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

EFFECT OF DOSE

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

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

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

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

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

b. Calculate total clearance.
c. Calculate the renal clearance of the drug.
d. What's the fraction of the dose that is eliminated by renal excretion?

6. When 100 mg of a drug was given as an i.v. bolus, the following plasma concentration–time relationship (C in mg/L and t in hr) was observed,

$$C = 7.14\, e^{-0.173t}$$

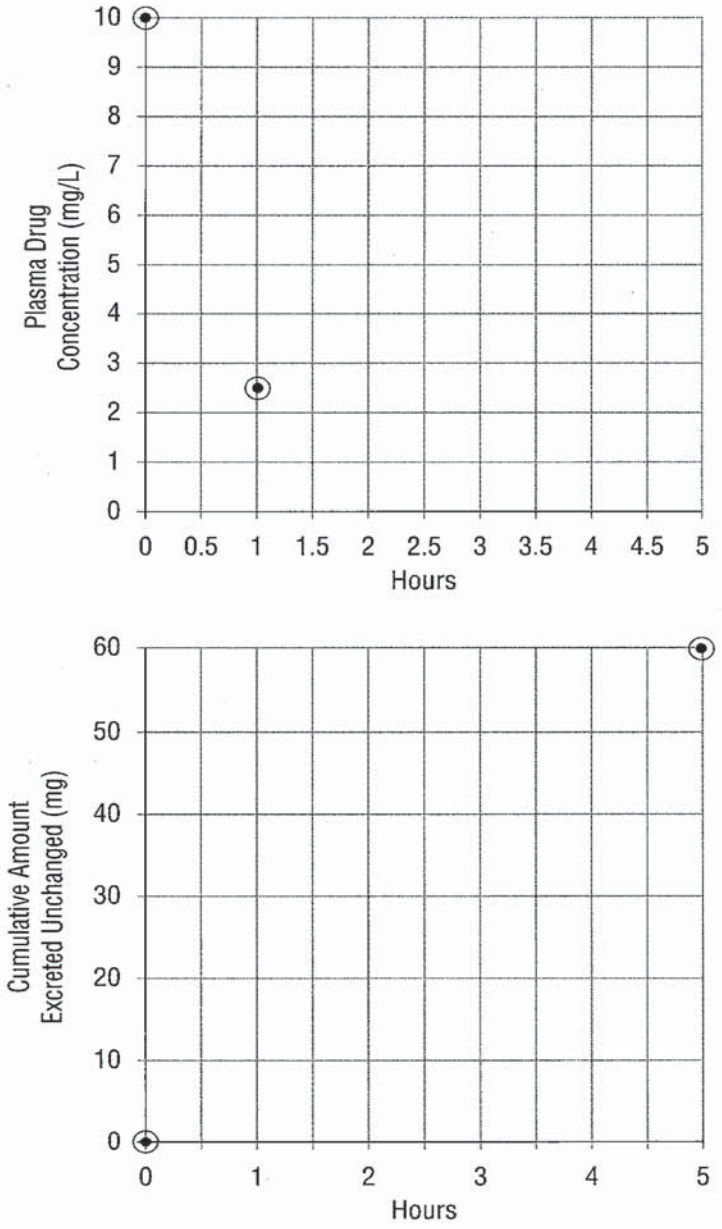

Fig. 3–7.

Calculate:
a. Volume of distribution
b. Elimination half-life
c. Total *AUC*
d. Total clearance
e. The plasma concentration 20 min after a 250-mg i.v. bolus dose.

7. Table 3–2 summarizes plasma data obtained after a bolus dose of ceftriaxone, a semisynthetic cephalosporin antibiotic, in a newborn infant. (Adapted from Schaad, U.B., Hayton, W.L., and Stoeckel, K.: Single-dose ceftriaxone kinetics in the newborn. Clin. Pharmacol. Ther., 37:522–528, 1985.)

Table 3–2. Plasma Concentrations of Ceftriaxone After i.v. Administration of a 184 mg (50 mg/kg) Dose

Time (hr)	1	6	12	24	48	72	96	144
Concentration (mg/L)	137	120	103	76	42	23	12	3.7

a. Prepare a semilogarithmic plot of the plasma concentration of ceftriaxone versus time. Estimate the half-life of the drug.
b. Estimate the total *AUC* of ceftriaxone.
c. Calculate total clearance.
d. Calculate the volume of distribution.

8. The data given in Table 3–3 are the plasma concentrations of cocaine as a function of time after i.v. administration of 33 mg cocaine hydrochloride to a subject. (Molecular weight of cocaine hydrochloride = 340 g/mole; molecular weight of cocaine = 303 g/mole.) (Adapted from Chow, M.J., Ambre, J.J., Ruo, T.I., Atkinson, A.J., Bowsher, D.J., and Fischman, M.W.: Kinetics of cocaine distribution, elimination, and chronotropic effects. Clin. Pharmacol. Ther., *38*:318–324, 1985.)

Table 3–3. Plasma Concentrations of Cocaine After a Single i.v. Dose of 33 mg

Time (hr)	0.16	0.5	1.0	1.5	2.0	2.5	3.0
Concentration (μg/L)	170	122	74	45	28	17	10

a. Prepare a semilogarithmic plot of plasma concentration versus time.
b. Estimate the half-life and total clearance of cocaine.
c. Given that the body weight of the subject is 75 kg, calculate the volume of distribution of cocaine in L/kg.

4

EXTRAVASCULAR DOSE

OBJECTIVES

The reader will be able to:

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

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

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

KINETICS OF ABSORPTION

The oral absorption of drugs often approximates first-order kinetics, especially when given in solution. The same holds true for the absorption of drugs from many other extravascular sites including subcutaneous tissue and muscle. Under these circumstances, absorption is characterized by an absorption rate constant, 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.

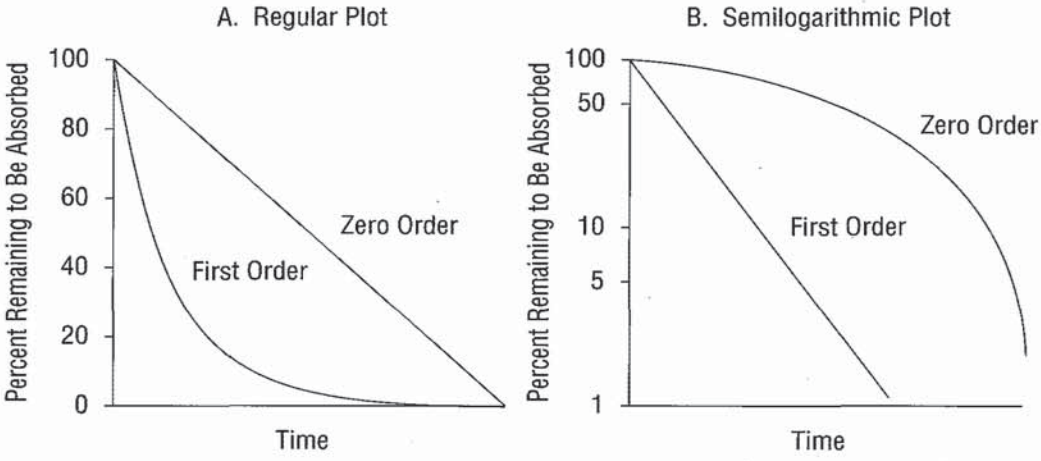

Fig. 4–1. A comparison of zero-order and first-order absorption processes. Depicted are: *A*, regular and *B*, semilogarithmic plots of the percent remaining to be absorbed against time.

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

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

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