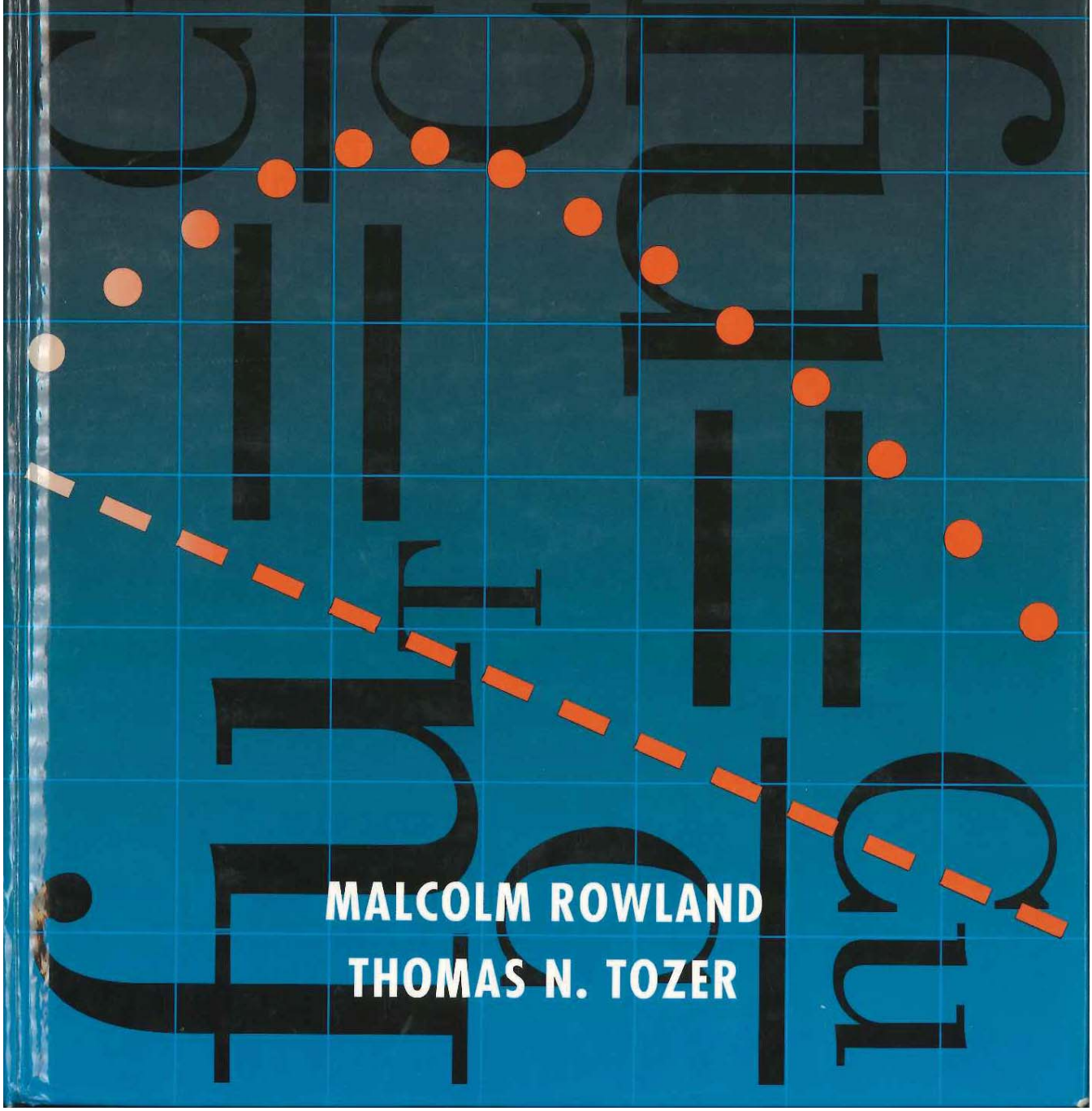
Clinical Pharmacokinetics

Concepts and Applications

third edition



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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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1

WHY CLINICAL PHARMACOKINETICS?

Those patients who suffer from chronic ailments such as diabetes and epilepsy may have to take drugs every day for the rest of their lives. At the other extreme are those who take a single dose of a drug to relieve an occasional headache. The duration of drug therapy is usually between these extremes. The manner in which a drug is taken is called a *dosage regimen*. Both the duration of drug therapy and the dosage regimen depend on the therapeutic objectives, which may be either the cure, the mitigation, or the prevention of disease. Because all drugs exhibit undesirable effects, such as drowsiness, dryness of the mouth, gastrointestinal irritation, nausea, and hypotension, successful drug therapy is achieved by optimally balancing the desirable and the undesirable effects. To achieve optimal therapy, the appropriate "drug of choice" must be selected. This decision implies an accurate diagnosis of the disease, a knowledge of the clinical state of the patient, and a sound understanding of the pharmacotherapeutic management of the disease. Then the questions How much? How often? and How long? must be answered. The question How much? recognizes that the magnitudes of the therapeutic and toxic responses are functions of the dose given. The question How often? recognizes the importance of time, in that the magnitude of the effect eventually declines with time following a single dose of drug. The question How long? recognizes that a cost (in terms of side effects, toxicity, economics) is incurred with continuous drug administration. In practice, these questions cannot be divorced from one another. For example, the convenience of giving a larger dose less frequently may be more than offset by an increased incidence of toxicity.

In the past, the answers to many important therapeutic questions were obtained by trial and error. The dose, interval between doses, and route of administration were selected, and the patient's progress followed. The desired effect and any signs of toxicity were carefully noted, and if necessary, the dosage regimen was adjusted empirically until an acceptable balance between the desired effect and toxicity was achieved. Eventually, after considerable experimentation on a large number of patients, reasonable dosage regimens were established (Table 1–1), but not without some regimens producing excessive toxicity or proving ineffective. Moreover, the above empirical approach left many questions unanswered. Why, for example, does tetracycline have to be given every 6 to 8 hours to be effective, while digoxin can be given once daily? Why must oxytocin be infused intravenously? Why is morphine more effective given intramuscularly than when given orally? Furthermore, this empirical approach contributes little, if anything, toward establishing a safe, effective dosage regimen of another drug. That is, our basic understanding of drugs has not been increased.

To overcome some of the limitations of the empirical approach and to answer some of the questions raised, it is necessary to delve further into the events that follow drug administration. *In vitro* and *in vivo* studies show that the magnitude of the response is a function of the concentration of drug in the fluid bathing the site(s) of action. From these observations the suggestion might be made that the therapeutic objective can be achieved by maintaining an adequate concentration of drug at the site(s) of action for the duration

of therapy. However, rarely is a drug placed at its site of action. Indeed, most drugs are given orally, and yet they act in the brain, on the heart, at the neuromuscular junction, or elsewhere. A drug must therefore move from the site of administration to the site of action. Simultaneously, however, the drug distributes to all other tissues including those organs, notably the liver and the kidneys, that eliminate it from the body.

Figure 1–1 illustrates the events occurring after a dose of drug is administered orally. The rate at which drug initially enters the body exceeds its rate of elimination; the concentrations of drug in blood and other tissues rise, often sufficiently high to elicit the desired therapeutic effects and sometimes even to produce toxicity. Eventually, the rate of drug elimination exceeds the rate of its absorption, and thereafter, the concentration of drug in both blood and tissues declines and the effect(s) subsides. To administer drugs optimally, therefore, knowledge is needed not only of the mechanisms of drug absorption, distribution, and elimination but also of the kinetics of these processes, that is, *pharmacokinetics*. The application of pharmacokinetic principles to the therapeutic management of patients is *clinical pharmacokinetics*.

Table 1–1. Empirically Derived Usual Adult Dosage Regimens of Some Representative Drugs *Before* the Introduction of Clinical Pharmacokinetics[a]

DRUG	INDICATED USE	ROUTE	DOSAGE REGIMEN
Tetracycline	Treatment of Infections	Oral	250 mg every 6–8 hr
Digoxin	Amelioration of congestive cardiac failure	Oral	1.5–2 mg initially over 24 hr, thereafter 0.25–0.5 mg once a day
Oxytocin	Induction and maintenance of labor	Intravenous	0.2–4 milliunits/min by infusion
Morphine sulfate	Relief of severe pain	Intramuscular	10 mg when needed
		Oral	Not recommended because of reduced effectiveness

[a]Taken from American Medical Association: Drug Evaluations. 2nd Ed., Publishers Science Group, Acton, MA, 1973.

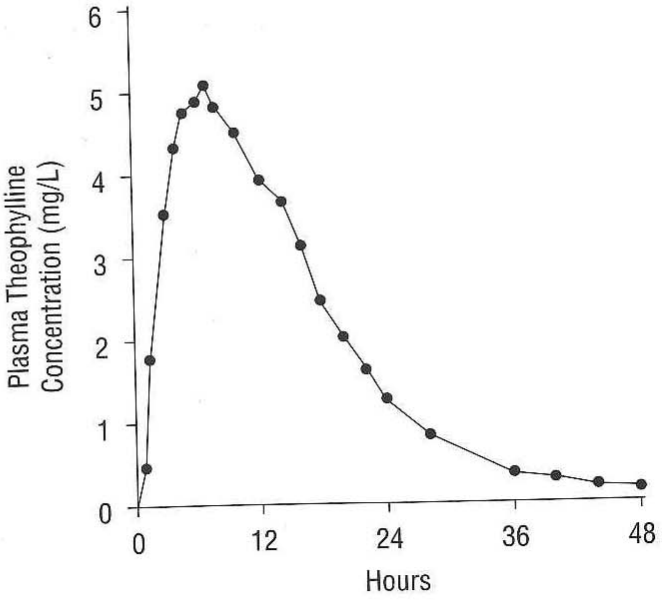

Fig. 1–1. Plasma concentration of theophylline in a subject following an oral dose of a 600-mg controlled-release formulation. Before the peak is reached, the rate of absorption exceeds that of elimination. At the peak, the two rates are equal; thereafter, the rate of elimination exceeds that of absorption. (Redrawn from Sauter, R., Steinijans, V.W., Diletti, E., Böhm, A., and Schulz, H.U.: Presentation of results in bioequivalence studies. Int. J. Clin. Pharmacol. Ther. Toxicol., *30*:S7–30, 1992.)

The events following drug administration can be divided into two phases, a *pharmacokinetic phase*, in which the adjustable elements of dose, dosage form, frequency, and route of administration are related to drug level–time relationships in the body, and a *pharmacodynamic phase*, in which the concentration of drug at the site(s) of action is related to the magnitude of the effect(s) produced (Fig. 1–2). Once both of these phases have been defined, a dosage regimen can be designed to achieve the therapeutic objective. Despite the greater amount of information required with this approach, it has several advantages over the empirical approach. First, and most obvious, distinction can be made between pharmacokinetic and pharmacodynamic causes of an unusual drug response. Second, the basic concepts of pharmacokinetics are common to all drugs; information gained about the pharmacokinetics of one drug can help in anticipating the pharmacokinetics of another. Third, understanding the pharmacokinetics of a drug often explains the manner of its use; occasionally such an understanding has saved a drug that otherwise may have been discarded or has suggested a more appropriate dosage regimen. Lastly, knowing the pharmacokinetics of a drug aids the clinician in anticipating the optimal dosage regimen for an individual patient and in predicting what may happen when a dosage regimen is changed.

A basic tenet of clinical pharmacokinetics is that the magnitudes of both the desired response and toxicity are functions of the drug concentration at the site(s) of action. Accordingly, therapeutic failure results when either the concentration is too low, giving ineffective therapy, or is too high, producing unacceptable toxicity. Between these limits of concentration lies a region associated with therapeutic success; this region may be regarded as a "therapeutic window." Rarely can the concentration of the drug at the site of action be measured directly; instead the concentration is measured at an alternative and more accessible site, *the plasma*.

Based on the foregoing considerations, an optimal dosage regimen might be defined as one that maintains the plasma concentration of a drug within the therapeutic window. For many drugs, this therapeutic objective is met by giving an initial dose to achieve a plasma concentration within the therapeutic window and then maintaining this concentration by replacing the amount of drug lost with time. One popular and convenient means of maintenance is to give a dose at discrete time intervals. Figure 1–3 illustrates the basic features associated with this approach by depicting the concentrations that follow the administration of two regimens, A and B. The dosing interval is the same but the dose given in regimen B is twice that given in regimen A. Because some drug always remains in the body from preceding doses, accumulation occurs until, within a dosing interval, the amount lost equals the dose given; a characteristic saw-toothed plateau is then achieved. With regimen A,

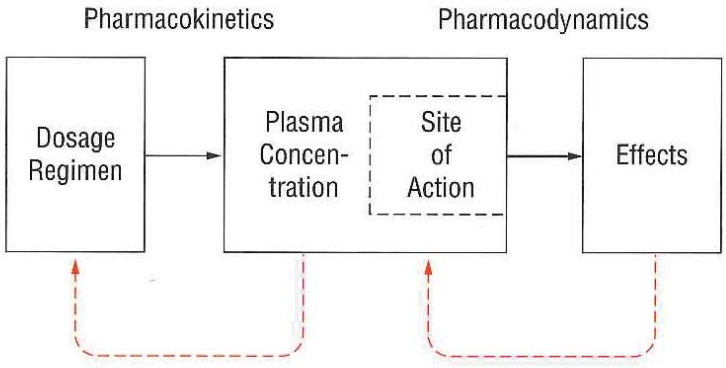

Fig. 1–2. An approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then, either the plasma drug concentration-time data or the effects produced are used via pharmacokinetics as a feedback (dashed lines) to modify the dosage regimen to achieve optimal therapy.

several doses had to be given before drug accumulation was sufficient to produce a therapeutic concentration. Had therapy been stopped before then, the drug might have been thought ineffective and perhaps abandoned prematurely. Alternatively, larger doses might have been tried, e.g., regimen B. Although a therapeutic response would have been achieved fairly promptly, toxicity would have ensued with continued administration when the concentration exceeded the upper limit of the therapeutic window.

The synthetic antimalarial agent, quinacrine, developed during World War II to substitute for the relatively scarce quinine, is an example. Quinacrine was either ineffective acutely against malaria or eventually produced unacceptable toxicity when a dosing rate sufficiently high to be effective acutely was maintained. Only after its pharmacokinetics had been defined was this drug used successfully. Quinacrine is eliminated slowly and accumulates extensively with repeated daily administration. The answer was to give large doses over the first few days to rapidly achieve therapeutic success, followed by small daily doses to maintain the plasma concentration within the therapeutic window.

The plateau situation in Fig. 1–3 shows that both the width of the therapeutic window and the speed of drug elimination govern the size of the maintenance dose and the frequency of administration. When the window is narrow and the drug is eliminated rapidly, small doses must be given often to achieve therapeutic success. Both cyclosporine and digoxin have a narrow therapeutic window, but because cyclosporine is eliminated much more rapidly than digoxin, it has to be given more frequently. Oxytocin is an extreme example; it also has a narrow therapeutic window but is eliminated within minutes. The only means of adequately ensuring a therapeutic concentration of oxytocin therefore is to infuse it at a precise and constant rate directly into the blood. This degree of control is not possible with other modes of administration. Besides, had oxytocin been given orally, this polypeptide hormone would have been destroyed by the proteolytic enzymes in the gastrointestinal fluids. Morphine, given orally, is also destroyed substantially before entering the general circulation, but for a reason different from that of oxytocin. Morphine is extensively metabolized on passage through the liver, an organ lying between the gastrointestinal tract and the general circulation.

Awareness of the benefits of understanding pharmacokinetics and concentration–response relationships has led in recent years to the extensive application of such information by the pharmaceutical industry to drug design, selection, and development. For example, a potent compound found to be poorly and unreliably absorbed and intended for oral administration may be shelved in favor of a somewhat less potent but more extensively and reliably absorbed compound. Also, many of the basic processes controlling both pharmacokinetics and response are similar across mammalian species such that data can be extrapolated from animals to predict quantitatively the likely behavior in humans. This quan-

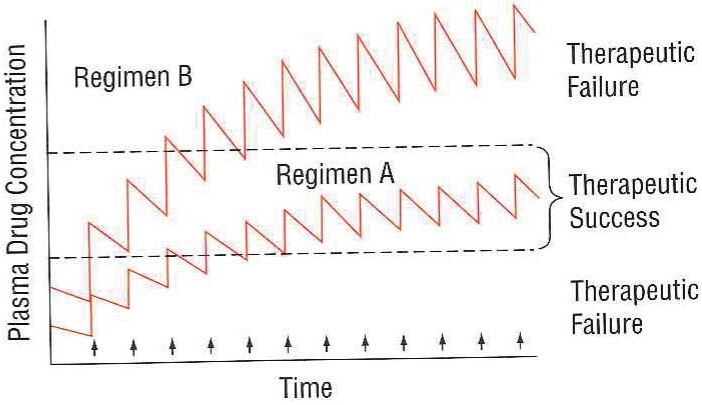

Fig. 1–3. When a drug is given in a fixed dose and at fixed time intervals (denoted by the arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved although not initially. With regimen B, the therapeutic objective is achieved more quickly, but the plasma drug concentration is ultimately too high.

titative framework improves the chances of selecting not only the most promising compounds but also the correct range of safe doses to first test in humans. Incorporation of a pharmacokinetic element with these early Phase I studies, usually in healthy subjects, together with assessment of any side effects produced, helps to define candidate dosage forms and regimens for evaluation in Phase II studies conducted in a small number of patients. These Phase II studies are aimed at defining the most likely safe and efficacious dosage regimens for use in the subsequent larger Phase III clinical trials, often involving many thousands of patients. Ultimately, some compounds prove to be of sufficient benefit and safety to be approved for a particular clinical indication by drug regulatory authorities. Even then the drug undergoes virtually continuous postmarketing surveillance to further refine its pharmacotherapeutic profile. This sequence of events in drug development and evaluation is depicted schematically in Fig. 1–4.

Figure 1–5 illustrates an important problem identified during drug development and therapy, variability. There is a wide range of daily dose requirements of the oral antico-

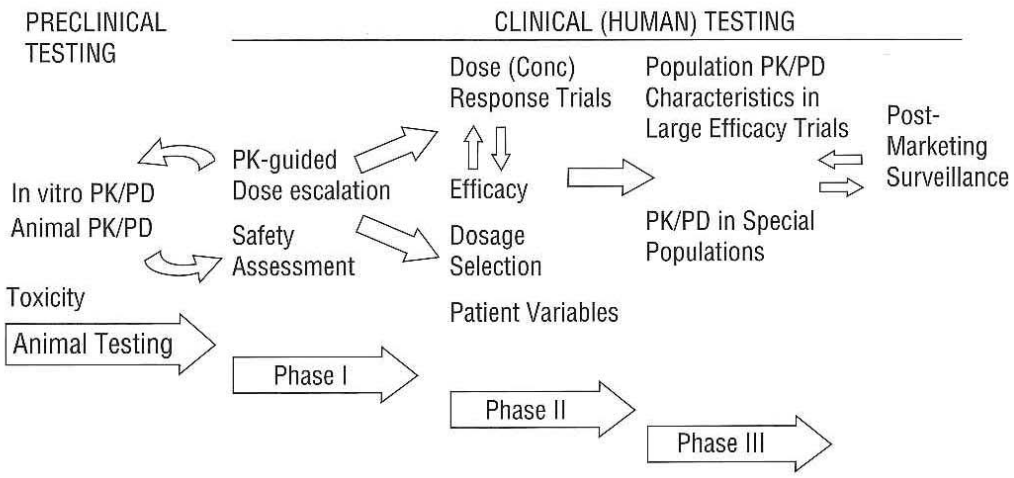

Fig. 1–4. The development and subsequent marketing of a drug. The prehuman data helps to identify promising compounds and to suggest useful doses for testing in humans. Phases I, II, and III of human assessment generally correspond to the first administration to humans, early evaluation in selected patients, and the larger trials, respectively. Pharmacokinetic (PK) and pharmacodynamic (PD) data gathered during all phases of drug development help to efficiently define safe and effective dosage regimens for optimal individual use. Postmarketing surveillance helps to refine the PK/PD information.

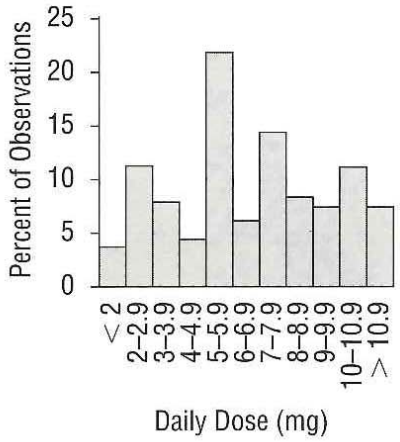

Fig. 1–5. The daily dose of warfarin required to produce similar prothrombin times in 200 adult patients varies widely. (1 mg/L = 3.3 μM). (Redrawn from Koch-Weser, J.: The serum level approach to individualization of drug dosage. Eur. J. Clin. Pharmacol. 9:1–8, 1975.)

agulant warfarin needed to produce a similar prothrombin time (an index of blood coagulability). Sources of variability in drug response include the patient's age, weight, degree of obesity, type and degree of severity of the disease, the patient's genetic makeup, other drugs concurrently administered, and environmental factors. The result is that a standard dosage regimen of a drug may prove therapeutic in some patients, ineffective in others, and toxic in still others. The need to adjust the dosage regimen of a drug for an individual patient is evident; this need is clearly greatest for drugs that have a narrow therapeutic window, that exhibit a steep concentration–response curve, and that are critical to drug therapy. Examples are digoxin, used to treat some cardiac disorders; phenytoin, used to prevent epileptic convulsions; theophylline, used to diminish chronic airway resistance in asthmatics; and cyclosporine, an immunosuppressant used in organ transplantation. With these drugs, and with many others, variability in pharmacokinetics is a major source of total variability in drug response.

It is becoming increasingly common to gain as much information on variability as possible during drug development by gathering, albeit limited, individual plasma concentration and response data in a large population of patients during Phase III clinical trials. Attempts are then made to account for this variability in terms of such patient characteristics as age and weight. These *population* pharmacokinetic/pharmacodynamic studies form a basis for dosage regimen recommendations in clinical practice.

Coadministration of several drugs to a patient, prevalent in clinical practice, can pose problems. Although the response produced by each drug alone may be predictable, that produced by the combination may be less certain and occasionally unpredictable. Ketoconazole, for example, devoid of immunosuppressant activity, potentiates the effect of cyclosporine. Possible causes of this kind of effect are many. In this instance, as in many others, the interaction involves a change in pharmacokinetics. Some drugs stimulate drug-

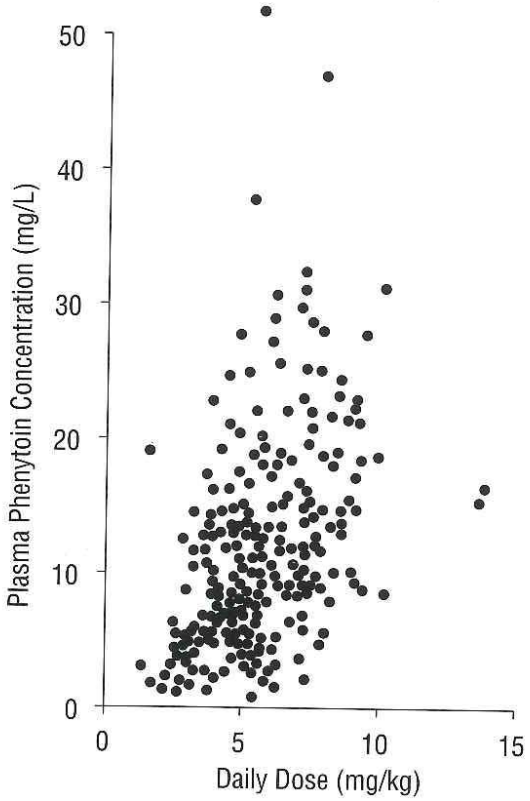

Fig. 1–6. Although the average plateau plasma concentration of phenytoin tends to increase with the dosing rate, there is considerable variation in the individual values. (One mg/L = 3.97 μM.) (Redrawn from Lund, L.: Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. *In* Biological Effects of Drugs in Relation to Their Plasma Concentration. Edited by D.S. Davies and B.N.C. Prichard, Macmillan, London and Basingstoke, 1973, pp. 227–238.)

metabolizing enzymes and hasten drug loss; others inhibit these enzymes and slow elimination. Still others interfere with drug absorption. Such interactions are graded; the change in the pharmacokinetics of a drug varies continuously with the plasma concentration of the interacting drug and hence with time. Indeed, given in sufficiently high doses, almost any drug can interact with another. It is always a question of degree. Understanding the quantitative elements of interactions ensures the more rational use of drugs that may need to be coadministered.

Figure 1–6 illustrates a situation in which monitoring of the drug concentration may be beneficial. Over the narrow range of the daily dose of the antiepileptic drug phenytoin, the plateau plasma drug concentration varies markedly within the patient population. Yet the therapeutic window of phenytoin is narrow, 7 to 20 mg/L; beyond 20 mg/L, the frequency and the degree of toxicity increase progressively with concentration. Here again, pharmacokinetics is the major source of variability. A pragmatic approach to this problem would be to adjust the dosage until the desired objective is achieved. Control on a dosage basis alone, however, has proved difficult. Control is achieved more readily and accurately when plasma drug concentration data and the pharmacokinetics of the drug are known.

Drug selection and therapy have traditionally been based solely on observations of the effects produced. In this chapter, the application of pharmacokinetic principles to decision making in drug therapy has been illustrated. Both approaches are needed to achieve optimal drug therapy. This book emphasizes the pharmacokinetic approach. It begins with a consideration of kinetic concepts basic to pharmacokinetics and ends with a section containing selected topics.

2

BASIC CONSIDERATIONS

OBJECTIVES

The reader will be able to:

1. Define the following terms:
   Pharmacokinetics, intravascular and extravascular administration, absorption, disposition, distribution, metabolism, excretion, first-pass effect, enterohepatic cycling, compartment
2. Discuss the limitations to interpretation of pharmacokinetic data imposed by assays that fail to distinguish between compounds administered (e.g., R- and S-isomers) or between drug and metabolite.
3. Show the general contribution of mass balance concepts to drug absorption and drug and metabolite disposition.

Pharmacokinetics has many useful applications that stem from basic concepts. These concepts are developed in this section of the book. This chapter specifically defines terms and describes a basic model for drug absorption and disposition.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Measurement of a drug in the body is limited usually to blood or plasma. Nonetheless, the information obtained has proved very useful. Such usefulness can be explained by anatomic and physiologic features that affect a drug following its administration.

Blood or plasma, in addition to being a practical and convenient site of measurement, is the most logical one for determining drug in the body. Blood receives drug from the site of administration as well as carries it to all the organs, including those in which the drug acts and those in which it is eliminated. This movement of drug is depicted schematically in Fig. 2–1. This scheme forms a basis for *physiologic modeling in pharmacokinetics*. Such modeling has applications not only in clinical pharmacokinetics but in drug development, veterinary medicine, and in assessing risk associated with exposures to environmental and occupational substances.

Sites of Administration

There are several sites at which drugs are commonly administered. These sites may be classified as either intravascular or extravascular. *Intravascular* administration refers to the placement of a drug directly into the blood, either intravenously or intra-arterially.

Extravascular modes of administration include the oral, sublingual, buccal, intramuscular, subcutaneous, dermal, pulmonary, and rectal routes. To enter the blood, drug ad-

ministered extravascularly must be absorbed: No absorption step is required when a drug is administered intravascularly.

Drug may also be administered regionally, e.g., into the pleural or peritoneal cavities or into the cerebrospinal fluid. Regional administration includes intra-arterial injection into the vessel leading to a tissue to be treated, e.g., one containing a cancerous tumor. It is a potential means of gaining a selective therapeutic advantage. This advantage, in comparison with other routes of administration, comes about by increasing drug exposure locally, where it is needed, and decreasing or producing little or no change in exposure throughout the rest of the body, where it is not wanted.

Disposition

Once absorbed, a drug is distributed to the various organs of the body. Distribution is influenced by how well each organ is perfused with blood, organ size, binding of drug within blood and in tissues, and permeability of tissue membranes.

The two principal organs of elimination, the liver and the kidneys, are shown separately in Fig. 2–1. The kidneys are the primary site for excretion of the chemically unaltered, or unchanged, drug. The liver is the usual organ for drug metabolism; however, the kidneys and other organs can also play an important metabolic role for certain drugs. The metabolites so formed are either further metabolized or excreted unchanged. The liver may also secrete unchanged drug into the bile. The lungs are, or may be, an important route for

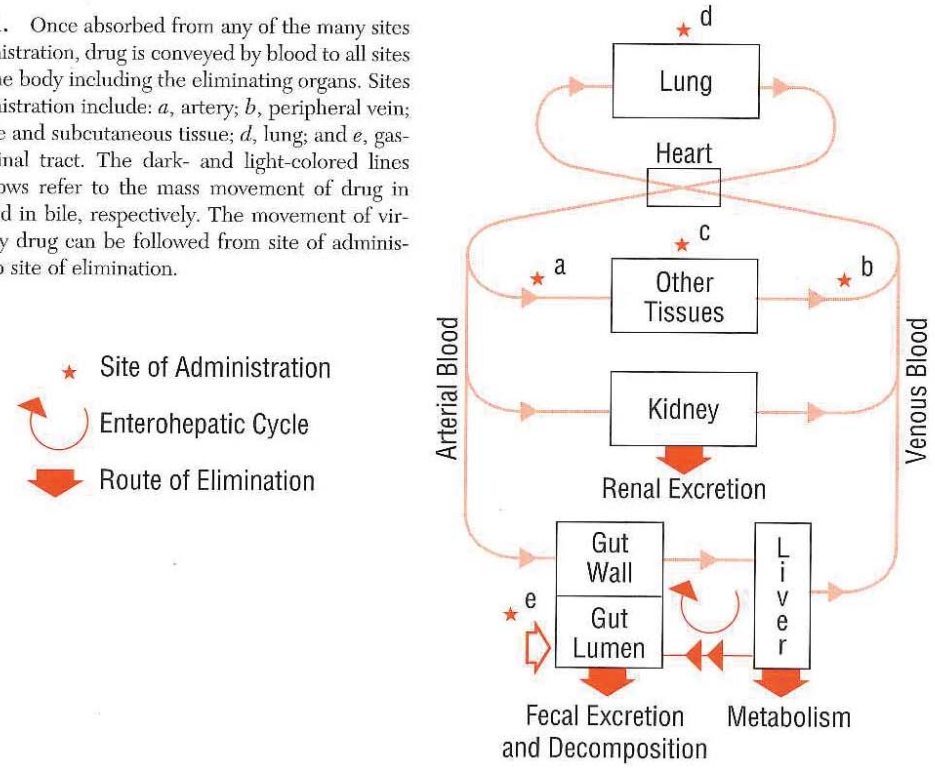

Fig. 2–1. Once absorbed from any of the many sites of administration, drug is conveyed by blood to all sites within the body including the eliminating organs. Sites of administration include: *a*, artery; *b*, peripheral vein; *c*, muscle and subcutaneous tissue; *d*, lung; and *e*, gastrointestinal tract. The dark- and light-colored lines with arrows refer to the mass movement of drug in blood and in bile, respectively. The movement of virtually any drug can be followed from site of administration to site of elimination.

eliminating volatile substances, for example, gaseous anesthetics. Another potential route of elimination is via a mother's milk. Although an insignificant route of elimination in the mother, drug in the milk may be consumed in sufficient quantity to affect the suckling infant.

CHEMICAL PURITY AND ANALYTIC SPECIFICITY

A general statement needs to be made about the chemical purity of prescribed medicines and the specificity of chemical assays.

Over the years, a major thrust of the pharmaceutical industry has been to produce therapeutic agents that are not only as safe and effective as possible but also are well characterized to ensure reproducible qualities. The majority of administered drugs today are therefore essentially pure materials, and coupled with specific analytic techniques for their determination in biologic fluids, definitive information about their pharmacokinetics can be gained. However, a large number of drug substances are not single chemical entities but rather mixtures. This particularly applies to stereoisomers and proteins. The most common stereoisomers found together in medicines are optical isomers, or compounds for which their structures are mirror images; the drug substance is usually a racemate, a 50:50 mixture of the R- and S-isomers. Some drug substances contain geometric isomers, and still others, especially proteins of high molecular weight derived from natural products or through fermentation, may be a mixture of structurally related, but chemically distinct, compounds. Each chemical entity within the drug substance can have a different pharmacologic, toxicologic, and pharmacokinetic profile. Sometimes these differences are small and inconsequential, other times the differences can be therapeutically important. For example, dextroamphetamine (S-isomer) is a potent central nervous stimulant, whereas the R-enantiomer is almost devoid of such activity. Despite such differences, many commonly employed chemical assays do not distinguish between stereoisomers. Obviously, under these circumstances, attempting to quantify the various processes and to relate plasma concentration to response has many problems with no simple solutions. Notwithstanding these problems, specific information about each chemical entity should be sought whenever possible. Increasingly, stereoisomers are being produced as single chemical entities, such as S-naproxyn, which avoid these problems. In contrast, many new protein and polypeptide drugs are being introduced that may, in many instances, lack purity. Furthermore, these substances are often measured by assays that lack specificity.

An added problem exists following drug administration, namely, the formation of metabolites. To be of value, an analytic procedure must distinguish between drug and metabolite(s). Today, most assays have this desired specificity, except for some of those used to measure many proteins and polypeptides.

A potential problem exists when using radiolabeled drugs. Incorporation of one or more radionuclides, usually ^{14}C and ^{3}H, into the molecular structure allows for simple and ready detection within a complex biologic milieu, but not necessarily of the administered drug. Complete recovery of all of a radiolabeled dose in urine, following oral drug administration, is useful in identifying the ultimate location of drug-related material but may provide little to no information about the drug. For example, almost all of an orally administered drug may have been destroyed in the gastrointestinal tract, from which the degradation products enter the body and are eventually excreted in urine. A basic lesson is learned here. Distinguish carefully between drug and metabolite(s). Many metabolites are of interest, especially if they are active or toxic. Each chemical entity must be considered separately for kinetic data to be meaningful.

DEFINITIONS

Although the processes of absorption and elimination are descriptive and their meanings are apparent at first glance, it is only within the context of experimental observation that they can be quantified (Chaps. 3, 4, and 6). General definitions of the processes follow.

Absorption

Absorption is defined as the process by which unchanged drug proceeds from site of administration to site of measurement within the body. To illustrate why absorption is defined in this way, consider the events depicted in Fig. 2–2 as a drug, given orally, moves from the site of administration to the general circulation. There are several possible sites of loss. One site is the gastrointestinal lumen where decomposition may occur. Suppose, however, that a drug survives destruction in the lumen only to be completely metabolized by enzymes as it passes through the membranes of the gastrointestinal tract. One would ask, Is the drug absorbed? Even though the drug leaves the gastrointestinal tract, it would not be detected in the general circulation. Hence, the drug is not absorbed systemically. Taking this argument one step further, Is the drug absorbed if all of the orally administered drug were to pass through the membranes of the gastrointestinal tract into the portal vein only to be metabolized completely on passing through the liver? In an experiment performed *in vitro* in which the passage of a drug across the intestinal membranes is studied separately, the answer would be positive. If, however, as is common, blood or plasma in an arm vein is the site of measurement, then, because no drug would be detected, the answer would be negative. Indeed, loss at any site prior to the site of measurement contributes to a decrease in the systemic absorption. The gastrointestinal tissues and the liver, in particular, are often sites of elimination. The requirement for an orally administered drug to pass through these tissues, prior to reaching the site of measurement, makes the extent of

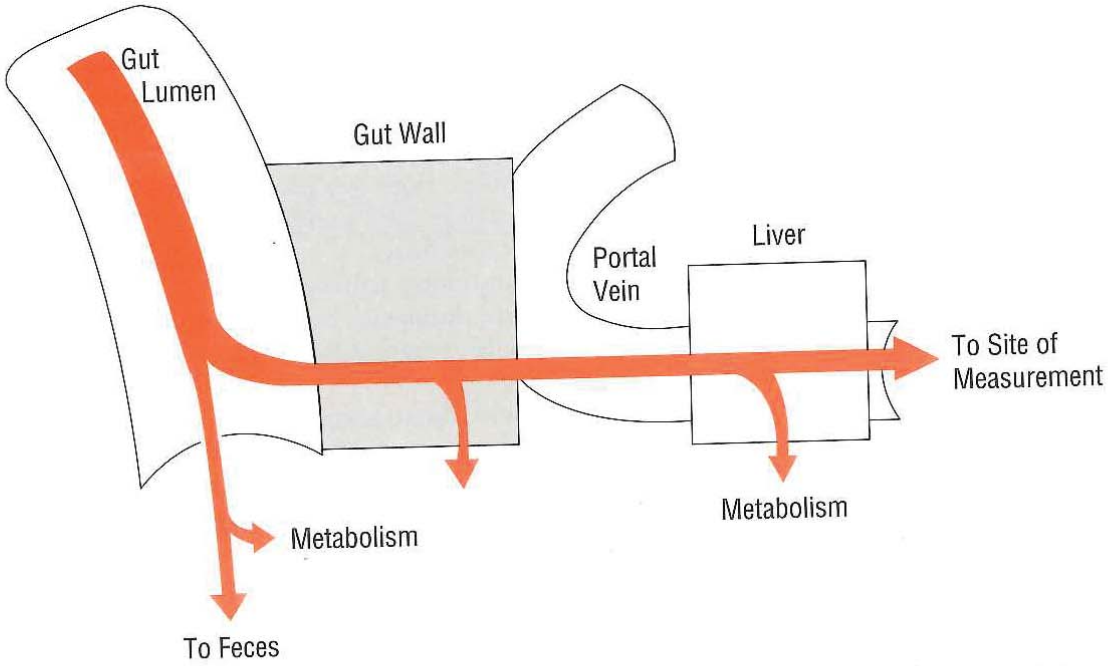

Fig. 2–2. A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement during gastrointestinal absorption. Incomplete dissolution or metabolism in the gut lumen or by enzymes in the gut wall is a cause of poor absorption. Removal of drug as it first passes through the liver further reduces absorption.

absorption dependent on elimination. The loss as drug passes, for the first time, through sites of elimination, such as the gastrointestinal membranes and the liver, during absorption is known as the *first-pass effect*.

Absorption is not restricted to oral administration. It occurs as well following intramuscular, subcutaneous, and other extravascular routes of administration. Monitoring intact drug in blood or plasma offers a useful means of assessing the entry of drug into the systemic circulation.

Disposition

As absorption and elimination of drugs are interrelated for physiologic and anatomic reasons, so too are distribution and elimination. Once absorbed, a drug is delivered simultaneously by arterial blood to all tissues, including organs of elimination. Distinguishing between elimination and distribution as a cause for a decline in concentration in blood or plasma is often difficult. *Disposition* is the term used to embrace both processes. *Disposition* may be defined as all the processes that occur subsequent to the absorption of a drug. By definition, the components of disposition are distribution and elimination.

Distribution. Distribution is the process of reversible transfer of a drug to and from the site of measurement, usually the blood or plasma. An example is distribution between blood and muscle. The pathway for return of drug need not be the same as that leaving the circulation. For example, drug may be excreted in the bile, stored in and released from the gallbladder, transit into the small intestine, and be reabsorbed into the circulation. By doing so, the drug completes a cycle, the *enterohepatic cycle* (see Fig. 2–1). If all the drug is reabsorbed in this manner, biliary secretion is not a route of elimination; the cycling is then a component of distribution. The situation is analogous to one in which water is pumped from one reservoir into another, only to drain back into the original reservoir. Biliary secretion is truly a route of elimination only to the extent that the drug fails to be reabsorbed. This failure may result from decomposition in the intestine, poor absorption characteristics, or other complications. Unchanged drug in bile that is neither reabsorbed nor decomposed in the intestinal tract is eventually excreted in the feces.

Elimination. Elimination is the irreversible loss of drug from the site of measurement. Elimination occurs by two processes, excretion and metabolism. *Excretion* is the irreversible loss of chemically unchanged drug. *Metabolism* is the conversion of one chemical species to another. Occasionally, metabolites are converted back to the drug. As with enterohepatic cycling, this *metabolic interconversion* is a route of elimination only to the extent that the metabolite is excreted or otherwise irreversibly lost from the body.

BASIC MODEL FOR DRUG ABSORPTION AND DISPOSITION

The complexities of human anatomy and physiology would appear to make it difficult, if not impossible, to model how the body handles a drug. Perhaps surprisingly then, it is a simple pharmacokinetic model, depicted in Fig. 2–3 which has proved useful in many applications and is emphasized throughout much of this book. More complex models are necessary to describe the pharmacokinetics of some drugs. Examples of such models are described in Chaps. 10, 19, and 22.

The boxes in Fig. 2–3 represent *compartments* that logically fall into two classes, transfer and chemical. The site of administration, the body, and excreta are clearly different places. Each place may be referred to as a location or transfer compartment. In contrast, metabolism involves a chemical conversion; the metabolite in the body and in excreta are therefore in compartments that differ chemically from the drug.

The model is based on amounts of drug and metabolite. However, the amounts of drug and metabolite can only be measured in urine directly. The total amount of drug metabolized includes metabolites in, as well as eliminated from, the body. The amount in the body is usually determined from measurement of the blood or plasma concentration. Estimates of drug in the absorption compartment are also usually made indirectly from either blood or urine data. Drug at the absorption site includes that which is never absorbed, for example, drug that is ultimately decomposed in the gastrointestinal tract or lost in the feces after oral administration.

The model is readily visualized from mass balance considerations. The dose is accounted for at any one time by the molar amount of substance in each of the compartments:

$$\text{Dose} = \begin{matrix}\text{Amount of}\\ \text{drug at}\\ \text{absorption site}\end{matrix} + \begin{matrix}\text{Amount}\\ \text{of drug}\\ \text{in body}\end{matrix} + \begin{matrix}\text{Amount}\\ \text{of drug}\\ \text{excreted}\end{matrix} + \begin{matrix}\text{Amount of}\\ \text{metabolite}\\ \text{in body}\end{matrix} + \begin{matrix}\text{Amount of}\\ \text{metabolite}\\ \text{eliminated}\end{matrix} \quad 1$$

The mass balance of drug and related material with time is shown in Fig. 2–4. Since the sum of the molar amounts of drug in transfer and chemical compartments is equal to the dose, the sum of the rates of change of the drug in these compartments must be equal to zero so that:

$$\begin{matrix}\text{Rate of change of}\\ \text{drug in body}\end{matrix} = \begin{matrix}\text{Rate of}\\ \text{absorption}\end{matrix} - \begin{matrix}\text{Rate of}\\ \text{elimination}\end{matrix} \quad 2$$

The relationships expressed in Eqs. 1 and 2 apply under all circumstances, regardless of the nature of the absorption and elimination processes. They are particularly useful in developing more complex models for quantifying drug absorption and disposition. *Pharmacokinetics* is the quantitation of the time course of a drug and its metabolites in the body

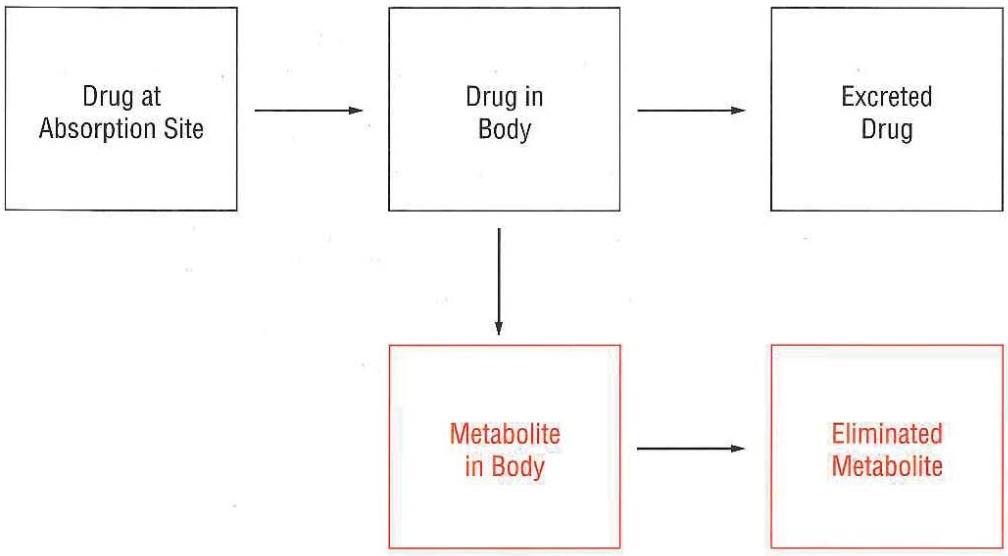

Fig. 2–3. A drug is simultaneously absorbed into the body and eliminated from it by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with boxes. The compartments represent different locations and different chemical species (color = metabolite). Metabolite elimination may occur by further metabolism (not shown) or excretion.

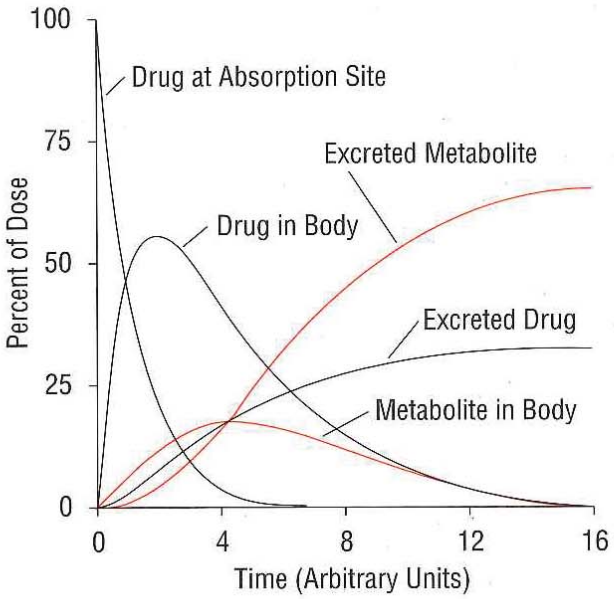

Fig. 2–4. Time course of drug and metabolite in each of the compartments shown in Fig. 2–3. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed.

and the development of appropriate models to describe observations and predict outcomes in other situations.

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. Define the terms listed in the first objective at the beginning of this chapter.
2. Briefly state why an analytical method that does not distinguish between R- and S-isomers can lead to problems in the interpretation of plasma data following administration of a racemic mixture.
3. Using Figs. 2–3 and 2–4, speculate on how an assay that measures the sum of drug and inactive metabolite might influence a correlation between plasma concentration and therapeutic response.
4. Following oral administration of a drug labeled with a radioactive atom, all of the radioactivity is recovered in urine. Can one conclude that the drug is completely absorbed?
5. Answer each of the following questions, which relate to Fig. 2–4 and Eqs. 1 and 2.
   a. Does a 100% recovery of unchanged drug in urine following oral administration indicate that drug is completely absorbed and not metabolized?
   b. When does drug in body reach a peak following administration of an oral dose?
   c. Can the amount of drug absorbed up to a given time be determined?
   d. When is rate of change of drug in body equal to rate of drug elimination?
   e. When does rate of change of drug in body approach rate of absorption?

3

INTRAVENOUS DOSE

OBJECTIVES

The reader will be able to:

1. Define the meaning of half-life, elimination rate constant, first-order process, volume of distribution, clearance, renal clearance, and fraction excreted unchanged.
2. Estimate the values of half-life, elimination rate constant, volume of distribution, and clearance from plasma or blood concentrations of a drug following an intravenous dose.
3. Estimate the values of half-life, elimination rate constant, and fraction excreted unchanged from urinary excretion data following an intravenous dose.
4. Estimate the value of the renal clearance of a drug from combined plasma and urine data.
5. Calculate the concentration of drug in the plasma and the amount of drug in the body with time following an intravenous dose, given values for the pharmacokinetic parameters.

Administering a drug intravascularly ensures that all of the dose enters the general circulation. By rapid injection, elevated concentrations of drug in the blood can be promptly achieved; by infusion at a controlled rate, a constant concentration can be maintained. With no other route of administration can blood concentration be as promptly and efficiently controlled. Of the two intravascular routes, the intravenous (i.v.) one is the most frequently employed. Intra-arterial administration, which has greater inherent manipulative dangers, is reserved for situations in which drug localization in a specific organ or tissue is desired.

The disposition characteristics of a drug are defined by analyzing the temporal changes of drug and metabolites in blood, plasma, and occasionally urine following i.v. administration.

How this information is obtained following a rapid injection of the drug forms the basis of this chapter. The remaining chapter in this section deals with events following an extravascular dose. The pharmacokinetic information so derived forms a basis for making rational decisions in therapeutics, the subject of subsequent sections.

DISPOSITION VIEWED FROM PLASMA

Several methods are employed for graphically displaying plasma concentration-time data. One common method, shown with theophylline in Fig. 3–1A, is to plot concentration against time on regular (Cartesian) graph paper. Depicted in this manner, the plasma concentration is observed to fall rapidly immediately after a 500-mg bolus, in this case from approximately 29 to 18 mg/L within 30 min. Thereafter, the rate of decline becomes much slower, taking almost another 4 hrs before the concentration falls 50% to 9 mg/L. Another method of display is a plot of the same data on semilogarithmic paper (Fig. 3–1B). The time scale is the same as before, but now the ordinate (concentration) scale is logarithmic.

Notice the sharp break at about 1 hr when the plasma concentration is about 16 mg/L. Before this time, the fall is rapid. Thereafter, the decline is slower and, on this semilogarithmic plot, appears to continue linearly. The early phase is commonly called the *distribution phase* and the latter, the *elimination phase*. This distinction is sometimes not clear-cut, an aspect more completely discussed in Chap. 19, Distribution Kinetics.

Distribution Phase

The distribution phase is so called because distribution primarily determines the early rapid decline in plasma concentration. For theophylline, distribution is extremely rapid and occurs significantly even by the time of the first measurement, 5 min. This must be so because the amount of theophylline in plasma at the end of this period is only 99 mg. This value is calculated by multiplying the highest plasma concentration, 33 mg/L, by the plasma volume, 3 L. The majority, 401 mg or 80% of the total (500 mg) dose, must have already left the plasma and been distributed into other tissues. Among these tissues are the liver and the kidneys, which also clear drug from the body. However, although some drug is eliminated during the early moments, the fraction of the administered dose lost during the distribution phase is small for theophylline and many other drugs.

Elimination Phase

During the distribution phase, changes in the concentration of drug in plasma reflect primarily movement of drug within, rather than loss from, the body. However, with time, distribution equilibrium of drug in tissue with that in plasma is established in more and more tissues, and eventually, changes in plasma concentration reflect a proportional change in the concentrations of drug in all other tissues and, hence, in the amount of drug in the body. During this proportionality phase, the body acts kinetically as a single container or compartment. As decline of the plasma concentration is now due only to elimination of drug from the body, this phase is often called the elimination phase.

Elimination Half-Life. The elimination phase is characterized by two parameters, the *elimination half-life* ($t_{1/2}$) and *the apparent volume of distribution* (V). The elimination half-

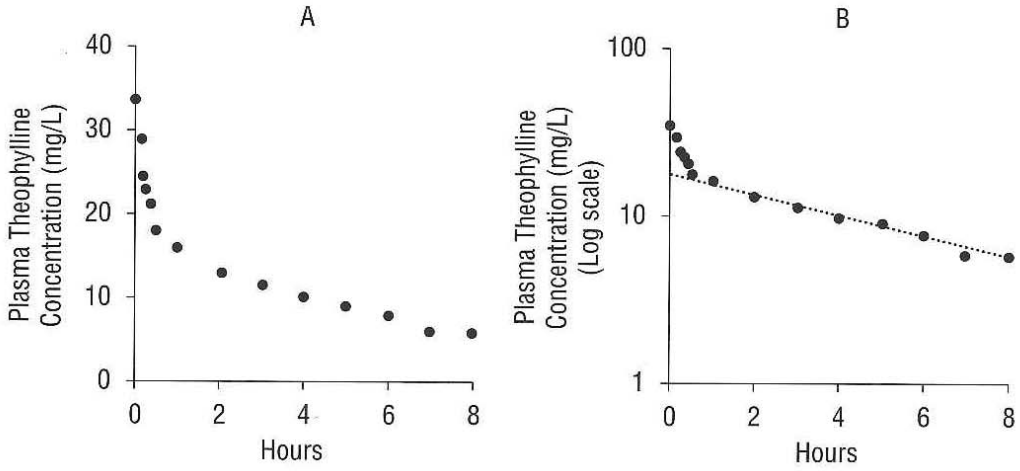

Fig. 3–1. *A*. Plasma concentration of theophylline with time after a 500-mg i.v. bolus injection into a 70-kg patient. *B*. The data in *A* are redisplayed as a semilogarithmic plot. Note the short distribution phase (1 mg/L = 5.5 μM). (Modified from the data of Mitenko, P.A., and Ogilvie, R.I.: Pharmacokinetics of intravenous theophylline. Clin. Pharmacol. Ther., *14*:509–513, 1973.)

life is the time taken for the plasma concentration, as well as the amount of the drug in the body, to fall by one-half. The half-life of theophylline, determined by the time taken to fall from 16 to 8 mg/L, is 5.0 hrs (Fig. 3–1B). This is the same time that it takes for the concentration to fall from 12 to 6 mg/L. In other words, for theophylline at the dose administered, the elimination half-life is independent of the amount of drug in the body. It follows, therefore, that less drug is eliminated in each succeeding half-life. Initially there are 500 mg in the body. After 1 half-life (5 hr), 250 mg remain. After 2 half-lives (10 hr), 125 mg remain, and after 3 half-lives (15 hr), 62.5 mg remain. In practice, all the drug (97%) may be regarded as having been eliminated by 5 half-lives (25 hr).

Volume of Distribution. The concentration in plasma achieved after distribution is complete is a function of dose and extent of distribution of drug into tissues. This extent of distribution can be determined by relating the concentration obtained with a known amount of drug in the body. This is analogous to the determination of the volume of a reservoir by dividing the amount of dye added to it by the resultant concentration, after thorough mixing. The volume measured is, in effect, a dilution space.

The apparent volume into which a drug distributes in the body at equilibrium is called the *(apparent) volume of distribution*. Plasma, rather than blood, is usually measured. Consequently, the volume of distribution, V, is the volume of plasma at the drug concentration, C, required to account for all the drug in the body, A.

$$V = A/C \qquad 1$$

$$\text{Volume of distribution} = \frac{\text{Amount in body}}{\text{Plasma drug concentration}}$$

Volume of distribution is useful in estimating plasma concentration when a known amount of drug is in the body or, conversely, in estimating the dose required to achieve a given plasma concentration.

Calculation of volume of distribution requires that distribution equilibrium be achieved between drug in tissues and that in plasma. The amount of drug in the body is known immediately after an i.v. bolus; it is the dose administered. However, distribution equilibrium has not yet been achieved. An estimate is needed of the plasma concentration that would have resulted had all drug spontaneously distributed into its final volume of distribution. To do this, use is made of the linear decline during the elimination phase seen in the semilogarithmic plot (Fig. 3–1B).

Decline in plasma concentration during the elimination phase can be characterized by the linear equation

$$\ln C = \ln C(0) - kt \qquad 2$$

where k is the slope of the line in Fig. 3–1B and $C(0)$ is the concentration one would determine from this equation at zero time. The negative sign arises because concentration declines with time. The term $C(0)$ is an extrapolated value and is an estimate of the concentration which when multiplied by the volume term, V, accounts for the dose administered, i.e.,

$$\text{Dose} = V \cdot C(0) \qquad 3$$

In the example with theophylline, $C(0)$ is 18 mg/L. Since 500 mg was administered to the patient, the volume of distribution of theophylline is 28 L. Knowing the volume of distribution, the amount in the body can now be estimated at any time during the elimi-

nation phase. For example, when the concentration of theophylline in plasma is 5 mg/L, there are 140 mg in the body.

Volume of distribution is a direct measure of the extent of distribution. It rarely, however, corresponds to a real volume, such as plasma volume (3 L), extracellular water (16 L), or total body water (42 L). Drug distribution may be to any one or a combination of the tissues and fluids of the body. Furthermore, binding to tissue components may be so great that the volume of distribution is many times the total body size.

To appreciate the effect of tissue binding, consider the distribution of 100 mg of a drug in a 1-L system composed of water and 10 g of activated charcoal, and where 99% of drug is adsorbed onto the charcoal. When the charcoal has settled, the concentration of drug in the aqueous phase would be 1 mg/L; thus, 100 L of the aqueous phase would be required to account for all the drug in the system, a volume much greater than that of the total system. Volumes of distribution for selected drugs are shown in Fig. 3–2. The causes for this wide range of values are discussed in Chap. 10, Distribution.

First-Order Elimination. Why the elimination for theophylline (and for most other drugs) is linear when displayed semilogarithmically can be appreciated as follows. Taking the antilogarithm of both sides of Eq. 2 yields

$$C = C(0) \cdot e^{-kt} \qquad 4$$

And multiplying both sides by V, gives

$$A = \text{Dose} \cdot e^{-kt} \qquad 5$$

since $C \cdot V$ and $C(0) \cdot V$ are the amount in the body and the dose administered, respectively. Equations 4 and 5 enable the concentration and amount in the body at any time to be estimated. When decline in the plasma concentration or amount in the body can be described by a single exponential term as given by Eqs. 4 and 5, it is said to be (mono)exponential. Since the elimination half-life ($t_{1/2}$) is the time taken for the concentration and the amount in the body to fall by one-half, e.g., from $C(0)$ to 1/2 $C(0)$, it follows from Eq. 4 that:

$$0.5 = e^{-k \cdot t_{1/2}} \qquad 6$$

or, on inversion

$$e^{k \cdot t_{1/2}} = 2$$

Taking the natural logarithm of both sides,

$$k \cdot t_{1/2} = \ln 2 = 0.693$$

one obtains the important relationship,

$$t_{1/2} = \frac{0.693}{k} \qquad 7$$

Although the constant k is in the exponent in Eq. 4 and can be calculated from Eq. 7, its meaning may be better understood by examining the rate at which the amount in the body, A, is changing with time. This is obtained by differentiating Eq. 5,

$$\frac{dA}{dt} = -k \cdot \text{Dose} \cdot e^{-kt} \qquad 8$$

but since $A = \text{Dose} \cdot e^{-kt}$, it follows that

$$\frac{dA}{dt} = -k \cdot A \qquad 9$$

The term on the left-hand side of Eq. 9 is the rate of change of the amount in the body. This is also the rate of elimination of drug from the body. Processes such as this, in which

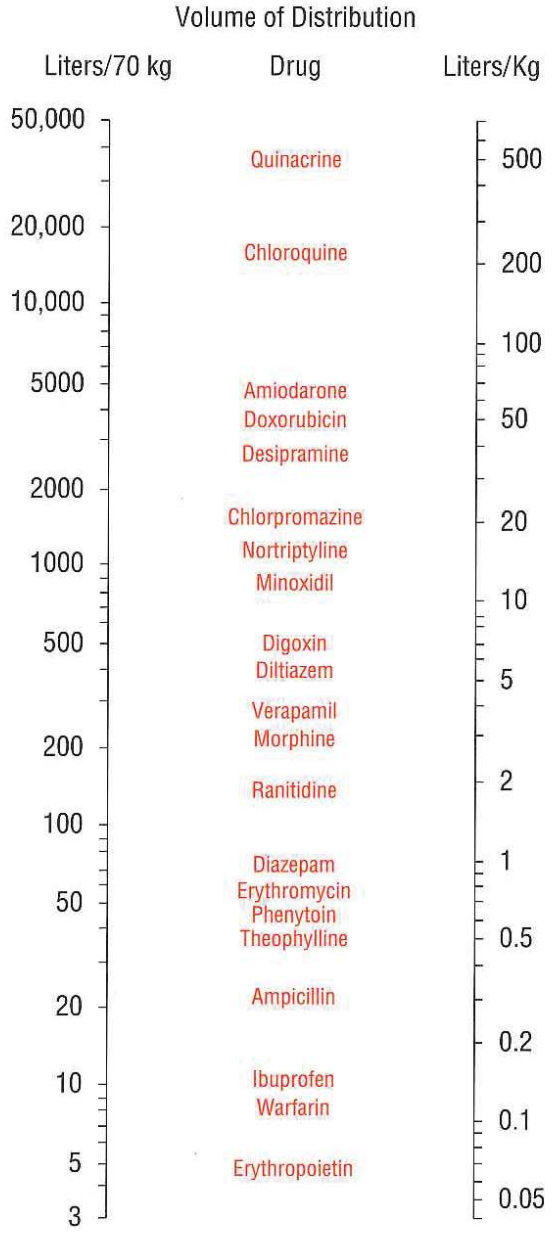

Fig. 3–2. The apparent volume into which drugs distribute varies widely.

the rate of reaction is proportional to the amount present, are known as *first-order processes*. The proportionality constant is known as the *first-order rate constant* with dimensions of time^{-1}. Because k characterizes the elimination process, it is known as the *elimination rate constant*. Since the rate constant can also be defined by rearranging Eq. 9 to yield

$$k = \frac{\text{Rate of elimination}}{\text{Amount in body}} \qquad 10$$

the elimination rate constant may simply be regarded as the *fractional rate of drug removal*. For example, since the half-life of theophylline is 5 hr, the value of its elimination rate constant is 0.14 hr^{-1}. Hence, the speed of the elimination process of theophylline can be characterized either by its half-life, 5 hr, or by saying that the fractional rate of elimination is 0.14 (or 14%) of the drug in the body per hour.

Fraction of Dose Remaining. Another view of the kinetics of drug elimination may be gained by examining how the fraction of the dose remaining in the body (A/Dose) varies with time. By reference to Eq. 5,

$$\text{Fraction of dose remaining in the body} = \frac{A}{\text{Dose}} = e^{-kt} \qquad 11$$

The fraction of the dose remaining is, therefore, given by e^{-kt}. Sometimes, it is useful to express time relative to the half-life. The value of doing so is seen by letting n be the number of half-lives elapsed after a bolus dose ($n = t/t_{1/2}$). Then, as $k = 0.693/t_{1/2}$,

$$\text{Fraction of dose remaining in the body} = e^{-kt} = e^{-0.693n} \qquad 12$$

Since $e^{-0.693} = {}^1/_2$, it follows that

$$\text{Fraction of dose remaining in the body} = ({}^1/_2)^n \qquad 13$$

Thus, ${}^1/_2$ or 50% of the dose remains after 1 half-life, and ${}^1/_4$ (${}^1/_2 \times {}^1/_2$) or 25% remains after 2 half-lives, and so on.

Total Clearance. Just as the parameter volume of distribution is needed to relate concentration to amount in the body, so there is a need to have a parameter to relate concentration to rate of drug elimination. Clearance (total), denoted by CL, is that proportionality factor. Thus,

$$\text{Rate of elimination} = CL \cdot \text{Concentration} \qquad 14$$

The units of clearance, like those of flow, are volume per unit time. For example, if the clearance value is 1 L/hr, then at a concentration of 1 mg/L, the rate of drug elimination is 1 mg/hr. Ordinarily, as the concentration of a drug increases, so does its rate of elimination; clearance remains the same. From Eq. 9, rate of elimination $= k \cdot A$. Since $A = V \cdot C$; from Eq. 1, it follows that

$$\text{Rate of elimination} = k \cdot V \cdot C \qquad 15$$

Comparison of Eqs. 14 and 15 leads to the relationship

$$\text{Clearance} = k \cdot V \qquad 16$$

Using Eq. 16, the (total) clearance of theophylline is calculated to be 4 L/hr or 67 mL/min. So that at a plasma concentration of 1 mg/L, e.g., the rate of elimination of theophylline from the body is 4 mg/hr.

Clearance and Elimination Half-life. It is more common to refer to the half-life rather than to the elimination rate constant of a drug. Recall that $t_{1/2} = 0.693/k$, so that half-life is related to clearance by:

$$t_{1/2} = \frac{0.693 \cdot \text{Volume of distribution}}{\text{Clearance}} \qquad 17$$

Equation 17 is purposely arranged in the above manner to stress that half-life (and elimination rate constant) reflects rather than controls volume of distribution and clearance, two independent parameters. To show the application of Eq. 17, consider the use of creatinine, a product of muscle catabolism, as a marker of renal function. Creatinine has a clearance of 7.2 L/hr and is evenly distributed throughout the 42 L of total body water. As expected by calculation using Eq. 17, its half-life is 4 hr. Inulin, a polysaccharide also used to assess renal function, has the same clearance as creatinine. However, inulin has a half-life of only 1.5 hr because it is restricted to the 16 L of extracellular water.

Clearance, Area, and Volume of Distribution. Thus far, clearance has been estimated from half-life and volume of distribution. Clearance can be better estimated in another way. By rearranging Eq. 14, it can be seen that during a small interval of time, dt,

$$\text{Amount eliminated in interval } dt = \text{Clearance} \cdot C \cdot dt \qquad 18$$

where the product $C \cdot dt$ is the corresponding small area under the plasma concentration-time curve. For example, if the clearance of a drug is 1 L/min and the area under the curve between 60 and 61 min is 1 mg-min/L, then the amount of drug eliminated in that minute is 1 mg. The total amount of drug eventually eliminated, which for an i.v. bolus equals the dose administered, is assessed by adding up or integrating the amounts eliminated in each time interval, from time zero to infinite time, and therefore,

$$\text{Dose} = \text{CL} \cdot AUC \qquad 19$$

where AUC is the total area under the concentration-time curve. Thus, once AUC is known (Appendix I-A), clearance is readily calculated. Note that there is no need to know the half-life or volume of distribution to calculate clearance. Furthermore, this calculation of clearance is independent of the shape of the concentration-time profile.

The relationship between area and elimination can be applied at any time following drug administration, as illustrated in Fig. 3–3. Thus, multiplying the area up to a given time, $[AUC(o, t)]$ by clearance gives the amount of drug that has been eliminated up to that time. Alternatively, when the area is expressed as a fraction of the total AUC, one obtains the fraction of the dose eliminated. And the fraction of the total area beyond a given time is a measure of the fraction of dose remaining to be eliminated. For example, in the case of theophylline, by 3.6 hr the area is 40% of the total AUC, and hence 40% of the administered 500-mg dose, or 200 mg, has been eliminated from the body; 300 mg has yet to be eliminated.

Volume of distribution (V) is used to relate plasma concentration to amount of drug in the body during the elimination phase. Often the value obtained by extrapolation (Eq. 3)

is a reasonable estimate of this volume term. Occasionally, when extensive elimination occurs in the distribution phase, it is not. The best method of calculating volume of distribution is to divide clearance by elimination rate constant

$$V = \frac{Cl}{k} = \frac{\text{Dose}}{AUC \cdot k} \qquad 20$$

Unlike extrapolation, this method of estimating V is not restricted to the i.v. bolus situation but can be used under a variety of conditions, e.g., long-term i.v. infusions. Consequently, the value of V, estimated using Eq. 20, is applied throughout the remainder of this book, although other volume terms are examined in Chap. 19, Distribution Kinetics.

RENAL CLEARANCE

Elimination occurs by renal excretion and extrarenal pathways, usually hepatic metabolism. Not only is renal excretion an important route of elimination for many drugs, but useful pharmacokinetic information can be obtained from analysis of urinary data. Central to this analysis is the concept of *renal clearance*.

Analogous to total clearance, renal clearance (CL_R) is defined as the proportionality term between urinary excretion rate and plasma concentration:

$$\text{Excretion rate} = CL_R \cdot C \qquad 21$$

Renal clearance, like total clearance, has units of flow, usually milliliters/minute or liters/hour.

Practical problems arise, however, in estimating renal clearance. Urine is collected over a finite period, e.g., 4 hr, during which the plasma concentration is changing continuously. Shortening the collection period reduces the change in plasma concentration but increases the uncertainty in the estimate of excretion rate owing to incomplete bladder emptying. This is especially true for urine collection intervals of less than 15 min. Lengthening the

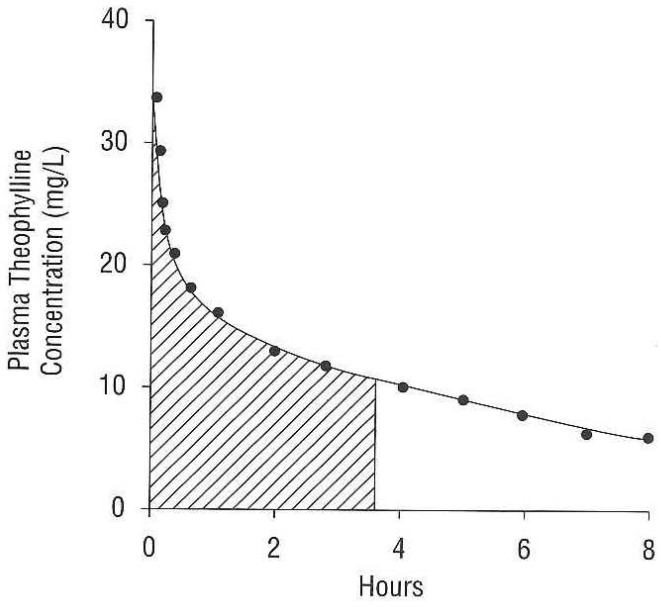

Fig. 3–3. A linear plot of the same plasma concentration-time data for theophylline as displayed in Fig. 3–1A. The area up to 3.6 hr is 40% of the total *AUC* indicating that 40% of the dose administered has been eliminated by then. The area beyond 3.6 hr represents the 60% of administered theophylline remaining to be eliminated.

collection interval, to avoid the problem of incomplete emptying, requires a modified approach for the estimation of renal clearance. This approach is analogous to that taken with total clearance. By rearranging Eq. 21, during a very small interval of time, dt,

$$\text{Amount excreted} = Cl_R \cdot C \cdot dt \qquad 22$$

where $C \cdot dt$ is the corresponding small area under the plasma drug concentration-time curve. The urine collection interval (denoted by Δt) is composed of many such very small increments of time, and the amount of drug excreted in a collection interval is the sum of the amounts excreted in each of these small increments of time, that is,

$$\text{Amount excreted in collection interval} = Cl_R \cdot [AUC \text{ within interval}] \qquad 23$$

The problem in calculating renal clearance therefore rests with estimating the AUC within the time interval (see Appendix I–A). The average plasma drug concentration during the collection interval is given by ($(AUC$ within interval$)/\Delta t$). This average plasma concentration is neither the value at the beginning nor at the end of the collection time but at some intermediate point. By assuming that the plasma concentration changes linearly with time, the appropriate concentration is that at the midpoint of the collection interval. Because the plasma concentration of drug is in fact changing exponentially with time, this assumption of linear change is reasonable only when loss during the interval is small. In practice, the interval should be less than an elimination half-life.

Extending Eq. 23 over all time intervals, from zero to infinity, one obtains the useful relationship

$$\text{Renal clearance} = \frac{\text{Total amount excreted unchanged}}{AUC} \qquad 24$$

where AUC is the total area under the plasma drug concentration-time curve. To apply Eq. 24, care must be taken to ensure that all urine is collected and for a sufficient period of time to gain a good estimate of the total amount excreted unchanged. In practice, the period of time must be at least 5 to 6 elimination half-lives of the drug (see Appendix I–B). Thus, if the half-life of a drug is in the order of a few hours, no practical difficulties exist in ensuring urine collections taken over an adequate period of time. Severe difficulties with compliance in urine collection occur, however, for drugs such as phenobarbital with a half-life of about a week, since all urine formed over a period of at least 1 month must be collected.

DISPOSITION VIEWED FROM URINE ONLY

Lack of sufficiently sensitive analytic techniques can and previously has prevented measurement of the concentration of many drugs in plasma. In the absence of plasma measurements, neither volume of distribution nor clearance can be determined. Nonetheless, useful information can still be obtained from urine data alone, when such is necessary.

Elimination Half-Life

The elimination half-life of the reversible cholinesterase inhibitor, galanthamine, can be estimated from urine data. The approach is to plot the average excretion rate against the midpoint of the collection time semilogarithmically and, from the slope of the straight line,

obtain an estimate of the half-life. Intuitively, the approach is easy to see. Assuming that renal clearance is constant, the urinary excretion rate is proportional to plasma concentration, and plotting urinary excretion rate against time is like plotting plasma concentration against time. The half-life is then taken as the time for the urinary excretion rate (or plasma concentration) to fall by one-half. For galanthamine this is approximately 6 hr in a healthy subject (Fig. 3–4). Conversely, when a straight line is obtained by plotting the urinary excretion rate against the midpoint time, constancy of renal clearance is inferred. The need for using midpoint time follows from the previous discussion; the measured urinary excretion rate reflects the average plasma concentration during the collection interval. Formal proof of the foregoing discussion is given in Appendix I–B.

Renal Excretion as a Fraction of Total Elimination

An important pharmacokinetic parameter is the fraction of the amount entering the general circulation that is excreted unchanged, *fe*. It is a quantitative measure of the contribution of renal excretion to overall drug elimination. Knowing *fe* aids in establishing appropriate modifications in the usual dosage regimen of a drug for patients with varying degrees of renal function. Among drugs, the value of *fe* ranges between 0 and 1.0. When the value is low, excretion is a minor pathway of drug elimination. Occasionally, renal excretion is the only route of elimination, in which case the value of *fe* is 1.0. By definition the difference, $1 - fe$, is the fraction of the amount entering the circulation that is eliminated by extrarenal mechanisms, usually metabolism.

An estimate of *fe* is most readily obtained from cumulative urinary excretion data following i.v. administration, since by definition.

$$fe = \frac{\text{Total drug excreted unchanged}}{\text{Dose}} \qquad 25$$

In practice, care should always be taken to ensure complete urinary recovery (i.e., collect

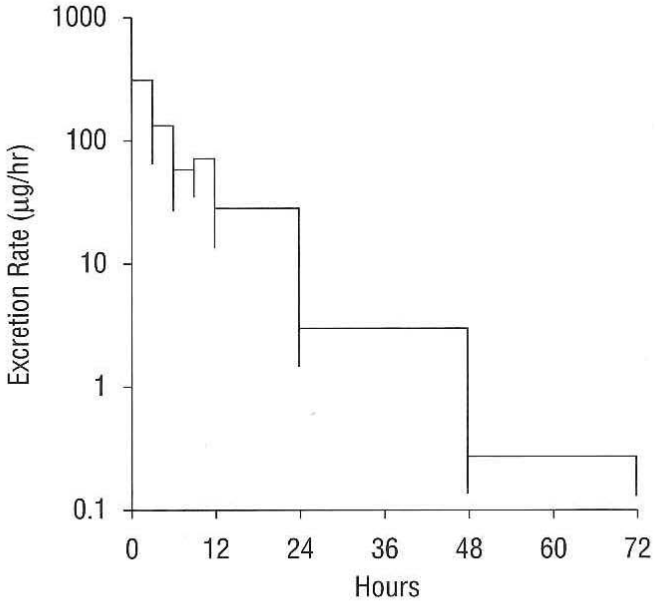

Fig. 3–4. Average urine excretion rate during each urine collection interval after an i.v. bolus dose of 10 mg of galanthamine to a healthy subject. (Redrawn from Bickel, U., Thomsen, T., Weber, W., Fischer, J.P., Bachus, R., Nitz, M., and Kewitz, H. Pharmacokinetics of galanthamine in humans and corresponding cholinesterase inhibition. Clin. Pharmacol. Ther., 50:420–428, 1991.)

urine for at least 5 elimination half-lives). In the case of galanthamine, *fe* is approximately 0.25 in subjects with normal renal function. At any instant, the fraction *fe* may be defined as the ratio of the rate of excretion to the rate of elimination,

$$fe = \frac{\text{Rate of excretion}}{\text{Rate of elimination}} \qquad 26$$

Appropriately substituting for numerator and denominator in Eq. 26, it is seen that

$$fe = \frac{CL_R \cdot C}{CL \cdot C} = \frac{CL_R}{CL} \qquad 27$$

Thus, *fe* may also be defined and estimated as the ratio of renal and total clearances. This is particularly useful in those situations in which total urine collection is not possible.

In practice, estimates of CL and CL_R are obtained directly, whereas extrarenal clearance is determined by difference. Thus, extrarenal clearance is $(1 - fe) \cdot CL$.

ESTIMATION OF PHARMACOKINETIC PARAMETERS

To appreciate how the pharmacokinetic parameters defining disposition are estimated, consider the plasma and urine data in Table 3–1 obtained following an i.v. bolus dose of 50 mg of a drug.

Table 3–1. Plasma and Urine Data Obtained Following an i.v. Bolus Dose

OBSERVATION					TREATMENT OF DATA		
PLASMA DATA		URINE DATA					
TIME (hr)	CONCENTRATION (mg/L)	TIME INTERVAL OF COLLECTION (hr)	VOLUME OF URINE (mL)	CONCENTRATION OF UNCHANGED DRUG IN URINE (mg/L)	AUC WITHIN TIME INTERVAL (mg-hr/L)	AMOUNT EXCRETED IN TIME INTERVAL (mg)	CUMULATIVE AMOUNT EXCRETED (mg)
1	2.0	0–2	120	133	4.00	16.0	16.0
3	1.13	2–4	180	50	2.26	9.0	25.0
5	0.70	4–6	89	63	1.40	5.6	30.6
7	0.43	6–8	340	10	0.86	3.4	34.0
10	0.20	8–12	178	18	0.80	3.2	37.2
18	0.025	12–24	950	2	0.43	1.9	39.1

Plasma Data Alone

A plot of plasma concentration versus time indicates that the values are dropping progressively, but only after the data are plotted semilogarithmically (Fig. 3–5) can the half-life and elimination rate constant be readily determined. The half-life, taken as the time for the concentration to fall in half (e.g., from 1.0 to 0.5 mg/L or 0.2 to 0.1 mg/L), is 2.8 hr, so that k is 0.25 hr^{-1}. Clearance is determined by dividing dose by AUC. The total AUC, estimated using the trapezoidal rule (Appendix I–A), is 10.2 mg-hr/L and when divided into the dose yields a value of 4.9 L/hr for clearance. Volume of distribution, estimated from CL/k (Eq. 20), is therefore 19.6 L. This value is virtually identical to that calculated by dividing dose by the intercept concentration at zero time, because no distinct distribution phase is apparent.

Plasma and Urine Data

Both plasma and urine data are required to estimate renal clearance. This parameter can be obtained from the slope of a plot of the amount excreted within a collection interval

against *AUC* within the same time interval (Fig. 3–6). The straight line implies that renal clearance is constant and independent of plasma concentration. The slope of the line indicates that the renal clearance of this drug is 4 L/hr. Essentially the same value is obtained by multiplying total clearance (5.0 L/hr) by *fe* (0.78) (cf. Eq. 27). The cumulative amount excreted is 39.1 mg, so the fraction of the dose excreted unchanged, *fe*, is 39.1 mg/50 mg, or 0.78.

Urine Data Alone

The elimination half-life of the drug can be obtained from either excretion rate or cumulative excretion data. The appropriate methods are dealt with in Appendix I–B.

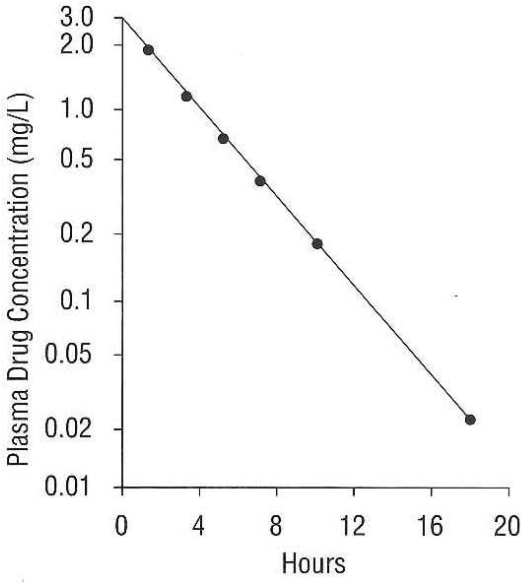

Fig. 3–5. Semilogarithmic plot of the plasma concentration-time data given in Table 3–1.

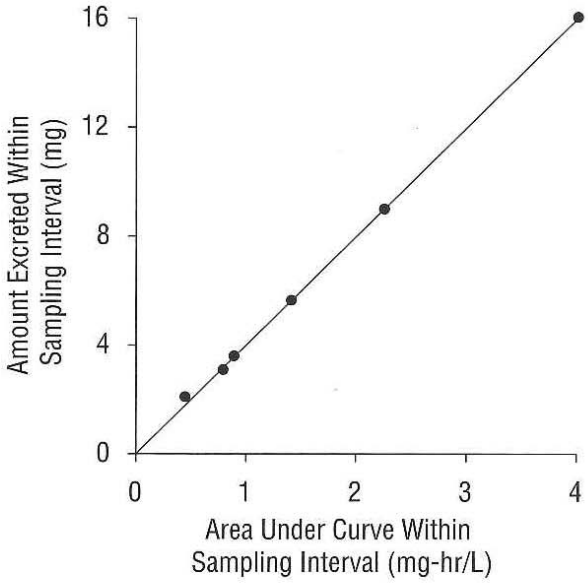

Fig. 3–6. The amount excreted is directly proportional to the *AUC* measured over the urine collection interval. Renal clearance is given by the slope of the line. Data from Table 3–1.

A Question of Precision

Had you, the reader, plotted the same data and calculated the pharmacokinetic parameters, you may have obtained answers that differ from those given. This is not unusual and will occur in many cases when you check your answers to the problems at the end of each chapter against those given in Appendix II. The reason lies in differences in the drawing of a line through data, after they have been plotted, and in rounding-off numbers. In addition, all measurements have errors associated with analytic methods, conditions of storage, and handling of samples prior to analysis.

Also, had the study just considered been repeated subsequently in the same individual, the estimated half-life may have been 3.1 hr instead of 2.8 hr. For almost all clinical situations, this degree of intraindividual variation is acceptable. To reflect the acceptable 5 to 10% variation, most answers here and throughout the remainder of the book are only given to two or three significant places.

In this chapter, many symbols are defined, as it is the first time that they are used. These symbols are reused repeatedly throughout the book. To avoid continually redefining them in every chapter and to facilitate reference to them, the Definitions of Symbols appear just before Chapter 1. Some infrequently used symbols that occur only in one chapter may not be included in the Definitions.

Measurement Fluid

So far, the pharmacokinetics of the drug within the body have been defined with reference to drug in plasma. Sometimes the reference is drug in serum or whole blood. The major difference between plasma and serum is the removal of fibrinogen in the latter case by clotting of blood, and as most drugs do not bind to fibrinogen, no difference between the concentrations of drug in plasma and serum is expected. Consequently, throughout the book the term *plasma* is taken to include serum.

Within blood, drug can bind to many constituents including plasma proteins and blood cells. Drug concentrations in whole blood and plasma can differ, thereby yielding different values for many pharmacokinetic parameters, an aspect discussed in some depth subsequently in the book (particularly Chap. 11, Elimination, and Chap. 12, Integration With Kinetics). Accordingly, unlike serum and plasma, blood and plasma cannot be considered to be equivalent, although for many applications in pharmacokinetics, the difference is relatively unimportant. Because of ease of clinical analysis, most measurements are made in plasma, rather than in blood.

Strictly speaking, one should use the terminology *concentration of drug in plasma (or blood, or plasma water)*. For expediency, in much of this chapter and throughout the rest of the book, this phrase is often shortened to *plasma (or blood) drug concentration*. Indeed, this is sometimes even further shortened to *plasma concentration (or blood concentration)* in many contexts in which concentration of a drug is understood. Similarly, the phrase *amount in body* refers to the amount of drug in the body.

Use of Computers

Today computers are used to analyze pharmacokinetic data and make predictions. Based upon statistical criteria, the pharmacokinetic parameter values are adjusted to give the best fit of the appropriate equation to the experimental data. This approach not only provides the best estimate of parameters but also increases one's confidence in them. Also, application of the same computer program results in the same answers independent of the operator. This consistency cannot be achieved by fitting graphical data by eye. Moreover, unlike an exponential equation, there are many situations in pharmacokinetics that require

equations that cannot be linearized. Then, obtaining a best fit by eye becomes virtually impossible. This limitation does not arise using a computer; any equation can be fitted directly to the experimental data. Nonetheless, a great deal about data is learned by displaying them graphically. One gains a feeling for the quality of the data and the equation that is most likely to describe them appropriately. The parameter values obtained by eye also generally serve as suitable starting values in a computer program. Because of the great benefits to learning pharmacokinetics gained by plotting data, this element is incorporated into many problems throughout the book.

EFFECT OF DOSE

An adjustment in dose is often necessary to achieve optimal drug therapy. Adjustment is made more readily when the values of the pharmacokinetic parameters of a drug do not vary with dose or with concentration. The possibility for a change with dose exists, however, for many reasons, and these are dealt with in Chap. 22 under the title of Dose and Time Dependencies. Throughout the majority of the book, however, pharmacokinetic parameters are assumed not to change with either dose or time.

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. Given that the disposition kinetics of a drug is described by a one-compartment model, which one(s) of the following statements is correct?
   The half-life of a drug following therapeutic doses in humans is 4 hr, therefore,
   a. The elimination rate constant of this drug is 0.173 hr^{-1}.
   b. It takes 16 hr for 87.5% of an i.v. bolus dose to be eliminated.
   c. It takes twice as long to eliminate 0.375 g following a 0.5-g bolus dose as it does to eliminate 0.5 g following a 1-g dose.
   d. Complete urine collection up to 12 hr is needed to provide a good estimate of the ultimate amount of drug excreted unchanged.
   e. The fraction of the administered dose eliminated by a given time is independent of the size of the dose.
2. Calculate the following:
   a. The fraction of an i.v. dose remaining in the body at 3 hr, when the half-life is 6 hr.
   b. The half-life of a drug, when 18% of the dose remains in the body 4 hr after an i.v. bolus dose.
3. Prepare a semilogarithmic plot of the following plasma concentration–time relationship:

$$C = 0.9\, e^{-0.347t}$$

   where C is in mg/L and time is in hours.
4. A drug that displays one-compartment disposition kinetics is administered as a single bolus dose. Depicted in the left-hand graph of Fig. 3–7 are the plasma concentrations of drug observed initially (10 mg/L) and 60 min later (2.5 mg/L). Depicted in the right-hand graph of Fig. 3–7 is the total urinary excretion of unchanged drug [Ae_∞ = 60 mg]. Complete the figure by drawing continuous lines that depict the fall of drug concentration in plasma and the accumulation of drug in urine with time.
5. From 0 to 3 hr after a 50-mg i.v. bolus dose of drug, the *AUC* is 5.1 mg-hr/L. The total *AUC* is 22.4 mg-hr/L and the cumulative amount excreted unchanged, Ae_∞, is 11 mg.
   a. What percent of the administered dose remains in the body as drug at 3 hr?

4

EXTRAVASCULAR DOSE

OBJECTIVES

The reader will be able to:

1. Describe the characteristics of, and the differences between, first-order and zero-order absorption processes.
2. Determine whether absorption or disposition rate limits drug elimination, given plasma concentration-time data following different dosage forms or routes of administration.
3. Anticipate the effect of altering rate of absorption, extent of absorption, clearance, or volume of distribution on the plasma concentration and amount of drug in the body following extravascular administration.
4. Estimate the bioavailability of a drug, given either plasma concentration or urinary excretion data following both extravascular and intravascular administration.
5. Estimate the relative bioavailability of a drug, given either plasma concentration or urinary excretion data following different dosage forms or routes of administration.
6. Estimate the renal clearance of a drug from plasma concentration and urinary excretion data following extravascular administration.

For systemically acting drugs, absorption is a prerequisite for therapeutic activity when they are administered extravascularly. The factors that influence drug absorption are considered in Chap. 9, Absorption. In this chapter the following aspects are examined: the impact of rate and extent of absorption on both plasma concentration and amount of drug in the body; the effect of alterations in absorption and disposition on body level-time relationships; and the methods used to assess pharmacokinetic parameters from plasma and urinary data following extravascular administration.

The term *bioavailability* is commonly applied to both rate and extent of drug input into the systemic circulation. Throughout this book the term will be limited to the extent of drug input and can be considered as the fraction, or percent, of the administered dose absorbed intact.

KINETICS OF ABSORPTION

The oral absorption of drugs often approximates first-order kinetics, especially when given in solution. The same holds true for the absorption of drugs from many other extravascular sites including subcutaneous tissue and muscle. Under these circumstances, absorption is characterized by an absorption rate constant, ka, and a corresponding half-life. The half-lives for the absorption of drugs administered orally in solution or in a rapidly disintegrating dosage form usually range from 15 min to 1 hr. Occasionally, they are longer.

Sometimes, a drug is absorbed at essentially a constant rate. The absorption kinetics are then called *zero order*. Differences between zero-order and first-order kinetics are illustrated in Fig. 4–1. For zero-order absorption, a plot of amount remaining to be absorbed against time yields a straight line, the slope of which is the rate of absorption (Fig. 4–1A). Recall from Chap. 3 that the fractional rate of decline is constant for a first-order process; the amount declines linearly with time when plotted semilogarithmically. In contrast, for a zero-order absorption process, the fractional rate increases with time, because the rate is constant but the amount remaining decreases. This is reflected in an ever-increasing gradient with time in a semilogarithmic plot of the amount remaining to be absorbed (Fig. 4–1B). A graphical method of examining the kinetics of absorption from plasma data following extravascular administration is given in Appendix I–C.

For the remainder of this chapter, and for much of the book, absorption is assumed to be first order. If absorption is zero order, then the equations developed in Chap. 6 (Constant-Rate Regimens) apply.

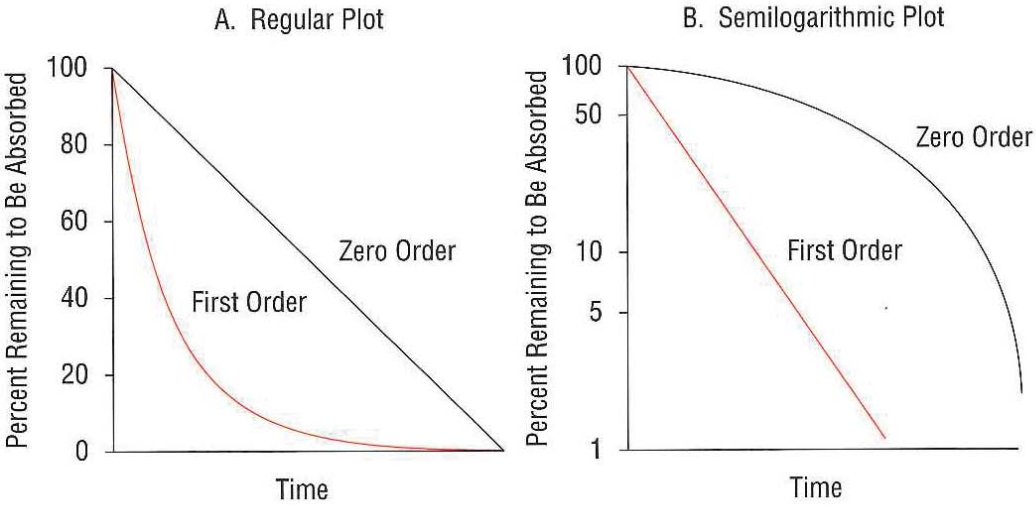

Fig. 4–1. A comparison of zero-order and first-order absorption processes. Depicted are: *A*, regular and *B*, semilogarithmic plots of the percent remaining to be absorbed against time.

BODY LEVEL-TIME RELATIONSHIPS

Comparison With an Intravenous Dose

Absorption delays and reduces the *magnitude of the peak* compared to that seen following an equal i.v. bolus dose. These effects are portrayed for aspirin in Fig. 4–2. The rise and fall of the drug concentration in plasma are best understood by remembering (Chap. 2, Eq. 2, p. 16) that at any time

$$\underset{\text{Rate of change of drug in body}}{\frac{dA}{dt}} = \underset{\text{Rate of absorption}}{\frac{dAa}{dt}} - \underset{\text{Rate of elimination}}{k \cdot A} \qquad 1$$

where Aa is the amount of drug at the absorption site remaining to be absorbed. When absorption occurs by a first-order process, the rate of absorption is given by $ka \cdot Aa$.

Initially, with all drug at the absorption site and none in the body, rate of absorption is maximal and rate of elimination is zero. Thereafter, as drug is absorbed, its rate of absorption decreases, whereas its rate of elimination increases. Consequently, the difference between the two rates diminishes. However, as long as the rate of absorption exceeds that of elimination the plasma concentration continues to rise. Eventually, a time t_{max}, is reached when the rate of elimination matches the rate of absorption; the concentration is then at a maximum, C_{max}. Subsequently, the rate of elimination exceeds the rate of absorption and the plasma concentration declines.

The peak plasma concentration is always lower following extravascular administration than the initial value following an equal i.v. bolus dose. In the former case, at the peak time some drug remains at the absorption site and some has been eliminated, while the entire dose is in the body immediately following the i.v. dose. Beyond the peak time, the plasma concentration exceeds that following i.v. administration of the same dose because of the continual entry of drug into the body.

Frequently, the rising portion of the plasma concentration-time curve is called the *absorption phase* and the declining portion, the *elimination phase*. As will be seen, this description may be misleading. Also, if bioavailability is low, the drug concentration may remain lower than that observed after i.v. administration at all times.

Lag time, the delay between drug administration and the beginning of absorption, may be particularly important when a rapid onset of effect is desired. The lag time can be anywhere from a few minutes to many hours. Long lag times have been observed following ingestion of enteric-coated tablets. The coating is resistant to the gastric environment, thus protecting an acid-labile drug or preventing gastric irritation by a drug. Factors contributing to the lag time are the delay in emptying the product from the stomach and the time taken for the protective coating to dissolve or to swell and release the inner contents into the intestinal fluids. Once absorption begins, however, it may be as rapid as with uncoated tablets. Clearly, enteric-coated products should not be used when a prompt and predictable response is desired. A method for estimating lag time is discussed in Appendix I–C.

Bioavailability and *area* are also important factors. As discussed more fully in Chaps. 7 and 9, the completeness of absorption is of primary importance in therapeutic situations.

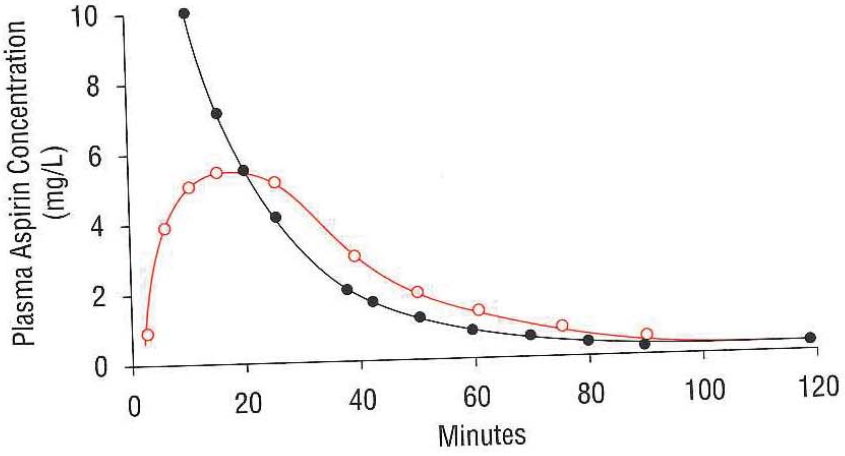

Fig. 4–2. Aspirin (650 mg) was administered as an intravenous bolus (●) and as an oral solution (○) on separate occasions to the same individual. Absorption causes a delay and a lowering of the peak concentration (1 mg/L = 5.5 μM). (Modified from the data of Rowland, M., Riegelman, S., Harris, P. A., and Sholkoff, S.D.: Absorption kinetics of aspirin in man following oral administration of an aqueous solution. J. Pharm. Sci., 67:379–385, 1972. Adapted with permission of the copyright owner.)

The bioavailability, F, is proportional to the total area under the plasma concentration-time curve (AUC) irrespective of its shape. This must be so. Recall from Chap. 3 that:

$$\text{Total amount eliminated} = \text{Clearance} \cdot AUC \qquad 2$$

but the total amount eliminated is the amount absorbed, $F \cdot \text{Dose}$, therefore:

$$\underset{\text{absorbed}}{F \cdot \text{Dose}} = \underset{\text{eliminated}}{\text{Clearance} \cdot AUC} \qquad 3$$

Thus, knowing dose, clearance, and area, bioavailability may be determined.

Changing Dose

Unless absorption half-life or bioavailability is altered, increasing the dose produces a proportional increase in plasma concentration at all times. The value of t_{max} remains unchanged, but C_{max} increases proportionally with dose.

Changing Absorption Kinetics

Alterations in either absorption or disposition produce changes in the time profiles of the amount in the body and the plasma concentration. This point is illustrated by the three situations depicted in the semilogarithmic plots of Fig. 4–3 involving only a change in the

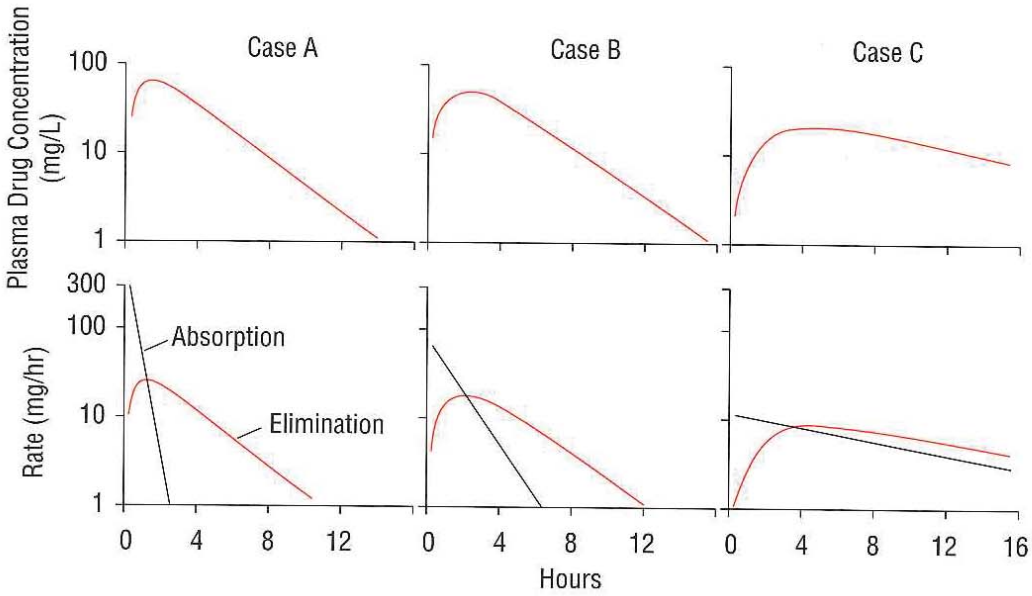

Fig. 4–3. A slowing (from left to right) of drug decline at the absorption site (lower graphs) delays the attainment and decreases the magnitude of the peak plasma drug concentration (top graphs). In Cases A and B (bottom two graphs), absorption (black line) is a faster process than elimination (colored line). In Case C (third graph on bottom), absorption (black line) rate limits elimination so that decline of drug in plasma reflects absorption rather than elimination; because there is a net elimination of drug during the decline phase, the rate of elimination is slightly greater than the rate of absorption. In all three cases, bioavailability is 1.0 and clearance is unchanged. Consequently, the areas under the plasma concentration-time curves (corresponding linear plots of the top three graphs) are identical. The AUCs of the linear plots of the rate data are also equal because the integral of the rate of absorption, amount absorbed, equals the integral of the rate of elimination, amount eliminated.

absorption half-life. All other factors (bioavailability, clearance, and volume of distribution and hence elimination half-life) remain constant.

In Case A, the most common situation, absorption half-life is much shorter than elimination half-life. In this case, by the time the peak is reached, most of the drug has been absorbed and little has been eliminated. Thereafter, decline of drug in the body is determined primarily by the disposition of the drug, that is, *disposition is the rate-limiting step*. The half-life estimated from the decline phase is, therefore, the elimination half-life.

In Case B, absorption half-life is longer than in Case A but still shorter than elimination half-life. The peak occurs later because it takes longer for the amount in the body to reach the value at which rate of elimination matches rate of absorption; the C_{max} is lower because less drug has been absorbed by that time. Even so, absorption is still essentially complete before the majority of drug has been eliminated. Consequently, disposition remains the rate-limiting step, and the terminal half-life remains the elimination half-life.

Absorption Rate-Limited Elimination

Occasionally, absorption half-life is much longer than elimination half-life, and Case C prevails (Fig. 4–3). The peak occurs later and is lower than in the two previous cases. The half-life of decline of drug in the body now corresponds to the absorption half-life. During the rise to the peak, the rate of elimination increases and eventually, at the peak, equals the rate of absorption. However, in contrast to the previous situations, absorption is so slow that much of the drug remains to be absorbed well beyond the peak time. The drug is either at the absorption site or has been eliminated; little is in the body. In fact, during the decline phase, the drug is eliminated as fast as it is absorbed. *Absorption is now the rate-limiting step*. Under these circumstances, since the rate of elimination essentially matches the rate of absorption, the following approximation ($\approx$) can be written

$$\underset{\text{Rate of elimination}}{k \cdot A} \approx \underset{\text{Rate of absorption}}{ka \cdot Aa} \qquad 4$$

that is,

$$\underset{\text{in body}}{\text{Amount}} \approx \left(\frac{ka}{k}\right) \cdot \underset{\text{be absorbed}}{\text{Amount remaining to}} \qquad 5$$

Accordingly, amount in the body (and plasma concentration) during the decline phase is directly proportional to the amount remaining to be absorbed. For example, when amount remaining to be absorbed falls by one-half, so does amount in body. However, the time for this to occur is the absorption half-life.

Absorption influences the kinetics of drug in the body; but what of the *AUC*? Because bioavailability and clearance were held constant, it follows from Eq. 3 that the *AUC* must be the same for Cases A, B, and C.

Distinguishing Absorption From Disposition Rate-Limited Elimination

Although disposition generally is rate-limiting, the preceding discussion suggests that caution may need to be exercised in interpreting the meaning of half-life determined from the decline phase following extravascular administration. Confusion is avoided if the drug is

also given intravenously. In practice, however, i.v. dosage forms of many drugs do not exist for clinical use. Distinguishing between absorption and disposition rate-limitations is achieved by altering the absorption kinetics of the drug. This is most readily accomplished by giving the drug either in different dosage forms or by different routes. To illustrate this point, consider data for theophylline and penicillin G.

Food and water influence the oral absorption kinetics of theophylline but not the half-life of the decline phase (Fig. 4–4). Here then, disposition rate-limits theophylline elimination. In contrast, for penicillin, with a very short elimination half-life, intramuscular (i.m.) absorption can become rate-limiting by formulation of a sparingly soluble salt (Fig. 4–5).

Changing Disposition Kinetics

What happens to the plasma concentration-time profile of a drug when the absorption kinetics remain constant, but modifications in disposition occur? When clearance is reduced, but bioavailability remains constant, the *AUC* must increase; so must both the time and magnitude of the peak concentration. These events are depicted in Fig. 4–6. With a

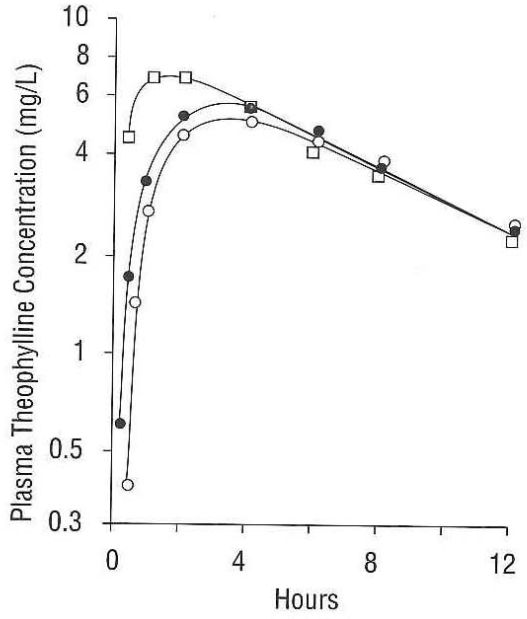

Fig. 4–4. Two tablets, each containing 130 mg theophylline, were taken by 6 healthy volunteers under various conditions. Absorption of theophylline was most rapid when the tablets were dissolved in 500 mL of water and taken on an empty stomach (□). Taking the tablets with 20 mL of water on an empty stomach (○) resulted in slower absorption than taking them with the same volume of water immediately following a standardized high carbohydrate meal (●). Despite differences in rates of absorption, however, the terminal half-life was the same (6.3 hours) and, therefore, it is the elimination half-life of theophylline (1 mg/L = 5.5 μM). (Modified from Welling, P.G., Lyons, L.L., Craig, W.A., and Trochta, G.A.: Influence of diet and fluid on bioavailability of theophylline. Clin. Pharmacol. Ther., 7:475–480, 1975.)

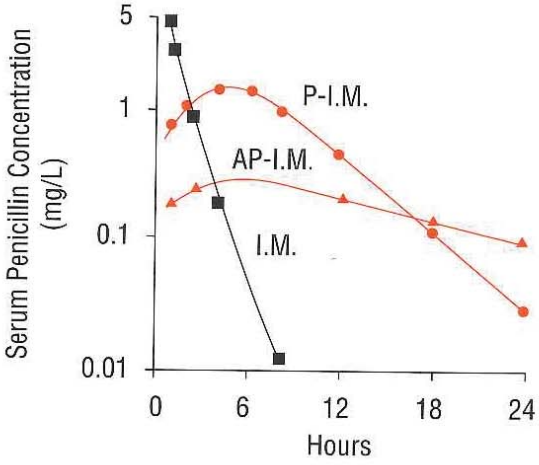

Fig. 4–5. Penicillin G (3 mg/kg) was administered intramuscularly to the same individual on different occasions as an aqueous solution (I.M.) and as procaine penicillin in oil (P-I.M.) and in oil with aluminum monostearate (AP-I.M.). The differing rates of decline of the plasma concentration of penicillin G point to an absorption rate-limitation when this antibiotic is given as the procaine salt in oil. Distinction between rate-limited absorption and rate-limited disposition following intramuscular administration of the aqueous solution can only be made by giving penicillin G intravenously. (1 mg/L = 3.0 μM). (Modified from Marsh. D.F.: Outline of Fundamental Pharmacology. Charles C. Thomas, Springfield, IL, 1951.)

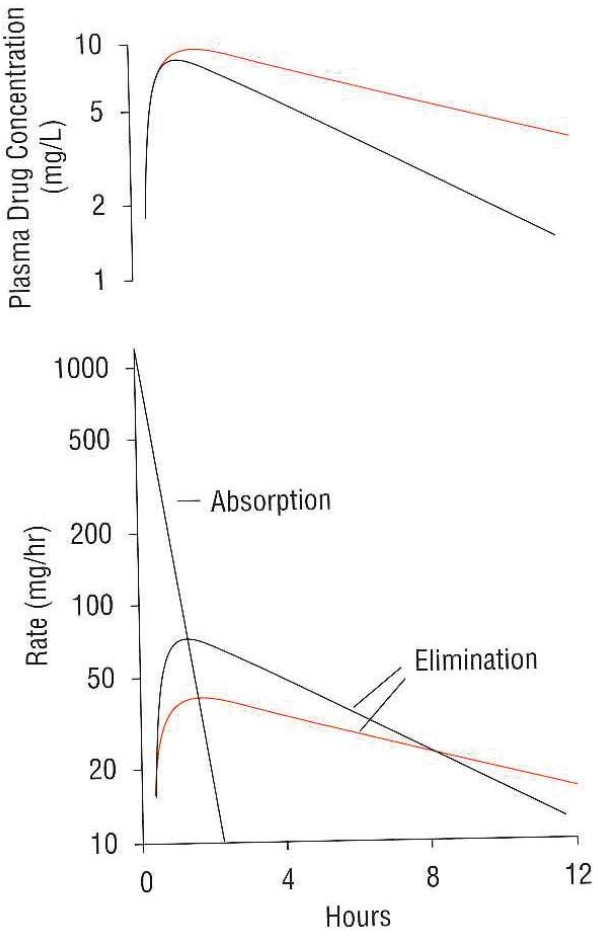

Fig. 4–6. A twofold reduction in clearance increases the area under the plasma concentration-time (colored line, top graph) twofold compared to that of the control (black line) after a single extravascular dose. With no change in absorption kinetics (and hence absorption rate profile with time) (colored line, bottom graph), the rate of elimination (colored line, bottom graph) is observed to be lower at first but to become greater than that of the control (black line, bottom graph), as the area under the corresponding linear plots of these rate curves must be equal to the dose (see Fig. 4–3). The decrease in clearance causes the peak concentration to be greater and to occur at a later time (only slightly different here). The peak time occurs when the rate of elimination equals the rate of absorption (bottom graph). The terminal slope reflects the increased elimination half-life.

reduction in clearance and, hence, elimination rate constant, a greater amount of drug must be absorbed, and the plasma concentration must be greater prior to the time when the rate of elimination equals the rate of absorption.

As shown in Fig. 4–7, the events are different when an increased volume of distribution is responsible for a longer elimination half-life. Under these circumstances the *AUC* is the same if bioavailability and clearance are unchanged. The peak occurs later and is lower, however. With a larger volume of distribution, more drug must be absorbed before the plasma concentration reaches a value at which the rate of elimination ($CL \cdot C$) equals the rate of absorption; the absorption rate is lower then and so is the plasma concentration.

Predicting Changes in Peak

Qualitative changes in C_{max} and t_{max} are difficult to predict when absorption or disposition is altered. To facilitate this prediction, a memory aid has been found to be useful. The basic principle of the method (Fig. 4–8) is simple; absorption increases and elimination decreases the amount of drug in the body. The faster the absorption process (measured by absorption rate constant), the greater is the slope of the absorption line, and the converse. The faster the elimination process (elimination rate constant), the steeper is the decline of the elimination line.

If absorption rate constant is increased, the new point of intersection indicates that peak amount is increased and that it occurs at an earlier time. If elimination rate constant is increased, the new point of intersection occurs at an earlier time, but at a lower amount.

The graph is designed for predicting changes in t_{max} and peak amount in the body. It applies as well to C_{max} with the exception of when volume of distribution is altered. An

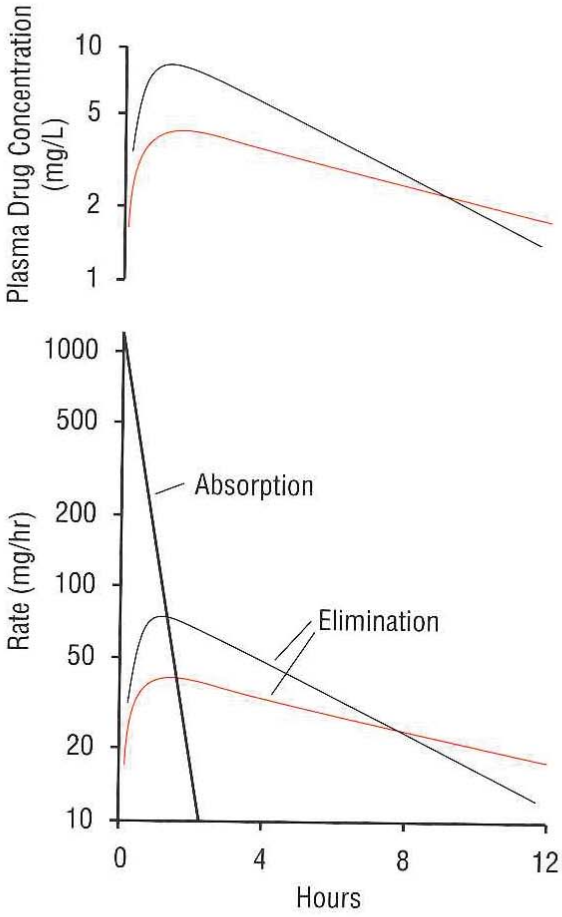

Fig. 4–7. A twofold increase in the volume of distribution causes a twofold increase in the elimination half-life and delays the time at which the peak plasma concentration occurs (colored line, top graph) compared to the control observation (black line) after a single extravascular dose. With no change in clearance, area (under linear concentration-time plot) is unchanged and peak concentration is thereby reduced. Because of a lower concentration, rate of elimination is initially slowed (colored line, bottom graph), but since the amount eliminated is the same (the dose), rate of elimination eventually is greater than that of the control (black line, bottom graph).

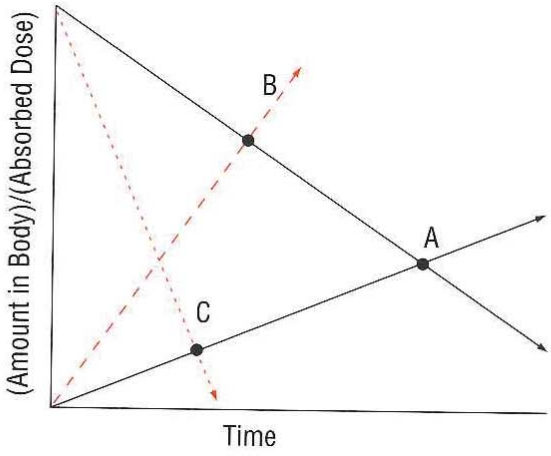

Fig. 4–8. Memory aid to assess changes in peak time and peak amount in the body after extravascular administration of a single dose when absorption or disposition is altered. The relative peak time and the relative peak amount are indicated by the intersection of the absorption and elimination lines (A) with slopes representing the absorption and elimination rate constants, respectively. The predictions for an increased absorption rate constant (colored dashed line and point B) and an increased elimination rate constant (colored dotted line and point C) are shown. (Modified from Øie, S. and Tozer, T.N.: A memory aid to assess changes in peak time and peak concentration with alteration in drug absorption or disposition. Am. J. Pharm. Ed., *46*:154–155, 1982.)

increase in volume of distribution causes a decrease in peak concentration, and the converse, as explained under Changing Disposition Kinetics. Specific relationships for estimating the values of C_{max} and t_{max} when absorption and disposition are first-order are given in Appendix I–C.

ASSESSMENT OF PHARMACOKINETIC PARAMETERS

How some parameter values are estimated following extravascular administration can be appreciated by considering both the plasma concentration-time curves in Fig. 4–9, obtained

following i.m. and oral administrations of 500 mg of a drug, and the additional information in Table 4–1.

Plasma Data Alone

Bioavailability. Supplemental data from i.v. administration allow calculation of bioavailability, F. The total AUC following extravascular administration is divided by the area following an i.v. bolus, appropriately correcting for dose. The basis for this calculation, which assumes that *clearance remains constant*, is as follows:

Intravenous (i.v.) dose

$$\text{Dose}_{\text{i.v.}} = \text{Clearance} \cdot AUC_{\text{i.v.}} \qquad 6$$

Extravascular (e.v.) dose

$$F_{\text{e.v.}} \cdot \text{Dose}_{\text{e.v.}} = \text{Clearance} \cdot AUC_{\text{e.v.}} \qquad 7$$

which upon division yields

$$F_{\text{e.v.}} = \left(\frac{AUC_{\text{e.v.}}}{AUC_{\text{i.v.}}}\right)\left(\frac{\text{Dose}_{\text{i.v.}}}{\text{Dose}_{\text{e.v.}}}\right) \qquad 8$$

For example, appropriately substituting the area measurements in Table 4–1 into Eq. 8

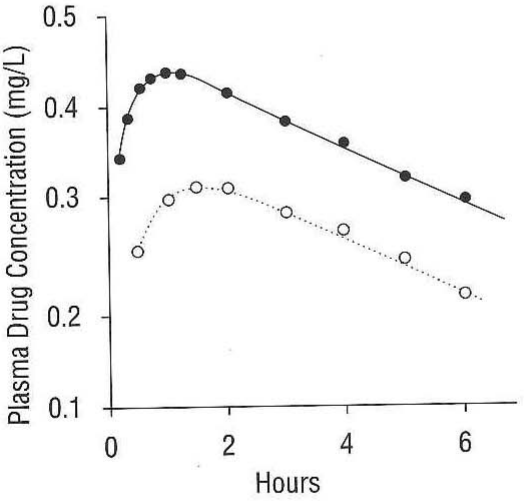

Fig. 4–9. A 500-mg dose is given intramuscularly (●—●) and orally (○· · ·○) to the same subject on separate occasions. The drug is less bioavailable and is absorbed more slowly from the gastrointestinal tract. A parallel decline, however, implies that disposition is rate-limiting in both instances.

Table 4–1. Data Obtained Following Administration of 500 mg of a Drug in Solution by Different Routes

	PLASMA DATA		URINE DATA
ROUTE	*AUC* (mg-hr/L)	HALF-LIFE; DECAY PHASE (min)	CUMULATIVE AMOUNT EXCRETED UNCHANGED (mg)
Intravenous	7.6	190	152
Intramuscular	7.4	185	147
Oral	3.5	193	70

indicates that the bioavailability of the i.m. dose is 97%. Virtually all drug injected into muscle is absorbed systemically. In contrast, only 46% is bioavailable when drug is given orally in solution.

An alternative method of estimating bioavailability, which gives the same answer, is to substitute the value for clearance directly into Eq. 7. Clearance can be estimated from blood (or plasma) data following either an i.v. bolus dose or a constant-rate i.v. infusion (Chap. 6).

Relative bioavailability is determined when there are no i.v. data. Cost, stability, solubility limitations, and potential hazards are major reasons for the lack of an i.v. preparation. Relative bioavailability is determined by comparing different dosage forms, different routes of administration, or different conditions (e.g., diet, disease state). As with the calculation of bioavailability, clearance is assumed to be constant.

Thus, taking the general case:

Dosage form A

$$\underset{\text{Amount absorbed}}{F_A \cdot \text{Dose}_A} = \underset{\text{Total amount eliminated}}{\text{Clearance} \cdot AUC_A} \qquad 9$$

Dosage form B

$$F_B \cdot \text{Dose}_B = \text{Clearance} \cdot AUC_B \qquad 10$$

So that,

$$\text{Relative bioavailability} = \frac{F_A}{F_B} = \left(\frac{AUC_A}{AUC_B}\right)\left(\frac{\text{Dose}_B}{\text{Dose}_A}\right) \qquad 11$$

The reference dosage form chosen is usually the one with the highest bioavailability, that is, the one having the highest area-to-dose ratio. In the example considered, this is the i.m. dose; the relative bioavailability of the oral dose is then 46%. If only two oral doses had been compared, they may have been equally, albeit poorly, bioavailable. It should be noted that all the preceding relationships hold, irrespective of route of administration, rate of absorption, or shape of the curve. Constancy of clearance is the only requirement.

Fraction Eliminated. Based on the relationship between area and amount eliminated presented in Chap. 3, *AUC* up to a given time, for example, t_{max}, reflects the amount eliminated up to that time (see Fig. 4–10). The area beyond t_{max} reflects the amount remaining to be eliminated. The latter area represents drug in the body if absorption is fast compared to elimination, because absorption is essentially finished. Conversely, it approximates amount remaining to be absorbed if absorption is rate-limiting.

Other Pharmacokinetic Parameters. Given only extravascular data, it is sometimes difficult to estimate pharmacokinetic parameters. Indeed, no pharmacokinetic parameter can be determined confidently from observations following only a single oral dose. Consider: Area can be calculated without knowing bioavailability, but clearance cannot. Similarly, although a half-life can be ascribed to the decay phase, without knowing whether absorption or disposition is rate-limiting, the value cannot be assigned to either absorption or elimination. Without knowing any of the foregoing parameters, the volume of distribution clearly cannot be calculated.

Fortunately, there is a sufficient body of data to determine at least the elimination half-life of most drugs. Failure of food, dosage form, and, in the example in Fig. 4–7, route of administration to affect the terminal half-life indicate that this must be the elimination half-life. Also, a drug is often fully bioavailable ($F = 1$) from i.m. or subcutaneous sites. Hence, clearance can be calculated knowing area (Eq. 3), and the volume of distribution can be estimated once the elimination half-life is known. Consider, for example, just the i.m. data in Table 4–1. Clearance, obtained by dividing dose (500 mg) by AUC (7.4 mg-hr/L), is 1.1 L/min. Dividing clearance by the elimination rate constant (0.693/185 min) gives the volume of distribution, in this case 300 L.

Previously, a range of likely absorption half-lives was quoted. The values were estimated indirectly from plasma concentration-time data. Direct measurements of absorption kinetics are impossible because plasma is the site of measurement for both absorption and disposition. To calculate the kinetics of absorption, a method must therefore be devised to separate these two processes. Two relatively simple methods for achieving this separation are discussed in Appendix I-C.

Urine Data Alone

Given only urine data, neither clearance nor volume of distribution can be calculated. If renal clearance of drug is constant, rate of drug excretion is proportional to its plasma concentration, and under these circumstances, theoretically, excretion rate data can be treated in a manner similar to that for plasma data. In practice, during the first collection of urine, usually 1 or 2 hr after drug administration, absorption of many well-absorbed drugs is virtually finished. A shorter collection interval is needed to characterize absorption kinetics but is impractical because of incomplete emptying of the bladder and an inability of a subject to produce a urine sample on demand so frequently. Urinary excretion rate data are then often of little use in estimating absorption kinetics.

Cumulative urine data can be used to estimate bioavailability. The method requires that the value of *fe* remains constant. Recall from Chap. 3 that *fe* is the ratio of the total amount excreted unchanged (Ae_∞) to the total amount absorbed.

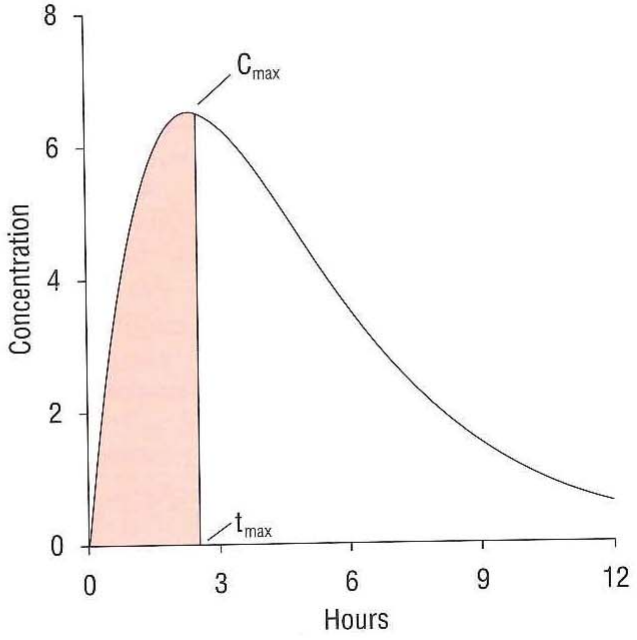

Fig. 4–10. The *AUC* up to t_{max}, the time of occurrence of the highest concentration, C_{max}, relative to the total *AUC* represents the amount eliminated at t_{max} relative to the total amount ultimately eliminated (see Fig. 3–3).

$$fe = \frac{Ae_{\infty}}{F \cdot \text{Dose}} \qquad 12$$

Then, using the subscripts A and B to denote two treatments, it follows that

$$F_A \cdot \text{Dose}_A = Ae_{\infty,A}/fe \qquad 13$$

$$F_B \cdot \text{Dose}_B = Ae_{\infty,B}/fe \qquad 14$$

Amount absorbed = Total amount eliminated

which upon division gives:

$$\frac{F_A}{F_B} = \left(\frac{Ae_{\infty,A}}{Ae_{\infty,B}}\right) \cdot \left(\frac{\text{Dose}_B}{\text{Dose}_A}\right) \qquad 15$$

The ratio of the dose-normalized cumulative amount excreted unchanged is therefore the ratio of the bioavailabilities. When Dose B is given intravenously, the ratio is the bioavailability of the drug. Otherwise the ratio gives the relative bioavailability. For example, from the cumulative urinary excretion data in Table 4–1, it is apparent that the i.m. dose is almost completely bioavailable; the corresponding value for the oral dose is only 46% [(70 mg/152 mg) × 100]. Notice that, as expected if *fe* is constant, this value is the same as that estimated from plasma data.

Urine data alone can be particularly useful for estimating bioavailability when the fraction excreted unchanged approaches 1. Under this condition, changes in renal clearance (and hence total clearance) affect *AUC*, but not the amount excreted, which is a direct measure of amount absorbed. The major problem here is in ensuring complete urine collection until virtually all the absorbed drug has been excreted.

Plasma and Urine Data

The renal clearance of a drug can be estimated when both plasma and urine data exist. The approach is identical to that taken for an i.v. dose (Chap. 3). Since no knowledge of bioavailability is required, the estimate of renal clearance from combined plasma and urine data following extravascular administration is as accurate as that obtained following i.v. drug administration.

BIOEQUIVALENCE

Laws mandate that new drug products be safe and effective. If a new product of a drug has the same molar dose and is of similar formulation to one already shown to be safe and effective, such laws allow marketing of the new product if it shows bioequivalence, i.e., similar efficacy and safety. The major concern is *switchability*, the ability of a patient to exchange one product for the other. Two products are considered to be bioequivalent if the concentration-time profiles are so similar that they are unlikely to produce clinically relevant differences in either therapeutic or adverse effects. The common measures used to assess differences in absorption are *AUC*, C_{max}, and t_{max}.

In practice, C_{max} and t_{max} are estimated from the highest concentration measured and the time of its occurrence. As the plasma concentration-time curve is quite flat near the peak and because of assay variability, the value of t_{max} chosen may not be a good representation of the actual value. Furthermore, the accuracy of the t_{max} estimate is limited by samples being obtained only at discrete times.

Bioequivalence testing usually arises when a patent on an innovator's drug expires. Other manufacturers may then wish to market the same formulation of the drug. Formulations that are bioequivalent with that of the innovator and bearing the generic name of the drug are called *generic* products. Bioequivalence testing is also performed during the course of development of new drugs, when a formulation is changed, or when the site or method of manufacture is altered.

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. Identify each of the statements below that are correct (see Fig. 4–8). For the one, or more, that is not correct, state why it is not or supply a qualification.
   a. All other parameters remaining unchanged, the slower the absorption process, the higher is the peak plasma concentration after a single oral dose.
   b. After a single oral dose, an increase in bioavailability causes the peak time to shorten.
   c. For a given drug in a subject, *AUC* is proportional to the amount of drug absorbed.
   d. If $ka << k$, then the terminal slope of the plasma concentration versus time curve reflects absorption, not elimination.
2. Graffner et al. (Graffner, C., Johnsson, G., and Sjögren, J.: Pharmacokinetics of procainamide intravenously and orally as conventional and slow-release tablets. Clin. Pharmacol. Ther., *17*:414–423, 1975), in evaluating different dosage forms of procainamide, obtained the following *AUC* and cumulative urine excretion data listed in Table 4–2.

Table 4–2.

ROUTE	DOSE (mg)	*AUC* (mg·hr/L)	AMOUNT EXCRETED (0–48 hr) (mg)
i.v.	500	13.1	332
Oral			
Formulation 1	1000	20.9	586
Formulation 2	1000	19.9	554

   a. Estimate both bioavailability and relative bioavailability of formulation 2 from both plasma and urine data. What are the assumptions made in your calculations?
   b. The half-life of procainamide found in this study was 2.7 hr. Was the urine collected over a long enough time interval to obtain a good estimate of the cumulative amount excreted at infinite time?
   c. Does renal clearance of procainamide vary much among the three treatments?
3. Depicted in Fig. 4–11 are curves of plasma concentration and amount in the body with time following the oral ingestion of a single dose of a drug. First draw five pairs of curves identical to those in Fig. 4–11. Then, draw another curve on each pair of these curves that shows the effect of each of the following alterations in pharmacokinetic parameters. In each case, the dose administered and all other parameters (among F, ka, V, and CL) remain unchanged.

5

THERAPEUTIC RESPONSE AND TOXICITY

OBJECTIVES

The reader will be able to:

1. Explain why effect (desired or toxic) of a drug is often better correlated with plasma concentration than with dose.
2. Define the terms: graded response, all-or-none response, therapeutic concentration range, utility curve, and tolerance.
3. List the range of plasma concentrations associated with therapy for any of the drugs given in Table 5–2.
4. Discuss briefly situations in which poor plasma drug concentration–response relationships are likely to occur.
5. Explain briefly why modality of administration of a given daily dose can affect therapeutic outcome.

The rational design of safe and efficacious dosage regimens is now examined. In this section, fundamental aspects of dosage regimens are covered primarily from the point of view of treating a patient population with a given disease. It is realized, of course, that individuals vary in their responses to drugs, and subsequently, in Section Four, focus is turned toward the establishment of dosage regimens in individual patients.

A therapeutic dosage regimen is basically derived from the kinds of information shown in Table 5–1. One consideration includes those factors that relate to both efficacy and safety of the drug, that is, its pharmacodynamics and toxicology. Another consideration is how the body acts on the drug and its dosage form, the essence of pharmacokinetics. A third consideration is that of the clinical state of the patient and his or her total therapeutic regimen. A fourth category includes all other factors such as genetic differences, tolerance, and drug interactions. All of these determinants are, of course, interrelated and interdependent.

Dosage regimens are designed to produce a therapeutic objective. This objective may be achieved by various modalities of drug administration, extending from a single occasional dose to continuous and constant input. An example of the former is the use of aspirin to treat an occasional headache; the continuous i.v. infusion of heparin to maintain a desired degree of anticoagulation is an example of the latter. More commonly, drugs are administered repeatedly in discrete doses. The frequency and duration vary with the condition being treated. Some drugs are administered relatively infrequently, producing large fluctuations in the plasma concentration. Reasons for this approach include the development of tolerance to the drug and the need to produce high concentrations for short periods of time, as occurs in some antibiotic and anticancer chemotherapies. In other situations, main-

tenance of a relatively constant concentration of drug is needed. In all cases, attempts are made to minimize undesirable and toxic effects and prevent ineffective therapy.

Evidence exists that response is often better correlated with plasma concentration than with dose administered. Accordingly, it would seem to be most appropriate to apply pharmacokinetic principles to the design of dosage regimens. Thus, given pharmacokinetic data following a single dose, the plasma concentration or amount of drug in the body following any dosing scheme can be estimated. Ultimately, however, the value of a dosage regimen must be assessed by the therapeutic and toxic responses produced. Pharmacokinetics facilitates the achievement of an appropriate dosage regimen and serves as a useful means of evaluating existing dosage regimens.

In this chapter, various elements of the concentration–response relationship are explored. Principles for attaining and maintaining a therapeutic level of drug in the body are discussed in the subsequent two chapters of this section.

RESPONSE AND CONCENTRATION

Response may be as vague as a general feeling of improvement or as precise as a lowering of the diastolic blood pressure by 30 mm Hg.

Information relating concentration to response is obtained at three levels: *in vitro* experiments, animal studies, and investigations in human volunteers and patients. The last level is the most relevant to human drug therapy but, unfortunately, only limited information is often obtainable here about the nature of the drug–receptor interaction. *In vitro* experiments, which include studies of the action of drugs on enzymes, receptors, microorganisms, and isolated tissues and organs, serve this purpose best. However, in isolating the variables, many of the complex interrelationships that exist *in vivo* are destroyed. Animal studies bridge much of the gap between *in vitro* experimentation and human investigation. Studies in animals introduce both the variable time, with all that it connotes, and

Table 5–1. Determinants of a Dosage Regimen

ACTIVITY-TOXICITY	PHARMACOKINETICS
Therapeutic window	Absorption
Side effects	Distribution
Toxicity	Metabolism
Concentration–response relationships	Excretion

CLINICAL FACTORS		
STATE OF PATIENT	MANAGEMENT OF THERAPY	OTHER FACTORS
Age, weight	Multiple drug therapy	Route of administration
Condition being treated	Convenience of regimen	Dosage form
Existence of other disease states	Compliance of patient	Tolerance-dependence
		Pharmacogenetics-idiosyncrasy
		Drug interactions
		Cost

the elements of absorption and disposition as well as the feedback control systems that operate to maintain homeostasis. Animal studies are often most useful for evaluating the pharmacologic spectrum of activity of a potential therapeutic agent and for determining aspects of its toxicity profile. Irrespective of the level of information, however, the conclusion is the same: A relationship, although sometimes complex, exists between the concentration of active agent at the site of measurement and the response.

The majority of drugs used clinically act reversibly in that the effect is reversed upon reducing concentration at the site of action. Many responses produced are *graded*, so called because the magnitude of the response can be scaled or graded. An example of a graded response, shown in Fig. 5–1, is the improvement of pulmonary function produced by the bronchodilator terbutaline, after its s.c. administration. The intensity of the response varies with the drug concentration in plasma. Many other pharmacologic and toxic responses do not occur on a continuous basis; these are known as *quantal* or *all-or-none* responses. An obvious but extreme example is death. Another is the suppression of an arrhythmia. The arrhythmia either is or is not suppressed. Sometimes, a limit is set on a graded response below which an effect is said not to occur clinically. For example, a potentially toxic effect of antihypertensive therapy is an excessive lowering of blood pressure. The lowering of blood pressure produced by the antihypertensive agents is a graded response, but hypotensive toxicity is said to occur only if the blood pressure falls to too low a value. Here the clinical endpoint is all-or-none, but the pharmacologic response is graded.

Returning to terbutaline, Fig. 5–1 is a plot of the forced expiratory volume in 1 second, a measure of pulmonary function, against plasma concentration. The plot is characteristic of most graded response curves. A nearly linear relationship between the intensity of response and the concentration at low concentrations and a tendency to reach a maximal response at high concentrations are apparent.

Unlike a graded response, the correlation between a quantal response and concentration is explored by examining the *frequency* of the event with concentration. This is illustrated in Fig. 5–2 by a plot of frequency of the suppression of ventricular arrhythmias as a function of the plasma concentration of the antiarrhythmic agent procainamide. In most patients

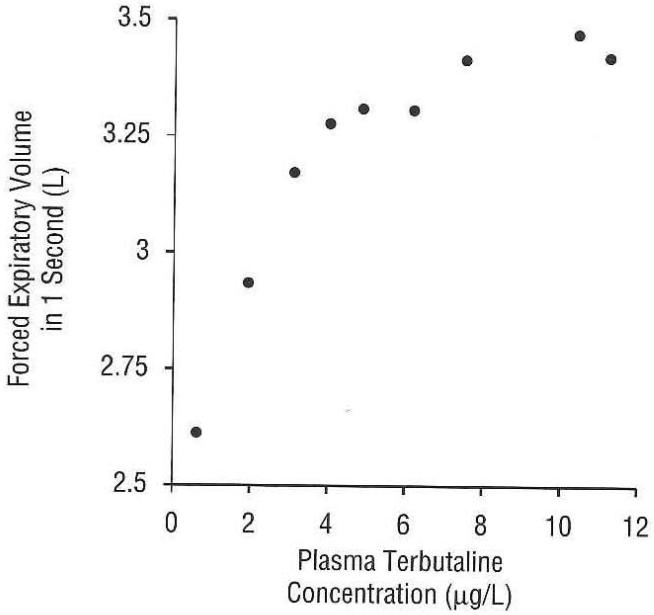

Fig. 5–1. The mean forced expiratory volume in 1 second (FEV_1) increases with the mean plasma concentration at preselected times in 10 patients given 0.75 mg of terbutaline subcutaneously. The improvement in pulmonary function increases with plasma concentration but appears to approach a limiting value. (Redrawn from Oosterhuis, B., Braat, P., Roos, C.M.J., and Van Boxtel, C.J.: Pharmacokinetic-pharmacodynamic modeling of terbutaline bronchodilation in asthma. Clin. Pharmacol. Ther., *40*:469–475, 1986.)

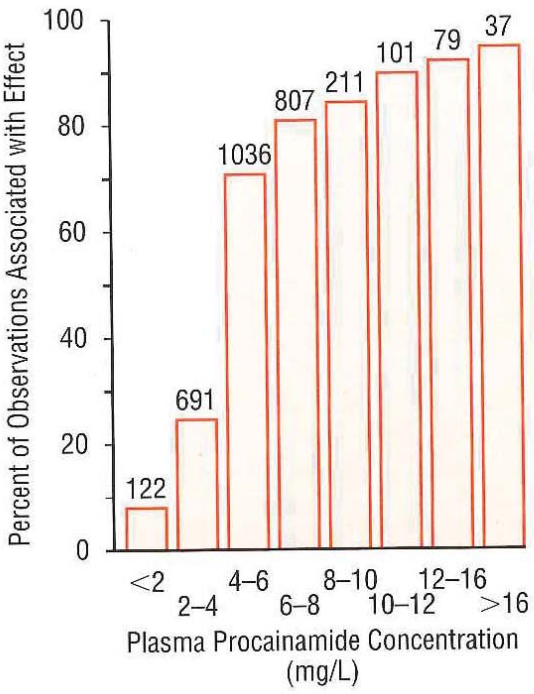

Fig. 5–2. The concentration of procainamide was determined in over 3000 plasma samples obtained from 291 patients receiving this drug for the treatment of cardiac arrhythmias. The frequency, expressed as a percent of the number of plasma samples with which a serum concentration correlates with effective therapy, increases with each interval of increasing concentration. The value above each bar refers to the number of samples within the respective concentration range (1 mg (base)/L = 4.3 μM). (From Koch-Weser, J.: *In* Pharmacology and the Future: Problems in Therapy. Edited by G.T. Okita and G.H. Archeson. Karger, Basel, 1973, Vol. 3, pp. 69–85.)

the arrhythmias are suppressed at concentrations of 2 to 8 mg/L. However, this belies the entire picture.

THERAPEUTIC PLASMA CONCENTRATION RANGE

Figure 5–3 shows the percent of those patients who did not respond to procainamide, those who responded, those who exhibited minor side effects, and those who exhibited serious toxicity. Side effects were considered minor when cessation of the drug was unnecessary and serious when disturbances of cardiovascular function or other adverse effects necessitated discontinuation of the drug. It should be noted in particular that serious toxicity begins to appear above 8 mg/L and occurs with increasing frequency at higher concentrations. Above 16 mg/L, the toxic effects may prove fatal. From these data, it can be concluded that the range of plasma concentrations of procainamide associated with effective therapy and without undue toxicity is 4 to 8 mg/L. This range is commonly known as the *therapeutic concentration range* of the drug.

Clearly, not all patients receiving procainamide for the treatment of ventricular arrhythmias need plasma concentrations between 4 and 8 mg/L. In a few, the arrhythmias are suppressed at concentrations below 4 mg/L; in others, toxicity occurs before efficacy, and for them procainamide is certainly not the drug of choice. Thus, a therapeutic concentration is most appropriately defined in terms of an individual patient's requirement. Usually, this information is unknown, and on initiating therapy, the therapeutic concentration must be estimated from consideration of the probability of therapeutic success within the typical patient population.

Also shown in Fig. 5–3 is a curve that represents the frequency of therapeutic effectiveness, i.e., the frequency of effective therapy minus the frequency of all toxic effects. This may be an inappropriate means of estimating the concentration at which therapeutic success is most probable. Perhaps the minor toxic effects should not be weighted equally against the desired response. Obviously, the major toxic effects should be given more weight. These are considerations requiring judgment.

Therapeutic Window

Let us expand philosophically on this concept of weighting developed for procainamide using the information in Fig. 5–3, adding hypersensitivity and assigning values to the responses according to our best judgment. Figure 5–4 shows the probabilities of the responses, plus that of hypersensitivity, each weighted by a judgmental factor versus the logarithm of the plasma concentration. The factor is negative for undesirable effects and positive for desirable effects. On algebraically adding the weighted probabilities, a *utility curve* is obtained that simply shows the chance of therapeutic success as a function of the plasma concentration. Both low and high concentrations have a negative utility; i.e., at these concentrations, the drug is potentially more harmful than helpful. There is an optimal concentration (8 mg/L) at which therapeutic success is most likely, and there is a range of concentrations (about 4 to 10 mg/L) within which the chances of successful therapy are high. This is the *therapeutic window* or *therapeutic concentration range*. Precise limits, of course, are not definable, particularly considering the subjective nature of the utility curve. Each drug produces its own peculiar responses, and the weighting assigned to these responses differ, but both the incidence of the drug effects and the relative importance of each effect must be evaluated to determine the therapeutic concentration range.

There are problems associated with the acquisition of the incidence of the various responses. For example, the procainamide data were obtained in patients who were sometimes titrated with the drug. That is, the dosage was adjusted when the patient had not adequately responded or when toxicity was present. However, patients even on the usual

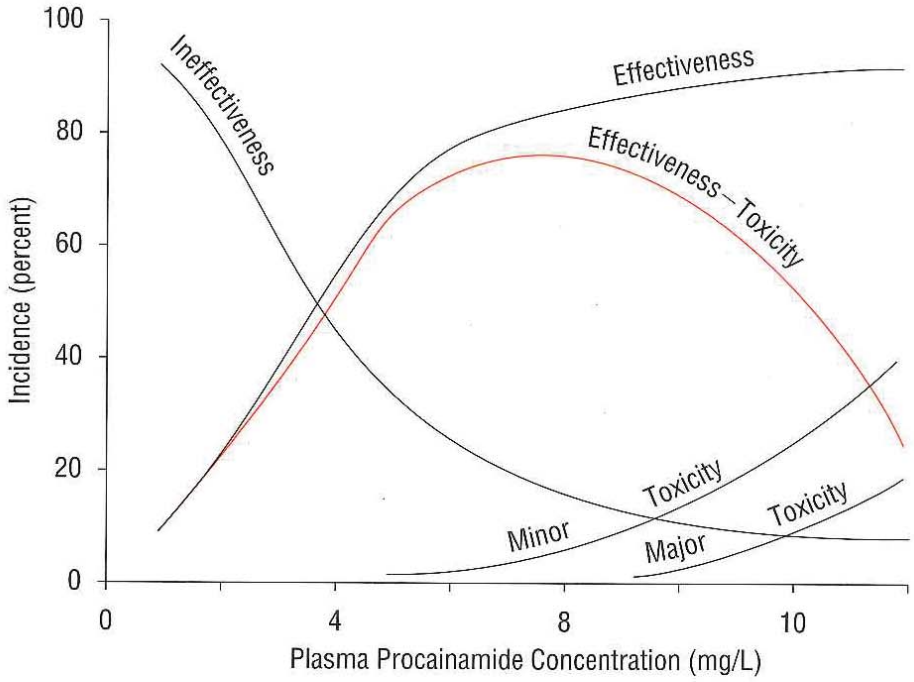

Fig. 5–3. Schematic representation of the frequency of ineffective therapy, effective therapy, minor side effects, serious toxicity, and "therapeutic effectiveness" with plasma concentration of procainamide in patients receiving this drug for the treatment of arrhythmias. Therapeutic effectiveness is defined arbitrarily as the difference in the frequency between effective therapy and toxic effects; the therapeutic effectiveness (colored line) of procainamide reaches a peak of 8 mg/L (1 mg/L = 4.3 μM). (Adapted from the data of Koch-Weser, J.: *In* Pharmacology and the Future: Problems in Therapy. Edited by G.T. Okita and G.H. Archeson. Karger, Basel, 1973, Vol. 3, pp. 69–85.)

dosage show a wide range of concentrations, leading one to question if selection of patients showing toxicity might have occurred. To avoid this bias, each of the patients should be titrated through all the responses. This is, of course, ethically unacceptable. Our information on toxicity must come from the patient who, for one reason or another, exhibits toxicity because the drug concentration is excessive or who has an unusual response at a low concentration.

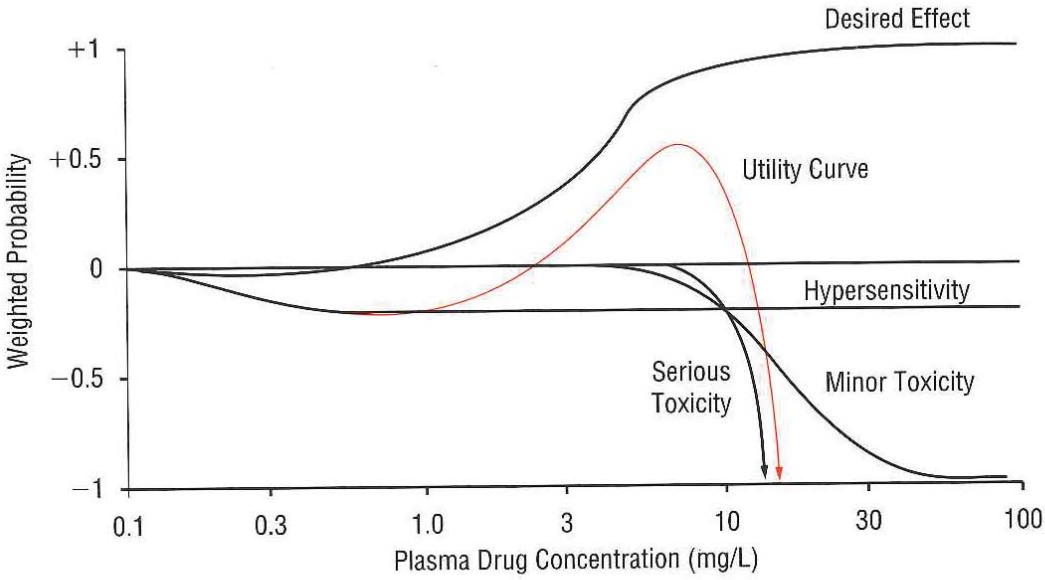

Fig. 5–4. Schematic diagram of the weighted probabilities of responses versus the plasma concentration of a drug. The probabilities from Fig. 5–3 (plus a hypothetical hypersensitivity reaction) are weighted by the following factors: desired effect, 1; hypersensitivity, −5; minor toxicity, −1; serious toxicity, −5. The algebraic sum of the weighted probabilities is the utility curve (colored line). According to this scheme, the highest weighted probability of therapeutic success occurs at 8 mg/L, and concentrations below 2 mg/L and above 12 mg/L are potentially more harmful than beneficial.

For the majority of patients, knowledge of a drug's therapeutic plasma concentration range and pharmacokinetics should lead to a more rapid establishment of a safe and efficacious dosage regimen. However, the narrower this range, the more difficult is the maintenance of values within it. The plasma concentration ranges associated with successful therapy of specific conditions are shown in Table 5–2 for a number of representative drugs.

Several points are worth noting about the data in Table 5–2. First, for most of these drugs, the therapeutic concentration range is narrow; the upper and lower limits differ by a factor of only 2 or 3. Of course, for many other drugs, this concentration range is much wider. Second, some drugs are used to treat several diseases, and the therapeutic plasma concentration range may differ with the disease. For example, a lower concentration of theophylline is needed to abolish episodes of recurring apnea in premature infants than is needed to substantially improve pulmonary function in patients with chronic airway diseases. Next, the upper limit of the plasma concentration may be either, like nortriptyline, a result of diminishing effectiveness at higher concentrations without noticeable signs of increasing toxicity or, like cyclosporine, a result of the possibility of nephrotoxicity. The upper limit may also be due to limiting effectiveness of the drug, as with the use of salicylic acid to relieve pain. Finally, toxicity may be either an extension of the pharmacologic property of the drug or totally dissociated from its therapeutic effect. The hemorrhagic tendency associated with an excessive plasma concentration of the oral anticoagulant, war-

farin, is an example of the former; the ototoxicity caused by the antibiotic gentamicin is an example of the latter.

Distinction also needs to be made between the steepness of a concentration–response curve and the width of a therapeutic window. This point is illustrated schematically in Fig. 5–5. Figure 5–5A shows a drug with a wide therapeutic window. The wide window occurs despite steep concentration–response curves for both efficacy and toxicity. Here toxicity occurs at concentrations well above those needed to achieve maximum desired effect. The normal strategy would be to ensure that all patients receive a dosage regimen that produces plasma concentrations that achieve maximal efficiency without toxicity. Figure 5–5B shows a drug with a narrow therapeutic window. The narrow window occurs despite shallow concentration–response curves for both efficacy and toxicity. This narrowness arises because the response curves overlap well below maximal efficacy, so that it is difficult to find plasma concentrations that produce efficacy without some degree of limiting toxicity.

It is to be stressed that significant interindividual variability may occur in both the efficacy and toxicity response curves, leading to differences among individuals in the location and width of the therapeutic window. This should be kept in mind when considering the therapeutic windows listed in Table 5–2. The values are derived from patient populations requiring the drugs and apply to the average patient within those populations. Also, keep in mind that the ultimate objective is to treat each individual patient as efficaciously and safely as possible and not to keep his or her plasma concentrations within the rec-

Table 5–2. Representative Drugs and Their Plasma Concentrations Usually Associated With Successful Therapy

DRUG	DISEASE/CONDITION	THERAPEUTIC WINDOW (mg/L)	THERAPEUTIC WINDOW (μM)
Acetazolamide	Glaucoma	10–30	50–150
Amikacin	Gram-negative infection	12–25[a]	—
Amitriptyline	Depression	0.12–0.25[b]	0.43–0.90
Carbamazepine	Epilepsy	4–12	17–51
Cyclosporine	Organ transplantation	0.15–0.4[c]	0.13–0.34
Desipramine	Depression	0.12[d]	0.45
Digitoxin	Cardiac dysfunction	0.01–0.02	0.013–0.026
Digoxin	Cardiac dysfunction	0.0006–0.002	0.0008–0.003
Ethosuximide	Epilepsy	25–75	180–540
Gentamicin	Gram-negative infection	4–12[a]	7–21
Lidocaine	Ventricular arrhythmias	2–6	4–25
Lithium	Manic and recurrent depression	—	0.4–1.4[e]
Nortriptyline	Endogenous depression	0.05–0.15	0.2–0.6
Phenobarbital	Epilepsy	10–30	40–120
Phenytoin	Epilepsy	10–20	30–60
	Ventricular arrhythmias	10–20	30–60
Procainamide	Ventricular arrhythmias	4–8	17–34
Propranolol	Angina	0.02–0.2	0.08–0.8
Salicylic Acid	Aches and pains	20–100	150–750
	Rheumatoid arthritis	100–300	750–2200
	Rheumatic fever	250–400	1800–3000
Theophylline	Asthma and chronic obstructive airway diseases	6–20	33–100
	Apnea	5–10	28–55
Tobramycin	Gram-negative infection	4–12[a]	35–120
Warfarin	Thromboembolic diseases	1–4	3–13
Valproic Acid	Epilepsy	40–100	280–690
Vancomycin	Penicillin-resistant infection	5–15[f]	3.3–10

[a] Thirty minutes after a 30-min infusion.
[b] Parent drug plus *N*-desmethyl metabolite.
[c] Whole blood, trough concentration.
[d] Suggested threshold concentration.
[e] Milliequivalents/liter.
[f] Sample obtained just before next dose.

ommended therapeutic window. This window does serve as a useful guide, however, particularly in the absence of additional information about the individual.

Therapeutic Correlates

So far, plasma concentration has been assumed to be a better correlate of a drug's therapeutic response and toxicity, in a population of patients needing a drug, than any other measure. However, since doses are administered, why not use dose as a therapeutic correlate? Certainly, in most cases, response, plasma concentration, and amount of drug in the body all increase with dose. Still, plasma concentration is expected to be a better

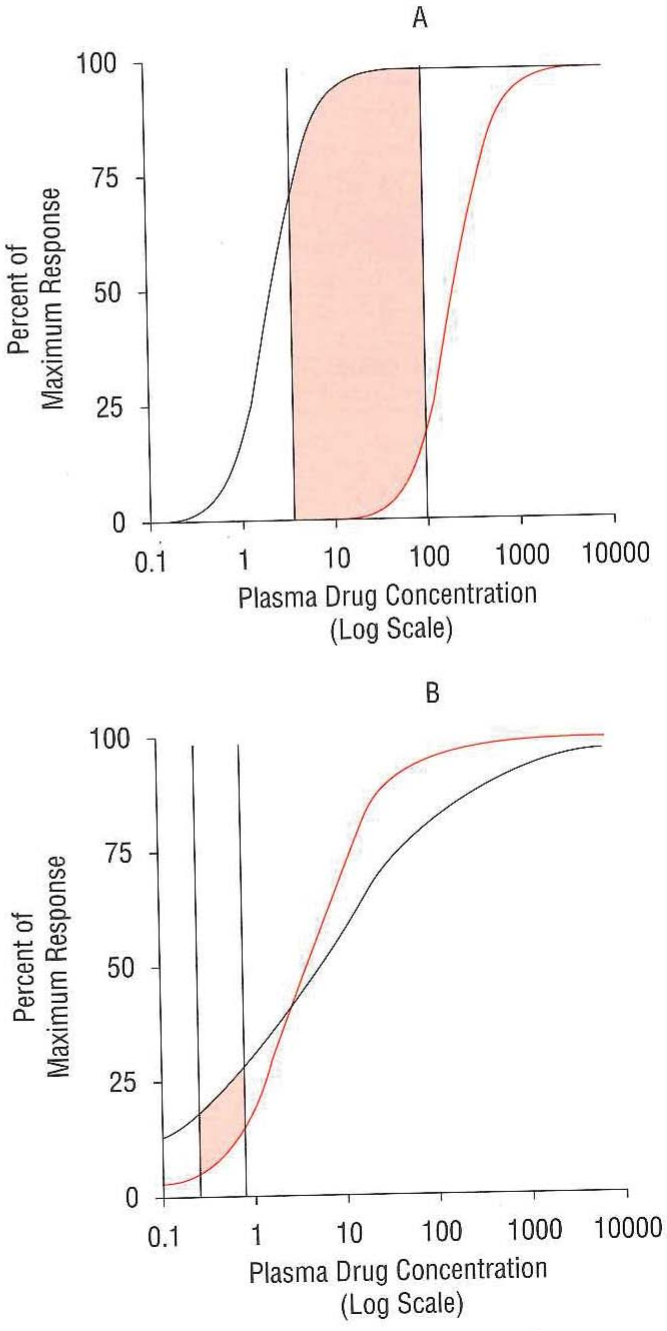

Fig. 5–5. The width of a therapeutic window depends on the degree of overlap of the efficacy (black lines) and toxicity (colored lines) concentration-response curves. *A*, The therapeutic window (shaded) is wide despite steep concentration-response curves for both efficacy and toxicity, as there is virtually no overlap between the two response curves. *B*, The therapeutic window (shaded) is narrow because of a high degree of overlap between efficacy and toxicity even though both the response curves are shallow.

correlate than dosage. This must be true following a single dose of drug, since with dose alone no account is taken of time. It may also be true for continuous drug administration but for a different reason.

The objective of most drug therapy is to maintain a stable therapeutic response, usually by maintaining an effective plasma concentration. Figure 1–6 (Chap. 1, p. 6) shows the relationship between the steady-state plasma concentration and the rate of administration of phenytoin, expressed as the daily dose per kilogram of body weight. There are large interindividual deviations in the plasma concentration at any dosing rate; in the patient cohort studied, the plasma concentration ranged from nearly 0 to 50 mg/L when the dosing rate is 6 mg/day/kg of body weight. Had no correction been made for body weight, the deviations would have been even greater. In contrast, plasma concentration correlates reasonably well with effect. Thus, seizures are usually effectively controlled at concentrations between 10 and 20 mg/L; side effects occur with increasing frequency and severity as the plasma concentration exceeds 20 mg/L, as shown in Fig. 5–6. The first sign of toxicity is usually nystagmus, which appears above a concentration of approximately 20 mg/L; gait ataxia usually appears with a concentration approaching 30 mg/L, and prolonged drowsiness and lethargy may be seen at concentrations in excess of 40 mg/L.

For phenytoin, plasma concentration is a better correlate than dose during chronic administration because pharmacokinetics is the major source of variability between dose and response. For other drugs, such as ampicillin, pharmacokinetic variability within the patient population is relatively small, and variability in the concentration–response curve is large. In such cases, plasma concentration is no better a correlate with response than dose and indeed may be worse if, for example, metabolites contribute to activity and toxicity (see below, Additional Considerations).

ADDITIONAL CONSIDERATIONS

Despite the appeal, measurement of plasma concentration is relatively uncommon in clinical practice (See Concentration Monitoring, Chap. 18). The major reason is the wide margin of safety of many drugs with direct and simple means of assessing the therapeutic and toxic responses. Another is that plasma concentration often correlates poorly with measured response. Some examples of poor correlations with explanations, where known, follow. This subject is considered further in Chap. 20, Pharmacologic Response.

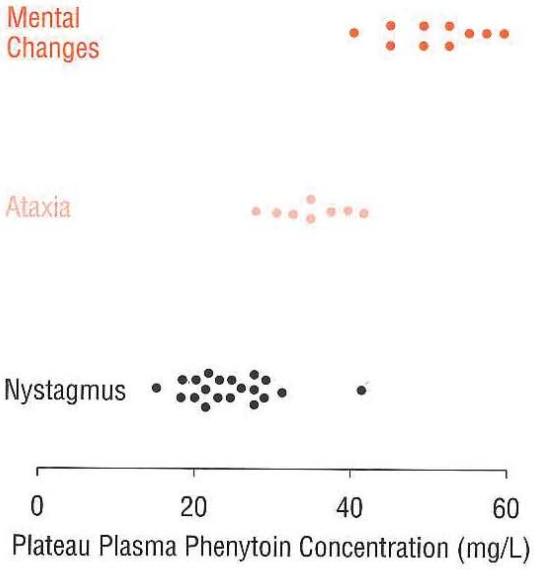

Fig. 5–6. The severity of the untoward effects of phenytoin increases in proportion to its concentration in plasma (1 mg/L = 4.0 μM). (Modified from Kutt, H., Winters, W., Kokenge, R., and McDowell, F.: Diphenylhydantoin metabolism, blood levels, and toxicity. Arch. Neurol., *11*:642–648, 1964. Copyright 1964, American Medical Association.)

Active Metabolites

Unless active metabolites are also measured, poor correlations may exist. For example, based on its plasma concentration, alprenolol is more active as a β-blocker when given as a single oral dose than when administered intravenously. This drug is highly cleared by the liver, and so in terms of the parent drug, the oral dose is poorly bioavailable. However, large amounts of metabolites, including an active species, 4-hydroxyalprenolol, are formed during the absorption process, which explains the apparent discrepancy. The tricyclic antidepressant amitriptyline offers a second example. Its antidepressant activity correlates poorly with the plasma concentration of parent drug. Only when the contribution of its active desmethyl metabolite is also considered can useful correlations be established. Other examples of active metabolites and the implications with respect to their pharmacologic response are discussed in Chap. 21, Metabolite Kinetics.

Chirality

About 40% of drugs contain one or more asymmetric (chiral) centers in the molecule. For each center, there are two possible mirror images or enantiomers, the R- and S-forms, which often differ in their pharmacokinetic and pharmacodynamic properties. Because of difficulty and cost of separation, the majority of synthetic chiral drugs are marketed as racemic mixtures. Failure to use a stereospecific chemical assay to measure the individual enantiomers can therefore lead to problems when attempting to correlate plasma concentration with response following administration of the racemate. Even when a stereospecific assay is employed, it is not always easy to know how to combine the enantiomer concentrations to relate to response when both enantiomers contribute to activity. For example, although R-warfarin is less potent than S-warfarin, it can still produce full anticoagulation. Thus, response cannot be related simply to the sum of the concentrations of warfarin enantiomers.

Tolerance and Acquired Resistance

The effectiveness of a drug can diminish with continual use. Acquired resistance denotes the diminished sensitivity of a population of cells (microorganisms, neoplasms) to a chemotherapeutic agent; tolerance denotes a diminished pharmacologic responsiveness to a drug. The degree of acquired resistance varies; it may be complete, thereby rendering the agent, e.g., an antibiotic, ineffective against a microorganism. The degree of tolerance also varies but is never complete. For example, within days or weeks of its repeated use, subjects can develop a profound tolerance but not total unresponsiveness to the pharmacologic effects (euphoria, sedation, respiratory depression) of morphine. Tolerance can develop slowly; e.g., tolerance to the central nervous system effects of ethanol takes weeks. Tolerance can also occur acutely (tachyphylaxis). Thus, tolerance, expressed by a diminished cardiovascular responsiveness, develops within minutes following repetitive administration of many β-phenethylamine-type sympathomimetics, such as isoproterenol. At any moment, a correlation might be found between the intensity of response and the plasma concentration of the drug, but the relationship varies with time.

Single-Dose Therapy

One dose of aspirin can often relieve a headache, which does not return even when all the drug has been eliminated. Other examples of effective single-dose therapy include the use of isoproterenol to relieve an acute asthmatic attack, colchicine to treat an acute gouty attack, nitroglycerin to relieve acute episodes of angina, and morphine to relieve acute pain. Although the specific mechanism of action is often poorly understood, the overall effect is

known; the drug returns an out-of-balance physiologic system to within normal bounds. Thereafter, feedback control systems within the body maintain homeostasis. The need for drug has now ended. In these instances of single-dose therapy, a correlation between effect and peak plasma concentration may exist, but beyond the peak, any such correlation is unlikely.

Duration Versus Intensity of Exposure

Some chemotherapeutic agents, e.g., methotrexate, exhibit peculiar relationships between response and dose. The response observed relates more closely to the duration of dosing than to the actual dose used or concentrations produced. This behavior for methotrexate can be explained by its activity as an antimetabolite. It inhibits dihydrofolate reductase, thereby preventing many methylation reactions in the body. These reactions can be inhibited for short periods of time, a few days, without causing irreversible damage. When the exposure is sufficiently prolonged, however, the damage is irreversible and potentially lethal.

Time Delays

It often takes some time for a measured response to fully reflect a given plasma concentration of drug. Until then, the continuously changing response makes any correlation between response and plasma concentration extremely difficult to establish. One source of the delay is the time required for equilibration to occur between drug in plasma and that at the site of action, usually in a tissue. This delay may be short if the drug enters the tissue rapidly; when effective, lidocaine suppresses ventricular arrhythmias within a few minutes of giving a bolus dose; thiopental induces anesthesia even more quickly. When the target organ resides in a slowly equilibrating tissue, the delay may be many hours. For example, the maximum cardiac effects of digoxin are not seen for an hour or more after administering an i.v. bolus of the drug.

Another source of delay can arise when the response monitored is an indirect measure of drug effect. A change in blood pressure is an indirect measure of either a change in peripheral resistance, in cardiac output, or in both. Plasma uric acid is another example; here, the direct effect is an alteration in uric acid synthesis or elimination. Yet another example of an indirect response is the change in the serum prothrombin complex activity produced by coumarin oral anticoagulants. The more direct effect of these anticoagulants is to inhibit synthesis of the prothrombin complex.

The delay between attainment of a plasma concentration and maximal indirect effect varies. Full response in blood pressure to a change in peripheral resistance or in cardiac output occurs within minutes, whereas maximal response of the prothrombin complex activity to warfarin is not seen for 1 to 2 days after an oral dose of this anticoagulant (Fig. 5–7).

Uric acid and the prothrombin complex are examples of endogenous materials. Such materials are continuously being renewed, with the pool size reflecting the balance between input and loss. The impact of changes in input and loss on the kinetics of endogenous compounds and the appropriate interpretation of such data are covered in greater detail in Chap. 23, Turnover Concepts.

MODALITY OF ADMINISTRATION AND THERAPEUTIC OUTCOME

As mentioned at the beginning of this chapter, maintenance of a plasma concentration is not always a desirable therapeutic objective. Sometimes, a fluctuating concentration is more desirable. Much depends on the pharmacodynamic features of efficacy and toxicity. This

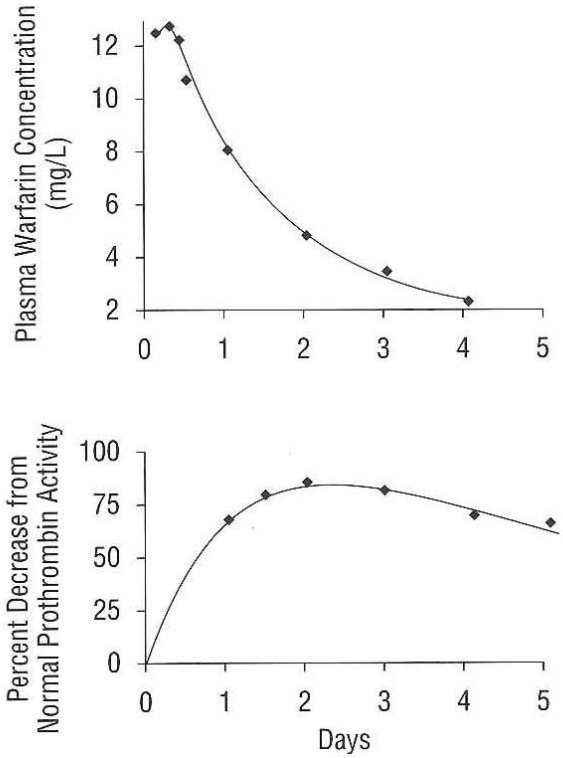

Fig. 5–7. The sluggish response in the plasma prothrombin complex activity to inhibition of its synthesis by warfarin reflects the indirect nature of the measurement and the slow elimination of this complex. For the first 2 days after giving a dose of warfarin, the complex activity steadily decreases. During the first day, the concentration of warfarin is sufficient to almost completely block complex synthesis. As warfarin concentration falls, the synthesis rate of the complex increases and by 48 hr equals the rate of degradation of the complex. Thereafter, with the synthesis rate exceeding the rate of degradation, the complex activity rises and eventually, when all the warfarin has been eliminated, returns to the normal prewarfarin steady-state level. The data points are the averages following the oral administration of 1.5 mg warfarin sodium per kg body weight in 5 male volunteers (1 mg/L = 3.3 μM). (From Nagashima, R., O'Reilly, R.A., and Levy, G.: Kinetics of pharmacologic effects in man: The anticoagulant action of warfarin. Clin. Pharmacol. Ther., *10*:22–35, 1969.)

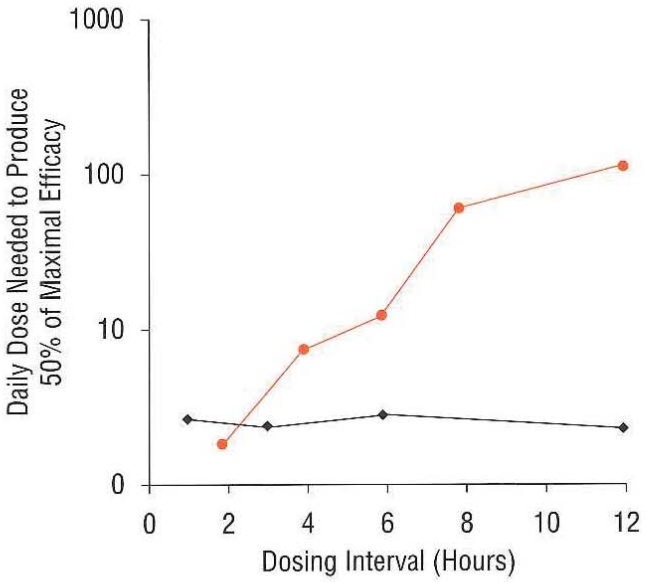

Fig. 5–8. The influence of lengthening the dosing interval on the daily dose needed to produce 50% of maximal efficacy in treating pneumonia due to *Klebsiella pneumoniae* in neutropenic mice varies with the antimicrobial agent. Whereas no change in daily dose is needed with gentamicin (black curve), much larger doses of ceftazidime (colored curve) are needed when administered less frequently. (From Leggett, J.E., Fantin, B., Ebert, S.C., Totsuka, K., Vogelman, R., and Craig, W.F.: Comparative antibiotic dose-effect relationships of several dosing intervals in murine pneumonitis and thigh-infection models. J. Infect. Dis., *159*:281–292, 1989.)

point is well illustrated with the antimicrobial agents. The purpose of antimicrobial therapy is the eradication of an infection with minimal toxicity. Figure 5–8 shows major differences in the effect of dosing frequency on the daily dose of ceftazidime and gentamicin required to produce 50% of maximal efficacy in pneumonia that is due to *Klebsiella pneumoniae* in neutropenic mice. Whereas decreasing the frequency of administration, and hence increasing the degree of fluctuation in plasma concentration, drastically diminished the efficacy of ceftazidime, it had minimal effect on gentamicin. The explanation lies in the different pharmacodynamic profiles of these two drugs.

Ceftazidime, like other β-lactam antibiotics, exhibits only minimal concentration-dependent bactericidal activity, so that bacterial killing is more dependent on time above the minimal bactericidal concentration than on the magnitude of the drug concentration. Greater benefit is therefore achieved with more frequent administration that minimizes the possibility of the plasma concentration falling too low. An additional reason for frequent administration is that the duration of the postantibiotic effect—whereby bacterial growth is suppressed for some time after intermittent exposure of bacteria to the antimicrobial agent—is very short with the β-lactam antibiotics.

In contrast to ceftazidime, gentamicin and other aminoglycosides produce a prolonged postantibiotic effect. They also exhibit marked concentration-dependent killing over a wide range of concentrations with higher values having a more pronounced effect on the rate and extent of bactericidal activity. Accordingly, large infrequent doses of gentamicin are as effective and potentially more so than smaller more frequent ones.

Although data in patients with infections, of necessity, are more variable than those obtained in the experimental mouse model, they do tend to bear out the findings in Fig. 5–8. Moreover, studies indicate that the nephrotoxicity of the aminoglycosides can be reduced by a once-daily regimen compared to more frequent administration. This may explain the tendency, in some quarters, to move from a thrice-daily to a once-daily administration of gentamicin.

ACHIEVING THERAPEUTIC GOALS

Chapters 6 and 7 present the basic principles for establishing and evaluating dosage regimens for those drugs that show reasonably valid correlations of response with dose and concentration. Chapter 6 examines features of constant-rate input, while Chap. 7 examines the principles underlying the administration of drug in discrete doses to attain and maintain therapeutic concentrations. Some additional complexities of the concentration–response relationship are addressed in Chap. 20, Pharmacologic Response.

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. Define the terms:
   a. All-or-none response.
   b. Graded response.
   c. Therapeutic window.
   d. Utility curve.
   e. Tolerance.
2. Explain why effect (desired or toxic) is often better correlated with plasma concentration than with dose.
3. List and briefly discuss four situations in which poor plasma drug concentration–response relationships are likely to occur.
4. List the plasma concentration ranges commonly associated with therapeutic responses of cyclosporine, digoxin, gentamicin, lithium, phenobarbital, phenytoin, and theophylline.
5. Briefly discuss, with examples, two situations for which frequency of administration of the same daily dose affects the therapeutic outcome.

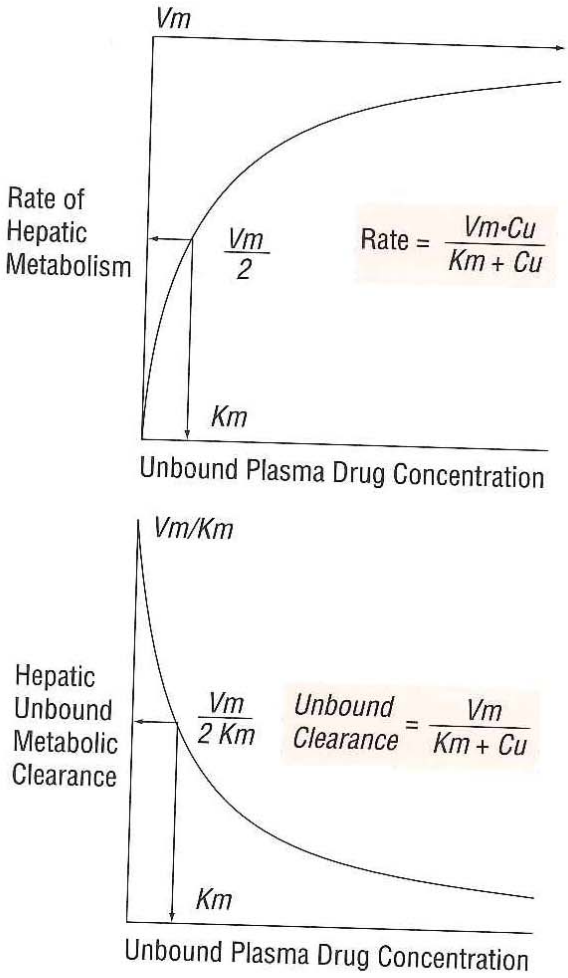

Fig. 11–5. When hepatic metabolism follows Michaelis-Menten kinetics, the rate of metabolism increases (top graph) toward a maximum value, *Vm*, as the plasma drug concentration is increased. The concentration at which the rate is one-half the maximum is the *Km* value. The unbound metabolic clearance (bottom graph) falls with increasing drug concentration. The concentration at which the clearance is one-half the maximum is also the *Km* value. The equations for the relationships are shown.

perfusion, plasma protein binding, and enzyme activity are altered. One of these models, the *well-stirred model*, in which instantaneous and complete mixing occurs within the liver, is particularly attractive because it can readily be used to summarize these principles. Even though it may not be quantitative, the model allows one to predict those situations in which either clearance or extraction ratio is affected and the expected direction of change.

The well-stirred model states that

$$CL_{b,H} = \frac{Q_H \cdot fu_b \cdot CL_{int}}{Q_H + fu_b \cdot CL_{int}} \qquad 13$$

where Q_H is the hepatic blood flow; CL_{int} is the intrinsic clearance that relates rate of metabolism to unbound concentration at the enzyme site, and fu_b is the fraction unbound in plasma. The hepatic extraction ratio, $CL_{b,H}/Q_H$, is then

$$E_H = \frac{fu_b \cdot CL_{int}}{Q_H + fu_b \cdot CL_{int}} \qquad 14$$

These two equations have the desired properties at the limits. Thus, when E_H approaches 1.0 (the perfusion rate-limited condition), $fu_b \cdot CL_{int}$ is much greater than Q_H,

and clearance approaches Q_H (Eq. 13). Changes in CL_{int} and fu here are not expected to influence CL_H and E_H much. Conversely, when E_H is small, Q_H must be much greater than $fu_b \cdot CL_{int}$. Now E_H and $CL_{b,H}$ are approximated by $fu_b \cdot CL_{int}/Q_H$ and $fu_b \cdot CL_{int}$, respectively; the value of the extraction ratio depends on all three factors, whereas clearance depends only on fu_b and CL_{int}.

Equation 14 offers an explanation for why the extraction ratios of most drugs appear to be either low ($E_H < 0.3$) or high ($E_H > 0.7$). Suppose, e.g., that the hepatocellular activity (intrinsic clearance) varied evenly from 0.01 to 100 L/min among a large group of compounds, i.e., over a 10,000-fold range, and that none is bound in plasma ($fu_b = 1.0$). Then substitution of these values into Eq. 14 shows that only those drugs with an intrinsic clearance in the narrow range of $0.43 \cdot Q_H$ to $2.3 \cdot Q_H$ have an intermediate extraction ratio, i.e. values between 0.3 and 0.7.

Strictly, as whole blood delivers drug to the liver, the fraction unbound in Eqs. 13 and 14 should refer to that in blood, not plasma. For didactic purposes, however, here and throughout remainder of the book where Eqs. 13 and 14 are applied, the two terms are equivalent. A major discrepancy occurs when the blood-to-plasma concentration ratio is much greater than 1.

First-Pass Considerations

To reach the general circulation, a drug given orally must pass through the liver via the portal system. The fraction escaping elimination by the liver, F_H, is the upper limit of the oral bioavailability. It may be calculated from the hepatic extraction ratio, E_H, since

$$\text{Maximum oral bioavailability} = 1 - \text{Hepatic extraction ratio} \qquad 15$$

Hepatic extraction ratio can be estimated if the hepatic (blood) clearance and hepatic blood flow are known or can be approximated.

For illustrative purposes, consider the following data obtained after an intravenous (i.v.) dose (500 mg) of a drug: Cumulative amount excreted unchanged (Ae_∞) = 152 mg, AUC = 385 mg-min/L, and the blood-to-plasma concentration ratio (C_b/C) = 1.2. Extrarenal elimination is assumed to occur only in the liver. The clearance (Dose/AUC) is then 1.3 L/min, and the blood clearance [$CL/(C_b/C)$] is 1.08 L/min. The fraction excreted unchanged (Ae_∞/Dose) is 0.304. Accordingly, the renal blood clearance ($fe \cdot CL_b$) is 0.32 L/min, and by difference, the hepatic blood clearance [$(1 - fe)CL_b$] is 0.76 L/min. Dividing by hepatic blood flow to obtain the hepatic extraction ratio, the maximum oral bioavailability is

$$F \simeq F_H = 1 - (1 - fe)\, CL_b/Q_H \qquad 16$$

which, in this example, is 0.56 for a hepatic blood flow of 1.35 L/min. Being physiologically determined, no amount of pharmaceutical manipulation can improve on this value for an oral dosage formulation. Any drug with a high hepatic extraction ratio (see Table 11–2) has a low oral bioavailability. There may be other factors that limit drug reaching the portal vein and so further decrease bioavailability, as described in Chap. 9, Absorption.

First-Pass Predictions

The effects of changing blood flow, intrinsic clearance, or protein binding on first-pass extraction can be predicted using the *well-stirred* model by substituting Eq. 14 into the relationship $F_H = 1 - E_H$. That is,

$$F_H = \frac{Q_H}{Q_H + fu_b \cdot CL_{int}} \quad 17$$

It should be re-emphasized that the prediction here, for changes in CL_H, E_H, and F_H with changes in Q_H, CL_{int}, or fu_b, are based on modest alterations. A low extraction ratio drug can become a high extraction ratio drug if CL_{int} or fu_b is increased or if Q_H is decreased by a sufficiently large factor (Fig. 11–4). The principles here refer to the relative tendencies that modest changes in these factors are likely to produce.

The effect on first-pass extraction can also be visualized by regarding perfusion and protein binding to be in competition with enzymatic activity; perfusion and protein binding help to move drug through the organ, making drug available to the general circulation, whereas enzyme activity removes drug from the perfusing blood.

Consider first the case of a drug with an E_H near zero, that is, Q_H much greater than $fu_b \cdot CL_{int}$. Then F_H is independent of changes in Q_H, CL_{int} or fu_b. This is not surprising as the extraction is so small that everything presented gets past the liver anyway. Consider next the condition in which $fu_b \cdot CL_{int}$ is much greater than Q_H, so that E_H approaches 1.0. In this case, $F_H = Q_H/(fu_b \cdot CL_{int})$, that is, bioavailability is low and dependent on all three factors. An increase in blood flow increases bioavailability by decreasing the time drug spends in the liver, where elimination occurs. An increase in either enzymatic activity or in fu_b (which raises the unbound concentration for a given incoming total concentration) decreases bioavailability by increasing the rate of elimination for a given rate of presentation to the liver.

Biliary Excretion and Enterohepatic Cycling

Small molecular weight drugs are found in bile; whereas protein drugs tend to be excluded. Drug in bile enters the intestine after storage in the gallbladder. In the intestine it may be reabsorbed to complete an enterohepatic cycle. Drug may also be metabolized in the liver, e.g., to a glucuronide. The glucuronide is then secreted into the intestine, where the β-glucuronidase enzymes of the resident flora may hydrolyze it back to the drug, which is then reabsorbed. Enterohepatic cycling of drugs directly and indirectly through a metabolite is represented schematically in Fig. 11–6. Recall from Chap. 2 that enterohepatic cycling is a component of distribution not elimination.

Any drug in bile not reabsorbed, either directly or indirectly via a metabolite, is excreted from the body via the feces. The efficiency of biliary excretion can be expressed by biliary clearance.

$$\text{Biliary clearance} = \frac{(\text{Bile flow}) \cdot (\text{Concentration in bile})}{(\text{Concentration in plasma})} \quad 18$$

Bile flow is a relatively steady 0.5 to 0.8 mL/min. Thus, for a drug with a concentration in the bile equal to or less than that in plasma, the biliary clearance is small. A drug that concentrates in the bile, however, may have a relatively high biliary clearance. Indeed, the bile-to-plasma concentration ratio can approach 1000. Therefore, biliary clearances of 500 mL/min or higher can be achieved. Eventually, of course, biliary clearance is limited by hepatic perfusion.

Bile is not a product of filtration, but rather of secretion of bile acids and other solutes. The pH of bile averages about 7.4. The biliary transport of drugs, however, is similar to active secretion in the kidneys (p. 172) in that it may be competitively inhibited.

A few generalizations can be made regarding the characteristics of a drug needed to ensure high biliary clearance. First, the drug must be actively secreted; separate secretory

mechanisms exist for acids, bases, and un-ionized compounds. Second, it must be polar, and, last, its molecular weight must exceed 250 g/mole. The latter two requirements may be a consequence of the apparent porous as well as lipophilic nature of bile cannaliculae. Both nonpolar and small molecules may be reabsorbed. These arguments do not aid in predicting the nature and specificity of the secretory mechanisms, but they do aid in predicting the likelihood of a high biliary clearance. For example, glucuronide conjugates of drugs are polar, ionized, *pKa* about 3, and have molecular weights exceeding 300 g/mole. They are often highly cleared into bile.

RENAL CLEARANCE

When the rate of urinary excretion is directly proportional to the plasma drug concentration,

$$\text{Rate of excretion} = Cl_R \cdot C \qquad 19$$

renal clearance is constant. This constancy forms the basis for the use of urine data to determine the time course of a drug in the body (Chap. 3). Interpretation of urine data with respect to plasma concentration is clearly complicated for drugs whose renal clearance varies. Factors that influence renal clearance include plasma drug concentration (see Chap. 22, Dose and Time Dependencies), plasma protein binding, urine flow, and urine pH. How these factors influence renal clearance is explained by the anatomy and physiology of the kidneys.

The Nephron: Anatomy and Function

The basic anatomic unit of renal function is the nephron (Fig. 11–7). Basic components are the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting tubule. The glomerulus receives blood first and filters about 120 mL of plasma water each minute. The filtrate passes down the tubule. Most of the water is reabsorbed; only 1 to 2 mL/min

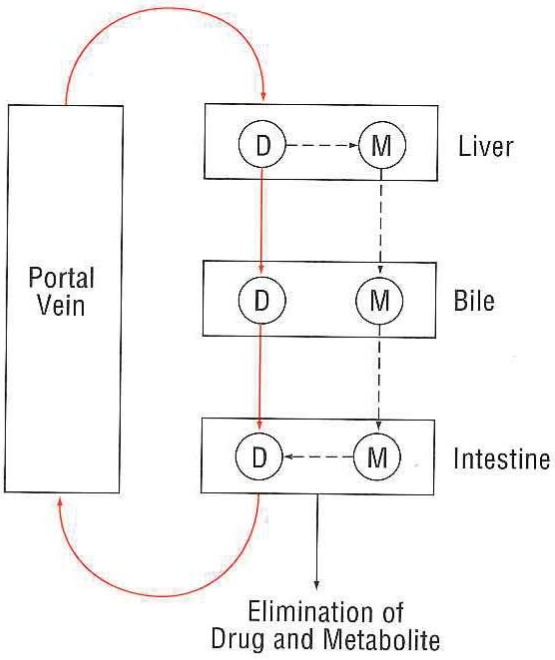

Fig. 11–6. When a drug (D) is absorbed from intestine, excreted in bile, and reabsorbed from intestine, it has undergone enterohepatic cycling (colored arrows), a component of distribution. Similarly, when a drug is converted to a metabolite (M) that is secreted in bile, converted back to drug in the intestine, and drug is reabsorbed (dashed arrows), the drug has also undergone enterohepatic cycling, in this case indirectly through a metabolite.

19

DISTRIBUTION KINETICS

OBJECTIVES

The reader will be able to:

1. State why the one-compartment model is sometimes inadequate to describe kinetic events within the body.
2. Compare the sum of two exponentials with the compartment model for representing plasma concentration data showing distribution kinetics.
3. Estimate clearance and the half-life of the phase associated with the majority of elimination given plasma concentration-time data of a drug showing distribution kinetics.
4. Define and estimate the distribution parameters: initial dilution volume (V_1), volume during the terminal phase (V), and volume of distribution at steady state (V_{ss}).
5. Describe the impact of distribution kinetics on the interpretation of plasma concentration-time data following administration of a single dose.
6. Explain the influence of distribution kinetics and duration of administration on the time-courses of concentration in plasma and amount in tissue during and after stopping a constant-rate infusion.
7. Describe how distribution kinetics influences the fluctuations of plasma and tissue levels with time during a multiple-dose regimen.
8. Explain how distribution kinetics can influence the interpretation of plasma concentration-time data and terminal half-life when clearance is altered.

The first four sections cover most of the fundamentals of pharmacokinetics. Section Five now expands on selected topics; it begins with chapters on distribution kinetics and pharmacologic response. Subsequent chapters deal with metabolite kinetics, dose and time dependencies, turnover concepts and dialysis. These topics do not build on each other as extensively as do the previous topics. Notable exceptions to this statement are found in applications of distribution kinetic concepts in the chapters on pharmacologic response, turnover concepts, and dialysis.

Portraying the body as a single compartment is appropriate for establishing the fundamental principles of pharmacokinetics but is an inaccurate representation of events that follow drug administration. A basic assumption of the concept of a one-compartment representation of distribution is that equilibration of drug between tissues and blood occurs spontaneously. In reality, distribution takes time. The time required depends on tissue perfusion, permeability characteristics of tissue membranes for drug, and its partitioning between tissues and blood (Chap. 10). Ignoring distribution kinetics is reasonable so long as the error incurred is acceptable. This error becomes unacceptable when the one-compartment representation fails to adequately explain observations following drug adminis-

tration; there is a danger of significant misinterpretation of the observations; and major discrepancies occur in the calculation of drug dosage. Such situations are most likely to arise when either substantial amounts are eliminated or response occurs before distribution equilibrium is achieved. This chapter deals with the pharmacokinetic consequence of distribution kinetics. The impact of distribution kinetics on pharmacologic response is dealt with in the next chapter, Pharmacologic Response.

EVIDENCE OF DISTRIBUTION KINETICS

Evidence of distribution kinetics is usually inferred from an early rapid decline in plasma (blood) concentration following an i.v. bolus dose; when little drug has been eliminated, and from the rapid onset and decline in the pharmacologic effect of some drugs during this early phase. Data in Fig. 19–1, which show the concentration of thiopental in various tissues after an i.v. bolus dose of this preoperative general anesthetic to a dog, provide direct evidence of distribution kinetics. Thiopental is a small, highly lipid-soluble drug for which distribution into essentially all tissues is perfusion rate-limited. The results seen with this drug are therefore typical of those observed with many other small lipophilic drugs.

Notice that thiopental in liver, a highly perfused organ, reaches distribution equilibrium with that in plasma by 5 min (the first observation), and thereafter, the decline in liver parallels that in plasma. The same holds true in other highly perfused tissues, including brain and kidneys.

Redistribution of thiopental from well-perfused tissues to less well-perfused tissues, such as muscle and fat, primarily accounts for the subsequent decline in plasma concentration over the next 3 hr; less than 20% of the dose is eliminated during this period. Due to a combination of poor perfusion and high partitioning, even by 3 hr distribution equilibrium in adipose tissue has not been established. Analysis of the situation indicates that this does not occur for several more hours, at which time the majority of thiopental remaining is in fat. Recall: The greater the partition of a drug into fat, or into any tissue, the longer is the time required to achieve distribution equilibrium (Chap. 10). However, only if the ap-

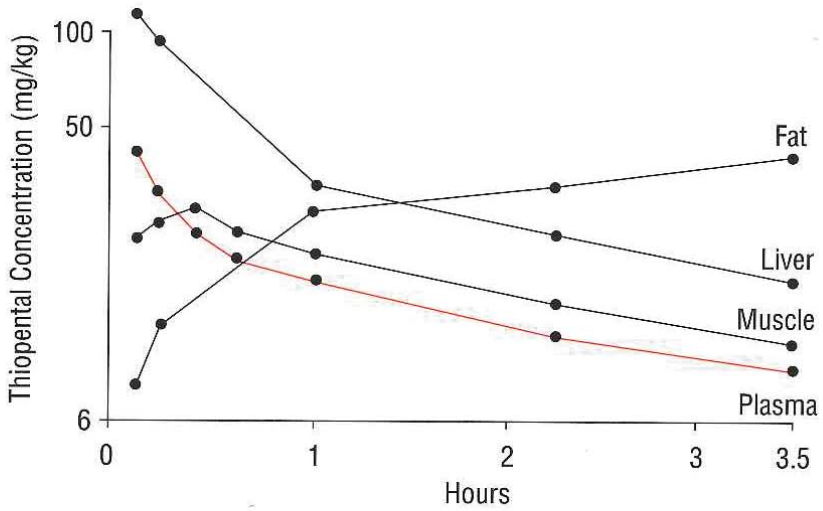

Fig. 19–1. Semilogarithmic plot of the concentration of thiopental in various tissues and plasma (colored line) following an i.v. bolus dose of 25 mg/kg to a dog. Note the early rise and fall of thiopental in the well-perfused tissues (e.g., liver) and in lean muscle tissue. After 3 hr much of the drug remaining in the body is in adipose tissue (1 mg/kg = 4.1 μmol/kg). (Redrawn from Brodie, B.B., Bernstein, E., and Mark, L.: The role of body fat in limiting the duration of action of thiopental. J. Pharmacol. Exp. Ther., *105*:421–426, 1952. © Williams & Wilkins (1952).)

parent volume of distribution of a tissue ($K_p \cdot V_T$) is a major fraction of the total volume of distribution does uptake into that tissue substantially affect events within plasma. With thiopental, which has an adipose-to-plasma partition coefficient of 10, fat (0.12 L/kg) constitutes approximately 40% of the total volume of distribution (2.3 L/kg). Accordingly, the plasma concentration of thiopental not only falls markedly, but distribution takes many hours. For other drugs, distribution may take even longer if partitioning into tissues is more extensive than for thiopental. In contrast, distribution is complete within 30 min after administration of theophylline (Fig. 3–1). Either theophylline does not enter poorly perfused tissues or if it does the partition coefficients are very low. It is impossible to distinguish between these two possibilities by measuring theophylline only in plasma, as events here may poorly reflect those that might occur elsewhere.

INTRAVENOUS BOLUS DOSE

Presentation of Data

Sum of Exponential Terms. The early rapid and subsequent slower decline in the plasma concentration of aspirin in an individual subject following a 650-mg i.v. bolus dose (Fig. 19–2) is typical of many drugs. Had no samples been taken during the first 10 min, the terminal linear decline of the plasma concentration when plotted on semilogarithmic graph paper would have been characterized by a monoexponential equation, and one-compartment disposition characteristics would have been applied to aspirin. Recall: The monoexponential equation is $C(0) \cdot e^{-kt}$, where k is the rate constant with an associated half-life, given by $0.693/k$, and $C(0)$ is the anticipated initial plasma drug concentration, given as the intercept on the plasma concentration axis when the line is extrapolated back to time zero. For aspirin k is 0.050 min^{-1}, the corresponding half-life is 14 min, and $C(0)$ is 33 mg/L. Going further, the volume of distribution [Dose/$C(0)$] is 20 L and clearance ($k \cdot V$) is 0.98 L/min.

Notice that the early plasma concentrations are higher than those anticipated by back extrapolation of the terminal slope and that the earlier the time, the greater is the difference. When the difference at each sample time is plotted on the same graph, all the difference values fall on another straight line, which can be characterized by a monoex-

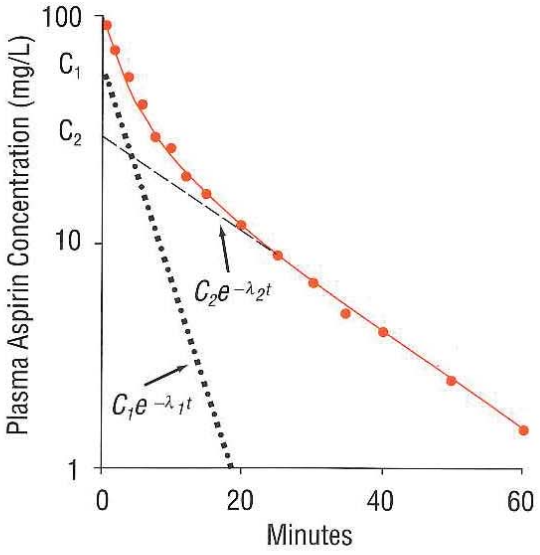

Fig. 19–2. When displayed semilogarithmically, the fall in the plasma concentration of aspirin is initially rapid but then slows after an i.v. bolus dose of 650 mg to a subject. The decline in concentration (——) can be characterized by the sum of two exponential terms: $C_1e^{-\lambda_1 t}$ (●■●■) and $C_2e^{-\lambda_2 t}$ (– – –) (1 mg/L = 5.5 μM). (Redrawn from Rowland, M., and Riegelman, S.: Pharmacokinetics of acetylsalicylic acid and salicylic acid after intravenous administration in man. J. Pharm. Sci., 57:1313–1319, 1968.)

ponential equation, $B(0)e^{-\alpha t}$, where α is the decay rate constant and $B(0)$ is the corresponding zero-time intercept. For aspirin, $\alpha = 0.23\ \text{min}^{-1}$, $t_{1/2} = 3.0$ min, and $B(0) = 67$ mg/L.

Because all the plasma concentrations at the later times can be fitted by one equation, $C(0)e^{-kt}$ and because at the earlier times, all the difference values can be fitted by another equation, $B(0)e^{-\alpha t}$, it follows that the entire plasma drug concentration (C) versus time data can be fitted by the *sum* of these two exponential terms. That is

$$C = B(0)e^{-\alpha t} + C(0)e^{-kt} \qquad 1$$

For example, the biexponential equation $C = 67e^{-0.23t} + 33e^{-0.050t}$, where t is time in minutes, adequately describes the decline in the plasma aspirin concentration following a 650-mg bolus dose. Sometimes, when using this difference procedure, known commonly as the *method of residuals*, a sum of three and occasionally four exponential terms is required to adequately fit the observed concentration-time data. Since the principles in approaching such data are the same as those used to analyze and interpret events described by a biexponential equation, only the simpler case is considered further in this book.

To facilitate the discussion a more uniform set of symbols is needed. Rather than using the different symbols α and k, the general symbol λ is used to denote the exponential coefficient. Thus, Eq. 1 can be rewritten as

$$C = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t} \qquad 2$$

where the subscripts 1 and 2 refer to the first and second exponential terms respectively, and C_1 and C_2 refer to the corresponding zero-time intercepts, or coefficients. By convention, the exponential terms are arranged in decreasing order of λ. For example, in the case of aspirin $C_1 = 67$ mg/L, $\lambda_1 = 0.23\ \text{min}^{-1}$, $C_2 = 33$ mg/L, and $\lambda_2 = 0.050\ \text{min}^{-1}$.

With aspirin, two exponential terms and hence two phases are seen when plasma concentration-time data are displayed on a semilogarithmic plot. Commonly, the last phase is called the *terminal phase*. With aspirin and many other drugs it is a correct description. Sometimes, however, there is an additional, still slower phase, indicating that distribution equilibrium has not been achieved with all tissues. The terminal phase is often missed because the assay procedure employed is insufficiently sensitive to measure the drug concentration at these later times. This certainly was the case with aminoglycosides and some amine drugs before the advent of more sensitive assays. With increased potency of many new compounds, analytical sensitivity continues to be an occasional problem in drug development. In the subsequent discussion, the observed terminal phase is assumed to be correctly designated.

At time zero the anticipated plasma concentration is, by reference to Eq. 2, equal to the sum of the coefficients, $C_1 + C_2$. At that time the amount in the body is the dose. Hence, by definition, the volume into which drug appears to distribute initially, the *initial dilution volume*, V_1, is given by

$$V_1 = \frac{\text{Dose}}{(C_1 + C_2)} \qquad 3$$

For aspirin, the anticipated initial concentration is 100 ($= 67 + 33$) mg/L so that the initial dilution volume of aspirin is 6.5 L.

It is important to realize that the time for concentration to fall by one-half is only equal to a half-life during the terminal phase. Before then, the plasma concentration falls in half in a period of less than one terminal half-life but more than one initial half-life. This is

clearly evident on comparing the fall in plasma aspirin concentration in the earlier moments with the decline of the first exponential term.

A Compartmental Model. Although for the majority of situations in pharmacokinetics the desired information can be obtained directly from modification of Eq. 2, it is sometimes conceptually helpful to represent disposition pictorially. Figure 19–3, a *two-compartment model*, is a common form of such a representation. Compartment 1, the initial dilution volume mentioned above, is also frequently called the central compartment because drug is administered into and distributed from it. As mentioned, the initial dilution volume of aspirin is 6.5 L; for many other drugs it is much larger. These values are clearly greater than the plasma volume, 3 L, and therefore this initial dilution volume must be composed of additional spaces into which drug distributes extremely rapidly. These spaces must be in well-perfused tissues, which probably include liver and kidneys, the major eliminating organs. Elimination is therefore usually depicted as occurring *directly* and *exclusively* from the central compartment. Drug distributes between this central compartment and a peripheral compartment, composed of tissues into which drug distributes more slowly.

Several points are worth mentioning here. First, the model is defined by the data. The number of compartments or pools required equals the number of exponential terms needed to describe the plasma concentration-time data. Thus, a three-compartment model is needed when the data are best fitted by a triexponential equation. Next, the model depicted in Fig. 19–3, or any other model for which drug elimination is portrayed as occurring exclusively from the central compartment, is not unique. Three two-compartment models can adequately describe a biexponential plasma concentration decay curve: the one depicted in Fig. 19–3, one with elimination occurring from both compartments, and one with loss occurring exclusively from the peripheral compartment. No distinction between these three possibilities can be made from plasma concentration-time data alone, and while the model depicted in Fig. 19–3 is the most favored one, based on such physiologic considerations as the initial dilution volume exceeding the plasma volume, elimination can sometimes occur in tissues of the peripheral compartment. Moreover, occasionally the liver (or kidneys) is not part of the central compartment. For example, the initial dilution volume of indocyanine green, a dye used as a dynamic test of hepatic function, is only 3 L, the plasma volume. The major peripheral tissue, in this instance the liver, is also the primary site of elimination via biliary excretion. A two-compartment model, with elimination occurring only from the peripheral compartment, therefore best describes the disposition kinetics of this dye. Last, drug distribution within a compartment is not homogenous. Although the concentrations of drug within and among such tissues usually vary enor-

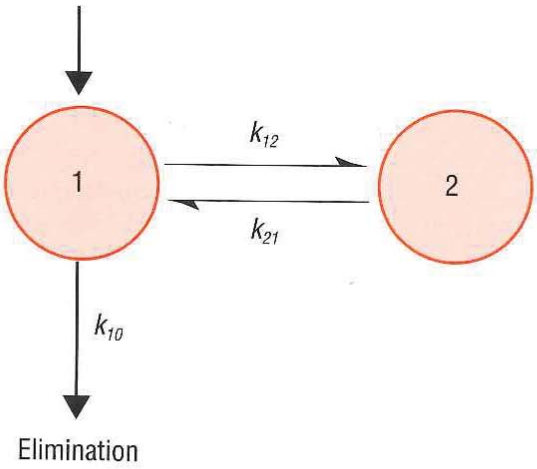

Fig. 19–3. A two-compartment model of the body. Drug is administered into and eliminated from compartment 1 and distributes between compartments 1 and 2. The rate constants for the processes are indicated.

mously, tissues are lumped together into a compartment because the times to achieve distribution equilibrium in each tissue are similar.

In Fig. 19–3 movement of drug between compartments can be characterized by transfer rate constants, where k_{12} denotes the rate constant associated with movement of drug from compartment 1 into compartment 2, and k_{21} is the rate constant associated with the reverse process. The rate constant k_{10} is associated with loss of drug from compartment 1 by metabolism and excretion. The unit of all three rate constants is reciprocal time.

Rate equations can be written for movement of amounts between the compartments and for drug elimination. Following an i.v. bolus dose these equations are

$$\begin{array}{lcccccc} \text{Rate of change of amount of drug in compartment 1} & = & -k_{12}\cdot A_1 & - & k_{10}\cdot A_1 & + & k_{21}\cdot A_2 \\ & & \text{Rate of movement from compartment 1 to compartment 2} & & \text{Rate of elimination} & & \text{Rate of movement from compartment 2 to compartment 1} \end{array} \quad 4$$

$$\begin{array}{lccccc} \text{Rate of change of amount of drug in compartment 2} & = & k_{12}\cdot A_1 & - & k_{21}\cdot A_2 \\ & & \text{Rate of movement from compartment 1 to compartment 2} & & \text{Rate of movement from compartment 2 to compartment 1} \end{array} \quad 5$$

where A_1 and A_2 are the amounts of drug in compartments 1 and 2, respectively. Integration of these rate equations provides a biexponential equation, of the same form as Eq. 2, for the decline of drug from plasma, except that the coefficients and exponents are recast in terms of the parameters defining the compartmental model. Equivalent relationships between the biexponential and two-compartment models are listed in Table 19–1.

Table 19–1. Equivalent Relationships Between the Biexponential and Two-Compartment Models[a]

PARAMETER/VARIABLE	SUM OF EXPONENTIALS	TWO-COMPARTMENT MODEL
Plasma concentration (C)	$C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t}$	$\left[\frac{\text{Dose}}{V_1}\cdot\frac{(k_{21}-\lambda_1)}{(\lambda_2-\lambda_1)}\right]e^{-\lambda_1 t} + \left[\frac{\text{Dose}}{V_1}\cdot\frac{(k_{21}-\lambda_2)}{(\lambda_1-\lambda_2)}\right]e^{-\lambda_2 t}$
	λ_1	$1/2[(k_{12}+k_{21}+k_{10}) + \sqrt{(k_{12}+k_{21}+k_{10})^2 - 4k_{21}k_{10}}]$
	λ_2	$1/2[(k_{12}+k_{21}+k_{10}) - \sqrt{(k_{12}+k_{21}+k_{10})^2 - 4k_{21}k_{10}}]$
	$\lambda_1+\lambda_2$	$k_{12}+k_{21}+k_{10}$
	$\lambda_1\cdot\lambda_2$	$k_{21}\cdot k_{10}$
Clearance (Cl)	$\text{Dose}/\left(\frac{C_1}{\lambda_1}+\frac{C_2}{\lambda_2}\right)$	$V_1\cdot k_{10}$
Initial dilution volume (V_1)	$\text{Dose}/(C_1+C_2)$	V_1
Volume of distribution (V) during terminal phase (V)	Cl/λ_2	$V_1\cdot k_{10}/\lambda_2$
Volume of distribution at steady state (V_{ss})	$\text{Dose}\left[\frac{C_1}{\lambda_1^2}+\frac{C_2}{\lambda_2^2}\right] \Big/ \left[\frac{C_1}{\lambda_1}+\frac{C_2}{\lambda_2}\right]^2$	$V_1\cdot(1+k_{12}/k_{21})$

[a]Model in which drug is eliminated from the initial dilution volume only.

Although expressing data in terms of a compartmental model and associated parameters may appear to give greater insight into the data, caution should be exercised in doing so. Remember that the compartmental model chosen is often not unique, and one can rarely assign a physical or physiologic meaning to the value of any of the rate constants. Accordingly, much of the subsequent discussion is related to describing drug disposition by the sum of exponentials. However, pharmacokinetic observations are discussed in terms of the compartmental model when this procedure facilitates general understanding.

Pharmacokinetic Parameters

Clearance. Elimination occurs at all times. Just as plasma concentration is highest immediately following an intravenous bolus dose, so is rate of elimination ($CL \cdot C$). Subsequently, both plasma concentration and corresponding rate of elimination fall rapidly. To calculate the amount eliminated in a small unit of time, dt, recall that

$$\text{Amount eliminated within interval } dt = \text{Clearance} \cdot C \cdot dt \qquad 6$$

where $C \cdot dt$ is the corresponding small area under the plasma concentration-time curve within the interval dt. The total amount eliminated, the dose administered, is the sum of all the small amounts eliminated from time zero to time infinity. Therefore,

$$\text{Dose} = \text{Clearance} \cdot AUC \qquad 7$$

where AUC is the *total* area under the plasma drug concentration-time curve. Accordingly, as with the simpler one-compartment model, clearance (CL) is most readily estimated by dividing Dose by AUC. The area may be determined from the trapezoidal rule (Appendix I–A) or, more conveniently, by realizing that the total area underlying each exponential term is the zero-time intercept divided by its corresponding exponential coefficient. Thus, the total area corresponding to Eq. 2 is given by

$$AUC = \underbrace{\frac{C_1}{\lambda_1}}_{\substack{\text{Area associated}\\ \text{with}\\ \text{initial term}}} + \underbrace{\frac{C_2}{\lambda_2}}_{\substack{\text{Area associated}\\ \text{with}\\ \text{last term}}} \qquad 8$$

When inserting the appropriate values for the aspirin example into Eq. 8, the value of AUC associated with the 650-mg dose is 951 mg-min/L, so that the total clearance of aspirin in the individual is 683 mL/min. Notice that clearance is considerably smaller than the value calculated assuming a one-compartment model, 985 mL/min. The latter is an overestimate of the true value, because more drug is eliminated during the attainment of distribution equilibrium than accounted for by the last term. If instead of the first phase a later phase is missed, the error in estimating clearance is large only if the missed area is a major fraction of the total area. Obviously, given the ease of estimating total area and provided that blood sampling times are adequate, the true value for clearance should always be calculated.

Volume of Distribution. One purpose of a volume term is to relate plasma concentration to amount in the body. The initial dilution volume fulfills this purpose initially. Subsequently, however, as drug distributes into the slowly equilibrating tissues, the plasma concentration declines more rapidly than does the amount in the body (A). Accordingly, as illustrated in Fig. 19–4 the effective volume of distribution (A/C) increases with time

until distribution equilibrium between drug in plasma and all tissues is achieved; this occurs during the terminal phase. Only then does decline in all tissues parallel that in plasma and is proportionality between plasma concentration and amount in body achieved.

The volume of distribution during the terminal phase (V) can be calculated as follows. During this phase the concentration is given by $C_2e^{-\lambda_2 t}$ (Fig. 19–2), and correspondingly,

$$\begin{matrix}\text{Amount of drug}\\ \text{in body during}\\ \text{terminal phase}\end{matrix} = V \cdot C = V \cdot C_2 e^{-\lambda_2 t} \qquad 9$$

Hence, extrapolating back to time zero, $V \cdot C_2$ must be the amount needed to give a plasma concentration of C_2, had drug spontaneously distributed into the volume, V. The amount, $V \cdot C_2$, remains to be calculated. When placed into the body, the amount, $V \cdot C_2$, is eventually matched by an equal amount eliminated. As the amount remaining to be eliminated is the product of clearance and area, and as C_2/λ_2 is the associated area, it follows that

$$\begin{matrix}V \cdot C_2\\ \text{Amount in body}\end{matrix} = \begin{matrix}Cl \cdot \dfrac{C_2}{\lambda_2}\\ \text{Amount remaining to be eliminated}\end{matrix} \qquad 10$$

or

$$\begin{matrix}V\\ \text{Volume of distribution}\end{matrix} = \begin{matrix}\dfrac{Cl}{\lambda_2}\\ \dfrac{\text{Total clearance}}{\text{Terminal exponential coefficient}}\end{matrix} \qquad 11$$

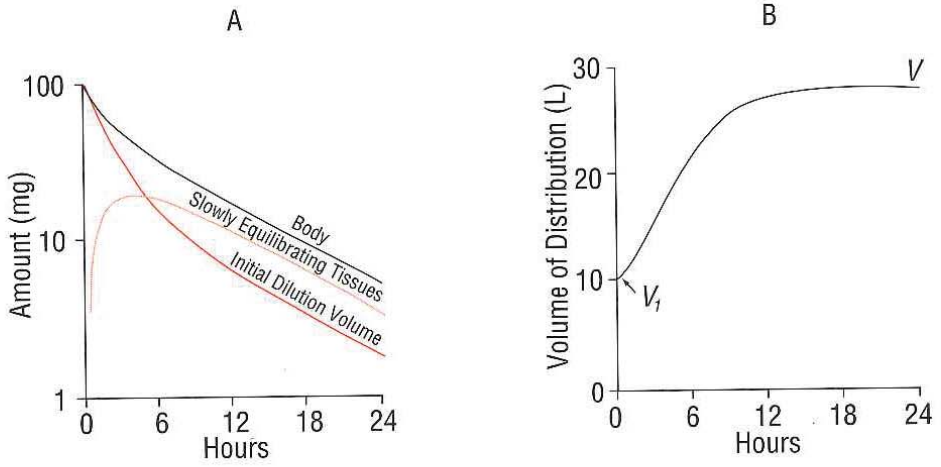

Fig. 19–4. Several events occur following a single i.v. bolus dose. A, Loss of drug from the initial dilution volume, of which plasma is a part, is due to both elimination from the body and distribution into the more slowly equilibrating tissues. The fall in amount of drug in the body is therefore initially less than the fall in the amount in the initial dilution volume. Only when distribution equilibrium has been achieved do the declines in the amounts in the initial dilution volume and in plasma parallel (same slope) that in the body. A, reflecting these events, the apparent volume of distribution (A/C), which just after giving the dose equals the initial dilution volume (V_1), increases with time approaching a limiting value (V), which occurs when distribution equilibrium is achieved.

Returning to the example of aspirin, $CL = 683$ mL/min and $\lambda_2 = 0.050\ min^{-1}$, therefore its volume of distribution is 13.7 L. That is, if during the terminal phase the plasma concentration is 10 mg/L, then the amount in the body is 137 mg. Since 65 mg (10 mg/L × 6.5 L) are in the initial dilution volume, the remaining 71 mg must be in the tissues with which aspirin slowly equilibrates.

A comparison of Eq. 11 with the one that has been used in all previous chapters to define the volume of distribution ($V = CL/k$) shows them to be the same, recognizing the equivalence of k and λ_2, the terminal exponential coefficient.

The ratio V_1/V gives an estimate of the degree of error in predicting the initial plasma concentration using a one-compartment model. For example, for aspirin, with values for V_1 and V of 6.5 and 13.7 L, respectively, the error in predicting initial concentrations from the plasma concentration-time data during the terminal phase can be relatively large. The error can be even larger when predicting conditions beyond the measured final phase if a still slower one exists. This last error is only of concern if there is an appreciable accumulation of drug in this phase during chronic administration, a point considered subsequently in this chapter.

Distribution Kinetics and Elimination

During the initial rapidly declining phase, more elimination occurs than would have been expected had distribution been spontaneous. Additional elimination is due to the particularly high concentrations of drug presented to organs of elimination during this period. For many drugs this increased elimination is small and, with respect to elimination, viewing the body as a single compartment is adequate. For other drugs, the additional elimination represents a major fraction of the administered dose, and approximating the kinetics with a one-compartment model is inappropriate. Area considerations are a basis for making this decision.

Recall from Eq. 9 that elimination associated with the concentrations defined by the terminal exponential term, $C_2e^{-\lambda_2 t}$, gives an amount equal to $CL \cdot C_2/\lambda_2$. Expressing this amount as a fraction, f_2, of the administered dose and utilizing the relationship in Eq. 8 gives

$$\text{Fraction of elimination associated with last exponential term} = f_2 = \frac{C_2/\lambda_2}{AUC} \qquad 12$$

The remaining fraction, f_1, must therefore have been eliminated as a result of concentrations above those expected had spontaneous distribution occurred, i.e., those concentrations defined by $C_1 \cdot e^{-\lambda_1 t}$.

Applying Eq. 12 to the case of aspirin, elimination of 69% of the dose is associated with the terminal slope; the remaining 31% therefore must be associated with plasma concentrations above those expected had spontaneous distribution occurred. Although distribution kinetics cannot be ignored, the majority of aspirin elimination is clearly associated with events defined by the terminal phase, which has a half-life of 14 min. Based on the same reasoning, the terminal half-life is the elimination half-life for most drugs. There are some drugs, however, for which the calculated value of f_2 is low. Gentamicin is an example. Over 98% of an i.v. bolus dose is eliminated before distribution equilibrium within the body has been achieved. In this case, the reason lies in a permeability-limited distribution of gentamicin into certain tissues. Clearly, for gentamicin and similar drugs, the appropriate half-life (biexponential model) defining elimination after a bolus dose is $0.693/\lambda_1$.

infusion is to match the net rate of movement into tissue. This rate is highest initially, when no drug is in tissue. However, as the tissue concentration rises toward plateau, the net movement into tissue progressively declines.

AN EXTRAVASCULAR DOSE

Often, absorption is slower than distribution, so approximating the body as a single compartment after an extravascular dose is reasonable. Occasionally, it is not, as illustrated with digoxin in Fig. 19–11. Following oral administration, digoxin is absorbed before much distribution has occurred, and consequently, the distribution phase is still evident beyond

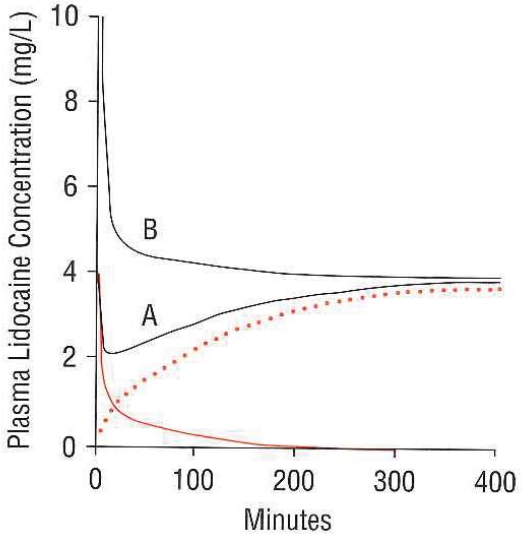

Fig. 19–10. Although a bolus ($V_1 \cdot C_d$) can be given to initially achieve a desired plasma lidocaine concentration of 4 mg/L, C_d, constant infusion at a rate required to maintain this value (rate = $CL \cdot C_d$) fails to do so in the early moments, owing to distribution kinetics. Note that the observed plasma concentration (———, *A*) is the sum of that associated with the bolus (colored solid line) (Eq. 2) and that associated with the constant-rate infusion (colored dotted line) (Eq. 20). A larger bolus dose can be given to prevent the concentration falling below 4 mg/L, but the resulting high initial plasma concentrations (———, *B*) may increase the chance of toxicity (1 mg/L = 4.3 μM).

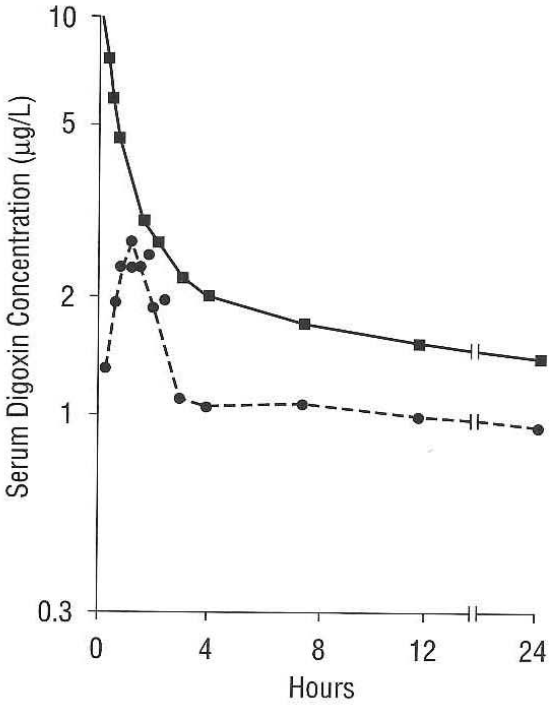

Fig. 19–11. Depicted is a semilogarithmic plot of the mean concentration of digoxin following 0.5 mg administered orally (two 0.25-mg tablets, ●) and i.v. (■) to four volunteers. Because absorption is much faster than distribution, a biphasic curve is still seen after attainment of the peak concentration following the oral dose (1 mg/L = 1.3 μM). (Taken from Huffman, D.H. and Azarnoff, J.: Absorption of orally given digoxin preparations. JAMA, 222:957–960, 1972. Copyright 1972, American Medical Association.)

the peak concentration. In this situation the peak concentration and the time of its occurrence depend on the kinetics of both absorption and distribution and minimally on elimination. The implication of these events to drug therapy and monitoring depends on whether the site of action resides in a rapidly or a slowly equilibrating tissue. Digoxin distributes slowly into the heart, the target organ. Accordingly, it is inappropriate to relate plasma concentration to effect until distribution equilibrium is achieved, 6 hr is a conservative estimate for this drug in most patients. Before then, response increases due to a rising cardiac concentration, even when plasma concentration is declining, making any interpretation of the plasma concentration extremely difficult (Chap. 20 p. 358). In contrast to digoxin, many drugs equilibrate rapidly with such highly perfused tissues as heart and brain; then plasma concentration correlates positively with response at all but the earliest times.

As with the simple one-compartment model, bioavailability is given by $F = CL \cdot AUC/\text{Dose}$, and relative bioavailability is estimated by comparison of AUC values following different formulations or routes of administration, correcting for dose.

MULTIPLE DOSING

The impact of distribution kinetics on events during multiple dosing is illustrated by the data in Fig. 19–12, obtained following an 8-hourly i.m. regimen of gentamicin administered

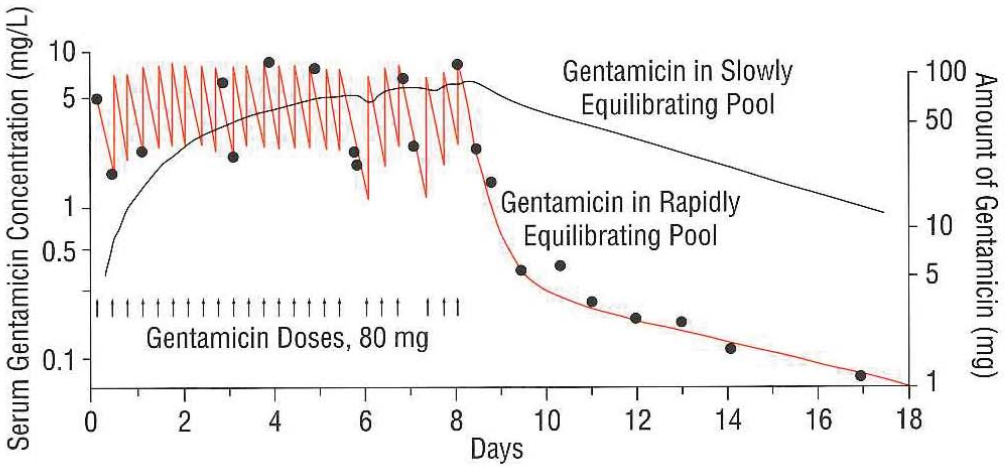

Fig. 19–12. Depicted are semilogarithmic plots of the levels of gentamicin in the body occurring during and after i.m. administration, 80 mg, almost every 8 hr (times indicated by arrows) to a patient for just over 8 days. The biphasic decline in serum concentration (●) when administration was stopped was fitted by a model that assumes that gentamicin distributes between a slowly equilibrating compartment and a rapidly equilibrating compartment from which elimination, entirely by renal excretion, occurs (see Fig. 19–3). The lines are the predicted concentrations (colored line, left-hand ordinate), the amount in the rapidly equilibrating compartment (colored line, right-hand ordinate), a value obtained by multiplying the serum concentration by the estimated initial dilution volume, and the predicted amount in the slowly equilibrating compartment (black line, right-hand ordinate). Little accumulation and large fluctuations of drug occur in plasma and the rest of the rapidly equilibrating pool. In contrast, the gentamicin slowly, but extensively, accumulates in the slowly equilibrating pool during drug administration, with little fluctuation within a dosing interval; disappearance of drug from the slowly equilibrating tissues is also slow on stopping gentamicin. During administration, the concentration in plasma after the Nth dose can be calculated from the formula

$$C = \frac{D_M}{V_1}\left\{f_1\left[\frac{1 - e^{N\lambda_1\tau}}{1 - e^{-\lambda_1\tau}}\right]e^{\lambda_1 t} + f_2\left[\frac{1 - e^{N\lambda_2\tau}}{1 - e^{-\lambda_2\tau}}\right]e^{-\lambda_2 t}\right\}$$

where D_M is the maintenance dose given every τ, t is the time since the last dose, and V_1 is the initial dilution volume. This equation can be derived using the multiple-dosing equation (Appendix I–D), assuming instantaneous absorption, and the mathematical aid (p. 322) (1 mg/L = 1.8 μM). (Adapted from Schentag, J.J., and Jusko, W.J.: Renal clearance and tissue accumulation of gentamicin. Clin. Pharmacol. Ther., 22:364–370, 1977. Reproduced with permission of C.V. Mosby.)

Appendix I–A

ASSESSMENT OF *AUC*

Several methods exist for measuring the area under the plasma concentration-time curve (*AUC*). One method, to be discussed here, is the simple numeric estimation of area by the *trapezoidal rule*. The advantage of this method is that it only requires a simple extension of a table of experimental data. Other methods involve either greater numeric complexity or fitting of an equation to the observations and then calculating the area by integrating the fitted equation.

General Case: Consider the blood concentration-time data, first two columns of Table A–1, obtained following oral administration of 50 mg of a drug. What is the total *AUC*?

Figure A–1 is a plot of concentration against time after drug administration. If a perpendicular line is drawn from the concentration at 1 hr (7 mg/L) down to the time-axis, then the area bounded between zero time and 1 hr is a trapezoid with an area given by the product of average concentration and time interval. The average concentration is obtained by adding the concentrations at the beginning and end of the time interval and dividing by 2. Since, in the first interval, the respective concentrations are 0 and 7 mg/L and the time interval is 1 hr, it follows that:

$$AUC_1 = \frac{0 + 7}{2}\ \text{mg/L} \times 1\ \text{hr}$$

AUC_1	$= \frac{0 + 7}{2}$ mg/L	$\times$ 1 hr
Area of trapezoid within the first time interval	Average concentration over the first interval	First time interval

or,

$$AUC_1 = 3.5\ \text{mg-hr/L}$$

In this example, the concentration at zero time is 0. Had the drug been given as an intra-

Table A–1. Calculation of Total *AUC* Using the Trapezoidal Rule

TIME (hr)	BLOOD CONCENTRATION (mg/L)	TIME INTERVAL (hr)	AVERAGE CONCENTRATION (mg/L)	AREA (mg-hr/L)
0	0	—	—	—
1	7	1	3.5	3.5
2	10	1	8.5	8.5
3	5	1	7.5	7.5
4	2.5	1	3.75	3.75
5	1.25	1	1.88	1.88
6	0.6	1	0.93	0.93
7	0.2	1	0.4	0.4
8	0	1	0.1	0.1
			Total Area =	26.60

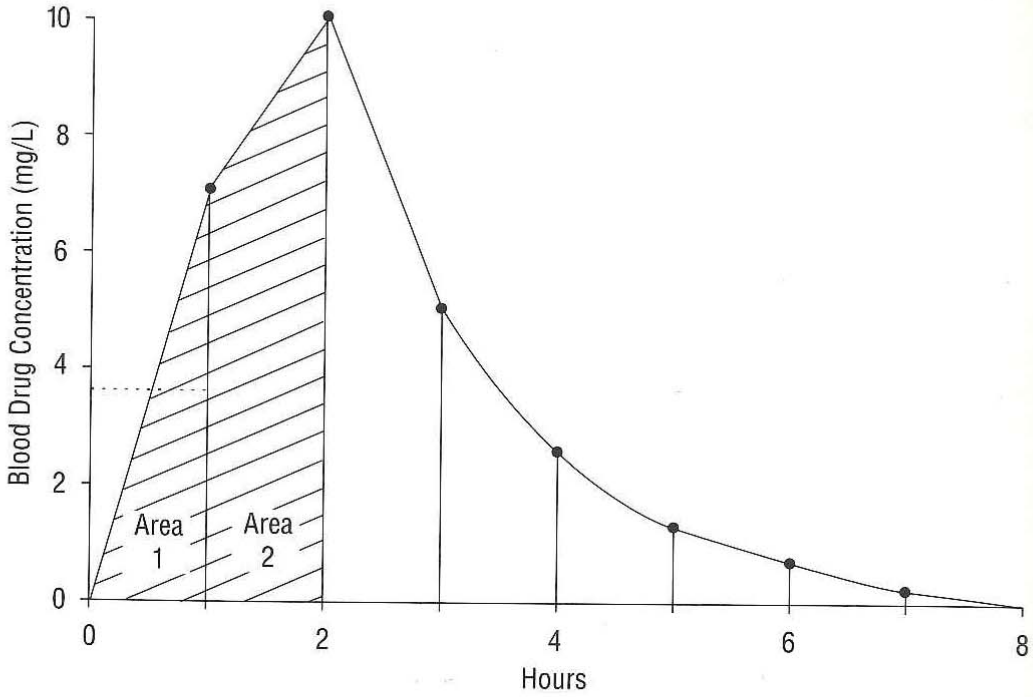

Fig. A–1. Plot of concentration-time data of Table A–1. The dotted line is the average concentration in the first interval.

venous (i.v.) bolus, the concentration at zero time might have been the extrapolated value, $C(0)$.

The area under each time interval can be obtained in an analogous manner to that outlined above. The total *AUC* over all times is then simply given by

$$\text{Total } AUC = \text{Sum of the individual areas}$$

Usually, *total AUC* means the area under the curve from zero time to infinity. In practice, infinite time is taken as the time beyond which the area is insignificant.

The calculations used to obtain the *AUC*, displayed in Fig. A–1, are shown in Table A–1. In this example the total *AUC* is 26.6 mg-hr/L.

SPECIAL CASE

An Intravenous Bolus. When a drug is given as an i.v. bolus and the decline in plasma concentration is monoexponential, total *AUC* is calculated most rapidly by dividing the extrapolated zero-time concentration ($C(0)$) by the elimination rate constant (k). For example, if $C(0)$ is 100 mg/L and k is 0.1 hr^{-1}, then the total *AUC* is 1000 mg-hr/L.

Proof: The total *AUC* is given by

$$\text{Total } AUC = \int_0^\infty C \cdot dt \qquad 1$$

But $C = C(0) \cdot e^{-kt}$, and since $C(0)$ is a constant, it follows that

$$\text{Total } AUC = C(0) \int_0^\infty e^{-kt} \cdot dt \qquad 2$$

which on integrating between time zero and infinity yields

$$\text{Total } AUC = \frac{C(0)}{-k} [e^{-k}]_0^\infty = \frac{C(0)}{-k} [0 - 1] = \frac{C(0)}{k} \qquad 3$$

When Decline Is Logarithmic. The numeric method used to calculate *AUC* by the trapezoid rule assumes a linear relationship between observations. Frequently, especially during the decline of drug concentration, the fall is exponential. Then a more accurate method for calculating area during the decline can be used, the *log trapezoidal rule*, as follows.

Consider, for example, two consecutive observations $C(t_i)$ and $C(t_{i+1})$ at times t_i and t_{i+1}, respectively. These observations are related to each other by

$$C(t_{i+1}) = C(t_i) \cdot e^{-k_i \cdot \Delta t_i} \qquad 4$$

where k_i is the rate constant that permits the concentration to fall exponentially from $C(t_i)$ to $C(t_{i+1})$ in the time interval $t_{i+1} - t_i$, that is, Δt_i. The value of k_i is given by taking the logarithm on both sides of Eq. 4 and rearranging, so that

$$k_i = \frac{\ln[C(t_i)/C(t_{i+1})]}{\Delta t_i} \qquad 5$$

Now the *AUC* during the time interval Δt_i, AUC_i, is the difference between the total areas from t_i to ∞ and from t_{i+1} to ∞, respectively. It therefore follows from events after an i.v. bolus that

$$AUC_i = \frac{C(t_i) - C(t_{i+1})}{k_i} \qquad 6$$

and, by appropriately substituting for k_i in Eq. 6, one obtains

$$AUC_i = \frac{[C(t_i) - C(t_{i+1})] \cdot \Delta t_i}{\ln[C(t_i)/C(t_{i+1})]} \qquad 7$$

This calculation is then repeated for all observations that lie beyond the peak concentration.

In practice, a large discrepancy arises between the method above and that using the (linear) trapezoidal rule only when consecutive observations differ by more than twofold.

STUDY PROBLEMS

1. The following data (Table A–2) were obtained following the ingestion of 50 mg of a drug.

Table A–2.

Time (hr)	0	0.5	1	1.5	2	3	4	6	8	12
Plasma concentration (mg/L)	0	0.38	0.6	0.73	0.85	0.95	0.94	0.87	0.66	0.37