Fifth Edition

CONCEPTS IN CLINICAL PHARMACOKINETICS

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Concepts in Clinical Pharmacokinetics

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Introduction to Pharmacokinetics and Pharmacodynamics

☑ OBJECTIVES

After completing Lesson 1, you should be able to:

1. Define and differentiate between *pharmacokinetics* and *clinical pharmacokinetics*.

2. Define *pharmacodynamics* and relate it to pharmacokinetics.

3. Describe the concept of the therapeutic concentration range.

4. Identify factors that cause interpatient variability in drug disposition and drug response.

5. Describe situations in which routine clinical pharmacokinetic monitoring would be advantageous.

6. List the assumptions made about drug distribution patterns in both one- and two-compartment models.

7. Represent graphically the typical natural log of plasma drug concentration versus time curve for a one-compartment model after an intravenous dose.

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

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

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

Similarly, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. Figure 1-3 is a simplified plot of the drug concentration versus time profile after an intravenous drug dose and illustrates this concept.
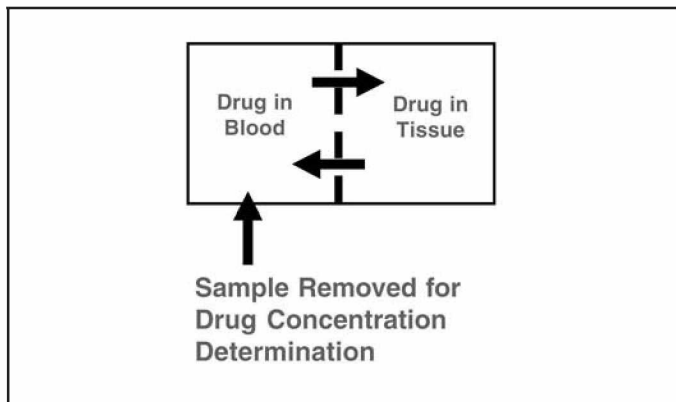
FIGURE 1-1.
Blood is the fluid most often sampled for drug concentration determination.

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

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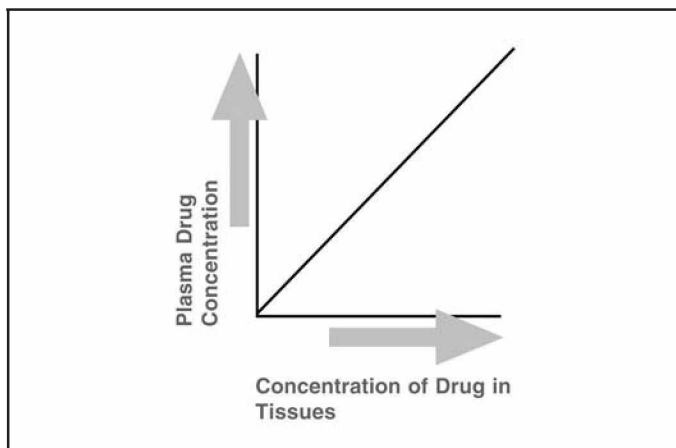

FIGURE 1-2.
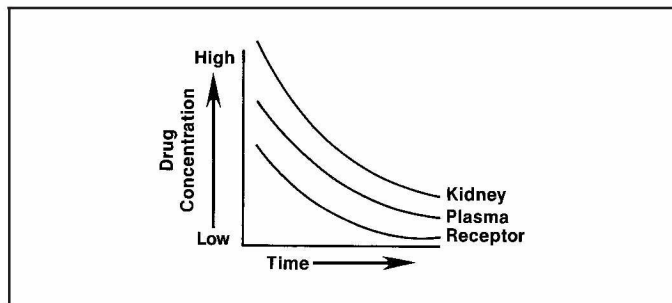Relationship of plasma to tissue drug concentrations.

FIGURE 1-3.
Drug concentration versus time.

BASIC PHARMACODYNAMIC CONCEPTS

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

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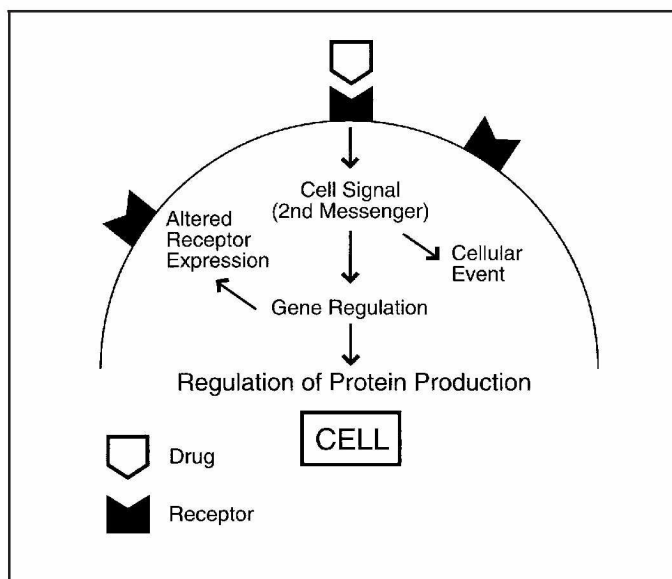

FIGURE 1-4.
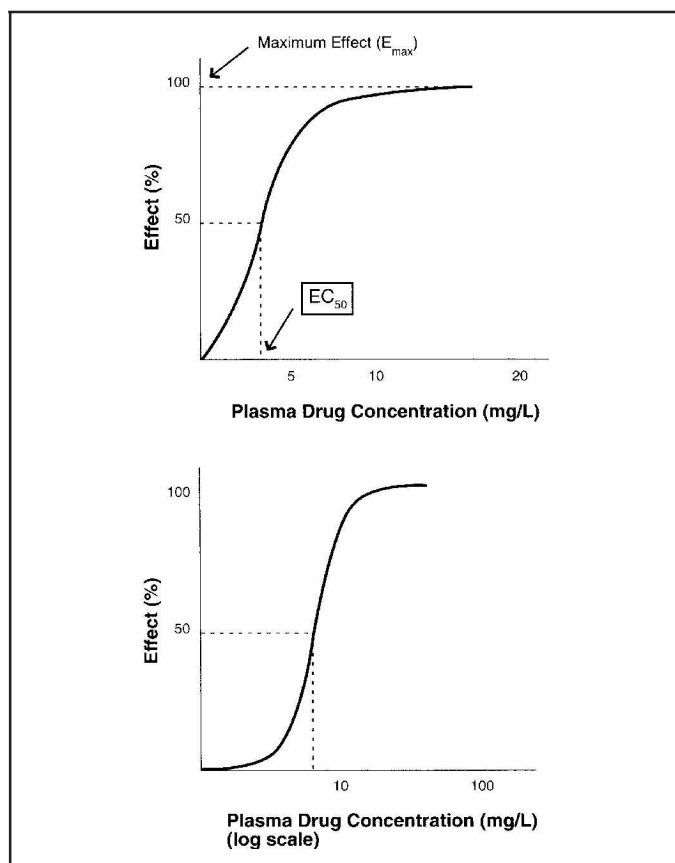Relationship of drug concentration to drug effect at the receptor site.

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

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

regulation results in variation of sensitivity to drug effect from one individual to another and also determines enhancement of or tolerance to drug effects.

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

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

The EC_{50} does not, however, indicate other important determinants of drug response, such as the duration of effect. Duration of effect is determined by a complex set of factors, including the time that a drug is engaged on the receptor as well as intracellular signaling and gene regulation.
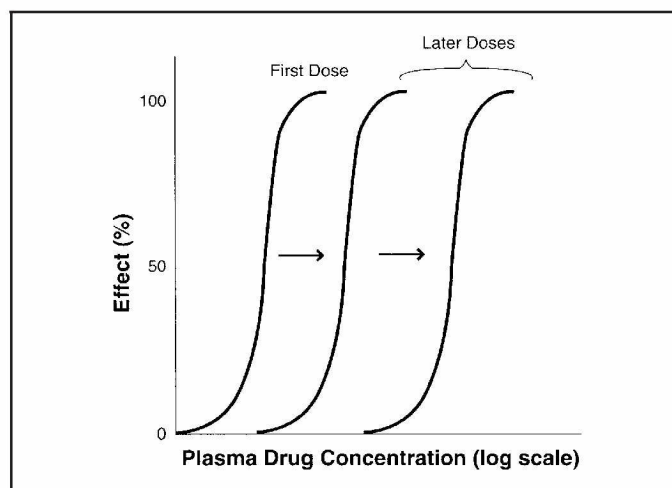
For some drugs, the effectiveness can decrease with continued use. This is referred to as *tolerance*. Tolerance may be caused by pharmacokinetic factors, such as increased drug metabolism, that decrease the concentrations achieved with a given dose. There can also be pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure. An example of drug tolerance is the use of opiates in the management of chronic pain. It is not uncommon to find these patients requiring increased doses of the opiate over time. Tolerance can be described in terms of the dose–response curve, as shown in Figure 1-6.

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

CLINICAL CORRELATE

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

CLINICAL CORRELATE

One way to compare potency of two drugs that are in the same pharmacologic class is to compare EC_{50}. The drug with a lower EC_{50} is considered more potent.
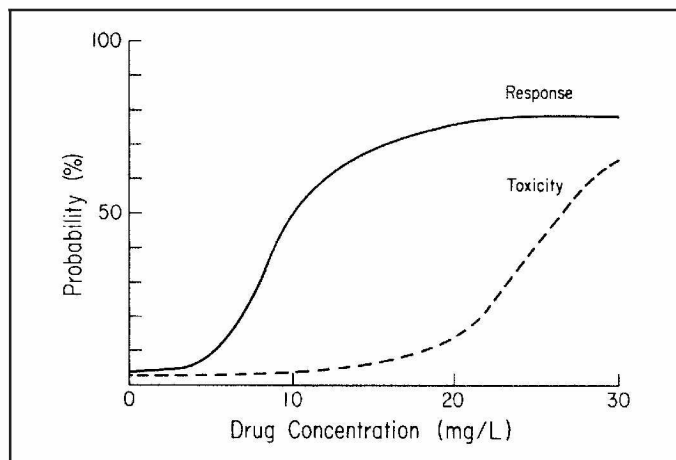
FIGURE 1-7.
Relationship between drug concentration and drug effects for a hypothetical drug. **Source:** Adapted with permission from Evans WE, editor. General principles of applied pharmacokinetics. In: *Applied Pharmacokinetics*, 3rd ed. Vancouver, WA: Applied Therapeutics; 1992. pp.1–3.

THERAPEUTIC DRUG MONITORING

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

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

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

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

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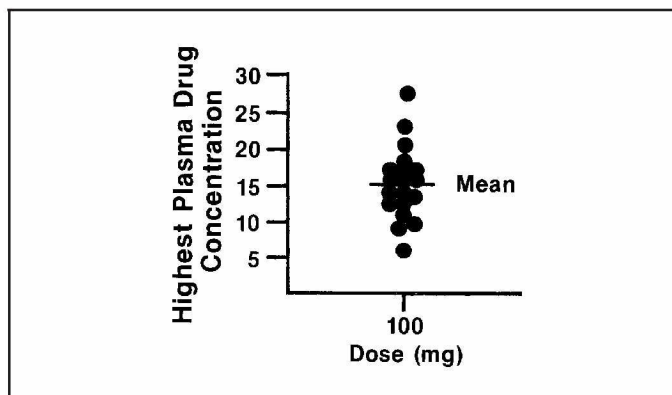
FIGURE 1-8.
Example of variability in plasma drug concentration among subjects given the same drug dose.

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

Therapeutic monitoring using drug concentration data is valuable when:

1. A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. This relationship allows us to predict pharmacologic effects with changing plasma drug concentrations (Figure 1-9).
2. Wide intersubject variation in plasma drug concentrations results from a given dose.
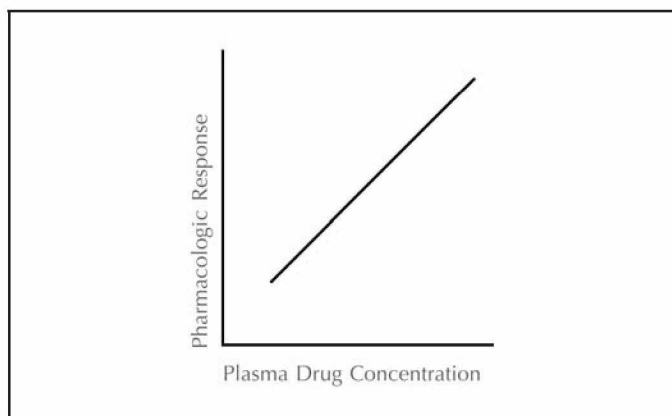
FIGURE 1-9.
When pharmacologic effects relate to plasma drug concentrations, the latter can be used to predict the former.

3. The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).
4. The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensives).

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

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

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

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

Examples of therapeutic ranges for commonly used drugs are shown in Table 1-1. As can be seen in this table, most drug concentrations are expressed as a unit of mass per volume.
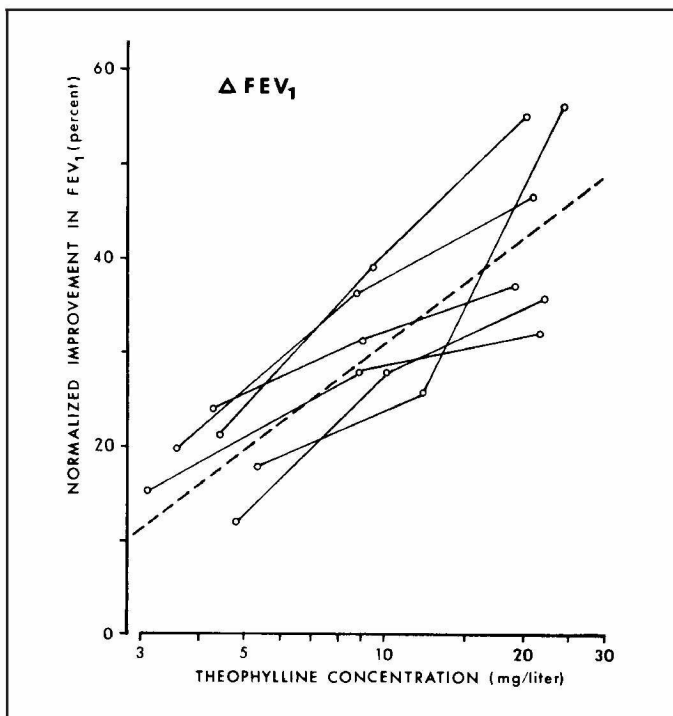
CLINICAL CORRELATE

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

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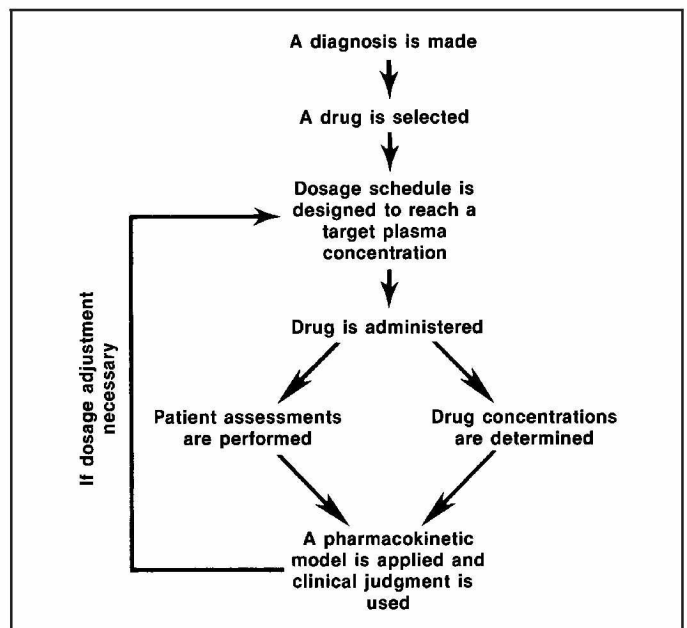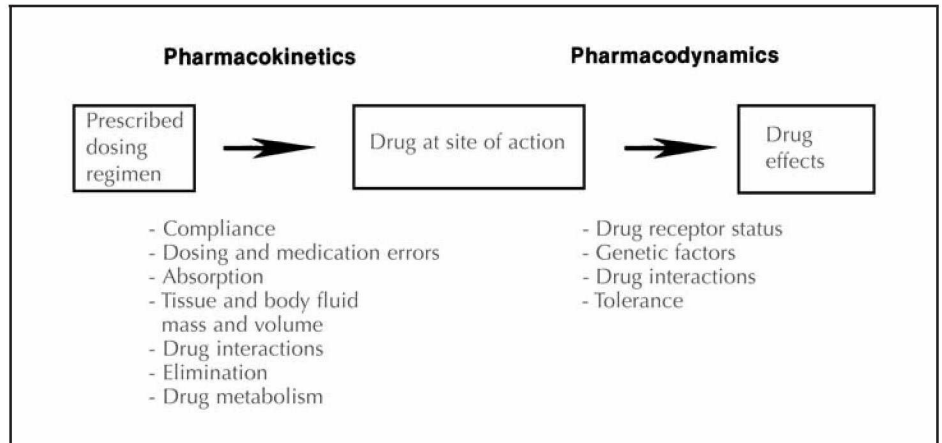

FIGURE 1-11.
Process for reaching dosage decisions with therapeutic drug monitoring.

FIGURE 1-12.

Relationship of pharmacokinetics and pharmacodynamics and factors that affect each.

PHARMACOKINETIC MODELS

The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Simplifications of body processes are necessary to predict a drug's behavior in the body. One way to make these simplifications is to apply mathematical principles to the various processes.

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

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

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

TABLE 1-1.

Therapeutic Ranges for Commonly Used Drugs

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

Source: Adapted with permission from Bauer LA. Clinical pharmacokinetics and pharmacodynamics. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. *Pharmacotherapy: a Pathophysiologic Approach,* 7th ed. New York: McGraw-Hill; 2008. p. 10.
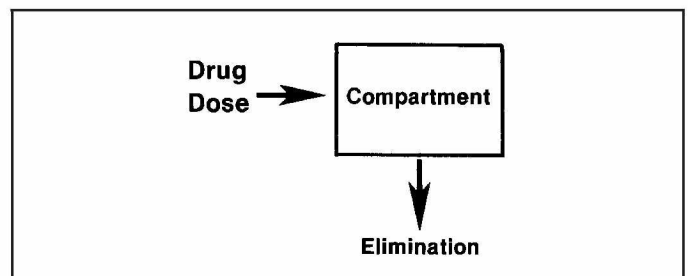
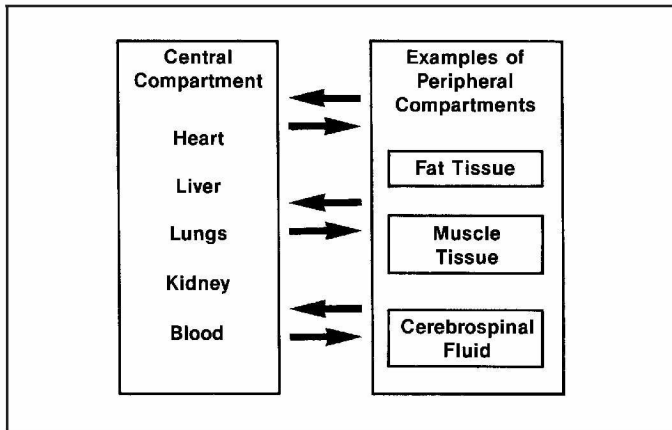**FIGURE 1-13.**

Simple compartmental model.

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

FIGURE 1-15.
One-compartment model.

and cerebrospinal fluid is the peripheral compartment, which is less well perfused than the central compartment.

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

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

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

COMPARTMENTAL MODELS

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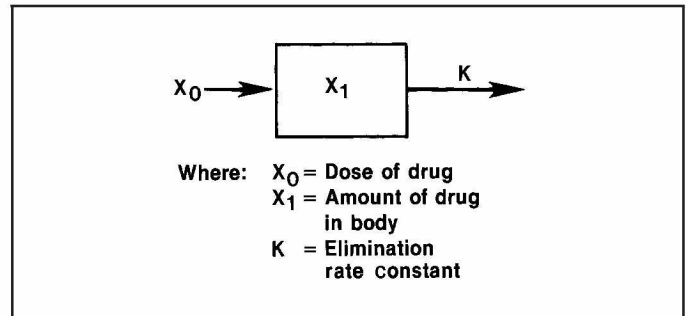
ment is represented by an enclosed square or rectangle, and rates of drug transfer are represented by straight arrows (Figure 1-15). The arrow pointing into the box simply indicates that drug is put into that compartment. And the arrow pointing out of the box indicates that drug is leaving the compartment.

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

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

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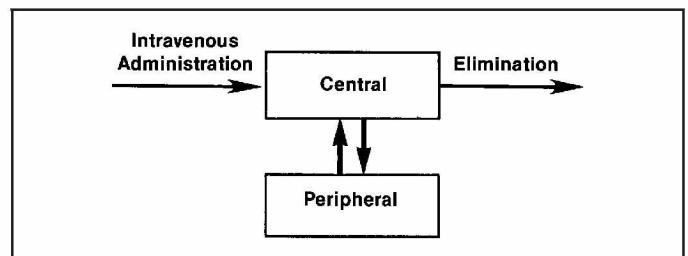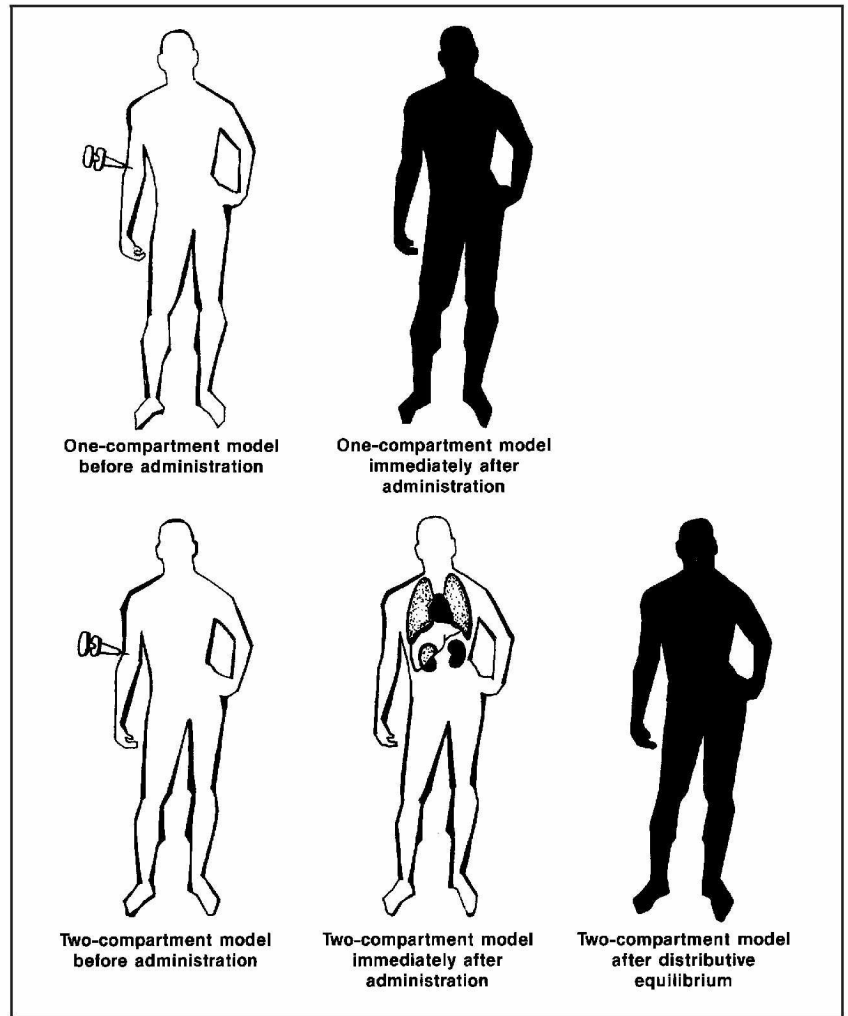

FIGURE 1-16.
Compartmental model representing transfer of drug to and from central and peripheral compartments.

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

One-compartment model before administration

One-compartment model immediately after administration

Two-compartment model before administration

Two-compartment model immediately after administration

Two-compartment model after distributive equilibrium

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

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

CLINICAL CORRELATE

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

Volume of Distribution

Until now, we have spoken of the amount of drug (X) in a compartment. If we also consider the volume of the
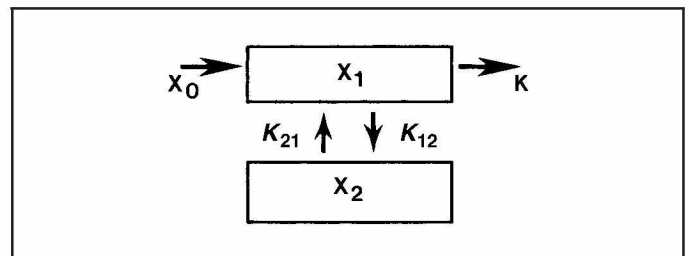
FIGURE 1-18.
Two-compartment model.

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

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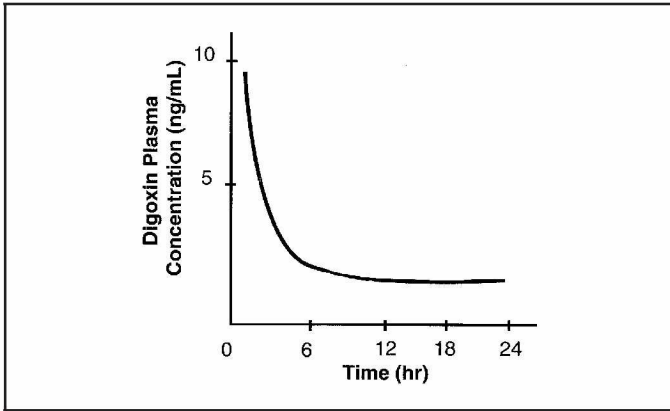**Approximate Volumes of Distribution of Commonly Used Drugs**

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

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

compartment, we can describe the concept of drug concentration. *Drug concentration* in the compartment is defined as the amount of drug in a given volume, such as mg/L:

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

1-1

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

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

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

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

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

To illustrate the concept of volume of distribution, let us first imagine the body as a tank filled with fluid, as

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

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

X = amount of drug in body
V = volume of distribution
C = concentration in the plasma

As with other pharmacokinetic parameters, volume of distribution can vary considerably from one person to another because of differences in physiology or disease states. Something to note: The dose of a drug (X_0) and
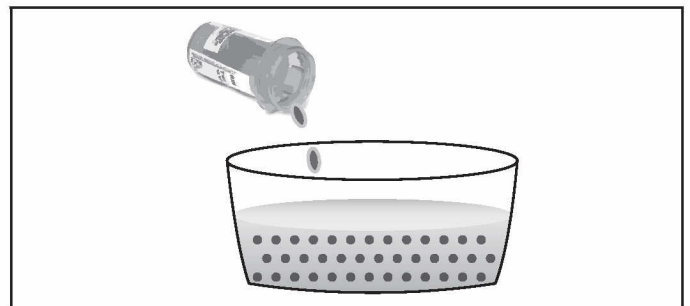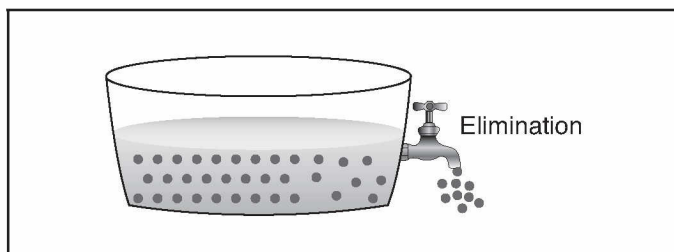

FIGURE 1-20.
The volume of a tank can be determined from the amount of substance added and the resulting concentration.

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

FIGURE 1-22.
One-compartment model.

the amount of drug in the body (X) are essentially the same thing because all of the dose goes into the body.

In this example, important assumptions have been made: that instantaneous distribution occurs and that it occurs equally throughout the tank. In the closed tank, there is no elimination. This example is analogous to a one-compartment model of the body after intravenous bolus administration. However, there is one complicating factor—during the entire time that the drug is in the body, elimination is taking place. So, if we consider the body as a tank with an open outlet valve, the concentration used to calculate the volume of the tank would be constantly changing (Figure 1-21).

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

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

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

CLINICAL CORRELATE

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

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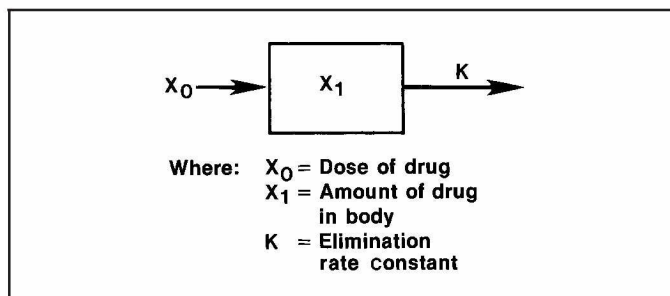
CLINICAL CORRELATE

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

PLASMA DRUG CONCENTRATION VERSUS TIME CURVES

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

Because of cost limitations and patient convenience in clinical situations, only a small number of plasma samples can usually be obtained for measuring drug concentrations (Figure 1-24). From these known values, we are able to predict the plasma drug concentrations for the times when we have no samples (Figure 1-25). In clinical situations, it is rare to collect more than two samples after a dose.
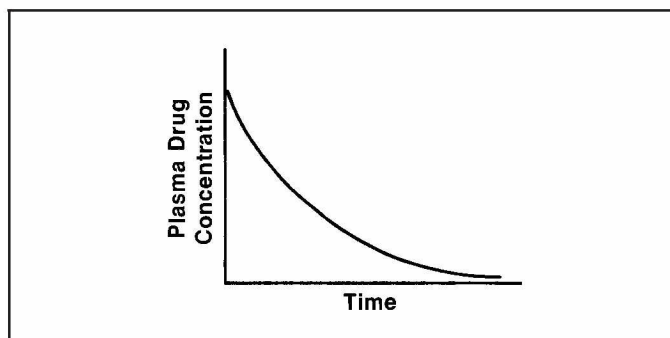
FIGURE 1-23.
Typical plasma drug concentration versus time curve for a one-compartment model.
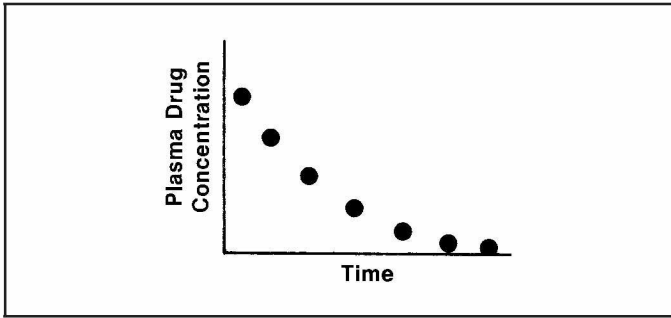
FIGURE 1-24.
Plasma drug concentrations determined at specific time points.

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

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

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

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

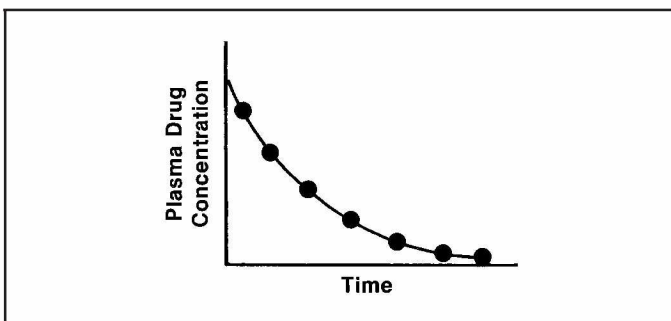An alternative to calculating the natural log values is to plot the actual concentration and time values on semilogarithmic (or semilog) paper (Figure 1-27), a special graph paper that automatically adjusts for the logarithmic relationship by altering the distance between lines on the *y*-axis. The lines on the *y*-axis are not evenly spaced but rather are logarithmically related within each log cycle (or multiple of 10). So when the actual values of plasma drug concentrations are plotted against the time values, a straight line results. The *x*-axis has evenly spaced lines; there is no logarithmic conversion of those values. (The term *semilogarithmic* indicates that only one axis is converted.) The numbers on the *y*-axis may be used to represent 0.1 through 1, 1 through 10, 10 through 100, or any series with a 10-fold difference in the range of values.

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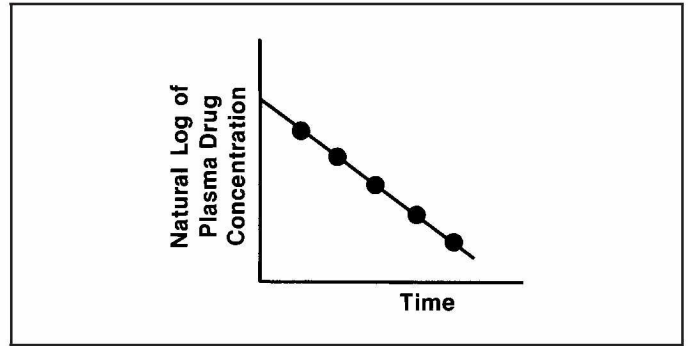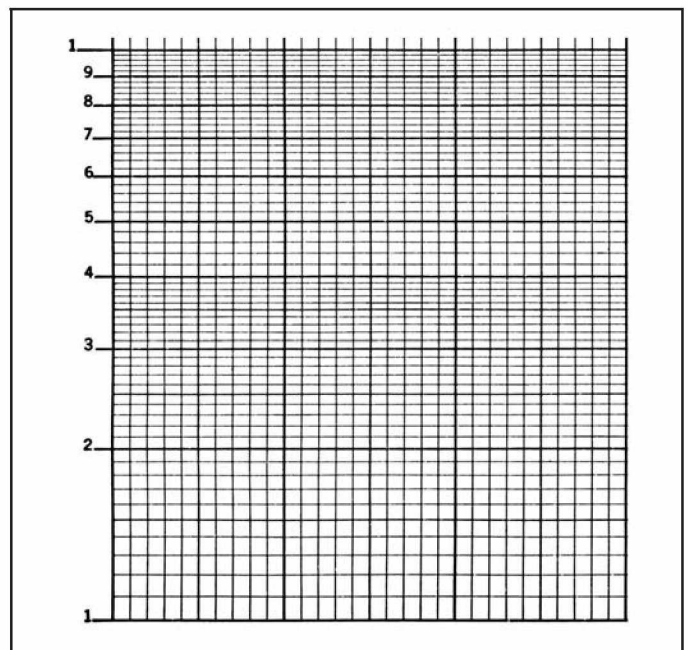

FIGURE 1-27.
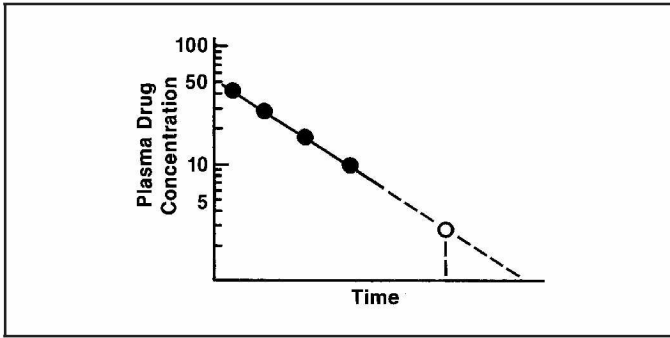Paper with one log-scale axis is called *semilog paper*.

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

> ### CLINICAL CORRELATE
>
> Semilog graph paper can be found via google.com

If a series of plasma concentration versus time points are known and plotted on semilog paper, a straight line can be drawn through the points by visual inspection or, more accurately, by linear regression techniques. Linear regression is a mathematical method used to determine the line that best represents a set of plotted points.
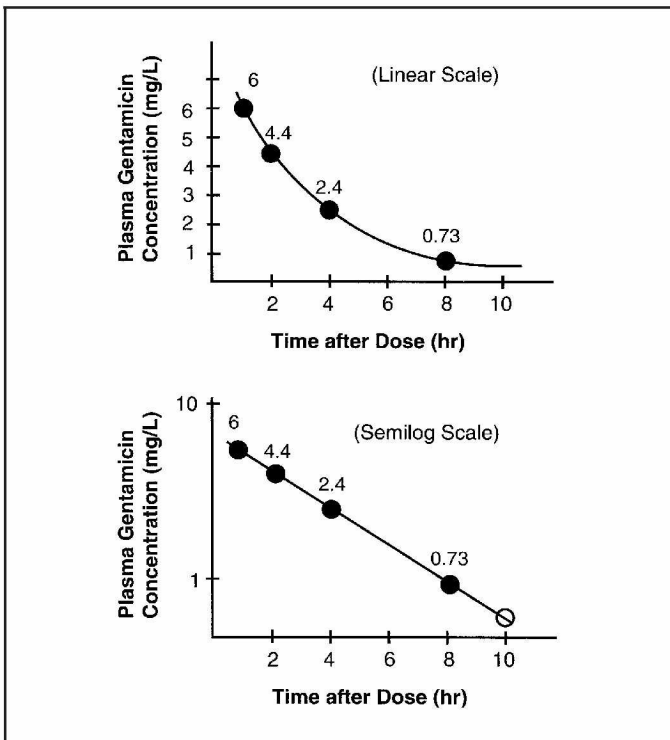

FIGURE 1-29.
Predicting plasma drug concentrations with semilog scale.

TABLE 1-3.
Time Course of Plasma Gentamicin Concentration

Concentration (mg/L)	Time after Dose (hours)
6	1
4.4	2
2.4	4
0.73	8

From this line, we can predict plasma drug concentrations at times for which no measurements are available (Figure 1-28).

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

MATH PRINCIPLE

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

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

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

USING THE CALCULATOR WITH NATURAL LOG AND EXPONENTIAL KEYS

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

■ Review Questions

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

A. pharmacodynamics.

B. drug concentration.

C. pharmacokinetics.

D. kinetic homogeneity.

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

A. pharmacodynamics.

B. clinical pharmacokinetics.

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

A. True

B. False

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

A. dose to drug concentration in plasma.

B. dose to drug concentration at the receptor site.

C. concentrations to drug effect.

D. dose to drug effect.

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

A. True

B. False

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

A. one-half the maximum response is achieved.

B. the maximal effect is achieved.

C. tolerance is likely to be observed.

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

A. True

B. False

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

A. True

B. False

1-9. Factors that cause variability in plasma drug concentrations after the same drug dose is given to different patients include variations in the:

A. drug absorption.

B. EC_{50} of the drug.

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

A. a wide variation in plasma drug concentrations is achieved in different patients given a standard drug dose.

B. the toxic plasma concentration is many times the therapeutic concentration range.

C. correlation between a drug's plasma concentration and therapeutic response is good.

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

A. True

B. False

1-12. In pharmacokinetics, the term *rate* refers to a change in which of the following measurements over time.

A. drug dose

B. drug elimination

C. concentration of drug in plasma

1-13. Highly perfused organs and blood comprise what is usually known as the peripheral compartment.

A. True

B. False

1-14. The most commonly used model in clinical pharmacokinetic situations is the:

A. one-compartment model.

B. two-compartment model.

C. multicompartment model.

1-15. Instantaneous distribution to most body tissues and fluids is assumed in which of the following models?

A. one-compartment model

B. two-compartment model

C. multicompartment model

1-16. The amount of drug per unit of volume is defined as the:

A. volume of distribution.

B. concentration.

C. rate.

1-17. If 3 g of a drug are added and distributed throughout a tank and the resulting concentration is 0.15 g/L, calculate the volume of the tank.

A. 10 L

B. 20 L

C. 30 L

D. 200 L

1-18. For a drug that has first-order elimination and follows a one-compartment model, which of the following plots would result in a curved line?

A. plasma concentration versus time

B. natural log of plasma concentration versus time

1-19. A drug that follows a one-compartment model is given as an intravenous injection, and the following plasma concentrations are determined at the times indicated:

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

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

A. 18 mg/L

B. 30 mg/L

C. <1 mg/L

▮ Answers _____

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

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

C. CORRECT ANSWER

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

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

B. CORRECT ANSWER

1-3. A. Incorrect answer. The plasma drug concentration is not the same as that in the tissue but rather is related to the tissue concentration by the volume of distribution (V). Plasma drug concentrations are commonly used because blood, being

readily accessible via venipuncture, is the body fluid most often collected for drug measurement.

B. CORRECT ANSWER

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

C. CORRECT ANSWER

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

1-5. A. CORRECT ANSWER

B. Incorrect answer

1-6. A. CORRECT ANSWER

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

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

1-7. A. Incorrect answer. Although the therapeutic range of a drug describes a range of plasma drug concentrations generally considered safe and effective in a patient population, no absolute boundaries

divide subtherapeutic, therapeutic, and toxic drug concentrations for an individual patient. Both pharmacodynamic and pharmacokinetic factors influence a patient's response.

B. CORRECT ANSWER

1-8.   A. CORRECT ANSWER

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

1-9.   A. CORRECT ANSWER

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

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

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

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

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

B. Incorrect answer

1-12. A. Incorrect answer. The dose is the amount of drug given at one time or in divided amounts within a given period.

B. Incorrect answer. Most pharmacokinetic models assume that elimination does not change over time.

C. CORRECT ANSWER

1-13. A. Incorrect answer. The peripheral compartment is generally made up of less well-perfused tissues, such as muscle and fat.

B. CORRECT ANSWER

1-14. A. CORRECT ANSWER

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

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

1-15. A. CORRECT ANSWER

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

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

1-16. A. Incorrect answer. The volume of distribution refers to the dose over the resulting concentration.

B. CORRECT ANSWER

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

1-17. A, C, D. Incorrect answers. A math error must have been made. The answer can be found by dividing 3 g by 0.15 g/L.

B. CORRECT ANSWER

1-18. A. CORRECT ANSWER

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

1-19. A, C. Incorrect answers. These results might have been determined if linear graph paper was used or if the points were plotted incorrectly.

B. CORRECT ANSWER

Discussion Points

D-1. An H_2-receptor antagonist is given to control gastric pH and prevent stress bleeding. The following gastric pHs were observed when steady-state concentrations of the drug were achieved. What are the E_{max} and EC_{50} of this drug?

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

D-2. The relationship shown in Figure 1-30 is observed from a clinical study. What are some of the likely reasons for this result?
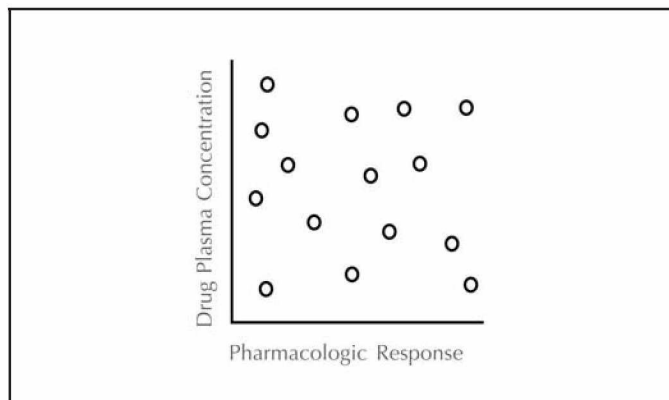

FIGURE 1-30.
Pharmacologic response versus drug plasma concentration.

D-3. The models shown in Figure 1-31 both well represent actual plasma concentrations of a drug after a dose. Which one should be preferred to predict plasma levels? Provide a justification for your answer.
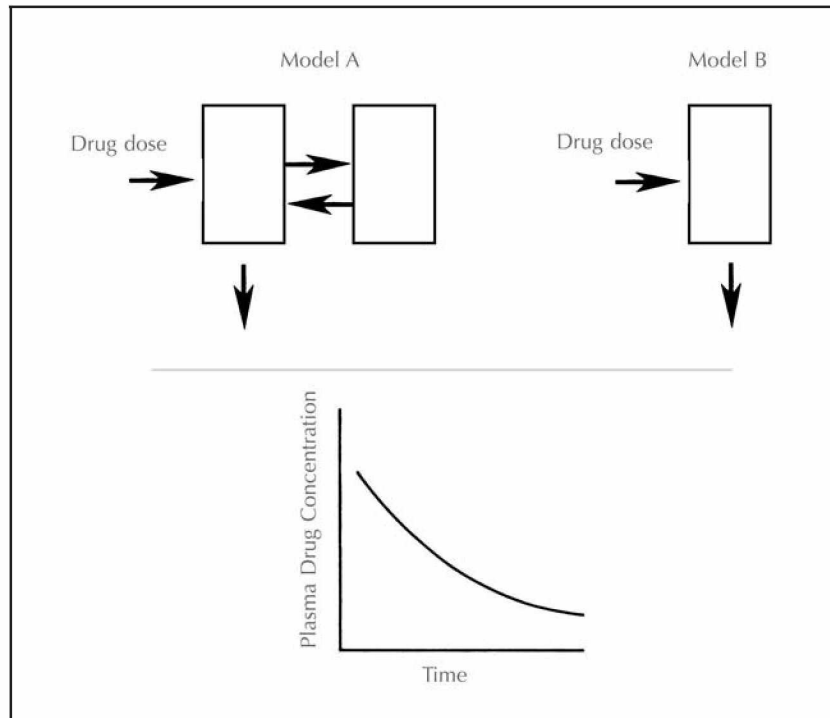

FIGURE 1-31.
Models for predicting plasma drug concentrations over time.

D-4. Would you expect a large drug molecule that does not cross physiologic membranes very well and is not lipid soluble to have a relatively high or low volume of distribution? Explain your answer.

D-5. When plotting plasma drug concentration (y-axis) versus time (x-axis), what are the advantages of using a natural log scale for the y-axis rather than a linear scale?