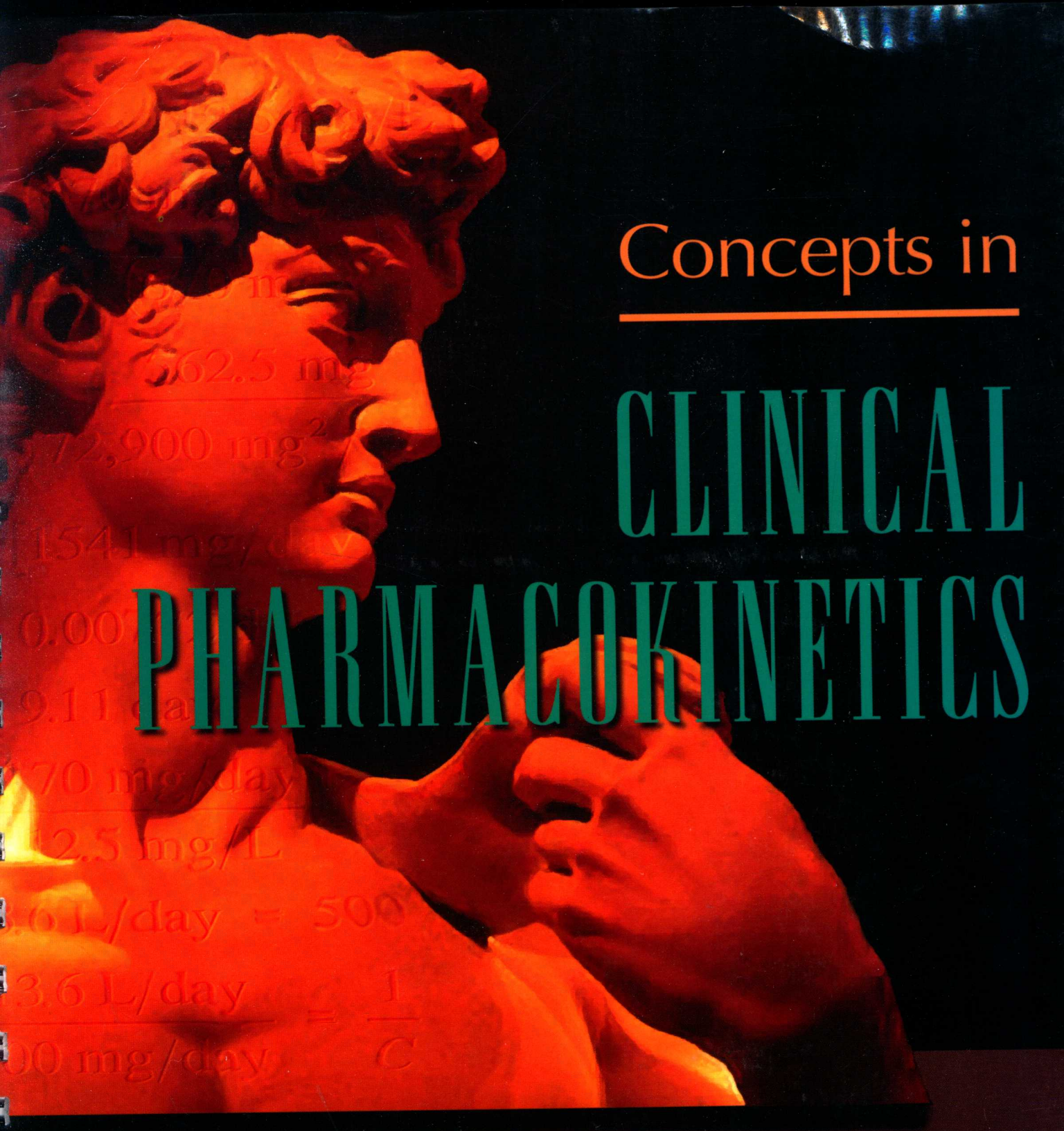

Concepts in CLINICAL PHARMACOKINETICS

Joseph T. DiPiro
William J. Spruill
Robert A. Blouin
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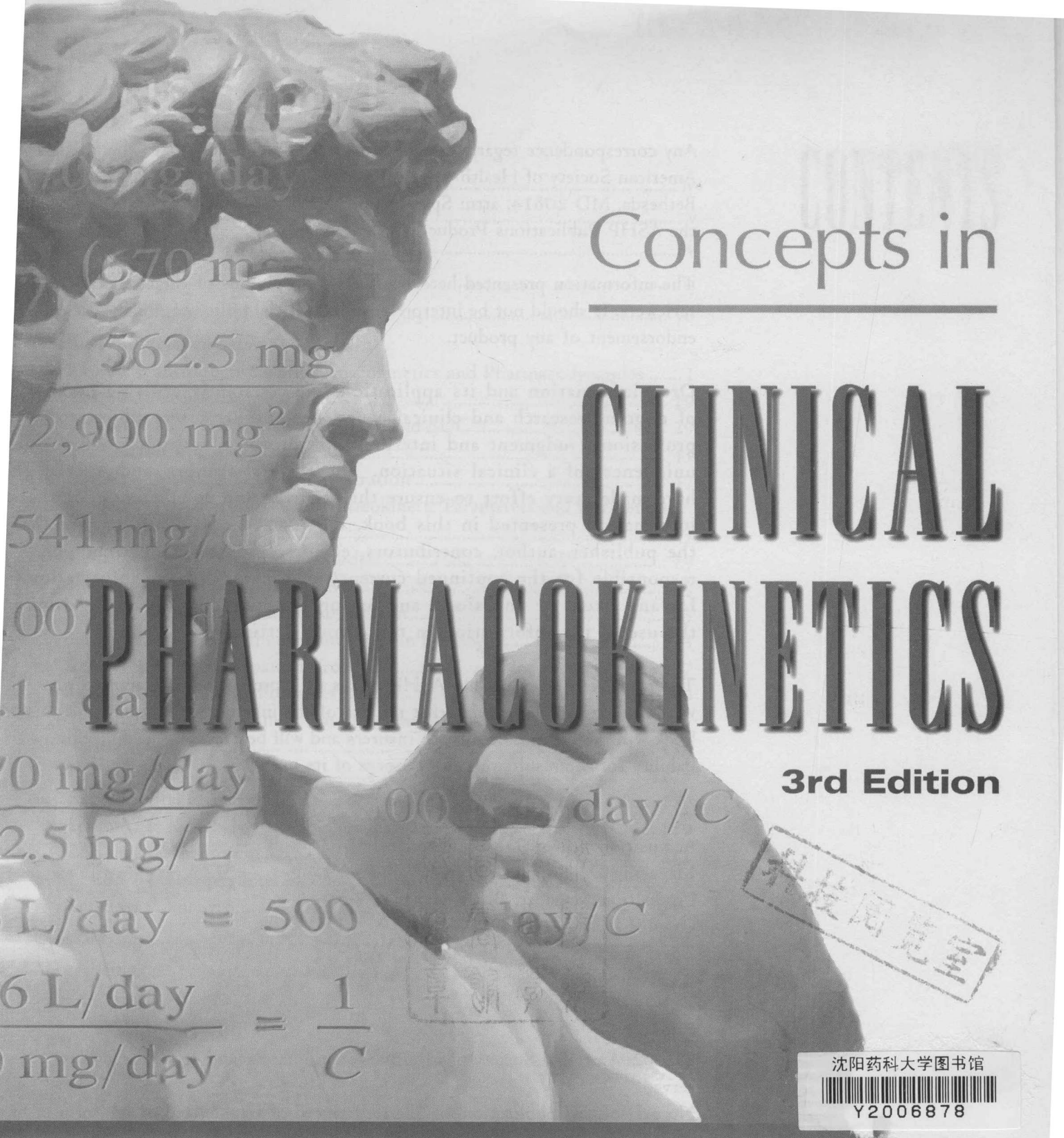
3rd Edition

American Society of Health-System Pharmacists®



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PREFACE

This programmed manual presents basic pharmacokinetic concepts and procedures that are useful in pharmacy, medicine, and other health professions. Most of the material relates to individualization of drug dosing regimens. Although this text is not intended to create a practitioner fully competent in clinical pharmacokinetics, it will provide an orientation to the concepts involved.

After completing this text, the reader should be prepared to begin learning the pharmacokinetic techniques for clinical situations. The reader should participate in structured educational settings, such as a formal clinical pharmacokinetics course or a clerkship under an experienced clinical practitioner to develop clinical skills related to pharmacokinetics. Readers who want in-depth understanding of the derivations of pharmacokinetic equations should consult an appropriate text.

In this third edition, the manual is divided into 15 lessons to allow progression on a typical semester schedule of 15 weeks. The first 11 lessons include pharmacokinetic and pharmacodynamic principles as well as an overview of biopharmaceutic principles. Each of these lessons begins with a list of educational objectives and concludes with a series of questions. Answers and feedback for incorrect responses have been provided for the short-answer questions. Discussion questions have been added. Lessons 12 through 15 present brief patient case studies with aminoglycosides, theophylline, vancomycin, digoxin, and phenytoin so the reader can practice the use of pharmacokinetic equations.

This edition will be accompanied by a Web-based version that will provide lessons to parallel each of the lessons in the print version. The Web-based version will include dynamic figures and simulators, calculators for applying pharmacokinetic equations, links to important web pages, and interactive capability for discussion questions. Although the print version may be used independently, we believe that concurrent use of both versions will enhance learning.

Joseph T. DiPiro
William J. Spruill
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January 2002

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CONTENTS

LESSON 1

INTRODUCTION TO PHARMACOKINETICS AND PHARMACODYNAMICS

Educational Objectives

After completing Lesson 1, you should be able to:

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

The discipline of clinical pharmacokinetics was first introduced in the 1920s by Torsten Tiorell. The term "pharmacokinetics" was first used more than 40 years ago and is currently defined as the study of the *time course* of drug absorption, distribution, metabolism, and excretion. *Clinical pharmacokinetics* deals with the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an *individual patient*.

A principal application of clinical pharmacokinetics is to increase the effectiveness or to decrease the 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 related to its concentration at the site of action, so it would be useful to monitor this concentration. However, because receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, we often cannot directly measure drug concentration at the

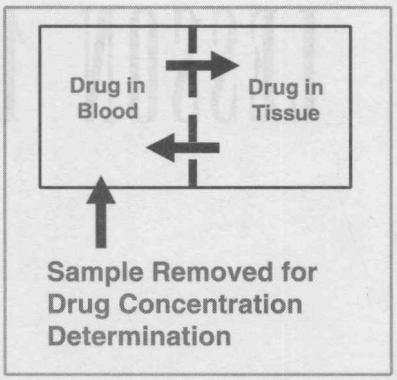

Figure 1.1. Blood is the fluid most often sampled for drug concentration determination.

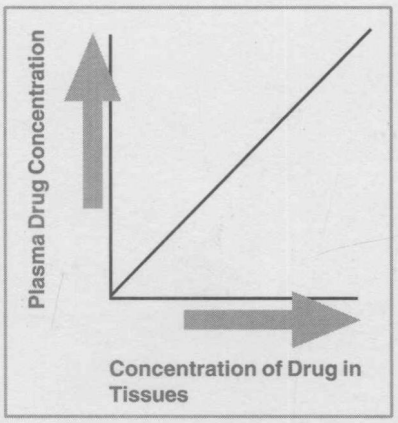

Figure 1.2. Relationship of plasma to tissue drug concentrations.

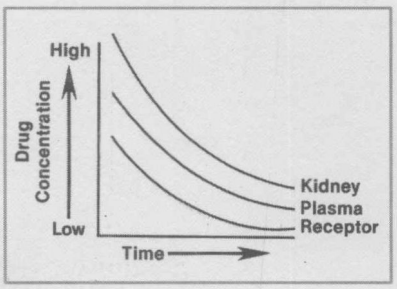

Figure 1.3. Drug concentration versus time.

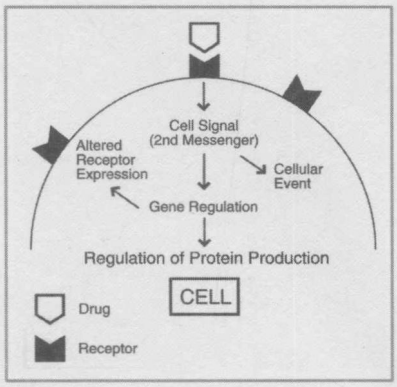

Figure 1.4. Relationship of drug concentration to drug effect at the receptor site.

receptor site. For example, the receptor sites for digoxin are believed to be within the myocardium, and 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**).

The term "kinetic homogeneity" describes the predictable relationship between plasma drug concentration and concentration at the receptor site (**Figure 1.2**). As the concentration of drug in plasma increases, the concentration of drug in most tissues will increase proportionally.

Changes in the plasma drug concentration reflect changes in drug concentrations in other tissues. However, the plasma drug concentration does not equal the concentration at other sites but rather indicates how it changes with time. Generally, 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 following an intravenous drug dose and illustrates the property of kinetic homogeneity.

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.

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 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. The drug's effect may ultimately be determined by the 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 that transmit signals from receptors), or regulatory factors that control gene translation and protein production. This multilevel regulation of drug effect 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.

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 dose. There can also be pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect after the initial treatment. 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.

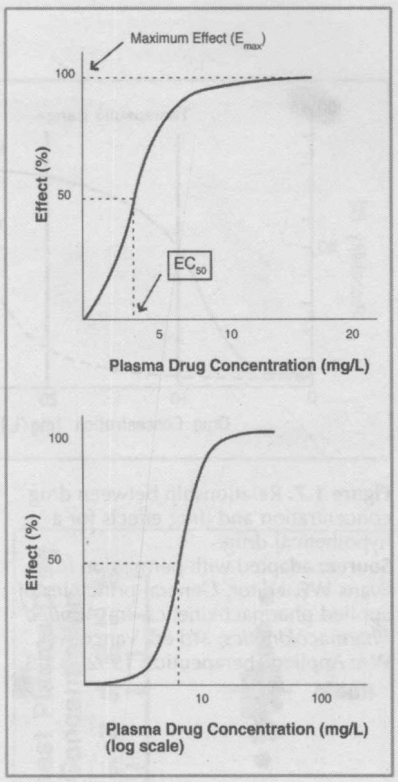

Figure 1.5. Relationship of drug concentration at the receptor site to effect (as a percentage of maximal effect).

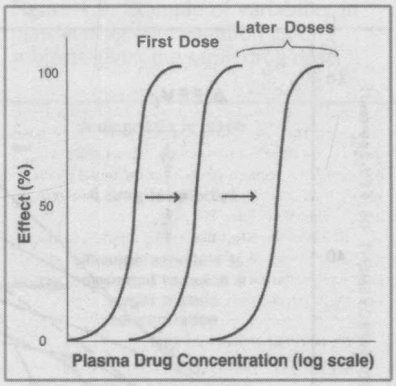

Figure 1.6. Demonstration of tolerance to drug effect with repeated dosing.

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.

For some patients with diabetes mellitus, there is a reduction in the number of insulin receptors on the surface of cells using glucose. These patients then become relatively insensitive to insulin and require higher doses. Therefore, the pharmacologic response for one person can be quite different from another, even with the same insulin concentrations at the receptor site.

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.

Therapeutic Drug Monitoring

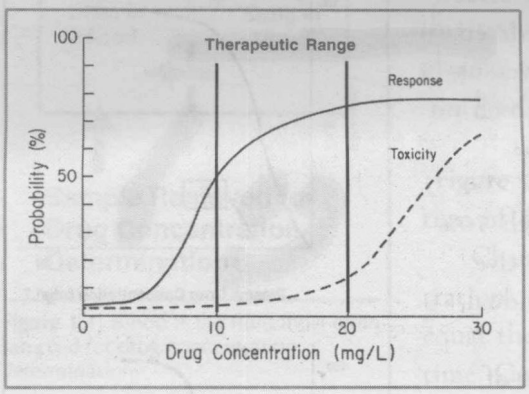

Figure 1.7. Relationship between drug concentration and drug effects for a hypothetical drug.
Source: adapted with permission from Evans WE, editor. General principles of applied pharmacokinetics. In: *Applied Pharmacokinetics*, 3rd ed. Vancouver, WA: Applied Therapeutics; 1992. p.1-3.

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; it is called the "therapeutic range" for the drug (**Figure 1.7**). Within this therapeutic range, the desired effects of the drug are seen. 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. Since individual patient response often plays an important role, there is a "gray area" where these concentrations overlap. Variability in a patient's response is influenced by both pharmacodynamic and pharmacokinetic factors.

Although this course will focus on pharmacokinetics, it is important to remember the fundamental relationship between drug pharmacokinetics and pharmacologic response. The pharmacokinetics of a drug determine the blood concentration achieved from a prescribed dosing regimen. It is generally assumed that after continued drug dosing, the blood concentration will mirror the drug concentration at the receptor site; and it is the receptor site concentration that should principally determine the intensity of a drug's effect. Consequently, both the pharmacokinetics and pharmacologic response characteristics of a drug and the relationship between them must be understood before predicting a patient's response to a drug regimen.

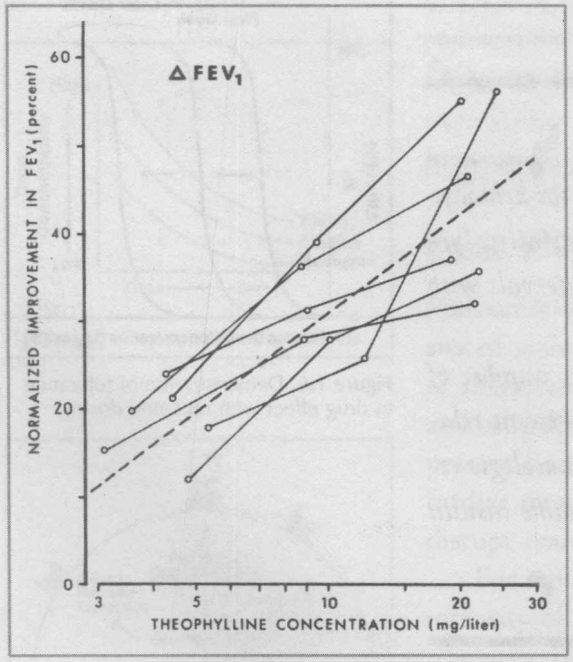

Figure 1.8. Relationship between plasma theophylline concentration and change in forced expiratory volume (FEV) in asthmatic patients.
Source: reproduced with permission from Mitenko PA, Ogilvie RI. Rational intravenous doses of theophylline. *N Engl J Med* 1973; 289:600–3. Copyright 1973, Massachusetts Medical Society.

Theophylline is an excellent example of a drug whose pharmacokinetics and pharmacodynamics are fairly well understood. When theophylline is administered at a fixed dosage to numerous patients, the blood concentrations achieved vary greatly. That is, wide interpatient variability exists in the pharmacokinetics of theophylline. This fact by itself would not be important unless subtle changes in the blood concentration resulted in significant changes in drug response.

Figure 1.8 shows the relationship between theophylline concentration (x-axis, on a logarithmic scale) and its pharmacologic effect, the change in pulmonary function (y-axis). Figure 1.8 illustrates that as the concentration of theophylline increases, so does the intensity of the response for some patients.

Theophylline concentrations below 5–8 mg/L are generally considered inadequate for a desired therapeutic effect, and side effects (tachycardia, nausea and vomiting, and nervousness) are more likely to occur at concentrations above 20 mg/L. Drugs like theophylline possess a narrow therapeutic index because the concentrations that may produce toxic effects are close to those required for therapeutic effects. The importance of considering both pharmacokinetics and pharmacodynamics is clear. Examples of therapeutic ranges for commonly used drugs are shown in **Table 1.1**.

Table 1.1. Therapeutic Ranges for Commonly Used Drugs

Drug	Range
Digoxin	0.9–2 ng/ml
Gentamicin	< 2 mg/L (trough), 5–10 mg/L (peak)
Lidocaine	1.5–5 mg/L
Lithium	0.6–1.4 mEq/L
Phenobarbital	15–40 mg/L
Phenytoin	10–20 mg/L
Quinidine	2–5 mg/L
Theophylline	10–20 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.* 4th ed. New York: McGraw-Hill; 1999. p. 22.

Most drug concentrations are expressed as a unit of mass per volume (e.g., mg/L or µg/ml [micrograms per milliliter], which are equivalent).

Many pharmacokinetic factors cause variability in the plasma drug concentration and, consequently, the pharmacologic response following a dosage regimen. Among these factors are:

- differences in an individual's ability to metabolize and eliminate the drug (e.g., genetics);
- variations in drug absorption;
- disease states or physiologic states (e.g., extremes of age) that alter drug absorption, distribution, or elimination; and
- drug interactions.

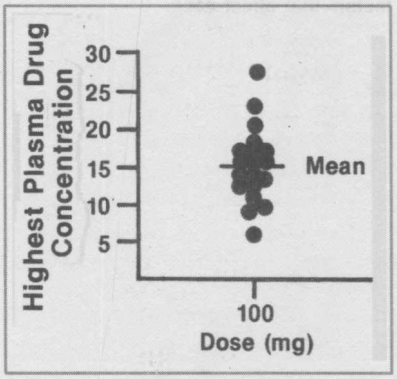

Figure 1.9. Example of variability in plasma drug concentration among subjects given the same drug dose.

We could study a large group of patients by measuring the highest plasma drug concentrations resulting after administration of the same drug dose to each patient. For most drugs, the intersubject variability is likely to result in differing plasma drug concentrations (**Figure 1.9**). This variability is primarily attributed to factors influencing drug absorption, distribution, metabolism, or excretion. Disease states (e.g., renal or hepatic failure) and other conditions (e.g., obesity and aging) that may alter these processes must be considered for the individualization of drug dosage regimens.

Determination of plasma drug concentrations to optimize a patient's drug therapy is known as "therapeutic drug monitoring." If performed properly, this monitoring allows the rapid and safe attainment of plasma concentrations within the therapeutic range. Together with observations of the drug's clinical effects, it should provide the safest approach to optimal drug therapy.

Two components make up the process of therapeutic drug monitoring:

- assays for determination of the drug concentration in plasma, and
- interpretation and application of the resulting concentration data to develop a safe and effective drug regimen.

The major potential advantages of therapeutic drug monitoring are the maximization of therapeutic drug benefits as well as the minimization of toxic drug effects. The formulation of drug therapy regimens by therapeutic drug monitoring involves a process for reaching dosage decisions (**Figure 1.10**).

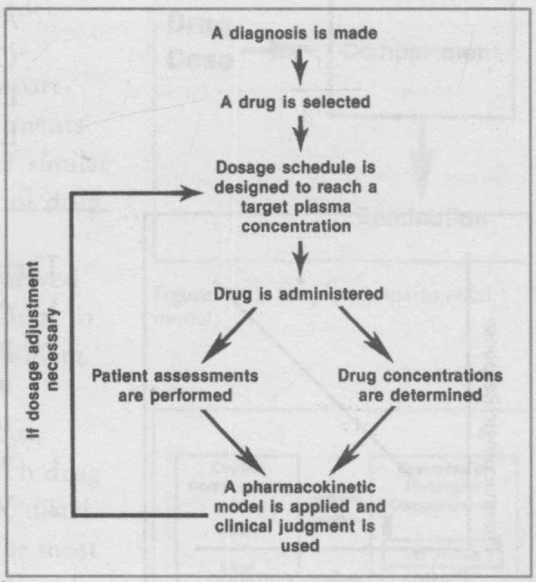

Figure 1.10. Process for reaching dosage decisions with therapeutic drug monitoring.

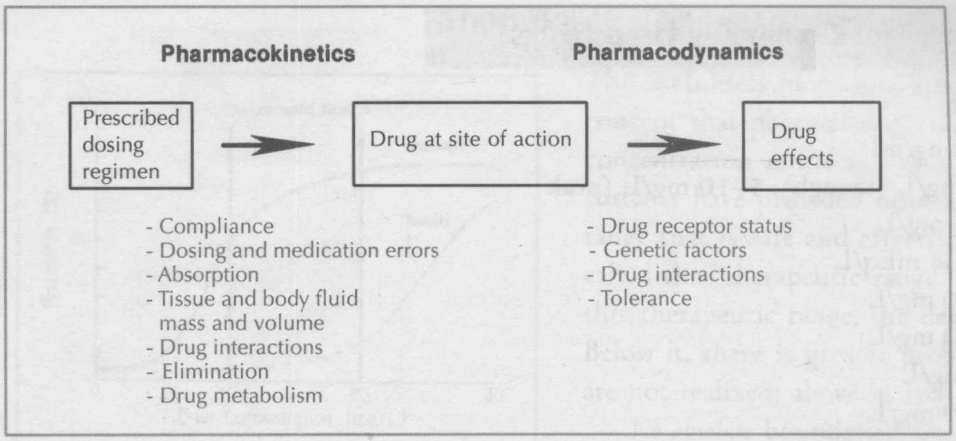

Figure 1.11. Relationship of pharmacokinetics and pharmacodynamics and factors that affect each.

Recall the definition of pharmacodynamics as the relationship between drug concentration at the site of action and pharmacologic response. As demonstrated in Figure 1.10, pharmacodynamics and pharmacokinetics are closely interrelated (**Figure 1.11**).

Some drugs lend themselves to clinical pharmacokinetic monitoring because their concentrations in plasma correlate well with pharmacologic response; for other drugs, this approach is not valuable. It is advantageous to know the plasma theophylline concentration of a patient with asthma. Because plasma theophylline concentration is related to pharmacologic effect, knowing that the plasma concentration is well below the therapeutic range could justify giving more theophylline. However, it is of little value to determine the plasma concentration of an antihypertensive agent, since it may not correlate well with pharmacologic effects and the end-point of treatment, blood pressure, is much easier to measure than the plasma concentration. Plasma levels are often monitored for the drugs listed in **Table 1.2**.

Table 1.2. Drugs for Which Plasma Levels Are Often Monitored

Aminoglycosides	Lithium	Quinidine
Antidepressants	Methotrexate	Theophylline
Cyclosporine	Phenobarbital	Valproic acid
Digoxin	Phenytoin	Vancomycin
Lidocaine	Procainamide	

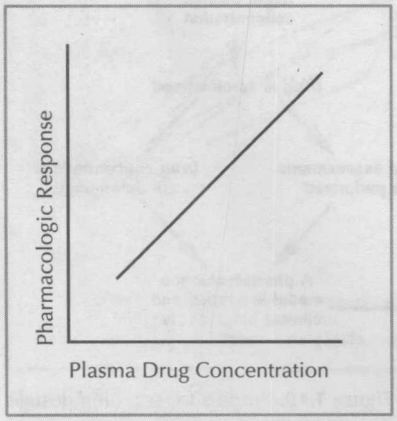

Figure 1.12. When pharmacologic effects relate to plasma drug concentrations, the latter can be used to predict the former.

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 1.12**).
2. Wide intersubject variation in plasma drug concentrations results from a given dose.
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.

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.

Pharmacokinetic Models

The handling of a drug by the body can be very complex, since 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**).

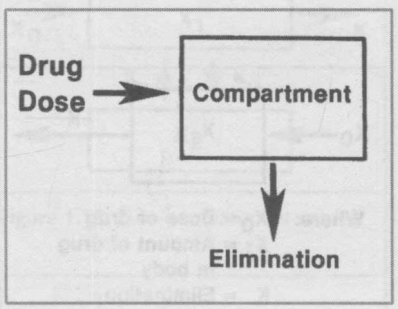

Figure 1.13. Simple compartmental model.

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**).

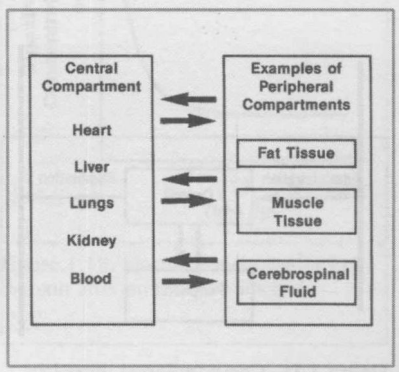

Figure 1.14. Typical organ groups for central and peripheral compartments.

Another simplification of body processes concerns the expression of

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

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

Clinical Correlate

Drugs that do not extensively distribute into extravascular tissues, such as aminoglycosides, are generally well described by one-compartment models. Extent of distribution is partly determined by the chemistry of the agents. Aminoglycosides are polar molecules, so their distribution is limited primarily to extracellular water. Drugs extensively distributed in tissue (such as lipophilic drugs like the benzodiazepines) or those 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. Discussion of this model will help define important pharmacokinetic parameters and develop the concept of compartmental models. In structuring the model, a visual representation is helpful. The compartment is represented by an enclosed square or rectangle, and rates of drug transfer are represented by straight arrows (**Figure 1.15**). The arrow pointing into the box simply indicates that drug is put into that compartment. And the arrow pointing out of the box indicates that drug is leaving the compartment.

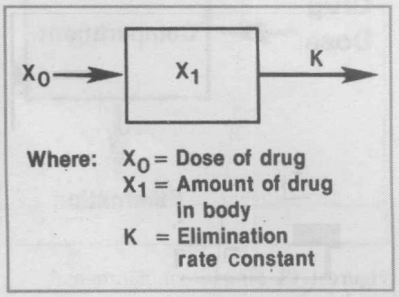

Figure 1.15. One-compartment model.

This model is the simplest because there is only one compartment. All body tissues and fluids are considered a part of this compartment. Furthermore, it is assumed that after a dose of drug is administered, it distributes instantaneously to all body areas. Common abbreviations are shown in Figure 1.15.

Some drugs do not distribute instantaneously to all parts of the body, however, even after intravenous bolus administration. Recall that "bolus" means a drug dose given over a very short time. 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*. The rapidly distributing tissues are called the "central" compartment, and the slowly distributing tissues are called the "peripheral" compartment. Drug moves back and forth between these tissues to maintain equilibrium (**Figure 1.16**).

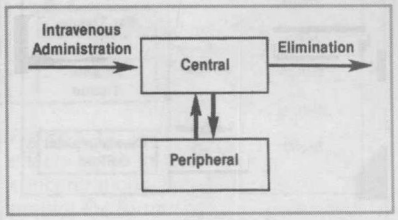

Figure 1.16. Compartmental model representing transfer of drug to and from central and peripheral compartments.

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.

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, and
K_{21} = elimination rate constant of drug from peripheral compartment to central compartment.

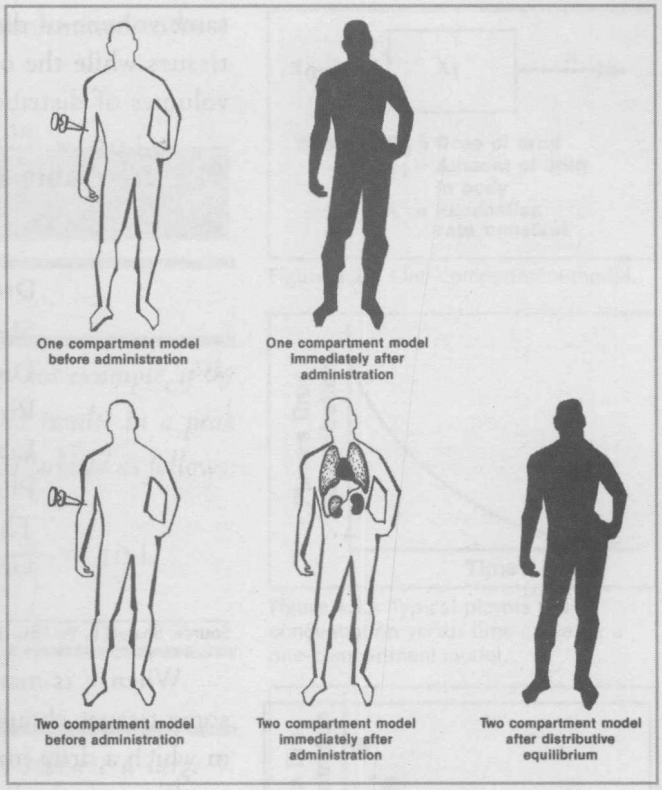

Figure 1.17. Drug distribution in one- and two-compartment models.

Clinical Correlate

*Digoxin, particularly when given intravenously, is an example of a drug that is well described by two-compartment pharmacokinetics. After an intravenous dose is administered, plasma concentrations rise and then rapidly decline as drug distributes out of plasma and into muscle tissue. After equilibration between drug in tissue and plasma, plasma concentrations decline less rapidly (**Figure 1.19**). The plasma would be the central compartment and muscle tissue would be the peripheral compartment.*

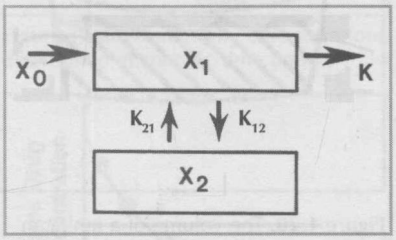

Figure 1.18. Two-compartment model.

Until now, we have spoken of the "amount" of drug (X) in a compartment. If we consider the volume of the compartment, we can refer to drug concentration. The drug concentration in the compartment is defined as the amount of drug in a given volume:

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

An important indicator of the extent of drug distribution into body fluids and tissues is called the *volume of distribution* (V); 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:

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

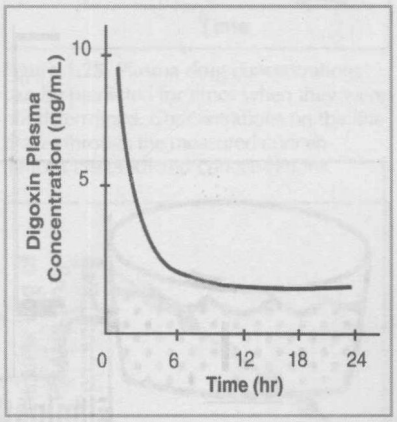

Figure 1.19. Plasma concentrations of digoxin after an intravenous dose.

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, as little as into the plasma only.

Volume of distribution indicates the extent of distribution but not the tissues or fluids into which the drug is distributing. Two drugs can have the