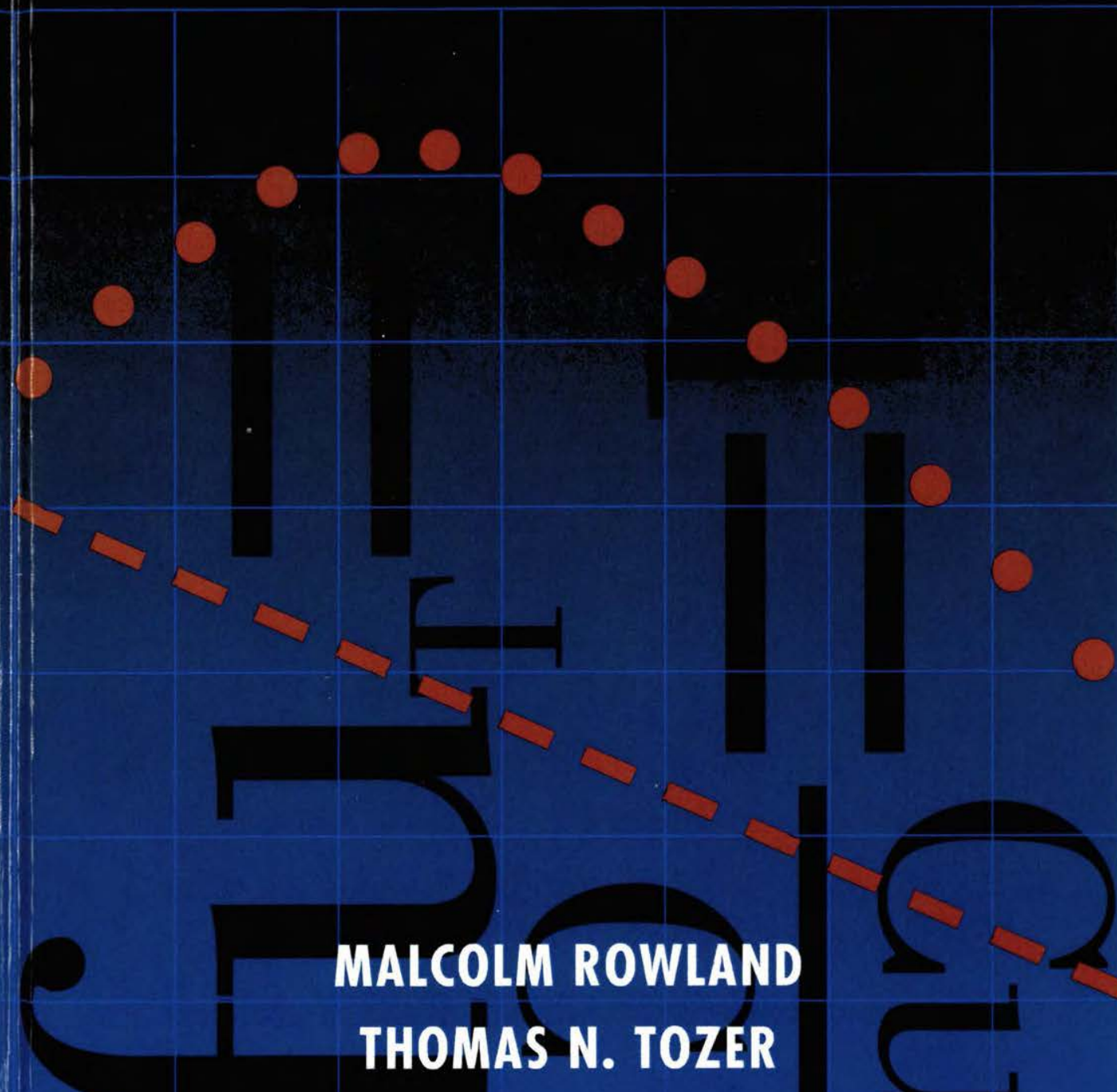


Clinical Pharmacokinetics

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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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.

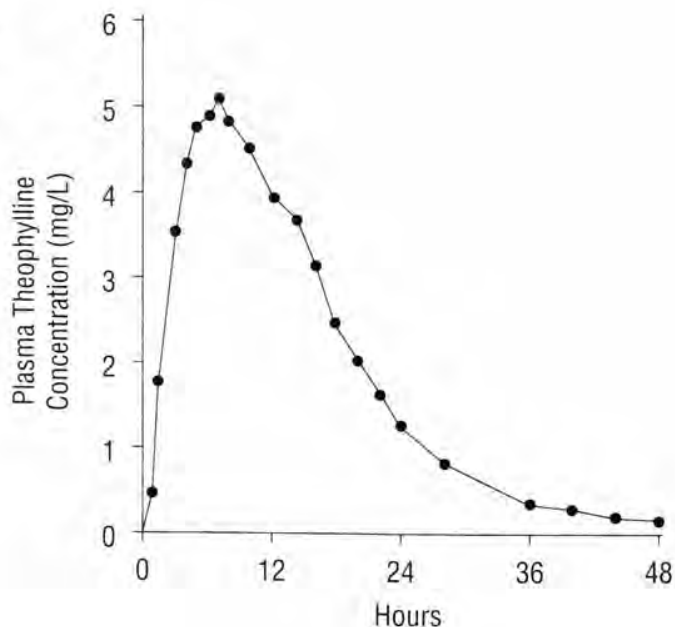
Figure 1-1 illustrates the events occurring after a dose of drug is administered orally. The rate at which drug initially enters the body exceeds its rate of elimination; the concentrations of drug in blood and other tissues rise, often sufficiently high to elicit the desired therapeutic effects and 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 Oral	10 mg when needed Not recommended because of reduced effectiveness

^aTaken 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.*, 30:57–30, 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,

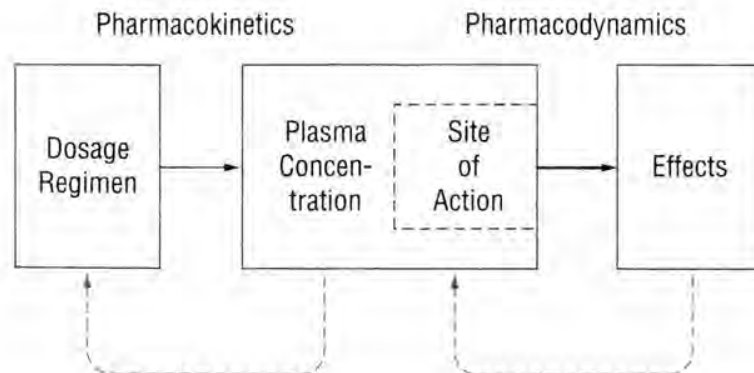


Fig. 1–2. An approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then, either the plasma drug concentration–time data or the effects produced are used via pharmacokinetics as a feedback (dashed lines) to modify the dosage regimen to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

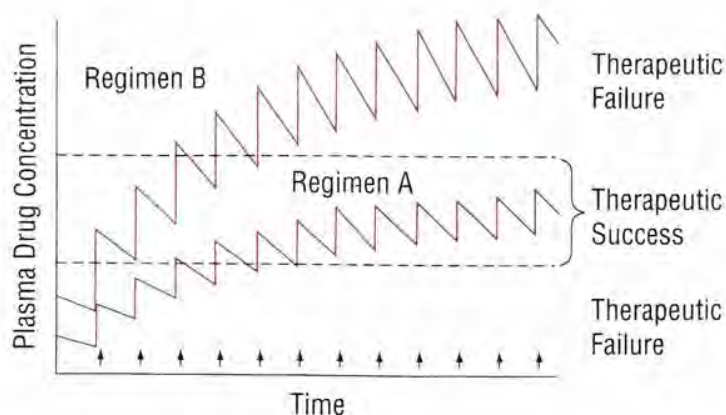
several doses had to be given before drug accumulation was sufficient to produce a therapeutic concentration. Had therapy been stopped before then, the drug might have been thought ineffective and perhaps abandoned prematurely. Alternatively, larger doses might have been tried, e.g., regimen B. Although 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-

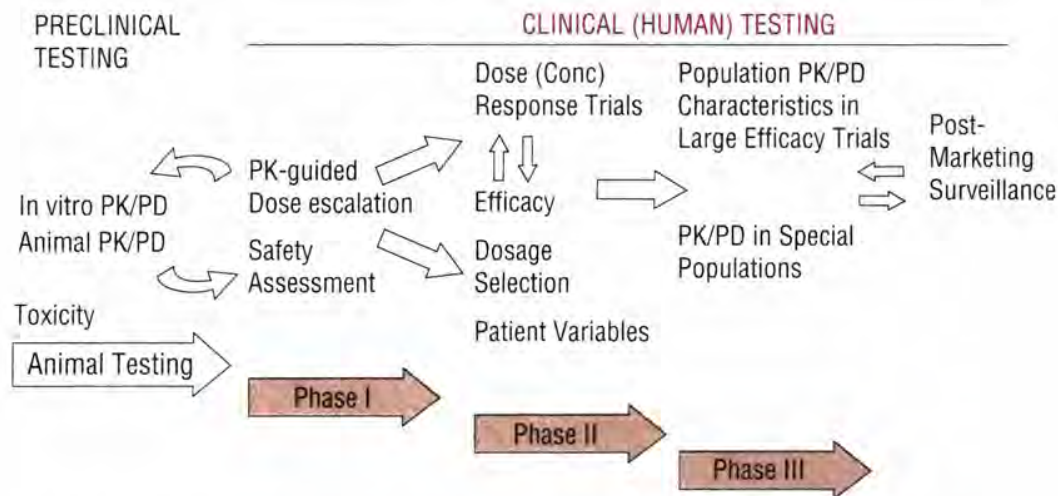


Fig. 1–4. The development and subsequent marketing of a drug. The prehuman data helps to identify promising compounds and to suggest useful doses for testing in humans. Phases I, II, and III of human assessment generally correspond to the first administration to humans, early evaluation in selected patients, 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.

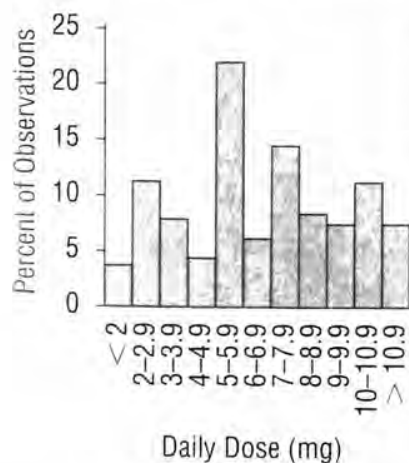


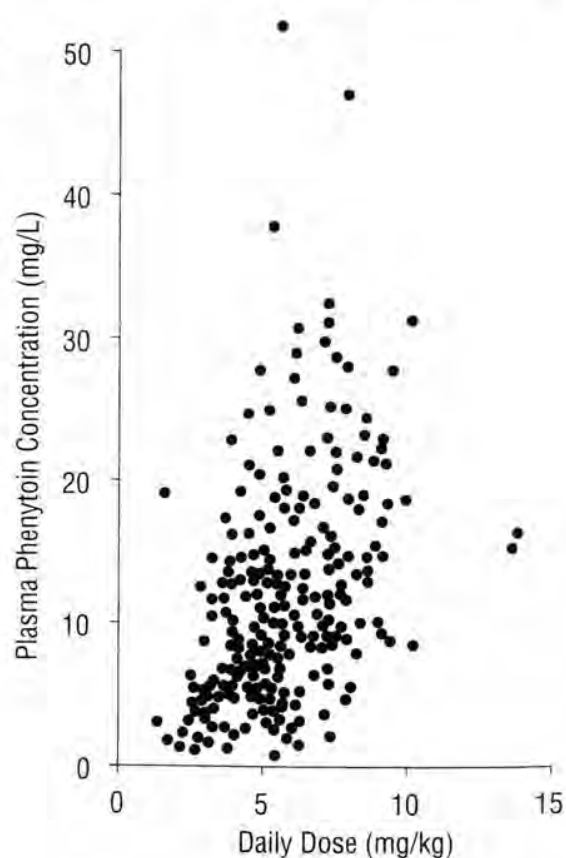
Fig. 1–5. The daily dose of warfarin required to produce similar prothrombin times in 200 adult patients varies widely. (1 mg/L = 3.3 μ M). (Redrawn from Koch-Weser, J.: The serum level approach to individualization of drug dosage. *Eur. J. Clin. Pharmacol.* 9:1–8, 1975.)

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 μ M.) (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.

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, k_a , 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.

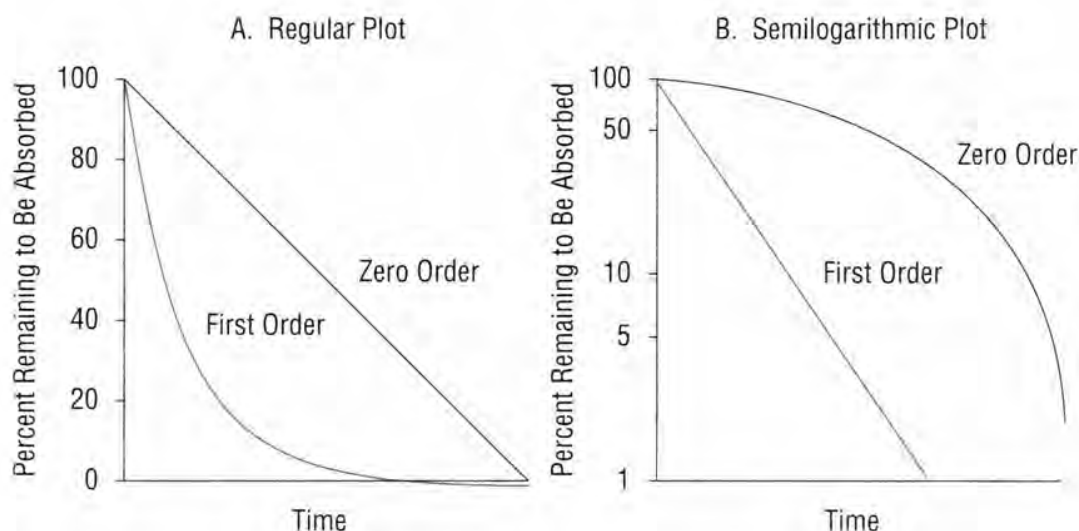


Fig. 4-1. A comparison of zero-order and first-order absorption processes. Depicted are: A. regular and B. semilogarithmic plots of the percent remaining to be absorbed against time.

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

$$\frac{dA}{dt} = \frac{dA_a}{dt} - k \cdot A \quad 1$$

Rate of change of drug in body Rate of absorption Rate of elimination

where A_a 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 $ka \cdot A_a$.

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.

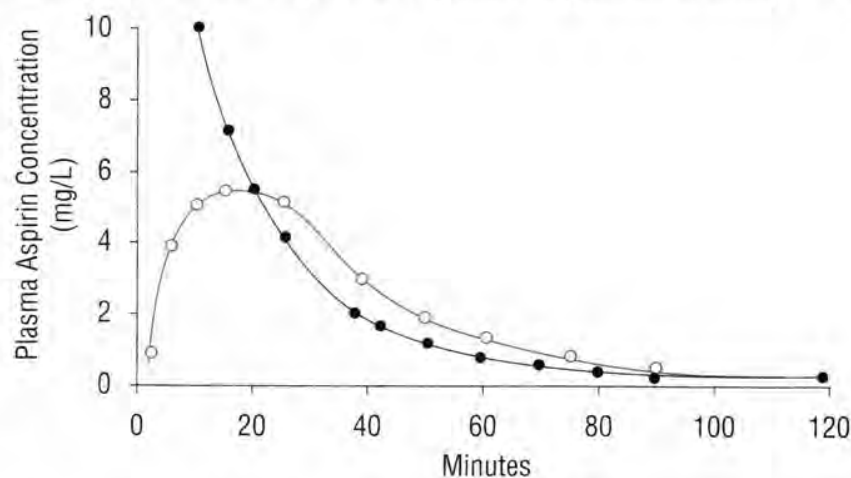


Fig. 4-2. Aspirin (650 mg) was administered as an intravenous bolus (●) and as an oral solution (○) on separate occasions to the same individual. Absorption causes a delay and a lowering of the peak concentration (1 mg/L = 5.5 μM). [Modified from the data of Rowland, M., Riegelman, S., Harris, P. A., 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:

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

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

$$\begin{array}{l} F \cdot \text{Dose} = \text{Clearance} \cdot AUC \\ \text{Amount} \quad \text{Total amount} \\ \text{absorbed} \quad \text{eliminated} \end{array} \quad 3$$

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

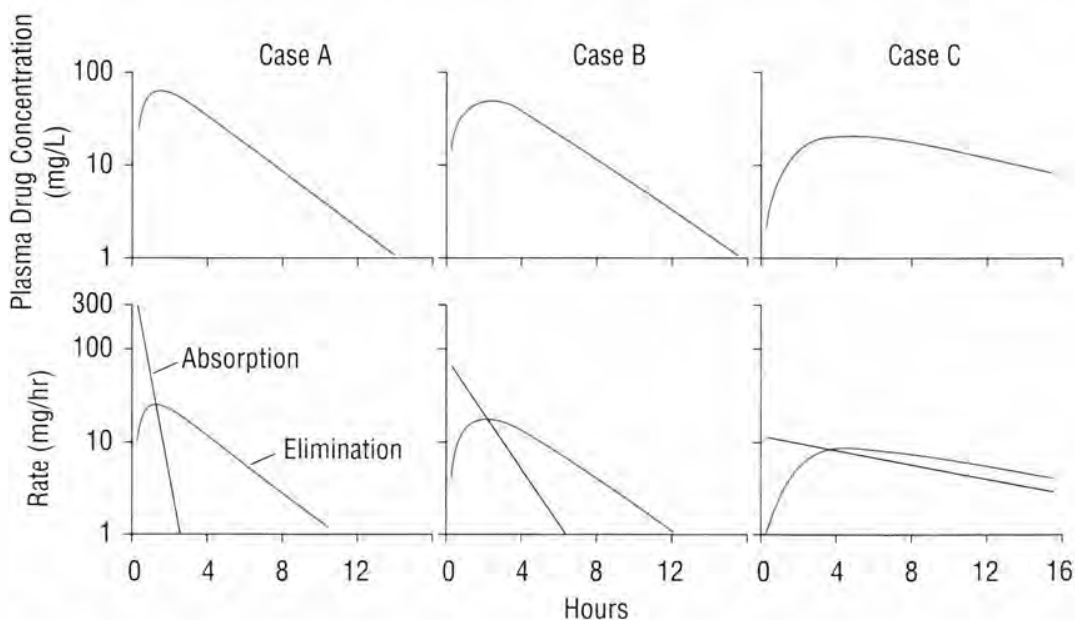


Fig. 4-3. A slowing (from left to right) of drug decline at the absorption site (lower graphs) delays the attainment and decreases the magnitude of the peak plasma drug concentration (top graphs). In Cases A and B (bottom two graphs), absorption (black line) is a faster process than elimination (colored 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 AUC s 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

$$\begin{array}{ccc} k \cdot A & \approx & ka \cdot A_a \\ \text{Rate of} & & \text{Rate of} \\ \text{elimination} & & \text{absorption} \end{array} \quad 4$$

that is,

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

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

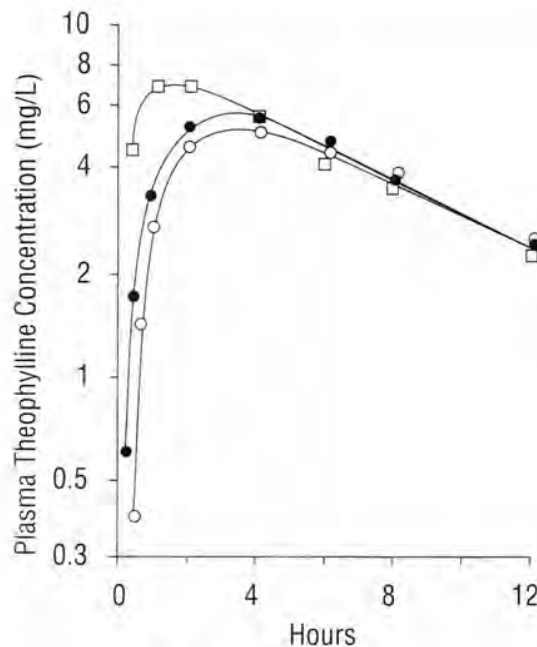


Fig. 4-4. Two tablets, each containing 130 mg theophylline, were taken by 6 healthy volunteers under various conditions. Absorption of theophylline was most rapid when the tablets were dissolved in 500 mL of water and taken on an empty stomach (□). Taking the tablets with 20 mL of water on an empty stomach (○) 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 ($1 \text{ mg/L} = 5.5 \text{ } \mu\text{M}$). (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.)

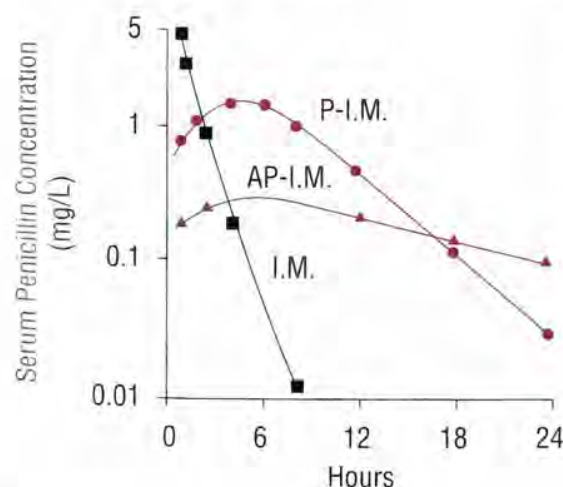
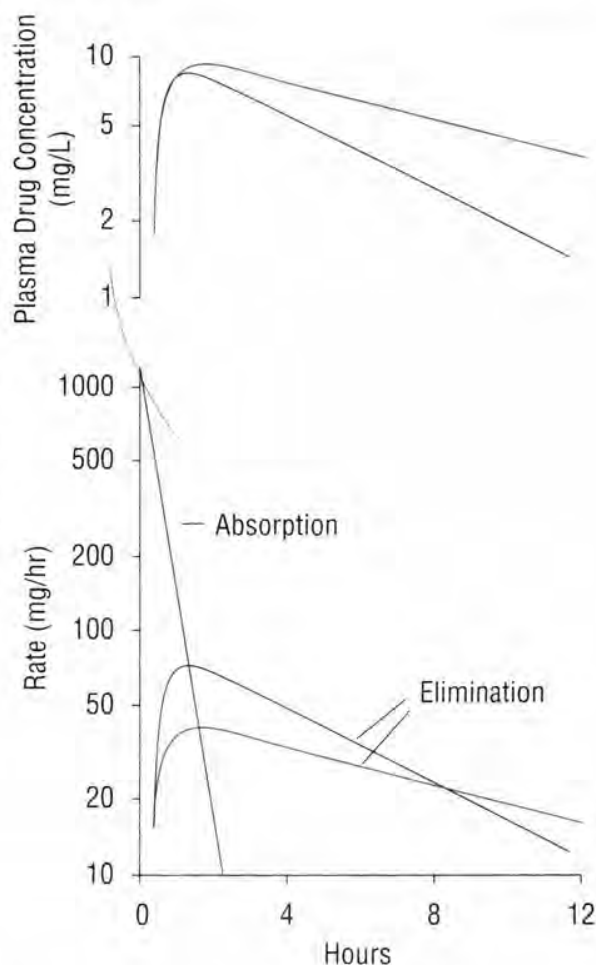


Fig. 4-5. Penicillin G (3 mg/kg) was administered intramuscularly to the same individual on different occasions as an aqueous solution (I.M.) and as procaine penicillin in oil (P-I.M.) and in oil with aluminum monostearate (AP-I.M.). The differing rates of decline of the plasma concentration of penicillin 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. ($1 \text{ mg/L} = 3.0 \text{ } \mu\text{M}$). (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

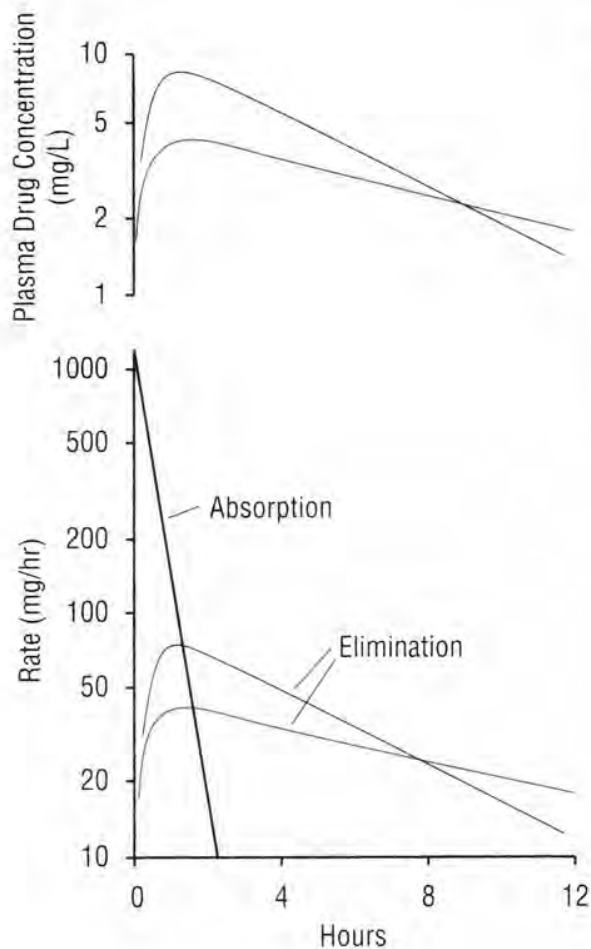


Fig. 4-7. A twofold increase in the volume of distribution causes a twofold increase in the elimination half-life and delays the time at which the peak plasma concentration occurs (colored line, top graph) compared to the control observation (black line) after a single extravascular dose. With no change 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).

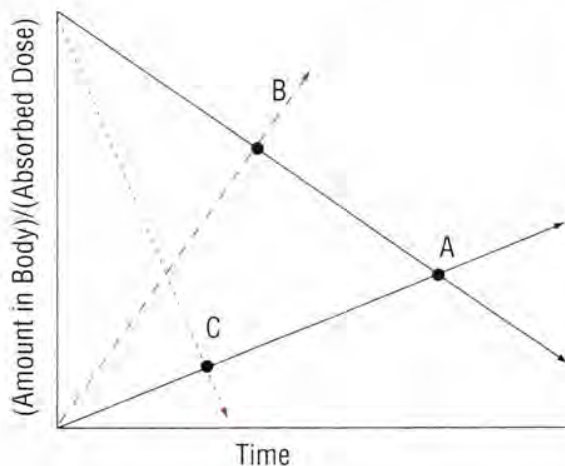


Fig. 4-8. Memory aid to assess changes in peak time and peak amount in the body after extravascular administration of a single dose when absorption or disposition is altered. The relative peak time and the relative peak amount are indicated by the intersection of the absorption and elimination lines (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

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.

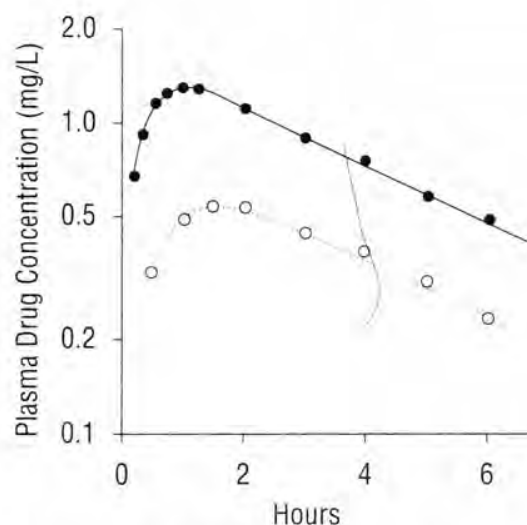


Table 4-1. Data Obtained Following Administration of 500 mg of a Drug in Solution by Different Routes

ROUTE	PLASMA DATA		URINE DATA
	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

following i.v. 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

$$\text{Dose}_{i.v.} = \text{Clearance} \cdot \text{AUC}_{i.v.} \quad 6$$

Extravascular (e.v.) dose

$$F_{e.v.} \cdot \text{Dose}_{e.v.} = \text{Clearance} \cdot \text{AUC}_{e.v.} \quad 7$$

which upon division yields

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

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

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

$$\begin{array}{l} F_A \cdot \text{Dose}_A = \text{Clearance} \cdot AUC_A \\ \text{Amount} \qquad \text{Total amount} \\ \text{absorbed} \qquad \text{eliminated} \end{array} \qquad 9$$

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.

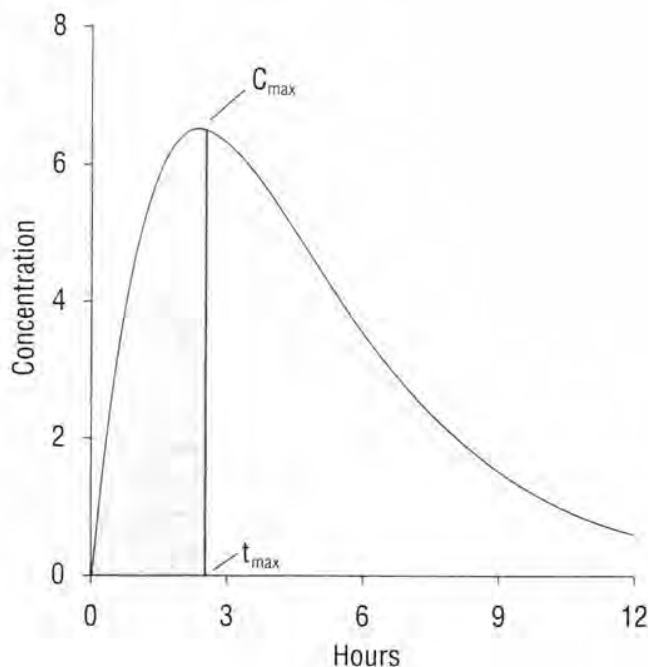
Previously, a range of likely absorption half-lives was quoted. The values were estimated indirectly from plasma concentration-time data. Direct measurements of absorption kinetics are impossible because plasma is the site of measurement for both absorption and disposition. To calculate the kinetics 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 f_e remains constant. Recall from Chap. 3 that f_e 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).



$$f_e = \frac{Ae_{\infty}}{F \cdot \text{Dose}} \quad 12$$

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

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

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

Amount Total amount
absorbed eliminated

which upon division gives:

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

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 f_e 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.)

- 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.
 - All other parameters remaining unchanged, the slower the absorption process, the higher is the peak plasma concentration after a single oral dose.
 - After a single oral dose, an increase in bioavailability causes the peak time to shorten.
 - For a given drug in a subject, AUC is proportional to the amount of drug absorbed.
 - If $ka \ll k$, then the terminal slope of the plasma concentration versus time curve reflects absorption, not elimination.
- 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

- Estimate both bioavailability and relative bioavailability of formulation 2 from both plasma and urine data. What are the assumptions made in your calculations?
 - 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?
 - Does renal clearance of procainamide vary much among the three treatments?
- 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.

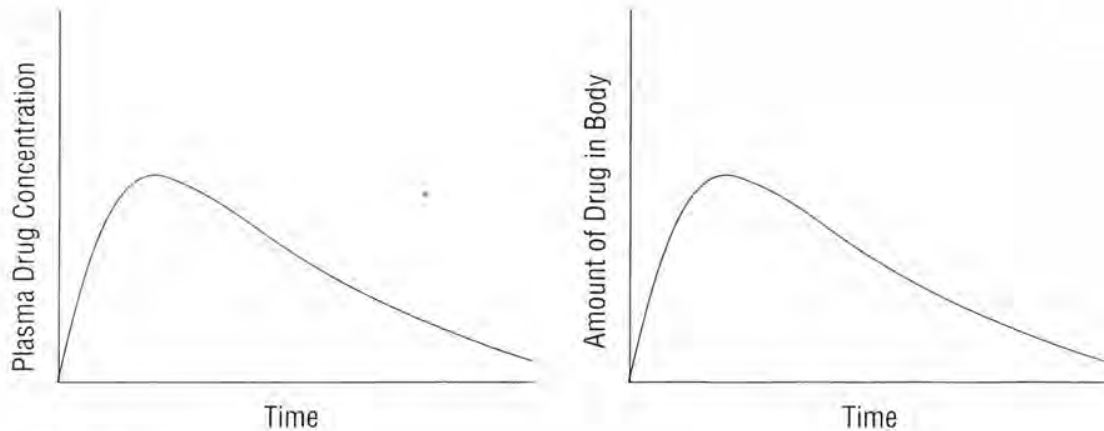


Fig. 4-11.

- F decreased
 - k_a increased
 - CL increased, k increased by same factor
 - CL decreased, k decreased by same factor
 - V increased, k decreased by same factor
4. Kampf et al. studied the pharmacokinetics of recombinant human erythropoietin, a glycosylated protein (M.W. = 34,000 g/mole) used to increase red blood cell formation, in patients with end-stage renal disease after single i.v. and subcutaneous (s.c.) administrations of 40 units/kg on separate occasions. Table 4-3 lists the salient findings of these studies. The mean weight of the patients was 60 kg.

Table 4-3. Mean AUC, Maximum Plasma Concentration, and Terminal Half-life of Erythropoietin in End-Stage Renal Disease Patients Following i.v. and s.c.^A Administration

ADMINISTRATION	AUC (Units·hr/L)	MAXIMUM CONCENTRATION (Units/L)	TIME OF MAXIMUM CONCENTRATION	TERMINAL HALF-LIFE (hr)
Intravenous	3010	417	5 min ^B	6.7
Subcutaneous	1372	40.5	12 hr	16.1

^AAbstracted from Kampf, D., Eckardt, K.U., Fischer, H.C., Schmalisch, C., Elmer, B., and Schostak, M. Pharmacokinetics of recombinant human erythropoietin in dialysis patients after single and multiple subcutaneous administration. *Nephron*, 61:393-398, 1992.

^BTime when first blood sample was taken.

- Determine the clearance and volume of distribution of this drug.
 - Calculate the bioavailability of erythropoietin after s.c. administration in these patients. How might you explain your answer?
 - The maximum concentration observed was much lower after the s.c. dose. How do you explain this observation?
5. Channer and Roberts (1985) studied the effect of delayed esophageal transit on the absorption of acetaminophen. Each of 20 patients awaiting cardiac catheterization swallowed a single tablet containing acetaminophen (500-mg) and barium sulfate. The first 11 subjects swallowed the tablet while lying down; in 10 of these subjects, transit of the tablet was delayed, as visualized by fluoroscopy. In the other 9 subjects who swallowed the tablet while standing, it entered the stomach immediately. In both groups the tablet was taken with a sufficient volume of water to ease swallowing. Table 4-4 lists the average plasma acetaminophen data obtained over 6 hr after swallowing the tablet.

Table 4-4.^a

TIME (min)	PLASMA ACETAMINOPHEN CONCENTRATION (mg/L) ^b	
	SUBJECTS STANDING	SUBJECTS LYING DOWN
0	0	0
10	2.1	0.1
20	5.6	0.3
30	5.8	1.1
40	6.3	1.9
50	4.7	2.8
60	4.1	3.2
90	3.5	3.9
120	2.8	3.1
150	2.2	2.9
180	1.7	1.8
210	1.8	1.7
240	1.5	1.5
360	0.75	0.7

^aAbstracted from Channer, K.S. and Roberts, C.J.C.: Effect of delayed esophageal transit on acetaminophen absorption, *Clin. Pharmacol. Ther.*, 37:72-76, 1985.

^bOne mg/L = 6.6 μ M.

- What effect does delayed esophageal transit have on the speed and extent of absorption of acetaminophen?
 - What process, absorption or disposition, rate-limits the decline in plasma drug concentration?
 - Acetaminophen is used for the relief of pain. Do the findings of this study affect the recommendation for the use of this drug?
6. Beshyah et al. (Beshyah, S.A., Anyaoku, V., Niththyananthan, R., Sharp, P., and Johnston, D.G.: The effect of subcutaneous injection site on absorption of human growth hormone: Abdomen versus thigh. *Clin. Endocrinol.*, 35:409-412, 1991) examined the effect of s.c. injection site on the absorption of human growth hormone. Table 4-5 lists the mean serum concentrations in 11 subjects observed during the first 12 hr after the administration of 4 IU (international units) of biosynthetic human growth hormone. The drug was injected, on separate occasions, into a lifted fold of skin on the anterior thigh and a lower quadrant of the abdomen.

Table 4-5. Mean Serum Concentrations of Growth Hormone for 12 hr following s.c. Injection of 4 IU in the Abdomen and Thigh

TIME (hr)	0	1	2	3	4	5	6	7	8	9	10	11	12
INJECTION SITE	SERUM CONCENTRATION (milliunits/L)												
Abdomen	<2	34	55	92	84	75	74	51	31	24	20	12	8
Thigh	<2	16	27	27	37	28	28	23	20	19	14	12	10

- Is there information in these data, gleaned from graphical analysis, to suggest whether absorption or disposition of growth hormone rate-limits the terminal decline? Briefly discuss.
- Many proteins given subcutaneously or intramuscularly are partially degraded within the lymphatic system before reaching the systemic circulation. Calculate the relative bioavailability of the drug after s.c. injection into the thigh (relative to abdomen).
- The clearance of growth hormone has been reported in the literature to average about 5 L/hr. Roughly estimate the bioavailability of the drug following abdominal s.c. injection.

7. Phenylethylmalonide (PEMA) is one of the major metabolites of the antiepileptic drug primidone. As part of a program to assess the potential use of PEMA as an antiepileptic drug itself, its pharmacokinetics were studied following i.v. and oral administration of 500 mg. Table 4-6 below lists the resultant plasma concentrations in one subject. Also, 81% of the i.v. dose was recovered in urine unchanged.

Table 4-6. Plasma Concentrations following i.v. and Oral Administration of 500 mg of PEMA to a Subject^a

TIME (hr)		0.33	0.5	0.67	1	1.5	2	4	6	10	16	24	32	48
Plasma concentration	i.v.	14.7	12.6	11.0	—	9.0	8.2	7.9	6.6	6.2	4.6	3.2	2.3	1.2
(mg/L)	oral	—	2.4	—	3.8	4.2	4.6	8.1	5.8	5.1	4.1	3.0	2.3	1.3

^aAbstracted from Pisoni, F., and Richens, A.: Pharmacokinetics of phenylethylmalonide (PEMA) after oral and intravenous administration. Clin. Pharmacol. Ther., 8:272-276, 1983.

- From a semilogarithmic plot of the plasma concentrations, estimate the elimination half-life of PEMA in the subject.
 - Calculate the total AUC following i.v. and oral administration.
 - From the i.v. data, estimate the clearance and volume of distribution of PEMA.
 - Calculate the oral bioavailability of the drug.
 - Calculate the renal clearance.
8. Rowland *et al.* (Rowland, M., Epstein, W., and Riegelman, S.: Absorption kinetics of griseofulvin in man. J. Pharm. Sci., 57:984-989, 1968) gave griseofulvin orally, 0.5 g of a micronized drug formulation and, on another occasion intravenously, 100 mg, to volunteers. The plasma concentration-time data obtained in one subject are given in Table 4-7 below.

Table 4-7.

	ROUTE	TIME (hr)	0	1	2	3	4	5	7	8	12	24	28	32	35	48
Plasma Griseofulvin Concentration (mg/L) ^a	i.v.		0	1.4	1.1	0.98	0.90	0.80	—	0.68	0.55	0.37	—	0.24	—	0.14
	Oral		0	0.4	0.95	1.15	1.15	1.05	1.2	1.2	0.90	1.05	0.90	0.85	0.80	0.50

^aOne mg/L = 2.8 μM.

From appropriate plots and calculations, what can be concluded from these data with respect to:

- Rate of absorption of griseofulvin with time on oral administration in this individual?
 - Completeness of absorption?
9. Kostenbauder *et al.* (1975) measured plasma phenytoin concentrations after the administration of sodium phenytoin intramuscularly (500 mg) and intravenously (250 mg). The average data obtained in 12 subjects, each of whom received both treatments, are listed in Table 4-8.

Table 4-8.^a

TIME (hr)	ROUTE	0	1	2	4	6	8	12	24	48	72	96	120
Plasma Phenytoin Concentration (mg/L) ^b	Intramuscular	0	3.0	3.2	3.5	3.2	3.6	3.8	4.1	3.2	1.6	0.8	0.4
	Intravenous	5.6	5.4	5.2	4.9	—	3.9	3.2	2.2	0.88	0.42	—	—

^aAbstracted from Kostenbauder, H.B., Rapp, R.P., McCowen, J.F., Foster, T.S., Perrier, D.G., Blocker, H.M., Hulan, W.C., and Kinkel, A.W.: Bioavailability and single-dose pharmacokinetics of intramuscular phenytoin. Clin. Pharmacol. Ther., 18:449-456, 1975.

^bOne mg/L = 4.0 μM.

- a. Estimate the bioavailability of phenytoin from the i.m. site based on area comparisons.
- b. From an appropriate plot of the data, comment on the process limiting the decline of the plasma phenytoin concentration following i.m. administration.
- c. The authors analyzed the plasma concentration-time data and found that, following i.m. administration, 23% of the dose was absorbed within the first hour, and thereafter absorption was much slower. The cumulative absorption data are shown in Table 4-9. After the rapid absorption in the first hour, is the subsequent absorption better characterized by a zero-order or a first-order process?

Table 4-9.

TIME (hr)		6	19	40	65
Percent of bioavailable drug absorbed from i.m. site	23	40	60	80	90

MULTIPLE-DOSE REGIMENS

OBJECTIVES

The reader will be able to:

1. Predict the rate and extent of drug accumulation for a given regimen of fixed dose and fixed interval.
2. Develop a dosage regimen from knowledge of the pharmacokinetics and therapeutic window of a drug.
3. Evaluate the kinetics of a drug given in a multiple-dose regimen.
4. Evaluate the kinetics of a drug following a multiple-dose regimen of a controlled-release formulation.
5. Derive pharmacokinetic parameters for a drug from plasma concentration (or urine) data following a multiple-dose regimen.

The previous chapter dealt with constant-rate regimens. Although these regimens possess many desirable features, they are not the most common ones. The more common approach to the maintenance of continuous therapy is to give multiple discrete doses. This chapter covers the pharmacokinetic principles associated with such multiple-dose regimens.

DRUG ACCUMULATION

Drugs are most commonly prescribed to be taken on a fixed dose, fixed time interval basis; e.g., 100 mg three times a day. In association with this kind of administration, the plasma concentration and amount in the body fluctuate and, similar to an infusion, rise toward a plateau.

Consider the simplest situation of a dosage regimen composed of equal bolus doses administered intravenously at fixed and equal time intervals. Curve A of Fig. 7-1 shows how amount in the body varies with time when each dose is given successively twice every half-life. Under these conditions drug accumulates substantially. Accumulation occurs because drug from previous doses has not been completely removed.

Maxima and Minima on Accumulation to the Plateau

To appreciate the phenomenon of accumulation, consider what happens when a 100-mg bolus dose is given intravenously every elimination half-life. The amounts in the body just after each dose and just before the next dose can readily be calculated; these values correspond to the maximum (A_{max}) and minimum (A_{min}) amounts obtained within each dosing interval. The corresponding values during the first dosing interval are 100 mg ($A_{1,max}$) and 50 mg ($A_{1,min}$), respectively. The maximum amount of drug in the second dosing interval ($A_{2,max}$), 150 mg, is the dose (100 mg) plus the amount remaining from the previous dose

(50 mg). The amount remaining at the end of the second dosing interval ($A_{2,min}$), 75 mg, is that remaining from the first dose, 25 mg ($100 \text{ mg} \times \frac{1}{2} \times \frac{1}{2}$, because two half-lives have elapsed since its administration) plus that remaining from the second dose, 50 mg. Alternatively, the value, 75 mg, may simply be calculated by recognizing that one-half of the amount just after the second dose, 150 mg, remains at the end of that dosing interval. Upon repeating this procedure, it is readily seen (curve B, Fig. 7-1) that drug accumulation, viewed in terms of either maximum or minimum amount in the body, continues until a limit is reached. At the limit, the amount lost in each interval equals the amount gained, the dose. In this example, the maximum and the minimum amounts in the body at steady state are 200 mg and 100 mg, respectively. This must be so since the difference between the maximum and minimum amounts is the dose, 100 mg, and since at the end of the interval, one half-life, the amount must be half that at the beginning.

Following a constant rate input, the *plateau* is reached when rate of elimination matches rate of input. Then the level of drug in the body is constant. With discrete dosing, the level is not constant within a dosing interval, but the values at a given time within the interval are the same from one dosing interval to another, that is, when the amount lost equals the amount gained within the interval. The term *plateau* is also applied to this interdosing steady-state condition.

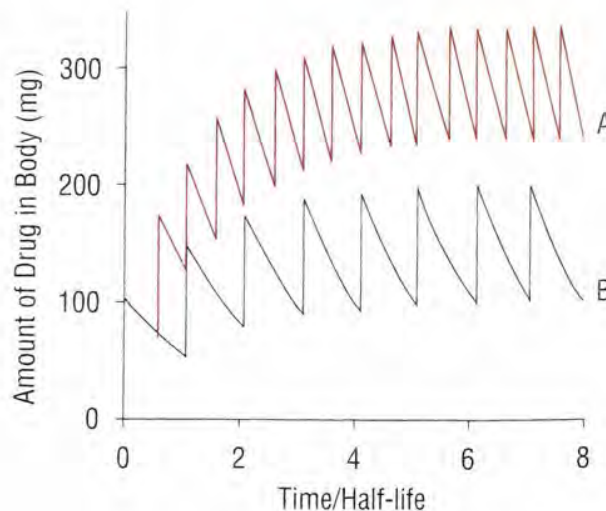
The foregoing considerations can be expanded for the more general situation in which a drug is given at a dosing interval, τ , which may differ from the half-life. The general equations derived in Appendix I-E for the maximum and minimum amounts in the body after the N th dose ($A_{N,max}$; $A_{N,min}$) and at plateau ($A_{ss,max}$; $A_{ss,min}$) are

$$\text{Maximum amount in body after } N\text{th dose, } A_{N,max} = \text{Dose} \cdot \left[\frac{1 - e^{-Nk\tau}}{1 - e^{-k\tau}} \right] \quad 1$$

$$\text{Minimum amount in body after } N\text{th dose, } A_{N,min} = A_{N,max} \cdot e^{-k\tau} \quad 2$$

$$\text{Maximum amount in body at plateau, } A_{ss,max} = \frac{\text{Dose}}{1 - e^{-k\tau}} \quad 3$$

Fig. 7-1. Dosing frequency controls the degree of drug accumulation. Curve A, i.v. bolus dose (100 mg) administered twice every half-life; curve B, same bolus dose administered once every half-life. Note that time is expressed in half-life units.



$$\text{Minimum amount in body at plateau, } A_{ss,min} = A_{ss,max} e^{-k\tau} = A_{ss,max} - \text{Dose} \quad 4$$

Recall from Chap. 3 that the function e^{-kt} is the fraction of the initial amount remaining in the body at time t . Similarly, the amount in the body at the end of a dosing interval τ of a multiple-dose regimen, ($A_{N,min}$), is obtained by multiplying the corresponding maximum amount by $e^{-k\tau}$, that is, $A_{N,min} = A_{N,max} e^{-k\tau}$ or $A_{ss,min} = A_{ss,max} e^{-k\tau}$.

To further appreciate the phenomenon of accumulation, consider an oral dosage regimen of 0.1 mg daily of digitoxin, used in the treatment of certain cardiac dysfunctions. Although not as widely used as the more popular drug, digoxin, digitoxin nicely illustrates many of the aspects of accumulation and design of dosage regimens. Given that absorption is complete and virtually instantaneous, oral administration can be simulated using i.v. bolus doses.

The average half-life of digitoxin is 6 days; therefore, from Eq. 3 the maximum amount at plateau is 0.92 mg, and from Eq. 4 the minimum amount at plateau is 0.82 mg. Digitoxin clearly undergoes considerable accumulation when given daily.

These calculations of the maximum and minimum values at plateau strictly apply only to intravascular bolus administration. They are reasonable approximations following extravascular administration, when absorption is complete and virtually instantaneous. The following discussion deals with a less restrictive view of accumulation, which applies to all routes of administration.

Average Amount and Concentration at Plateau

In many respects the accumulation of drugs, administered in multiple doses is the same as that observed following a constant-rate i.v. infusion. The average amount in the body at steady state, plateau, is readily calculated using the steady-state concept: Average *rate in* must equal average *rate out*. The average rate in is $F \cdot \text{Dose}/\tau$. The average rate out is $k \cdot A_{ss,av}$, where $A_{ss,av}$ is the average amount of drug in the body over the dosing interval at plateau. Therefore,

$$\frac{F \cdot \text{Dose}}{\tau} = k \cdot A_{ss,av} \quad 5$$

or

$$\frac{F \cdot \text{Dose}}{\tau} = CL \cdot C_{ss,av} \quad 6$$

where $C_{ss,av}$ is the average plasma concentration at the plateau. Since $k = 0.693/t_{1/2}$, it also follows that

$$A_{ss,av} = 1.44 \cdot F \cdot \text{Dose} \cdot t_{1/2}/\tau \quad 7$$

and

$$C_{ss,av} = \frac{F}{CL} \cdot \frac{\text{Dose}}{\tau} \quad 8$$

These are fundamental relationships; they show how the average amount in the body at

steady state depends on rate of administration (Dose/τ), bioavailability, and half-life, and how the corresponding average concentration depends on the first two factors and clearance.

Drug accumulation is not a phenomenon that depends on the property of a drug, nor are there drugs that are cumulative and others that are not. Accumulation, in particular the extent of it, is a result of the frequency of administration relative to half-life ($t_{1/2}/\tau$ or $1/k\tau$) as shown in Figs. 7-1 and 7-2.

Notice that the average amount of digitoxin (0.87 mg), calculated from Eq. 7, lies midway between the maximum 0.92 mg and the minimum 0.82 mg. Since calculating the average value is the much simpler procedure, under these circumstances the maximum and minimum values can easily be calculated by adding and subtracting one-half the maintenance dose absorbed, respectively, to the average value. With digitoxin, for example, $A_{ss,max}$ is $0.87 + 0.05 = 0.92$ mg; $A_{ss,min}$ is $0.87 - 0.05 = 0.82$ mg. This simple method is a reasonable approximation as long as the dosing interval does not exceed the half-life.

Comparison of Maximum, Average, and Minimum Amounts at Plateau

Fluctuation in the amount of drug in the body, like accumulation, depends on both frequency of drug administration and half-life. Fluctuation also depends on rate of absorption; it is greatest for i.v. bolus administration. Figure 7-2A illustrates how maximum, minimum, and average amounts in the body at plateau depend on the frequency of i.v. bolus administration. Several observations are pertinent: (1) The average amount increases in direct proportion to frequency of administration (inverse of the dosing interval). (2) The maximum amount is not much greater than dose if drug is administered less frequently than once every 3 half-lives, $t_{1/2}/\tau = 0.33$ or less. Then most of the drug from all previous doses has

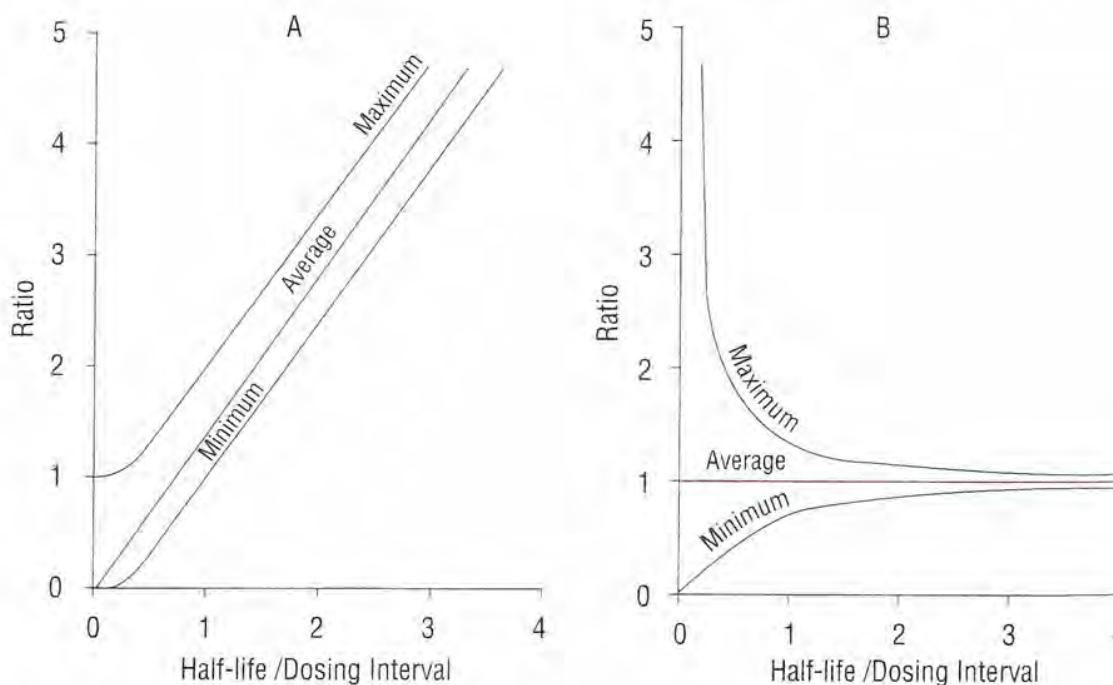


Fig. 7-2. More frequent administration results in a greater degree of drug accumulation and hence smaller relative differences among the maximum ($A_{ss,max}$), average ($A_{ss,av}$) and minimum ($A_{ss,min}$) amounts of drug in the body at plateau. Note that frequency is the reciprocal of the dosing interval expressed here in half-life units. A, Ratios of the maximum, average (colored line), and minimum amounts of drug at plateau to the maintenance dose following chronic i.v. bolus administration, as a function of the dosing frequency. B, Ratios of maximum to average (colored line), and minimum to average amounts of drug in the body as a function of the dosing frequency.

been eliminated before the next dose is administered. (3) Defining fluctuation as the ratio, $A_{ss,max}/A_{ss,min}$, given by $e^{k\tau}$ (Eq. 4), the greater the relative frequency of administration ($1/k\tau$) the smaller is the fluctuation. Figure 7-2B demonstrates how fluctuation at plateau depends on frequency of administration. The maximum and minimum amounts are each compared with the average amount in the body. Note that the average is arithmetically closer to the minimum than to the maximum value. This is particularly evident for low frequencies of administration.

Rate of Accumulation to Plateau

The amount in the body rises on multiple dosing just as it does following a constant-rate i.v. infusion (Chap. 6). That is, the approach to the plateau depends solely on the drug's half-life. The data for digitoxin, in Table 7-1 which show the ratio of the minimum amount during various dosing intervals to the maximum amount at plateau, illustrate this point. Observe that it takes 1 half-life (6 days), or 6 doses, to be at 50% of the value at plateau, 2 half-lives (12 days), or 12 doses, to be at 75% of the plateau value, and so on.

Accumulation of digitoxin takes a long time because of its long half-life. The degree of accumulation is extensive, because of relatively frequent administration. The frequency of administration also determines the small fluctuation in the amount of drug in the body at plateau; 0.1 mg is lost every dosing interval, when there is about 0.9 mg in the body.

The approach to steady state, observed for the minimum amounts of digitoxin in the body, also holds true for the maximum (proof in Appendix I-D), and average amounts, that is,

$$\frac{A_{N,max}}{A_{ss,max}} = \frac{A_{N,av}}{A_{ss,av}} = \frac{A_{N,min}}{A_{ss,min}} = 1 - e^{-Nk\tau} \quad 9$$

where $A_{N,av}$ is the average amount in the body in the dosing interval after the N th dose.

Accumulation Index

If the amounts at steady state are compared to the corresponding values at time τ after the first dose, then

$$\frac{A_{ss,max}}{A_{max,1}} = \frac{A_{ss,av}}{A_{av,1}} = \frac{A_{ss,min}}{A_{min,1}} = \frac{1}{(1 - e^{-k\tau})} \quad 10$$

The quantity, $1/(1 - e^{-k\tau})$, is an index of the extent of accumulation. For digitoxin ($k = 0.116 \text{ day}^{-1}$, $\tau = 1 \text{ day}$), the *accumulation index* (R_{ac}) is 9.2. Thus, the maximum, average, and minimum amounts (and for that matter the amount at any time within the dosing interval at plateau) are 9.2 times the values at the corresponding times after a single dose.

Table 7-1. Approach to Plateau on Daily Administration of Digitoxin

Time (days) ^a	0	1	2	3	6	12	18	24	30	∞
Number of doses (N)		1	2	3	6	12	18	24	30	∞
Minimum amount Minimum amount at plateau										
	0	0.11	0.21	0.29	0.5	0.75	0.875	0.94	0.97	1.00

^aTime after first dose

^b $A_{N,min}/A_{ss,min} = 1 - e^{-0.116N}$

Change in Regimen

Suppose that the decision is made to halve the amount of digitoxin in the body at plateau. The need for a twofold reduction in the rate of administration, to 0.05 mg/day, follows from Eq. 7.

As with i.v. infusion, it takes 1 half-life to go one-half the way from 0.90 to 0.45 mg, 2 half-lives to go three-quarters of the way, and so on. For digitoxin it would take about 12 days to go 75% of the way to the new plateau. (The same principle applies to an increase in the rate of digitoxin administration.) The fastest way to achieve 0.45 mg would be to discontinue drug for 1 week (approximately 1 half-life) before initiating the reduced rate of administration.

RELATIONSHIP BETWEEN INITIAL AND MAINTENANCE DOSES

It might be therapeutically desirable to establish the required amount of digitoxin in the body on the first day. When the first or initial dose is intended to be therapeutic it is referred to as the *priming* or *loading dose*. In this case, the patient would require 0.9 mg initially, followed by 0.1 mg daily. For digitoxin the initial dose is often administered in divided doses. Several procedures are followed, but the divided dose is commonly given every 6 hours until the desired therapeutic response is obtained. In this way each patient is titrated to the initial therapeutic dose required.

Instead of determining the loading dose when the maintenance dose is given, it is more common to determine the maintenance dose required to sustain a therapeutic amount in the body. The initial dose rapidly achieves the therapeutic response; subsequent doses maintain the response by replacing drug lost during the dosing interval. The maintenance dose, D_M , therefore, is the difference between the loading dose, D_L , and the amount remaining at the end of the dosing interval, $D_L \cdot e^{-k\tau}$. That is,

$$\text{Maintenance dose} = \left[\frac{\text{Loading dose}}{\text{dose}} \right] \cdot (1 - e^{-k\tau}) \quad 11$$

Likewise, if the maintenance dose is known, the initial dose can be estimated:

$$\text{Loading dose} = \frac{\text{Maintenance dose}}{(1 - e^{-k\tau})} \quad 12$$

Thus, for digitoxin, a daily maintenance dose of 0.1 mg requires a loading dose of 0.9 mg.

The similarity between Eqs. 3 and 11 should be noted. From the view point of accumulation, Eq. 3 relates to the maximum amount at plateau on administering a given dose repetitively. If the maximum amount were put into the body initially, then Eq. 11 indicates the dose needed to maintain that amount. The relationships are the same, although they were derived using different logic. These equations form the heart of multiple-dose drug administration and might well be called the "dosage regimen equations."

The ratio of loading to maintenance doses depends on the dosing interval and the half-life and is equal to the accumulation index, R_{ac} . For example, tetracycline has approximately an 8-hour half-life in man, and a dose in the range of 250 to 500 mg is considered to provide effective antimicrobial drug concentrations. Therefore, a reasonable schedule is 500 mg (two 250-mg capsules) initially, followed by 250 mg every half-life, as shown in Fig. 7-3. A dosage regimen consisting of a priming dose equal to twice the maintenance dose and a dosing interval of one half-life are convenient for drugs with half-lives between 8 and 24 hr. The frequency of administration for such drugs varies from 3 times a day to once daily.

respectively. For drugs with very short to short half-lives, less than 3 hr, or with very long half-lives, greater than 24 hr, this regimen is often impractical.

Although a loading or initial dose greater than the maintenance dose seems appropriate for drugs with half-lives longer than 24 hr, such is often not the case. There are a variety of reasons why this is so. For piroxicam, an analgesic/antipyretic with a half-life of 48 hr, the most common adverse effects are gastrointestinal reactions. Such reactions may be increased if the loading dose is three to four times the maintenance dose ($D_L = D_M/(1 - e^{-k\tau})$, $\tau = 1$ day). Another example is that of warfarin (half-life = 37 hr), for which the anticoagulant effect develops slowly with time. A third example is that of protriptyline (an antidepressant with a half-life of 78 hr), for which larger doses slow gastric emptying and gastrointestinal activity (anticholinergic effect), resulting in slower and more erratic absorption of this and other drugs. Furthermore, for protriptyline, the development of therapeutic effects is also delayed, usually for 2 to 3 weeks.

MAINTENANCE OF DRUG IN THE THERAPEUTIC RANGE

Dosage regimens that achieve therapeutic concentrations are listed in Table 7-2 for drugs with both medium to high and low therapeutic indices and with various half-lives.

Half-Lives Less Than 30 Min

Great difficulty is encountered in trying to maintain therapeutic concentrations of such drugs. This is particularly true for a drug with a low therapeutic index, e.g., heparin, which has a half-life of approximately 30 min. Such a drug must be either infused or discarded unless intermittent concentrations are permissible. Drugs with a high therapeutic index may be given less frequently, but the greater the dosing interval, the greater is the maintenance dose required to ensure that drug in the body stays above a minimum effective value. Penicillin is a notable example of a drug for which the dosing interval (4 to 6 hr) is many times longer than its half-life (approximately 30 min). The dose given greatly exceeds that required to yield plasma concentrations of antibiotic equivalent to the minimum inhibitory concentration for most microorganisms.

Half-Lives Between 30 Min and 8 Hr

For such drugs, the major considerations are therapeutic index and convenience of dosing. A drug with a high therapeutic index need only be administered once every 1 to 3 half-lives, or even less frequently. A drug with a low therapeutic index must be given approximately every half-life, or more frequently, or be given by infusion. Lidocaine, for example,

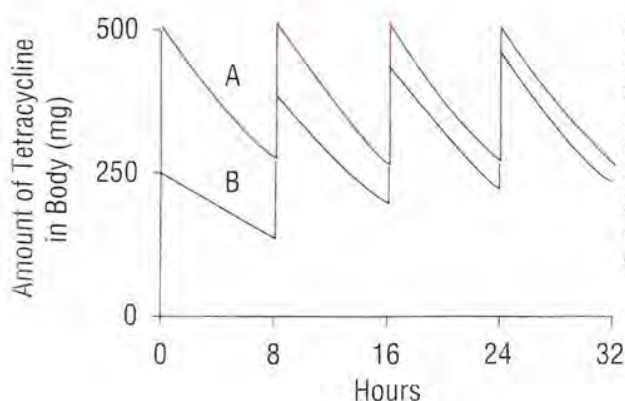


Fig. 7-3. Sketch of the amount of tetracycline in the body with time; simulation of the i.v. administration of 500 mg initially and 250 mg every 8 hr thereafter, curve A. When the initial and maintenance doses are the same, curve B, it takes approximately 30 hr (3 to 4 half-lives) before the plateau is practically reached. Thereafter, curves A and B are essentially the same.

has a half-life of 90 min, and the range of plasma concentrations associated with the treatment of cardiac arrhythmias is only about threefold. This drug must be given by infusion to ensure prolonged suppression of arrhythmias and minimal toxicity.

Half-Lives Between 8 and 24 Hr

Here, the most convenient and desirable regimen is one in which a dose is given every half-life. If immediate achievement of steady state is desired, then, as previously mentioned, the initial dose must be twice the maintenance dose; the minimum and maximum amounts in the body are equivalent to one and two maintenance doses, respectively.

Half-Lives Greater Than 24 Hr

For drugs with half-lives greater than 1 day, administration once daily is convenient and promotes patient compliance. If an immediate therapeutic effect is desired, a therapeutic dose needs to be given initially. Otherwise the initial and maintenance doses are the same, in which case several doses may be necessary before the drug accumulates to therapeutic levels. The decision whether or not to give larger initial doses is often a practical matter. Side effects to large oral doses (gastrointestinal side effects) or to acutely high concentrations of drug in the body may necessitate a slow accumulation.

Table 7-2. Dosage Regimens for Continuous Maintenance of Therapeutic Concentrations

THERAPEUTIC INDEX ^a	HALF-LIFE	RATIO OF INITIAL DOSE TO MAINTENANCE DOSE	RATIO OF DOSING INTERVAL TO HALF-LIFE	GENERAL COMMENTS	DRUG EXAMPLES
Medium to High	<30 min	—	—	Candidate for constant-rate administration and/or short-term therapy.	Nitroglycerin
	30 min to 3 hr	1	3-6	To be given any less often than every 3 half-lives, drug must have very high therapeutic index.	Cephalosporins
	3-8 hr	1-2	1-3		Tetracycline
	8-24 hr	2	1	Very common and desirable regimen.	Sulfamethoxazole
	>24 hr	>2	<1	Once daily is practical. Occasionally given once weekly, or less frequently. Initial dose may need to be much greater than maintenance dose.	Chloroquine (suppression of malaria)
Low	<30 min	—	—	Not a candidate except under very closely controlled infusion.	Nitroprusside
	30 min to 3 hr	—	—	Only by infusion.	Lidocaine
	3-8 hr	1-2	1	Requires 3-6 doses per day, but less frequently with controlled-release formulation.	Theophylline
	8-24 hr	2-4	0.5-1		Clonidine ^b
	>24 hr	>2	<1	Requires careful control; once toxicity is produced drug concentration and toxicity decline slowly.	Digitoxin

^aUsually toxic maintenance dose/usual therapeutic maintenance dose.

^bAs with many other drugs in this category, rather than administering a loading dose, dosage is progressively elevated until the desired response is achieved.

To summarize the foregoing discussion, consider the antibiotic drug tetracycline, the nasal congestant phenylpropanolamine, and the antiepileptic agent phenobarbital, and their dosage regimens given in Table 7-3. Listed in Table 7-4 are the corresponding fractions of the initial amount remaining at the end of a dosing interval, the average amounts at steady state, and the maximum and minimum values. Instantaneous and complete absorption is assumed.

Dosing intervals for all three drugs are identical. The doses of phenylpropanolamine and phenobarbital are also the same, but the amounts of them in the body with time are certainly not. The explanation is readily visualized with a sketch.

As with any graph, consideration should first be given to scaling the axes. The amount of drug in the body should be scaled to the maximum amount at steady state. The time axis should be scaled to 4 to 5 half-lives, by which time plateau is achieved.

For tetracycline the amount in the body immediately after the first dose is 500 mg. At the end of the dosing interval, the fraction remaining is 0.5, and the amount therefore is 250 mg. A maintenance dose of 250 mg returns the level to 500 mg and so on. Figure 7-3, curve A, is thus readily drawn. Now consider the sketch had no loading dose been given. The initial amount, 250 mg, would then decline to 125 mg at the end of the first interval. The amount in the body immediately after the next dose would be 375 mg. At the end of the second interval, 187 mg would remain, and so on (curve B of Fig. 7-3).

For phenylpropanolamine the maximum and minimum amounts in the body at plateau are 40 mg and 10 mg, respectively, and a period of 4 half-lives is 16 hr. The fraction remaining at the end of each dosing interval is 0.25; therefore, the values of $A_{ss,max}$ and $A_{ss,min}$ are:

Dose	Time (hr)	$A_{ss,max}$ (mg)	$A_{ss,min}$ (mg)
1	0	30	
	8		7.5
2	8+	37.5	
	16		9.4
3	16+	39.4	

By the third dose (24 hr), the plateau is virtually achieved. Being given every two half-lives, the accumulation of phenylpropanolamine is minimal. Figure 7-4 is a sketch of the amounts of phenylpropanolamine in the body with time.

Table 7-3. Dosage Regimens and Half-lives of Three Drugs

DRUG	LOADING DOSE (mg)	MAINTENANCE DOSE (mg)	DOSING INTERVAL (hr)	HALF-LIFE (hr)
Tetracycline	500	250	8	8
Phenylpropanolamine	30	30	8	4
Phenobarbital	30	30	8	100

Table 7-4. Amount of Drug in Body (mg) on Regimens Given in Table 7-3

DRUG	FRACTION REMAINING AT END OF INTERVAL ^a	AVERAGE AT STEADY STATE ^b	MAXIMUM AT STEADY STATE ^c	MINIMUM AT STEADY STATE ^d
Tetracycline	0.5	360	500	250
Phenylpropanolamine	0.25	22	40	10
Phenobarbital	0.946	540	556	526

^a Given by e^{-kt}

^b $\Delta A_{ss} = \frac{D}{1 - F}$

^c $A_{ss,max} = \frac{D}{1 - F}$

^d $A_{ss,min} = F \cdot A_{ss,max}$

The same dosage regimen for phenobarbital produces a dramatically different result. At the end of each dosing interval, the fraction remaining is 0.946. Accumulation then occurs until the 5.4% lost in each interval is equal to the dose, and the amount in the body at steady state is therefore about 19 times the dose. From the calculated value of the maximum amount at plateau (556 mg) and the half-life, it is apparent that a sketch must be scaled to 600 mg and to about 15 days (Fig. 7-5). The curve is similar to that obtained with constant-rate infusion. The amounts in the body at 100 hr is one-half of the steady-state amount, and at 200 hr the level is 75% of the plateau amount, and so on. Practically, there is little need to consider the minor fluctuations.

The clinical implications of these regimens are manifold. The tetracycline regimen is designed to attain and maintain therapeutic levels. The phenylpropanolamine regimen gives rise to large fluctuations that may be desirable. Tolerance to the drug develops readily; the maintenance of high, effective, decongesting concentrations is questionable. With pheno-

Fig. 7-4. Sketch of the amount of phenylpropanolamine in the body with time; simulation of 30 mg given i.v. every 8 hr. Because the half-life, 4 hr, is short relative to the dosing interval, the degree of accumulation is small and the fluctuation is large.

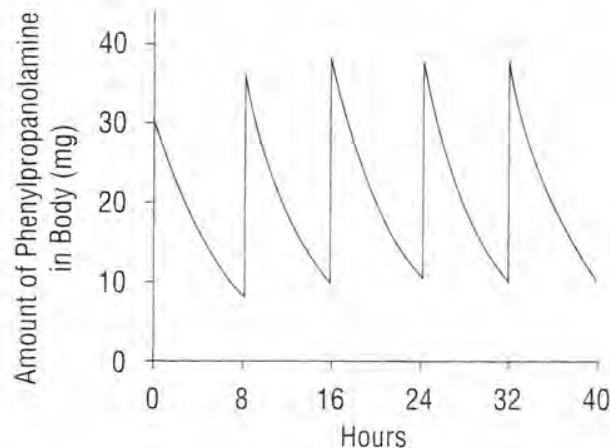
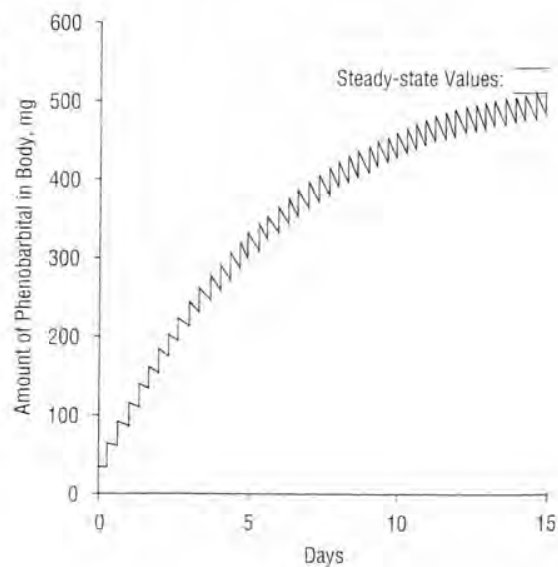


Fig. 7-5. Sketch of the amount of phenobarbital in the body with time; simulation of 30 mg given i.v. every 8 hr. Because the half-life, 4 days, is extremely long relative to the dosing interval, the degree of accumulation is large, and the fluctuation is low. The maximum and minimum values at steady state, 556 and 326 mg, are shown on the right.



barbital the appropriate regimen depends on whether the drug is used for sedation or as an antiepileptic. For sedation, the omission of a loading dose is desirable, in that tolerance to the sedative effect develops with time and a large priming dose, 600 mg, causes too great a central depressive effect. As an antiepileptic, however, a loading dose may be appropriate. Although previously prescribed as such, chronic administration of phenobarbital three times daily is unnecessary; once daily administration may lead to better chances of compliance.

Lack of compliance is a major problem in pharmacotherapy. The most frequent pattern of noncompliance is the occasional omitted dose or failure to take several consecutive doses. Regimens of multiple daily doses tend to produce greater frequencies of missed doses than those in which a drug is taken once or twice daily. However, decreasing the frequency of dosing (with corresponding increase in each dose) may not improve the maintenance of concentrations within the effective range. The impact of a missed dose is shown in Fig. 7-6 for regimens of 300-mg once daily and 100-mg every 8 hr. In both regimens the total daily dose is the same. Omission of a single daily 300-mg dose produces a much lower minimum concentration than omission of a 100-mg dose for two reasons. First, the amount lost during the longer interval of the former regimen is greater. Second, the average minimum concentration at steady state is lower for the once daily regimen. Thus, omitting a single dose during a once daily regimen may have a much greater impact on therapeutic response than omitting an 8-hourly dose.

Note that even omitting three consecutive doses of the 8-hourly regimen (the equivalent of a once-daily dose) does not produce as low a concentration as the omission of a single daily dose.

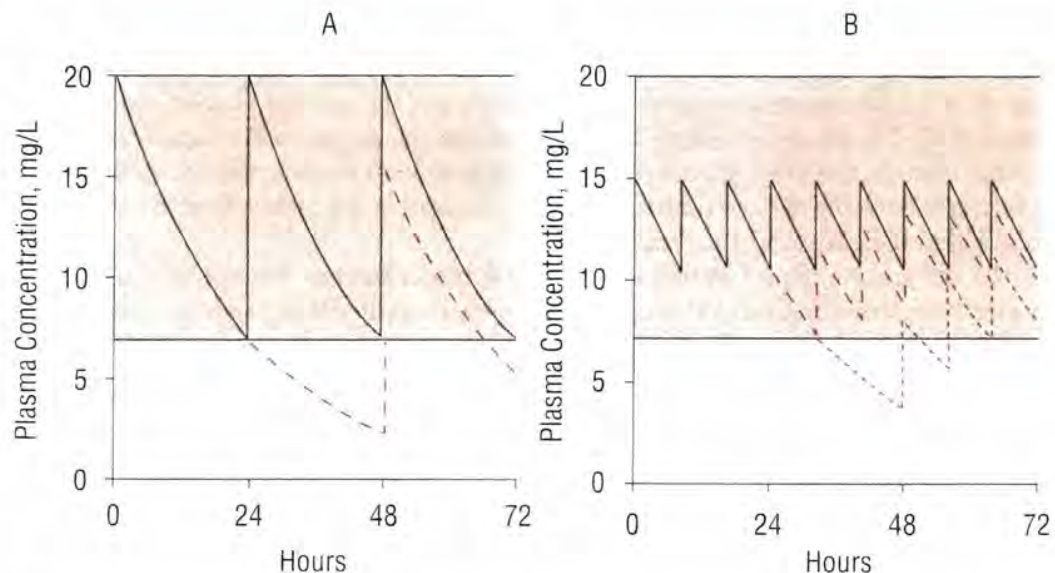


Fig. 7-6. From a kinetic perspective, the impact of a missed dose is greater the larger the dose and the less frequent the administration. Consider steady-state multi-dose conditions for a drug with a therapeutic window of 7 to 20 mg/L (color screened), a volume of distribution of 23.1 L, and a half-life of 15.9 hr. **Panel A:** When a 300-mg dose is given once daily to maintain therapeutic concentrations, a missed dose results in a trough concentration of 2.5 mg/L, a value well below the lower limit of the therapeutic window. **Panel B:** When a 100-mg dose is given every 8 hr (colored long dashed line), the lowest concentration achieved after a single missed dose is 7.3 mg/L, a value within the therapeutic concentration range. If 3 consecutive doses are missed (colored short-dashed line) the minimum concentration (3.7 mg/L) is still above that observed when a single daily dose of 300-mg is missed. The figure was adapted from concepts presented by Levy G., A pharmacokinetic perspective on medicament noncompliance. *Clin. Pharmacol. Ther.* 54:242-244, 1993.

The increased probability of compliance by once daily dosing is countered by kinetic arguments in favor of more frequent dosing. Where the optimum regimen lies depends on many factors. For example, for phenobarbital, with a half-life of 4 days, the omission of a single daily dose of 90 mg or an 8-hourly dose of 30 mg is of minor importance because the average amount in the body at steady state is 556 mg (see Fig. 7-5). Thus, the smaller the ratio of the dosing interval to half-life, the less the kinetic impact of a missed dose. Other determinants of the optimal regimen include factors such as those affecting the likelihood of compliance (severity and nature of disease, occupation of patient, personality of patient) and those relating to the pharmacodynamic characteristics of the drug (steepness of concentration-response curves, width of therapeutic window).

PRACTICAL ASPECTS OF MULTIPLE-DOSE ADMINISTRATION

So far, consideration has been given primarily to the amount of drug in the body following multiple i.v. bolus injections, or their equivalent, at equally spaced intervals. In practice, chronic administration is usually by the oral route. Furthermore, only drug concentration in plasma or in blood can be measured and not amount of drug in the body. These aspects are now considered. Problems related to unequal doses and dosing intervals and to missed doses are covered in Chap. 18, Concentration Monitoring.

Extravascular Administration

The oral (also intramuscular [i.m.], buccal, subcutaneous [s.c.], and rectal) administration of drugs requires an added step, absorption. Eqs. 1 to 4 apply to extravascular administration, provided that absorption has essentially ended within a small fraction of a dosing interval, a condition similar to i.v. bolus administration. Even so, a correction must be made if bioavailability is less than 1. When absorption continues throughout a dosing interval, or longer, then the relationships of Eqs. 7 and 8 still apply. These relationships allow estimation of the average plateau amount in the body and the average plateau concentration, respectively. The slowness of drug absorption affects the degree of fluctuation around, but not the value of, the average concentration. The exception is when absorption becomes so slow that there is insufficient time for complete absorption, e.g., when limited by the transit time within the gastrointestinal tract.

The therapeutic impact of differences in absorption kinetics, but not in bioavailability, of extravascularly administered drug products given repeatedly depends on the frequency of their administration. As illustrated in Fig. 7-7, major differences seen following a single dose only persist and are of potential therapeutic concern at plateau when the drug products are given infrequently, relative to the half-life of the drug. Differences between them almost disappear at plateau when the products are given frequently. In the latter case, as stated previously, with extensive accumulation of drug, the concentration at plateau is relatively insensitive to variations in absorption rate.

Plasma Concentration Versus Amount in Body

During multiple dosing, the plasma concentration can be calculated at any time by dividing the corresponding equations defining amount by volume of distribution. Distribution equilibrium between drug in the tissues and that in plasma takes time. Thus, observed maximum concentrations may be appreciably greater than those calculated by dividing Eqs. 1 and 3 by V (see Chap. 19).

The average plateau concentration may be calculated using Eq. 8. This equation is applicable to any route, method of administration, or dosage form, as long as bioavailability and clearance remain constant with both time and dose.

DESIGN OF DOSAGE REGIMENS FROM PLASMA CONCENTRATIONS

Dosage regimens can be designed to maintain concentrations within a therapeutic window. The window is defined by a lower limit (C_{lower}) and an upper limit (C_{upper}). The maximum dosing interval, τ_{max} , and maximum maintenance dose, $D_{M,max}$, can be readily computed from these limits as follows:

$$C_{lower} = C_{upper} \cdot e^{-k\tau_{max}} \quad 13$$

where τ_{max} is the maximum time interval over which these upper and lower concentrations can occur. By rearrangement of Eq. 13, the value of τ_{max} is

$$\tau_{max} = \frac{\ln(C_{upper}/C_{lower})}{k} \quad 14$$

and, from the relationship, $k = 0.693/t_{1/2}$,

$$\tau_{max} = 1.44 \cdot t_{1/2} \cdot \ln(C_{upper}/C_{lower}) \quad 15$$

The corresponding maximum maintenance dose, $D_{M,max}$, that can be given every τ_{max} is

$$D_{M,max} = \frac{V}{F} (C_{upper} - C_{lower}) \quad 16$$

When $D_{M,max}$ is administered every τ_{max} , there is an average concentration produced within the dosing interval, defined by

$$\frac{D_{M,max}}{\tau_{max}} = \frac{CL}{F} \cdot C_{ss,av} \quad 17$$

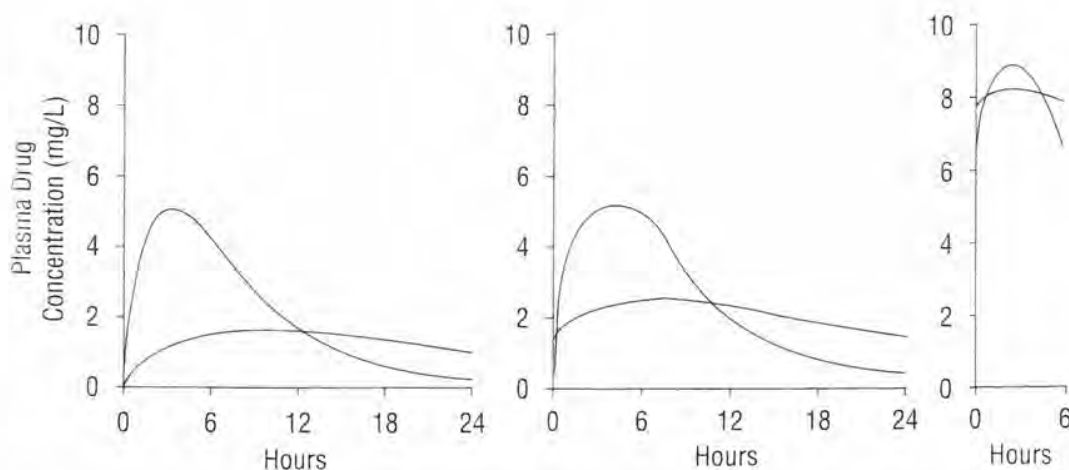


Fig. 7-7. Differences in the absorption rates between two dosage forms, exaggerated here for illustrative purposes, following a single extravascular dose (left panel) can have a major therapeutic impact at plateau during multiple dosing. The relative fluctuation of the plasma concentration when the drug products are given infrequently (middle panel) is much greater than when given frequently (right panel).

By dividing Eq. 16 by Eq. 14 and comparing this ratio to Eq. 17, it is apparent that the value of $C_{ss,av}$ is given by

$$C_{ss,av} = \frac{(C_{upper} - C_{lower})}{\ln(C_{upper}/C_{lower})} \quad 18$$

A dosage regimen may be designed by setting the dosing rate either to achieve the average concentration, $C_{ss,av}$, or to maintain a peak concentration. In both approaches, concentrations are maintained within the therapeutic window throughout the dosing interval.

Maintenance of an Average Concentration

Choosing the average concentration within the dosing interval at plateau to be $C_{ss,av}$ allows the greatest possible dosing interval. This dosing interval (Eq. 15) and the corresponding maintenance dose (Eq. 16) may not be practical, however. Both values may need to be adjusted to make the frequency of administration convenient for patient compliance and to accommodate the dose strengths of the drug products available. The guiding principle is to maintain the same rate of administration and therefore the same chosen average steady-state concentration.

Having chosen a convenient dosing interval, τ smaller than τ_{max} , the maintenance dose is

$$D_M = (D_{M,max}/\tau_{max}) \cdot \tau \quad 19$$

and the loading dose, appropriate to attain the steady-state concentration, initially, is

$$D_L = D_M/(1 - e^{-k\tau}) \quad 20$$

If more (or less) vigorous therapy is desired, resulting in the setting of the average targeted concentration to be higher (or lower) than $C_{ss,av}$, the dosing rate can be increased (or decreased) proportionately. However, one may wish to adjust the dosing interval to ensure that concentrations remain within the therapeutic window.

Maintenance of a Peak Concentration

The second approach to the design of dosage regimens is based on the desire to maintain a given peak concentration. The peak concentration chosen, C_{peak} , depends on how aggressively one wishes to pursue therapy but usually lies in the upper half of the therapeutic window. The maximum dosing interval is:

$$\text{Maximum dosing interval} = \frac{\ln(C_{peak}/C_{lower})}{k} \quad 21$$

On choosing a convenient interval, τ , less than the maximum defined in Eq. 21, the maintenance dose then becomes

$$D_M = V \cdot C_{peak}(1 - e^{-k\tau}) \quad 22$$

and the loading dose, if necessary, is $V \cdot C_{peak}$. Note that C_{peak} is the same as $C_{ss,max}$. This method of regimen design tends to be simpler than the previous one.

For example, consider a drug with a therapeutic window of 2–10 mg/L, a volume of distribution of 25 L and a 16-hr half-life ($k = 0.043 \text{ hr}^{-1}$). The maximum dosing interval is then 37 hr ($\ln(10/2)/0.043 \text{ hr}^{-1}$). If an interval of 12 hr is chosen, the maintenance dose needed is then about 100 mg ($V \cdot C_{peak}(1 - e^{-k\tau})$). The loading dose ($V \cdot C_{peak}$) is 250 mg. If the regimen is designed on the basis of attaining and maintaining the average concentration, the maintenance dose (Eqs. 17 and 19) is then 65 mg and the loading dose (Eq. 20) is 160 mg. Figure 7–8 illustrates the differences in these two approaches.

Following extravascular administration, fluctuations in the plasma concentration of drug are less than those after intravascular administration. Depending on the slowness of the absorption process, it may be possible to administer the drug less frequently than indicated in the regimens designed by either of the last two methods.

When Bioavailability and Volume Are Unknown

Oral dosage regimens can also be designed without determining bioavailability. This is accomplished using the area under the plasma concentration-time curve (AUC) following a single dose. From the relationship $F \cdot \text{Dose} = CL \cdot AUC$ after a single dose (Eq. 7, Chap. 4) and the relationship $F \cdot \text{Dose}/\tau = CL \cdot C_{ss,av}$ during steady state after multiple doses (Eq. 6), it follows that

$$C_{ss,av} = AUC(\text{single dose})/\tau \quad 23$$

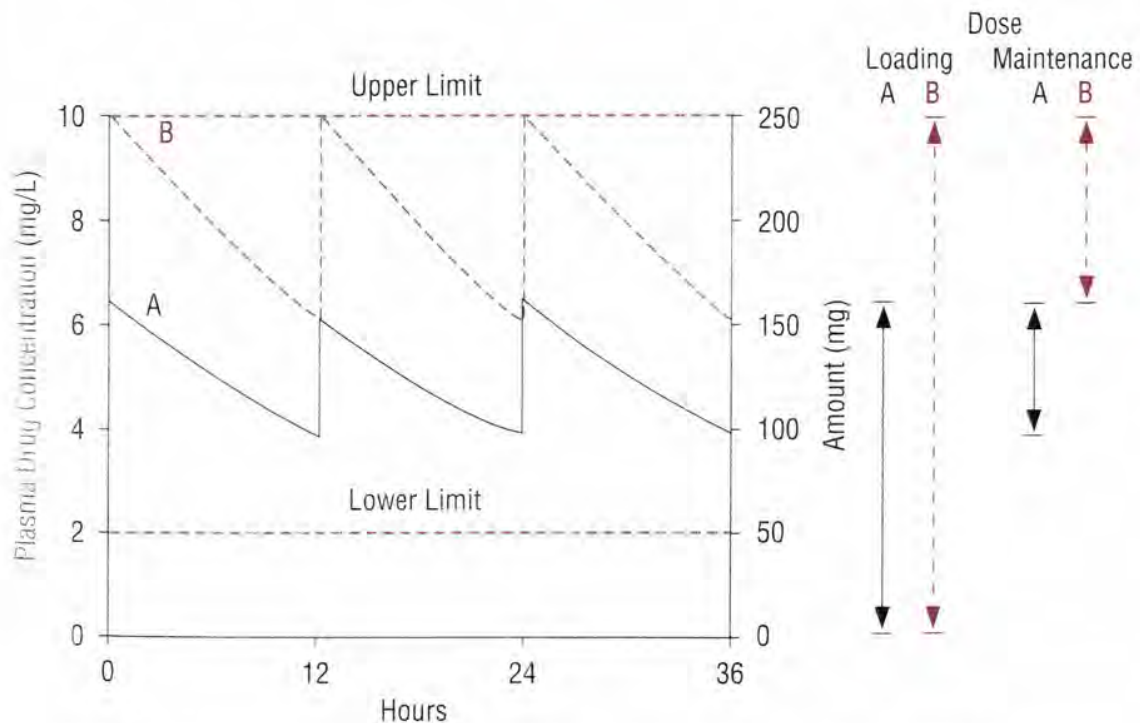


Fig. 7–8. Differences in two methods of dosage regimen design. Regimen A (solid black line) is designed to maintain the same average concentration as that obtained when the concentration fluctuates between the upper (10 mg/L) and lower (2 mg/L) limits. Regimen B (colored stippled line) is designed to ensure that the peak concentration does not exceed the upper limit. Of course, a lower peak value may have been chosen. The loading doses required to achieve the steady-state concentrations immediately and the maintenance doses for both regimens are indicated on the right side of the graph.

Consequently, either the dosing interval necessary to achieve a desired average steady-state concentration or the average concentration resulting from administering the dose every dosing interval can be calculated.

By definition of $C_{ss,av}$, the value of $\tau \cdot C_{ss,av}$ is the AUC within a dosing interval at steady state. Thus, this area is equal to that following a single dose. This principle is shown in Fig. 7-9, and a practical illustration is shown in Fig. 7-10.

Given the plasma concentrations with time after a single oral dose, the concentration at any time during repeated administration of the same dose can be readily calculated by adding the concentrations remaining from each of the previous doses. For example, if doses are given at 0, 12, and 24 hr, then the concentration at 30 hr is equal to the sum of the values at 30, 18, and 6 hr after a single dose.

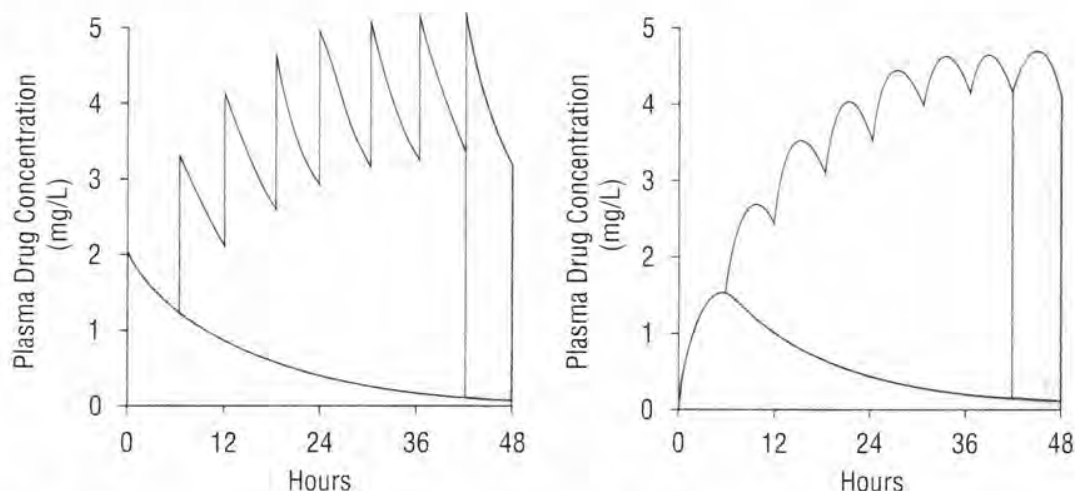
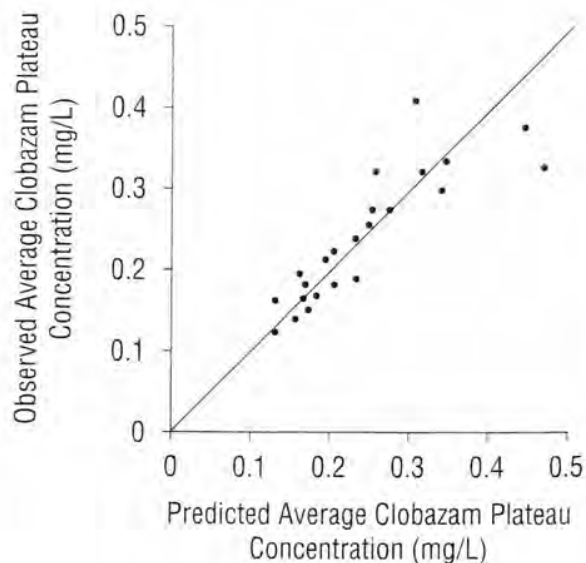


Fig. 7-9. Plasma concentrations of a drug given intravenously (left) and orally (right) on a fixed dose of 50 mg and fixed dosing interval of 6 hr. The half-life is 12 hr. Note that the AUC during a dosing interval at steady state (lighter shading) is equal to the total area under the curve following a single dose (darker shading). The fluctuation of the concentration is diminished when given orally (absorption half-life is 1.4 hr), but the average steady-state concentration is the same as that after i.v. administration, when, as in this example, $F = 1$. The equations used for the simulations are given in Appendix I-D.

Fig. 7-10. Twenty-four subjects each received a single 20-mg oral dose of the benzodiazepine, clobazam, followed 1 month later by an oral regimen of 10 mg of clobazam daily for 22 consecutive days. The observed average plateau clobazam concentration was well predicted by the value calculated from the single dose data, obtained by dividing the AUC by the dosing interval and correcting for dose. The solid line is the perfect prediction (1 mg/L = 33 μ M) (Redrawn from Greenblatt, D.J., Divoll, M., Puri, S.K., Ho, I., Zinny, M.A., and Shader, R.L.: Reduced single-dose clearance of clobazam in elderly men predicts increased multiple-dose accumulation. Clin. Pharmacokinet., 8:83-94, 1983. Reproduced with permission of ADIS Press Australasia Pty Limited.)



Useful relationships have been derived for designing and evaluating a dosage regimen in which the dose and the dosing interval are fixed. Table 7-5 summarizes some of the more important relationships and their limitations.

CONTROLLED RELEASE

The maintenance of a constant plasma concentration, and usually a relatively constant response, is achieved by constant-rate administration. While some constant-rate release systems have been developed (Chap. 6), other dosage forms exist from which drug release is much slower than from conventional dosage forms and for which the release kinetics are closer to first-order, than to zero-order. Such controlled-release products do not completely obliterate but do reduce considerably the fluctuation in the plasma concentration at plateau, when compared with conventional therapy, and are particularly useful when maintenance of therapeutic concentrations is difficult or inconvenient.

To illustrate the potential value of controlled-release products, consider the events at plateau simulated in Fig. 7-11 following oral administration of theophylline, which has a therapeutic window of 6–20 mg/L in a child with a half-life of 4 hr. With the usual dosage forms, absorption is rapid and, to maintain the plasma concentration within the therapeutic window, the drug must be administered every 6 hr, an inconvenience. Administering the controlled-release dosage form at the same frequency as the conventional formulation leads to a marked reduction in the fluctuation at plateau. Indeed, the controlled-release formulation can be given at a more convenient dosing interval, 12 hr, and still maintain the plasma concentration within the therapeutic window. To maintain the same average concentration at plateau for the 12-hr interval, the dose of the less frequently administered controlled-release product must be twice that of the conventional product. Obviously, controlled-release products must perform reliably. If all the drug were released immediately, an unacceptable fluctuation in the plasma concentration would result.

For oral administration, once or twice daily is desirable. Accordingly, for drugs with half-lives greater than 12 hr, oral controlled-release products may be of little value, not only

Table 7-5. Relationships for Evaluating Dosage Regimens^a

	RELATIONSHIP	I.V. BOLUS	EXTRAVASCULAR		
			RAPID ABSORPTION ($k_a \gg k$)	SLOW ABSORPTION	
				($k_1 > k$)	($k > k_d$)
Maintenance dose	$D_M = D_i \cdot (1 - e^{-k\tau})$	***b	***	**	N ^d
Accumulation index PLATEAU	$R_{AC} = \frac{1}{(1 - e^{-k\tau})}$	***	***	**	N
Average amount	$A_{ss,av} = 1.44 \cdot F \cdot D \cdot \left(\frac{h_{1/2}}{\tau}\right)$	***	***	***	***
Average concentration	$C_{av} = \frac{F \cdot D_M}{CL \cdot \tau}$	***	***	***	***
	$C_{ss,av} = \frac{AUC \text{ (single dose)}}{\tau}$	***	***	***	***
Maximum concentration	$C_{ss,max} = \frac{F \cdot D_M}{V(1 - e^{-k\tau})}$	c	**	*	N
Minimum concentration	$C_{ss,min} = \frac{F \cdot D_M \cdot e^{-k\tau}}{V(1 - e^{-k\tau})}$	***	***	**	N

^aFor regimens of equal doses and dosing intervals

*** Generally useful

** A reasonable approximation

* Limited usefulness

^bNot valid because distribution is not instantaneous

^cNot valid

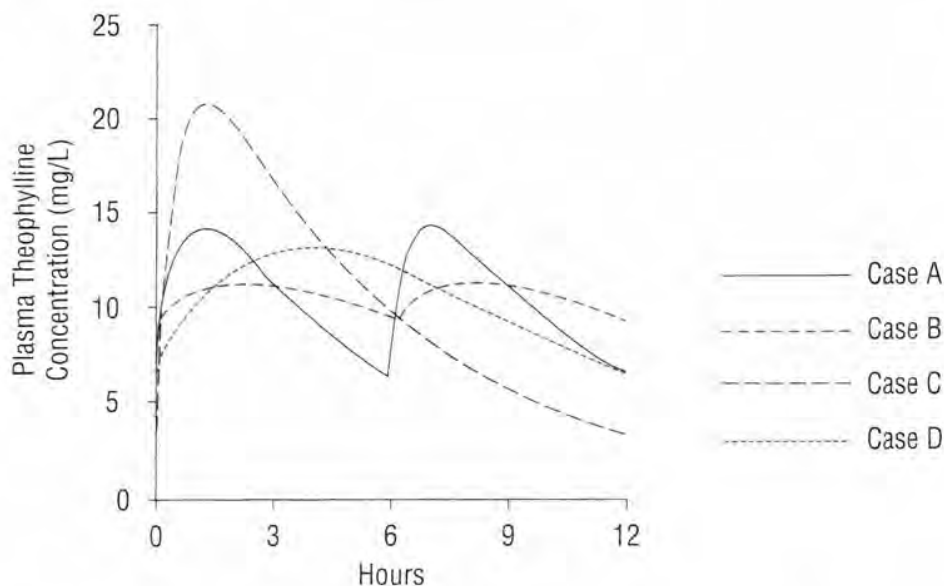


Fig. 7-11. Administering a drug, like theophylline, in a controlled-release dosage form (colored lines) may not only decrease the fluctuation in plasma concentration at plateau (Case B) compared to that seen with the usual regimen (Case A), but may also permit the drug to be given less frequently (Case D). Case C shows the concentration-time profile after the usual dosage form (360 mg) every 12 hr. In this example, $t_{1/2} = 4$ hr, $V = 35$ L, $F = 1$, the half-life of release from the controlled-release product is 3 hr, and the therapeutic window is 3 to 10 mg/L. The dosage regimens are 180 mg every 6 hr (Cases A and B) and 360 mg every 12 hr (Cases C and D).

because the usual regimen is convenient but because protracted release may put drug into the lower intestine or perhaps out of the body before the release is complete. Decreased bioavailability then becomes a major concern, especially in patients with diseases in which gastrointestinal transit is shortened.

For a drug that is usually given i.m. or s.c., multiple injections are inconvenient and a controlled-release injectable dosage form may be advantageous. Depending on the total dose required and on the local effects of the injection mixture, it may only be necessary to administer the injection weekly, monthly, or perhaps as a single dose.

Evaluation of a Multiple-Dose Regimen and Assessment of Pharmacokinetic Parameters

The development of dosage regimens proceeds in two stages. The first involves establishing whether the events on multiple dosing are predicted from single-dose data. Often there is good accord between observation and prediction, indicating that the pharmacokinetic parameters have not changed upon multiple dosing. Occasionally, prediction is poor, signifying that one or more pharmacokinetic parameters has changed, evidence of some dose or time dependency (see Chap. 22). If prediction is good, the second stage is relatively straightforward. It involves varying the regimen to achieve particular plasma concentration-time profiles, which can be evaluated against therapeutic response and toxicity. The task is much more difficult when dose and time dependencies prevail.

This section deals with how to both evaluate a multiple-dose regimen, with or without single-dose data, and estimate pharmacokinetic parameters. It builds on what has been covered in the preceding parts of the chapter.

Clearance/Bioavailability. Stability in this ratio (CL/F) on multiple dosing is given by the equation

$$AUC_{ss} = AUC \text{ (single)}$$

where AUC_{ss} is the AUC within a dosing interval at plateau. Equation 24 is a recasting of Eq. 23, where $AUC_{ss} = F \cdot \text{Dose}/CL$. A plateau is taken to be reached when several consecutive trough concentrations, determined from blood samples taken just before the next dose, show no trend with time. The accuracy of the estimates of AUC_{ss} and AUC (single) are heavily dependent on the number and timing of blood samples. If needed, the estimate of AUC_{ss} can be improved using several dosing intervals, which in turn improves the estimate of CL/F at plateau. As shown in Fig. 7-9 for clobazam, CL/F does not change on multiple dosing.

Half-Life. This parameter may be difficult to estimate during multiple dosing. Certainly, half-life cannot be estimated within a dosing interval with any confidence when the dosing interval is shorter than the half-life, as the decline in plasma concentration is too small over this time interval. The problem is made impossible if absorption continues throughout the dosing interval as often occurs with controlled-release products. Theoretically, half-life could be estimated from trough values taken on the approach to plateau, in much the same way as done with plasma data obtained on the rise to plateau following a constant-rate input regimen (pp. 70-71). In practice, however, this method is generally not very precise, especially when the dosing interval approaches the half-life, resulting in only a few trough values before plateau is reached.

The best way to estimate half-life is after stopping drug administration. At plateau, plasma concentrations are often much higher than those achieved after a single dose and so can be measured over much longer periods of time after stopping dosing, thereby facilitating an accurate estimate of half-life.

Degree of Accumulation. Accumulation always occurs. The major question is whether the degree of accumulation differs from that anticipated. One predictor of the degree of accumulation, given in Eq. 10, is the quantity $1/(1 - e^{-k\tau})$, the accumulation index (R_{ac}). This quantity predicts the ratio of the amount in the body at some time within the dosing interval at plateau to that at the same time after the first dose. However, plasma concentrations and not amounts are measured, and the ratio of amount to concentrations is only constant when the body acts as a single compartment. In practice, because distribution equilibrium between drug in tissues and that in plasma takes time, discrepancies arise between observed concentration and calculated values, assuming complete distribution. The discrepancy is greatest at early times. For this reason and because the value is difficult to estimate in practice, C_{max} is a poor choice to estimate the degree of accumulation. A trough value is a better choice, as distribution equilibrium is more likely to have been achieved at the end of the dosing interval. The observed degree of accumulation is $C_{ss,min}/C_{1,min}$, where $C_{1,min}$ is the trough concentration at the end of the first dosing interval. However, this last method relies on values obtained at only one time. This limitation is avoided using a commonly employed method based on AUC considerations, namely,

$$\text{Observed accumulation index} = \frac{AUC_{ss}}{AUC(1, \tau)} \quad 25$$

where $AUC(1, \tau)$ is the area under the plasma concentration-time profile during the first dosing interval to time τ . The procedure, analogous to the use of A_{at} values (Eq. 10), is illustrated in Fig. 7-12. Obviously, a prediction based on the ratio $AUC(\text{single})/AUC(1, \tau)$ will match the observed ratio if $AUC_{ss} = AUC(\text{single dose})$. The last term is the total AUC after a single dose. The value determined by Eq. 25 is approximately equal to $1/(1 - e^{-k\tau})$ if absorption is virtually complete at time τ after a single dose.

Degree of Fluctuation at Plateau. Fluctuation is an important consideration of any dosing regimen. It is usually evaluated at plateau. One common measure of the degree of

fluctuation is the ratio $(C_{ss,max} - C_{ss,min})/C_{ss,av}$. An advantage of this measure is that it deals with direct observations, $C_{ss,max}$, $C_{ss,min}$, which are thought to have relevance with respect to correlates of safety and minimum efficacy. A disadvantage of this measure, however, is that it relies on only two observations, one of which ($C_{ss,max}$) is often difficult to estimate accurately, unless many blood samples are taken within the dosing interval, a relatively uncommon clinical practice. Another more stable measure of fluctuation, which is less dependent on single observations, is given by

$$\text{Fluctuation} = \frac{AUC \text{ (above } C_{ss,av}) + AUC \text{ (below } C_{ss,av})}{AUC_{ss}} \quad 26$$

where $AUC \text{ (above } C_{ss,av})$ and $AUC \text{ (below } C_{ss,av})$ are the areas above and below the average concentration at plateau (AUC_{ss}/τ), respectively. Estimation of these values is shown in the inset to Fig. 7-12.

Other Parameters. Equation 27 forms a useful basis for determining relative bioavailability of a drug administered extravascularly (e.g., orally), between two treatments (e.g., dosage forms A and B). If clearance remains unchanged, then

$$\text{Relative bioavailability} = \frac{(AUC_{ss})_B}{(AUC_{ss})_A} \cdot \frac{(\text{Dose})_A}{(\text{Dose})_B} \quad 27$$

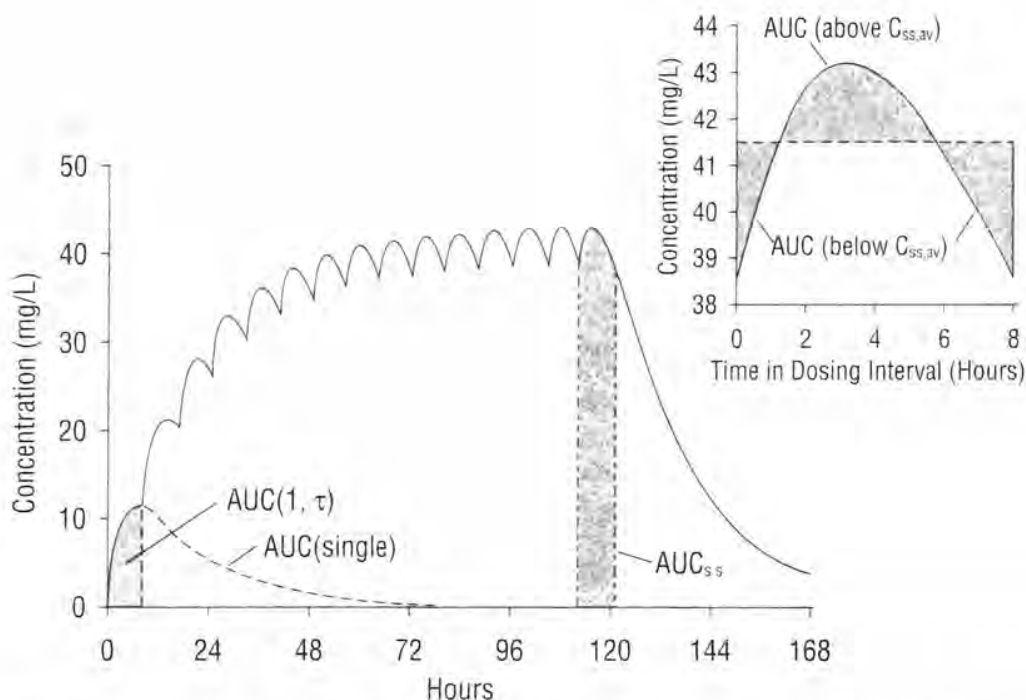


Fig. 7-12. Evaluation of a multiple-dose regimen. The stability of the CL/F ratio with dosing can be assessed by comparing the area during a dosing interval at plateau (AUC_{ss}) to that of the total area after a single dose ($AUC(\text{single})$). The degree of accumulation is taken as the ratio of AUC_{ss} to the area during the first dosing interval to time τ ($AUC(1, \tau)$). The half-life is best determined after stopping drug administration. The inset shows the method for estimating the degree of fluctuation based on AUC (Eq. 26) above and below the average concentration, $C_{ss,av}$, within the dosing interval at plateau. Alternatively, it can be calculated from the observed maximum and minimum concentrations at plateau, $C_{ss,max}$, $C_{ss,min}$; degree of fluctuation = $(C_{ss,max} - C_{ss,min})/C_{ss,av}$.

Renal clearance can be estimated from the amount of drug excreted unchanged in a dosing interval at steady state, $Ae_{ss,\tau}$ and the value of AUC_{ss} .

$$\text{Renal clearance} = \frac{Ae_{ss,\tau}}{AUC_{ss}} \quad 28$$

The relative bioavailability of an extravascular dose may be determined from urine, as well as plasma, data as follows.

$$\text{Relative bioavailability} = \frac{(Ae_{ss,\tau})_B}{(Ae_{ss,\tau})_A} \cdot \frac{(\text{Dose})_A}{(\text{Dose})_B} \quad 29$$

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

- Comment on the accuracy of the following statements with regard to drugs given as an oral multiple-dose regimen.
 - Accumulation always occurs.
 - The extent of accumulation increases when drug is given less frequently.
 - The time to reach plateau following a multiple-dose regimen depends on the frequency of drug administration.
 - At plateau, the amount of drug lost within a dosing interval equals the oral maintenance dose.
 - The larger the volume of distribution, the lower is the average plateau concentration.
 - The average plateau concentration depends on the absorption kinetics of the drug following administration of a regimen of a fixed daily dose.
- Gaffner et al. (Gaffner, 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) compared a rapid-release with a controlled-release formulation of procainamide at steady state. To ensure comparability, the data (presented in Table 7-6) were collected over an 8-hr interval at steady state after administration of 0.5 g every 4 hr as the rapid-release tablet and 1 g every 8 hr as the controlled-release formulation.

Table 7-6.

	AUC (0-8) (mg·hr/L)	Ae_{ss} (0-8) (mg)
Rapid-release formulation	22.6	664
Controlled-release formulation	21.1	667

- Calculate the relative bioavailability of the controlled-release formulation compared with the rapid-release product.
 - Calculate the renal clearance of procainamide.
- The population pharmacokinetics of the oral diuretic agent, chlorthalidone, for a 70-kg person are:

$$F = 0.64$$

$$V = 280 \text{ L}$$

$$CL = 4.5 \text{ L/hr}$$

- a. Given that absorption is instantaneous relative to elimination, calculate the following when a 50-mg dose of chlorthalidone is taken daily at breakfast.
 1. The maximum and minimum amounts of drug in the body at plateau
 2. The accumulation ratio
 3. The minimum plasma concentration at plateau
 4. The time required to achieve 50% of plateau
- b. Complete the table below for the dosage regimen of chlorthalidone given in (a).

	Amount of Chlorthalidone in Body (mg)							
Dose	1	2	3	4	5	6	7	∞
$A_{N,max}$								
$A_{N,min}$								

- c. Prepare a sketch on regular graph paper of the amount of chlorthalidone in the body with time. Show the salient features of accumulation of this drug during therapy.
 - d. If required, what is the loading dose of chlorthalidone needed to immediately attain the condition at plateau?
4. Mr. J.M., a nonsmoking 60-kg patient with chronic obstructive pulmonary disease, is to be started on an oral regimen of aminophylline (85% of which is theophylline). The pharmacokinetics parameter values for a typical patient population with this disease are:

$$F = 1.0 \text{ (for theophylline)}$$

$$V = 0.5 \text{ L/kg}$$

$$CL = 40 \text{ mL/hr/kg}$$

Design an oral dosage regimen of *aminophylline* (100- and 200-mg tablets are marketed) for this patient to *attain* and *maintain* a plasma concentration within the therapeutic window, 10 to 20 mg/L. The absorption of theophylline is complete and rapid.

5. Table 7-7 lists a typical plasma concentration-time profile obtained following an oral 500-mg dose of a drug. The AUC is 80.6 mg-hr/L, and the terminal half-life is 5 hr.

Table 7-7.

Time (hr)	0	1	2	4	8	12	24	36	48
Plasma drug concentration (mg/L)	0	2.3	4.7	5.2	4.0	2.8	0.6	0.14	0.03

- a. What oral dosing rate of drug is needed to maintain an average plateau concentration of 10 mg/L?
 - b. The decision has been made to give the drug once every 12 hr. What is:
 1. The unit dose strength of product needed?
 2. The plateau trough concentration expected?
6. The therapeutic dose of a rapidly (compared to elimination) and completely absorbed drug is 50 mg. A controlled-release dosage form to be given every 8 hr is designed to release its contents *evenly* and *completely* (no loading dose) over this dosing interval. Given that the half-life of the drug is 4 hr,

- b. To achieve a prompt effect, a rapidly absorbed dosage form is administered initially. When should the first controlled-release dosage form be given?
 - c. Following the dosage regimen in (b) what is the total dose (i) for day 1? (ii) for day 2?
 - d. In tabular form or on the same graph, provide the relative amounts of drug in the body versus time curves expected when the controlled-release preparation only is given (i) every 4 hr (ii) every 8 hr (iii) every 12 hr.
7. Adinazolam is a drug under investigation for the treatment of depression and panic disorders. Table 7-8 summarizes some of the salient pharmacokinetic information following single and multiple doses of immediate-release and controlled-release products.

Table 7-8. Mean Adinazolam Pharmacokinetic Information Following Single and Multiple Doses of Immediate-Release and Controlled-Release Preparations to a Group of 16 Subjects^a

	IMMEDIATE RELEASE		CONTROLLED RELEASE	
	SINGLE DOSE 40 mg	MULTIPLE DOSES 40 mg every 8 hr	SINGLE DOSE 60 mg	MULTIPLE DOSES 60 mg every 12 hr
AUC (mg·hr/L)	0.57 ^b	1.72 ^c	0.88 ^b	1.57 ^c
C _{max} (mg/L)	0.15	0.20	0.07	0.11
T _{max} (hr)	1.00	—	2.50	—
Terminal t _{1/2} (hr)	2.20	—	5.50	—

^aAbstracted from Fleishaker, J.C. and Wright, C.E. Pharmacokinetic and pharmacodynamic comparison of immediate-release and sustained-release adinazolam mesylate tablets after single-dose and multiple-dose administration. *Pharm. Res.* 9: 457-462, 1992.

^bAUC (0-∞)

^cAUC (0-24) after 7 days of dosing.

- a. What rate-limits the decline of plasma adinazolam concentration following the administration of the controlled-release product?
- b. On multiple dosing, have the immediate-release and controlled-release products been given long enough to ensure that a plateau should have been reached? In your answer, indicate whether any difference is expected in the time to reach plateau between the two products.
- c. For both products, are the plasma concentration data observed on multiple dosing (Table 7-8) those predicted from single-dose data?
- d. What is the relative bioavailability of adinazolam of the controlled-release product compared to the immediate-release product?
- e. Are the pharmacokinetics of adinazolam after administration of the immediate-release and the controlled-release products such that the terminal half-life can be determined within the respective dosing intervals at plateau?
- f. What are the degrees of accumulation associated with the immediate-release and the controlled-release regimens given that the AUC(0 to 8 hr) and AUC(0 to 12 hr) following the single 40-mg immediate-release product and the 60-mg controlled-release products are 0.45 and 0.44 mg·hr/L, respectively? Base your calculations on AUC considerations.