mg/L and $C_{min,ss}$ of 0.5 mg/L.

The patient is within 30% of his ideal body weight (IBW_{male} = 50 + 2.3 [72 in – 60] = 78 kg) and has stable kidney function, so the Cockcroft-Gault CL_{cr} estimation equation can be used:

$\mathrm{CL_{Cr}} = \frac{(140 - 65) \times 78}{72 \times 2.1} = 38\ \mathrm{mL/min}$CLCr=(140−65)×7872×2.1=38 mL/min

The patient's weight and estimated CL_{cr} are used to compute his V_D, k, and $t_{½}$ respectively:

$V_D = 0.26\ \mathrm{L/kg} \times 78\ \mathrm{kg} = 20.3\ \mathrm{L}$VD=0.26 L/kg× 78 kg=20.3 L

$k = 0.00293(38\ \text{mL/min}) + 0.014 = 0.125\ \text{hr}^{-1}$k=0.00293(38 mL/min)+0.014=0.125 hr−1

$t_{1/2} = \frac{0.693}{0.125\ h^{-1}} = 5.5\ \text{hr}$t12=0.6930.125 h−1=5.5 hr

The dosage interval and dose for the desired serum concentrations would then be calculated:

$\tau = \frac{\ln\ 25\ \text{mg/L} - \ln\ 0.5\ \text{mg/L}}{0.125\ h^{-1}} + 1\ h = 32\ \text{hr}$τ=ln 25 mg/L−ln 0.5 mg/L0.125 h−1+1 h=32 hr

The next reasonable dosage interval would then be every 36 hours.

$D = 1\ \text{hr} \times 0.125\ \text{hr}^{-1} \times 20.3\ \text{L} \times 25\ \text{mg/L} \times \frac{1 - e^{-0.125\ \text{hr}^{-1}(36\ \text{hr})}}{1 - e^{-0.125\ \text{hr}^{-1}(1\ \text{hr})}} = 534\ \text{mg}$D=1 hr×0.125 hr−1×20.3 L×25 mg/L×1−e−0.125 hr−1(36 hr)1−e−0.125 hr−1(1 hr)=534 mg

Rounding to the nearest 40 mg increment, we would arrive at a dose of 520 mg. Thus, the prescribed dose would be gentamicin 520 mg every 36 hours administered as a 1-hour infusion.

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 approximately 2 hours after a dose administered as an IV infusion of 1 hour to allow for drug distribution (C_{max}) and at one additional post-dose time (C_2) at least one estimated half-life after C_{max}, generally between 6 and 10 hours post-dose. The $t_{1/2}$ and k values are computed using C_{max} and C_2:

$k = \frac{ln\ C_{max} - ln\ C_2}{\Delta t}$k=ln Cmax−ln C2Δt

where Δt is the time that expired between the times C_{max} and C_2 were obtained. If the patient is at steady state, serum aminoglycoside concentrations can be obtained either in the method above or 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 $C_{min,ss}$:

$k = \frac{ln\ C_{max,ss} - ln\ C_{min,ss}}{\tau - T}$k= ln Cmax,ss−ln Cmin,ssτ−T

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

$V_D = \frac{D/T(1 - e^{-kT})}{k(C_{max,ss} - C_{min,ss}\ e^{-kT})}$VD=DT(1−e−kT)k(Cmax,ss−Cmin,ss e−kT)

where D is the dose, and T is the duration of infusion. Once these are known, the dose and dosage interval can be calculated for any desired $C_{max,ss}$ and $C_{min,ss}$ with the dose and interval formulas above, remembering to round the dose and dosage interval to provide clinically accepted values (every 24, 36, and 48 hours for dosage interval, nearest 20-40 mg for extended interval dosing).

To provide an example of this technique, the problem given previously will be extended to include steady-state concentrations. Patient JJ was prescribed gentamicin 560 mg every 36 hours (infused over 1 hour) for the treatment of Pseudomonas aeruginosa 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 3-5 estimated half-lives), respectively, and equaled $C_{min,ss}$ = 1.1 mg/L and $C_{max,ss}$ = 24.5 mg/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 µmol/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 targeted. The patient's elimination rate constant and half-life can be computed using the following formulas:

$k = \frac{\ln\ 24.5\ \text{mg/L} - \ln\ 1.1\ \text{mg/L}}{36\ \text{hr} - 1\ \text{hr}} = 0.089\ \text{hr}^{-1}$k=ln 24.5 mg/L−ln 1.1 mg/L36 hr−1 hr=0.089 hr−1

$t_{1/2} = \frac{0.693}{0.089\ \text{hr}^{-1}} = 7.8\ \text{hr}$t12= 0.6930.089 hr−1=7.8 hr

The patient's volume of distribution can be calculated using the following equation:

$V_D = \frac{520\ \text{mg}/1\ \text{hr}\ \left(1 - e^{-0.089\ \text{hr}^{-1} \times 1\ \text{hr}}\right)}{0.089\ \text{hr}^{-1}(24.5\ \text{mg/L} - [1.1\ \text{mg/L} \times e^{-0.089 \times 1\ \text{hr}}])} = 21.2\ \text{L}$VD=520 mg/1 hr (1−e−0.089 hr−1×1 hr)0.089 hr−1(24.5 mg/L−[1.1 mg/L×e−0.089×1 hr])=21.2 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 ($C_{min,ss}$ = 0.5 mg/L and $C_{max,ss}$ = 25 mg/L), the patient's actual kinetic parameters are used to compute a new dose and dosage interval:

$\tau = \frac{\ln\ 25\ \text{mg/L} - \ln\ 0.5\ \text{mg/L}}{0.089\ \text{hr}^{-1}} = 44\ \text{hr}$τ=ln 25 mg/L−ln 0.5 mg/L0.089 hr−1=44 hr

The next reasonable dose interval would be every 48 hours. Then, calculate the dose:

$D = 1\ \text{hr} \times 0.089\ \text{hr}^{-1} \times 21.2\ \text{L} \times 25\ \text{mg/L} \times \frac{1 - e^{-0.089\ \text{hr}^{-1}(48\ \text{hr})}}{1 - e^{-0.089\ \text{hr}^{-1}(1\ \text{hr})}} = 546\ \text{mg}$D=1 hr×0.089 hr−1×21.2 L×25 mg/L×1−e−0.089 hr−1(48 hr)1−e−0.089 hr−1(1 hr)=546 mg

This result could be rounded to the nearest 20 mg increment (540 mg) or rounded down to nearest 40 mg increment (520 mg, which the patient had previously reached goal $C_{max,ss}$). Given that the patient is improving, one could choose to round to previous dose, and the new regimen would be tobramycin 520 every 48 hours and infused over 1 hour, with the first dose given 48 hours (eg, the new dosage interval) after the last dose of the old dosage regimen.

To illustrate how the nomogram dosage would be used, the same patient example used previously will be repeated for this dosage approach. Patient JJ weighs 80 kg (176 lb) and has a CL_{cr} of 38 mL/min. Using the Harford nomogram, the patient would receive tobramycin 560 mg every 48 hours (7 mg/kg× 80 kg = 560 mg; the initial dosage interval for CL_{cr} = 38 mL/min is every 48 hours).[47] In addition to providing empiric dosing, the three referenced nomograms also contain a nomogram for adjusting interval based on a random serum concentration drawn between 6- and 14-hours post-dose, with each having slight variation in time frame.[47,50,51] The nomograms contain a concentration vs time graph that the concentration is plotted on that will suggest the recommended interval based on that concentration/time profile. For example, ten hours after the first dose was given, the serum tobramycin concentration for Patient JJ was 6.9 mg/L (mcg/mL; 8.6 nmol/L). According to the graph contained in the Hartford nomogram, the dosage interval should be changed to every 36 hours. The new dose is 560 mg every 36 hours.[47]

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.[52] 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. It has been known that the ideal PK/PD parameter for vancomycin activity is an AUC over 24 hours to MIC ratio of ≥400; however, in the recent past, monitoring of steady-state trough concentrations of vancomycin in patients with serious methicillin-resistant Staphylococcus aureus (MRSA) infections was seen as an appropriate surrogate marker of AUC/MIC ratio.[53] Previous consensus guidelines recommended a vancomycin trough of 15-20 mg/L (mcg/mL; 10.4-13.8 µmol/L) for serious infections, such as infective endocarditis, bacteremia, osteomyelitis, meningitis, and pneumonia, caused by MRSA. Other indications are often treated with a reduced trough goal of 10 to 15 mg/L (mcg/mL; 6.9-10.4 µmol/L), though there is little evidence to support either of these practices. It has been recommended that vancomycin troughs be maintained a >10 mg/L (mcg/mL; 6.9 µmol/L) in order to avoid development of resistance.[53]

Recent evidence and the increased availability of software programs that allow for clinicians to estimate $_{AUC_0^{24}}$AUC024 have led to a shift in consensus guidelines, which now recommend AUC-guided dosing for serious MRSA infections.[54] The goal AUC, assuming an MIC of 1 mg/L, is defined as 400 to 600 mg*hr/L. It should be noted that the consensus guidelines found insufficient evidence to recommend either AUC-guided or trough-guided dosing in patients with non-invasive MRSA or other infections requiring the use of vancomycin. As such, institutions may use one or both of these dosing strategies, and it is prudent that pharmacists understand both methods of dosing.

Regardless of method, the empiric dose of vancomycin for patients with normal kidney function is 15 to 20 mg/kg every 8 or 12 hours, with consideration for patient-specific factors.[54] For patients with impaired kidney function, the interval will need to be extended to prevent accumulation of drug. A loading dose of 20 to 35 mg/kg can be considered for patients in which therapeutic drug concentrations are needed quickly, such as critical illness.[54]

Trough-Guided Approach

Initial doses of vancomycin can be computed for adult patients using estimated kinetic parameters derived from population pharmacokinetic data. Several pharmacokinetic prediction models have been proposed to describe estimation of parameters; however, none have shown to be more reliable than the other.[55]

The most commonly used prediction model in practice is the Matzke equation, in which the elimination rate constant can be calculated with the following equation: $k = 0.00083(CL_{cr}) + 0.0044$.[56] The volume of distribution is computed assuming the standard value of 0.7 L/kg: $V_D = 0.7(Wt)$, where

Wt is the patient's weight.

Another prediction model, commonly referred to as the Bauer method, in which clearance is estimated using the patient's creatinine clearance in the following equation[57,58]: CL (in mL/min/kg) = 0.695 (CL_{cr} in mL/min/kg) + 0.05. The elimination rate constant is calculated using clearance and volume of distribution estimates, correcting for possible differences in units for these parameters: $k = CL/V_D$.

$C_{max,ss}$ values of between 20 and 40 mg/L (and $C_{min,ss}$ values of between 10 and 15 mg/L typically are used for patients with mild-to-moderate infections or sensitive bacteria with lower MIC values (less than 1 mcg/mL). For patients with pneumonia or other life- threatening infections due to multidrug-resistant organisms, $C_{min,ss}$ as high as 15 to 20 mg/L were previously suggested, though an AUC-guided approach is now recommended for invasive MRSA infections as above.[53,54] 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 (8, 12, 18, 24, 36, 48, or 72 hours):

$$\tau = \frac{\ln C_{max,ss} - \ln C_{min,ss}}{k}$$τ=ln Cmax,ss−ln Cmin,ssk

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 250 mg:

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

If desired, a loading dose can be computed using the following equation, with a goal of attaining a C_{max} that is similar to the desired $C_{max,ss}$:

$$LD = V_D C_{max,ss}$$LD=VDCmax,ss

The following case will illustrate the use of this dosage methodology. Patient HJ is a 65-year-old female (she/her) who weighs 68 kg (150 lb) and is 5 ft 10 in. (70 in. [178 cm]) tall. She has developed a skin and soft tissue infection with abscess; Staphylococcus aureus is the suspected pathogen with an anticipated MIC = 1 mg/L. Her serum creatinine concentration is 1.8 mg/dL (159 µmol/L) and is 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 12 mg/L (mcg/mL; 21 and 8 µmol/L), respectively.

The patient is at her ideal body weight (IBW_{female}= 45.5 kg + 2.3[70 in. – 60 in.] = 68 kg), and has stable kidney function, so the Cockcroft-Gault creatinine clearance estimation formula can be used: CL_{cr} = 0.85([140 – 65 y]68 kg)/(72[1.8 mg/dL]) = 33 mL/min (0.55 mL/s). The patient's weight and CL_{cr} are used to calculate her estimated V_D, k, and $t_{1/2}$ using the Matzke equation:

$$V_D = 0.7\ \text{L/kg} \times 68\ \text{kg} = 47.6\ \text{L}$$VD=0.7 L/kg×68 kg=47.6 L

$$k = 0.00083(CL_{cr}) + 0.0044 = 0.00083(33\ \text{mL/min}) + 0.0044 = 0.032\ \text{hr}^{-1}$$k=0.00083(CLcr)+0.0044=0.00083(33 mL/min)+0.0044=0.032 hr−1

$$t_{1/2} = \frac{0.693}{0.032} = 22\ \text{hr}$$t1/2=0.6930.032=22 hr

The dosage interval, maintenance dose, and loading dose for the desired serum concentrations can be computed:

$$\tau = \frac{\ln 30\ \text{mg/L} - \ln 12\ \text{mg/L}}{0.032\ \text{hr}^{-1}} = 28.6\ \text{hr}$$τ=ln 30 mg/L−ln 12 mg/L0.032 hr−1=28.6 hr

The closest reasonable interval would be every 24 hours. Next, the maintenance dose can be calculated:

$$D = 30\ \text{mg/L} \times 47.6\ \text{L} \times \left(1 - e^{-0.032\ \text{hr}^{-1} \times 24\ \text{hr}}\right) = 765\ \text{mg}$$D=30 mg/L×47.6 L ×(1−e−0.032 hr−1×24 hr)=765 mg

Rounded to nearest 250 mg, the dose would be 750mg. A loading dose could be used as follows:

$$LD = 47.6\ \text{L} \times 30\ \text{mg/L} = 1428\ \text{mg}$$LD=47.6 L×30 mg/L=1428 mg

Rounded to the nearest 250mg, the loading dose would be 1,500 mg. Therefore, the prescribed dose would be vancomycin 1,500 mg IV once as a loading dose, followed by vancomycin 750mg IV every 24 hours administered as a 1-hour infusion thereafter. If a loading dose is used, it would be given as the first dose, and the first maintenance dose would be administered one dosage interval later.

To calculate the expected $C_{max,ss}$ and $C_{min,ss}$, the following equations can be used:

$$C_{max,ss} = \frac{D}{V_D \cdot T \cdot k} \times \frac{(1 - e^{-kT})}{(1 - e^{-k\tau})}$$Cmax,ss=DVD · T · k×(1−e−kT)(1−e−kτ)

$$C_{min,ss} = C_{max,ss} e^{-k(\tau - T)}$$Cmin,ss=Cmax,sse−k(τ−T)

In the example above, a dose of vancomycin 750 mg IV every 24 hours administered over a 1-hour infusion would produce an estimated $C_{max,ss}$ and

$C_{min,ss}$ as below:

$C_{max,ss} = \frac{750\ mg}{47.6\ L \cdot 1\ h \cdot 0.032\ h^{-1}} \times \frac{\left(1 - e^{-0.032\ h^{-1} \times 1\ h}\right)}{\left(1 - e^{-0.032\ h^{-1} \times 24\ h}\right)} = 28.9\ mg/L$Cmax,ss=750 mg47.6 L · 1 h · 0.032 h−1×(1−e−0.032 h−1×1 h)(1−e−0.032 h−1×24 h)=28.9 mg/L

$C_{min,ss} = \frac{28.9\ mg}{L} \times e^{-0.032(24-1)} = 13.8\ mg/L$Cmin,ss=28.9 mgL×e−0.032(24−1)=13.8 mg/L

In this case, the calculated estimated $C_{max,ss}$ and $C_{min,ss}$ are within the designated parameters.

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 ≃ 1,000 mg for average-weight individuals). Also, toxic peak concentrations (generally greater than 80-100 mg/L [mcg/mL; 55-69 µmol/L]) are quite a bit higher than therapeutic peak concentrations, which adds a safety margin between effective concentrations and those yielding adverse drug effects.

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):

$\frac{D_{new}}{\tau_{new}} = \left(\frac{D_{current}}{\tau_{current}}\right)\left(\frac{C_{ss,new}}{C_{ss,current}}\right)$Dnewτnew=(Dcurrentτcurrent)(Css,newCss,current)

where new and current indicate the new target trough concentration and the current measured trough concentration, respectively. This equation is an approximation of the actual new steady-state trough concentration that will be attained in the patient because, mathematically, $C_{ss,new}$ is an exponential function of τ.

An example of this approach is given in the following case. Patient MK is a 72 year old man (he/him) who weighs 72 kg (158 lb) and measures 5 ft 9 in. (69 in. [175 cm]). He 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 ($C_{min,ss}$) value was obtained before the fifth dose was given (more than three to five estimated half-lives), and $C_{min,ss}$ = 19 mg/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 $C_{min,ss}$ = 10 mg/L was suggested.

$\frac{D_{new}}{\tau_{new}} = \left(\frac{1000\ mg}{12\ hr}\right)\left(\frac{10\ mg/L}{19\ mg/L}\right) = 44\ mg/hr$Dnewτnew=(1000 mg12 hr)(10 mg/L19 mg/L)=44 mg/hr

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: τ = 1,000 mg/44 mg/hr = 23 hr, rounded to 24 hours. The new prescribed dose for the patient would be 1,000 mg every 24 hours.

AUC-Guided Approach

The preferred method to implement AUC-guided dosing includes using Bayesian software to support dosing; however, these programs may be cost-prohibitive.[59] Alternatively, several other calculators and programs are available that use first-order pharmacokinetic equations, including spreadsheet-based, electronic health record-based, and commercial calculators.[59] These programs require multiple steady state serum concentrations to calculate patient-specific pharmacokinetic parameters. When Bayesian software is available, two serum concentrations can be drawn after the first dose and input into the model, which will recommend maintenance dosing to achieve AUC/MIC goals. If using first-order equations, two serum concentrations can be drawn and then patient-specific parameters to calculate an estimated AUC for patients with serious MRSA infections or dosed based on population parameters; however, two serum concentrations will need to be drawn at steady state in order to confirm AUC goals are achieved.

Remembering that AUC is equal to the dose divided by clearance,

$AUC = \frac{D}{CL}$AUC=DCL

The approach to dosing vancomycin based on an AUC-guided approach requires estimation of vancomycin clearance. As discussed previously in the chapter, clearance is the product of k and V_D:

$CL = k \times V_D$CL=k×VD

Where k and V_D can be calculated using the Matzke equation as in the trough-based approach section. Then, once clearance has been estimated, the AUC equation can be re-arranged to solve for total daily dose (TDD):

$$\text{TDD} = \text{CL} \times \text{AUC}_{\text{n}}^{24\ \text{goal}}$$ TDD=CL×AUC024 goal

As the goal is between 400 to 600 mg*hr/L, most clinicians choose 500 mg*hr/L to allow rounding of doses and interval in later steps while still remaining within AUC goal. Alternatively, a range could be calculated using the lowest and highest goal and selecting a dose that falls within that range. Next, the interval must be calculated. $C_{max,ss}$ values of 40 mg/L and $C_{min,ss}$ values of 10 mg/L are typically used to maximize efficacy while reducing nephrotoxicity and preventing resistance.[60] 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 (8, 12, 18, 24, 36, 48, or 72 hours):

$$\tau = \frac{\ln\ C_{\text{max,ss}} - \ln\ C_{\text{min,ss}}}{k}$$ τ=ln Cmax,ss−ln Cmin,ssk

Finally, a maintenance dose is chosen using calculated:

$$D = \frac{TDD}{24/\tau}$$ D=TDD24/τ

Using the patient case described above, this time with an AUC-guided approach, will illustrate the use of this dosage methodology. Patient CW is a 65-year-old female (she/her) who weighs 68 kg (150 lb) and is 5 ft 10 in. (70 in. [178 cm]) tall. She is found to have developed Methicillin-resistant Staphylococcus aureus bacteremia with an MIC = 1 mg/L. Her serum creatinine concentration is 1.8 mg/dL (159 µmol/L) and is stable. Compute a vancomycin dosage regimen that would provide approximate AUC of 400 to 600 mg*hr/L.

The patient is at her ideal body weight (IBW_{female}= 45.5kg + 2.3[70 in. – 60in.] = 68 kg) and has stable kidney function, so the Cockcroft-Gault creatinine clearance estimation formula can be used: CL_{cr} = 0.85([140 – 65 y]68 kg)/(72[1.8 mg/dL]) = 33 mL/min (0.55 mL/s). The patient's weight and CL_{cr} are used to calculate her estimated V_D, k, and $t_{1/2}$ using the Matzke equation:

$$V_D = 0.7\ \text{L/kg} \times 68\ \text{kg} = 47.6\ \text{L}$$ VD=0.7 L/kg×68 kg=47.6 L

$$k = 0.00083(\text{CL}_{\text{cr}}) + 0.0044 = 0.00083(33\ \text{mL/min}) + 0.0044 = 0.032\ \text{hr}^{-1}$$ k=0.00083(CLcr)+0.0044=0.00083(33 mL/min)+0.0044=0.032 hr−1

$$t_{1/2} = \frac{0.693}{0.032} = 22\ \text{hr}$$ t1/2=0.6930.032=22 hr

Using the population pharmacokinetic parameter estimate, clearance and subsequently TDD can be calculated.

$$CL = k \times V_D = 0.032\ \text{hr}^{-1} \times 47.6\ \text{L} = 1.52\ \text{L/hr}$$ CL=k×VD=0.032 hr−1×47.6 L=1.52 L/hr

$$TDD = \text{CL} \times \text{AUC}_{\text{n}}^{24\ goal} = 1.52\ \text{hr/L} \times 500\ \text{mg} \cdot \text{hr/L} = 762\ \text{mg}$$ TDD=CL×AUC024 goal=1.52 hr/L×500 mg · hr/L=762 mg

The dosage interval and maintenance dose for the desired serum AUC goal can then be computed:

$$\tau = \frac{\ln\ 40\ \text{mg/L} - \ln\ 10\ \text{mg/L}}{0.032\ \text{hr}^{-1}} = 43\ \text{hr}$$ τ=ln 40 mg/L−ln 10 mg/L0.032 hr−1=43 hr

The closest reasonable interval would be every 48 hours. Then, the maintenance dose to be given at the interval is calculated:

$$D = \frac{762\ \text{mg}}{24\ \text{hr}/48\ \text{hr}} = 1524\ \text{mg}$$ D=762 mg24 hr/48 hr=1524 mg

Rounded to nearest 250 mg, the dose would be 1500 mg. Therefore, the prescribed dose would be vancomycin 1,500 mg IV every 48 hours.

Once at steady state, two serum concentrations (which will be referred to as C_1 and C_2) can be obtained to ensure AUC goals are being met. Ideally, the first concentration should be drawn 1-2 hours after the end of the infusion and the second should be a trough, immediately preceding the next scheduled dose. Then, patient-specific elimination constant can be calculated using the following equations:

$$k = \frac{ln\ C_1 - ln\ C_2}{t_1 - t_2}$$ k= ln C1−ln C2t1−t2

Where t_1 and t_2 (often represented as Δt) are the time after the start of the infusion when C_1 and C_2 were drawn, respectively. Because serum concentrations are rarely drawn at the exact peak and trough of a dosing regimen, adjustments are needed to be able to calculate the $C_{max,ss}$ and $C_{min,ss}$. Once the patient's pharmacokinetic parameters are known, the true $C_{max,ss}$ can be calculated as follows:

$$C_{max,ss} = \frac{C_1}{e^{-k(\Delta t)}}$$ Cmax,ss=C1e−k(Δt)

Where Δt is the difference between the time C1 was drawn and the end of the infusion. Then, $C_{min,ss}$ can be calculated:

$$C_{min,ss} = C_2 \times e^{-k(\Delta t)}$$ Cmin,ss=C2×e−k(Δt)

Where Δt is the difference between the time C_2 was drawn and the end of the dosing interval. As a reminder, the trough should be maintained >10

mg/L. The patient-specific V_D can then be calculated using the $C_{max,ss}$:

$V_D = \frac{(D/T)(1 - e^{-kT})}{k(C_{max,ss})(1 - e^{-k\tau})}$VD=(D/T)(1−e−kT)k(Cmax,ss)(1−e−kτ)
Then, the AUC can be calculated:

$AUC_0^{24} = \frac{TDD}{k \times V_D}$AUC024=TDDk×VD
If AUC is within goal range of 400 to 600 mg*hr/L, the current dose should continue. If it is not within goal, the dose may be adjusted using the following equation:

$TDD_{new} = \frac{TDD_{current}}{AUC_{current}} \times AUC_{goal}$TDDnew= TDDcurrentAUCcurrent×AUCgoal
As an illustration of responding to two-concentration AUC monitoring, the following case will be used. Patient LG was started on vancomycin 1,000 mg IV every 12 hours administered as a 1-hour infusion for treatment of MRSA infective endocarditis. At steady state, two concentrations were obtained: 35.1 mg/L drawn 1.5 h after the end of the infusion and 11.1 mg/L drawn 10.5 h after the end of the infusion (0.5 h before the end of the dosing interval).

First, the patient specific k should be calculated:

$k = \frac{\ln 35.1 \text{ mg/L} - \ln 11.1 \text{ mg/L}}{10.5 - 1.5} = 0.128 \text{ hr}^{-1}$k=ln 35.1 mg/L−ln 11.1 mg/L10.5−1.5=0.128 hr−1
Then, $C_{max,ss}$ and $C_{min,ss}$ can be calculated:

$C_{max,ss} = \frac{35.1 \text{ mg/L}}{e^{-0.128 \text{ hr}^{-1}(1.5 \text{ hr})}} = 42.5 \text{ mg/L}$Cmax,ss=35.1 mg/Le−0.128 hr−1(1.5 hr)=42.5 mg/L
$C_{min,ss} = 11.1 \times e^{-0.128 \text{ hr}^{-1}(0.5 \text{ hr})} = 10.4 \text{ mg/L}$Cmin,ss=11.1×e−0.128 hr−1(0.5 hr)=10.4 mg/L
The V_D can then be calculated:

$V_D = \frac{\frac{1000 \text{ mg}}{1 \text{ hr}}\left(1 - e^{-0.128 \text{ hr}^{-1} \times 1 \text{ hr}}\right)}{0.128 \text{ hr}^{-1}(35.1 \text{ mg/L})\left(1 - e^{-0.128 \text{ hr}^{-1} \times 12 \text{ hr}}\right)} = 34.1 \text{ L}$VD=1000 mg1 hr(1−e−0.128 hr−1×1 hr)0.128 hr−1(35.1 mg/L)(1−e−0.128 hr−1×12 hr)=34.1 L
Finally, the AUC can be calculated, remembering that in this equation total daily dose is used instead of single dose:

$AUC_0^{24} = \frac{2000 \text{ mg}}{0.128 \text{ hr}^{-1} \times 34.1 \text{ L}} = 458 \text{ mg} * \text{hr/L}$AUC024=2000 mg0.128 hr−1×34.1 L=458 mg*hr/L
Because the AUC is within goal of 400 to 600 mg*hr/L, the patient's previous dosing of vancomycin 1,000 mg IV every 12 hours should be continued.

Knowledge of pharmacokinetic principles will help the clinician individualize vancomycin dosing to maximize efficacy and minimize toxicity for optimized patient care.

CLINICAL PHARMACODYNAMICS

17 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 pharmacotherapy, decreases in heart rate during beta 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:

$Drug + receptor \leftrightarrow drug - receptor\ complex \leftrightarrow response$Drug+receptor↔drug−receptor complex↔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.

E_{max} and Sigmoid E_{max} Models

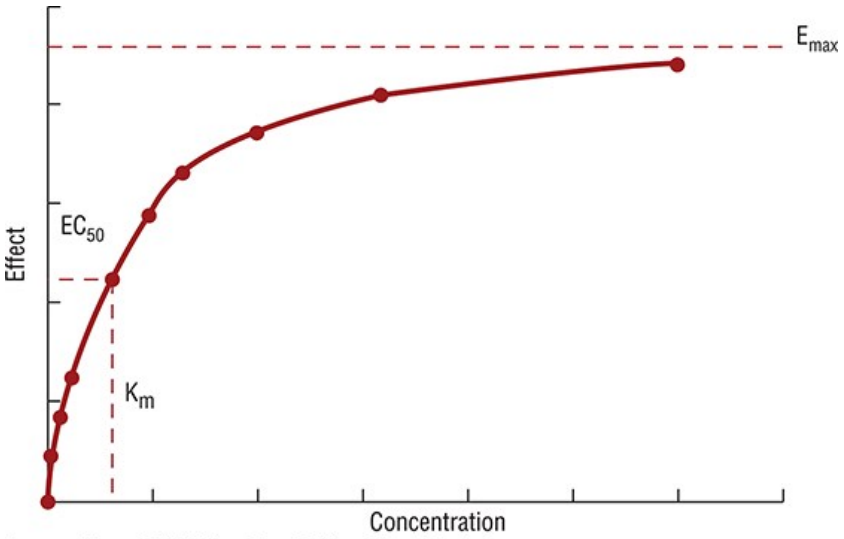
The mathematical model that comes from the classic drug–receptor theory shown previously is known as the E_{max} model:

$E = \frac{E_{max} \times C}{EC_{50} + C}$E=Emax×CEC50+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) or maximal capacity to which a given drug can produce an effect. If pharmacologic effect is plotted against concentration in the $_{max}$ equation, a hyperbola results with an asymptote equal to E_{max} (Fig. e6-10). At a concentration of zero, no measurable effect is present.

FIGURE e6-10

The E_{max} model 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 or cell culture in a laboratory setting.

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:

$E = \frac{E_{max} \times C^n}{EC_{50}^n + C^n}$E=Emax×CnEC50n+Cn

where *n* is an exponent that changes the shape of the concentration–effect curve. When n greater than 1, the concentration–effect curve is S- or sigmoid-shaped at lower serum concentrations. When *n* less than 1, the concentration–effect curve has a steeper slope at lower concentrations.

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. 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 × 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 $S = E_{max}/EC_{50}$.

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 × (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.[61]

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=E0+Emax×CEC50+C

$E = E_0 + \frac{E_{max} \times C^n}{EC_{50}^n + C^n}$ E=E0+Emax×CnEC50n+Cn

$E = E_0 + S \times C$ E=E0+S×C

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.[62,63] 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.[63] 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=E0−Emax×CIC50+C

$E = E_0 - \frac{E_{max} \times C^n}{IC_{50}^n + C^n}$ E=E0−Emax×CnIC50n+Cn

$E = E_0 - S \times C$ E=E0−S×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 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 (eg, 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:

$E = E_0\left(1 - \frac{C}{IC_{50} + C}\right)$E=E0(1−CIC50+C)
This form of the model relates drug concentration to the fraction of the maximum effect.

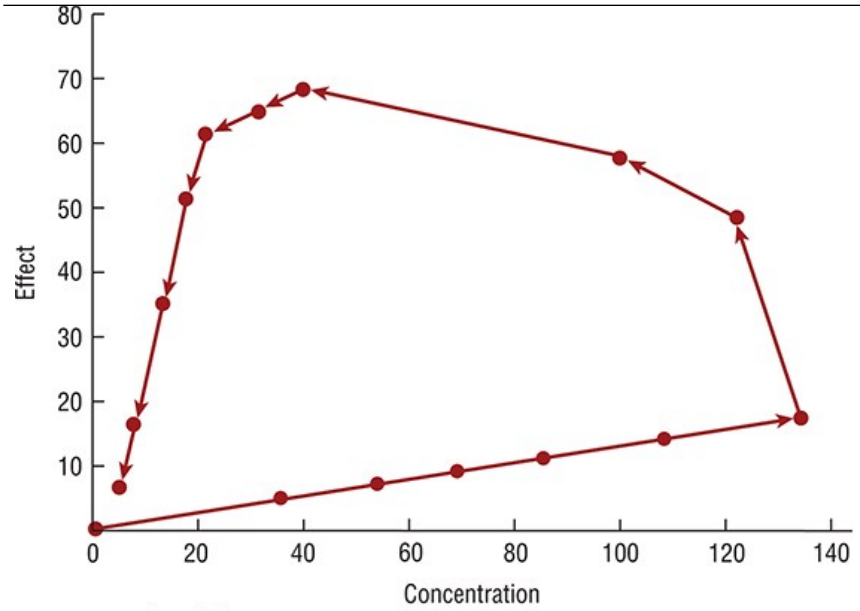
An alternative approach to the pharmacodynamic modeling of drugs that alter baseline effects is to transform the effect data so that they represent a percentage increase or decrease from the baseline value.[63] For drugs that increase the effect, the following transformation equation would be used: percent effect $_t$ = ([treatment$_t$ –baseline]/baseline) × 100. For drugs that decrease the effect, the following formula would be applied to the data: percent inhibition$_t$ = ([baseline – treatment$_t$]/baseline) × 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 (heart rate determined 2 hours after placebo and 2 hours after drug treatment) could be used in the appropriate transformation equation.[63] 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. e6-11). When individual concentration–effect pairs are joined in time sequence, this results in clockwise and counterclockwise hysteresis loops.

FIGURE e6-11

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.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

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. In this case, the same concentration will cause an increased effect upon prolonged systemic drug exposure. Combined pharmacokinetic/pharmacodynamic models have been devised that allow equilibration lag times to be taken into account.

CONCLUSION

The availability of inexpensive, rapidly achievable serum drug concentration measurements has changed the way clinicians monitor pharmacotherapy in patients. The therapeutic range for many drugs is known and can be used to guide therapy or pharmacokinetic principles can be applied to determine dose adjustments; however, clinicians must remember that significant pharmacodynamic variability exists between patients and 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 ($LD = V_D C_0$), 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 pharmacotherapy 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.

As the use of increasingly complex drug therapies expands and the role of therapeutic drug monitoring evolves, it is becoming more imperative than ever that clinicians understand the principles of pharmacokinetics and pharmacodynamics. Therapeutic monitoring is no longer relegated to a consultant kinetics services—it impacts the day-to-day practice of many healthcare professionals. Whether managing immunosuppressants in a transplant clinic, adjusting antiepileptic pharmacotherapy for a patient with seizures to manage a drug-drug interaction, or initiating AUC-guided vancomycin to treat a serious bacterial infection, clinical pharmacokinetics is being utilized across the healthcare system every day. By thoughtfully considering these principles, clinicians can select the drug dose, route, and frequency that will provide the optimal balance of safety and efficacy for the patient and promote positive outcomes. In all, clinical pharmacokinetics and pharmacodynamics help healthcare professionals provide optimal, individualized care to patients.

ABBREVIATIONS

α	distribution rate constant
AUC	area under serum or blood-concentration-versus-time curve
β	terminal rate constant
C	serum concentration
C_{max}	maximum serum or blood concentration
C_{min}	minimum serum or blood concentration
C_0	initial concentration
C_{SS}	steady-state concentration
$C_{ss,\ ub}$	steady-state concentration of unbound drug
CL	clearance
CLcr	creatinine clearance
CL_{int}	intrinsic clearance
D	dose
E	extraction ratio
F	fraction of drug absorbed into the systemic circulation
f_u	fraction of drug in the blood that is unbound
k	elimination rate constant
k_a	absorption rate constant
K_m	serum concentration at which the rate of metabolism equals $V_{max}/2$
LD	loading dose
MD	maintenance dose
P-gp	P-glycoprotein
Q	blood flow
R_0	IV infusion rate

τ	dosage interval
t'	post-infusion time
$t_{1/2}$	half-life
V_D	volume of distribution
V_{max}	maximum rate of drug metabolism

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SELF-ASSESSMENT QUESTIONS

1. Systemic clearance is the pharmacokinetic parameter that describes:

   A. Absorption

   B. Bioavailability

   C. Distribution

   D. Elimination

2. In pharmacokinetic studies, it is found that 80% of the drug reaches systemic circulation. The *F* for this drug would be:

   A. 0.2

   B. 0.8

   C. 1.2

   D. 1.8

3. A drug that is given as an IV bolus is found to produce serum concentrations of 10 mg/L when measured 4 hours after the dose and 5 mg/L when measured 10 hours after the dose. The half-life of the drug can be calculated as:

   A. 2 hrs

   B. 5 hrs

   C. 6 hrs

   D. 15 hrs

4. Phenytoin displays saturable Michaelis-Menten kinetics. If the dose is increased, the serum concentration is predicted to be _____ than expected in linear kinetics.

   A. Proportionally higher

   B. Disproportionally higher

   C. Proportionally lower

   D. Disproportionally lower

5. Which of the following is most likely to undergo extensive first-pass metabolism?

   A. Low extraction ratio drug given IV

   B. High extraction ratio drug given IV

   C. Low extraction ratio drug given orally

   D. High extraction ratio drug given orally

6. Most drugs follow nonlinear pharmacokinetics:

   A. True

B. False

7. The enzyme system responsible for the metabolism of most drugs is:

A. P-glycoprotein

B. Serum creatinine

C. Cytochrome P450

D. HMG-CoA

8. Pharmacodynamics is best described as:

A. Relationship of dose and serum concentration

B. Relationship of serum concentration and response

C. Relationship of dose over time

D. Relationship of half-life and steady state

9. For a drug that is renally eliminated, which would be the most appropriate to assess to determine if dose adjustments are needed?

A. Estimated glomerular filtration rate

B. Child-Pugh score

C. International normalized ratio (INR)

D. Adjusted body weight

10. Compartmental models are helpful in order to:

A. Predict plasma drug concentrations with a dosage regimen

B. Correlate drug concentrations with activity or toxicity

C. Estimate how a disease state may affect drug concentrations in the body

D. All of the above

11. The area under the curve is best defined as:

A. Total exposure of the body to the drug over time

B. Time to reduce serum concentrations by one-half

C. Proportionality constant that relates the amount of drug in the body to the serum concentration

D. Volume of plasma cleared of the given drug over time

12. The half-life is best defined as:

A. Total exposure of the body to the drug over time

B. Time to reduce serum concentrations by one-half

C. Proportionality constant that relates the amount of drug in the body to the serum concentration

D. Volume of plasma cleared of the given drug over time

13. The range of concentrations within which the pharmacologic response is produced and adverse effects prevented in most patients is referred to as the:

A. E_{max}

B. Steady-state concentration

C. Fraction unbound drug

D. Therapeutic window

14. The volume of distribution is best defined as:

A. Total exposure of the body to the drug over time

B. Time to reduce serum concentrations by one-half

C. Proportionality constant that relates the amount of drug in the body to the serum concentration

D. Volume of plasma cleared of the given drug over time

15. For a drug that is hepatically eliminated, which would be the most appropriate to assess to determine if dose adjustments are needed?

A. Estimated creatinine clearance

B. Child-Pugh score

C. Alkaline phosphatase

D. Adjusted body weight

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Systemic clearance is a pharmacokinetic parameter that describes the process of elimination.

2. **B.** The bioavailability (F), which is defined as the proportion of drug absorbed into systemic circulation, has a maximum value of 1. Thus, the percentage (80%) needs to be converted to ratio form –0.8.

3. **C.** The half-life is calculated by determining the amount of time for the serum concentration to reduce by one-half. The serum concentration in this example goes from 10 mg/L to 5 mg/L (a 50% reduction) in 6 hours, so this is the half-life.

4. **A.** Michaelis-Menten kinetics are nonlinear kinetics that result from saturable elimination processes. As such, increases in dose would result in disproportionately higher than expected serum concentrations than a drug with linear kinetics.

5. **D.** High extraction ratio drugs are very effectively metabolized by the liver. When drugs are given orally, they pass through the liver prior to reaching systemic circulation, thus limiting the bioavailability of high extraction ratio drugs. This does not occur with intravenously administered drugs, which enter the bloodstream directly.

6. **B.** Most drugs follow linear kinetics.

7. **C.** The group of enzymes primarily responsible for drug metabolism are the Cytochrome P450 enzymes. There are many unique enzymes within this group.

8. **B.** Pharmacodynamics is the interaction of the serum concentration and response, ie, what the drug does to the body.

9. **A.** Estimated GFR or creatinine clearance can be used for assessing kidney function.

10. **C.** Compartmental models are useful for all of the listed items—predicting plasma (or tissue) drug concentrations with a dosage regimen, correlating drug concentrations with activity or toxicity, and estimating how a disease state may affect drug concentrations in the body

11. **A.** The area under the curve is the measurement of the total exposure (area) of the drug to the body over the entire course of time, from administration of the drug to the end of elimination.

12. **B.** The half-life is the time to reduce the serum concentration by one-half. The time it takes to reduce serum concentration from 20 mg/L to 10 mg/L as it takes to reduce from 2 mg/L to 1 mg/L.

13. **D.** The therapeutic window describes the range of serum concentrations in which there is maximal effect with minimal adverse effects in the large population. This does not guarantee safety and efficacy in an individual patient.

14. **C.** The volume of distribution is a pharmacokinetic parameter that describes distribution and is a proportionality constant of that relates the serum concentration to the total amount of drug in the body.

15. **B.** The Child-Pugh score can be used to estimate degree of liver impairment in patients with hepatic disease. Alkaline phosphatase may be elevated in acute hepatitis and is not reliably indicative of the metabolizing ability of the liver.