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## CLINICAL PHARMACOKINETIC EQUATIONS AND CALCULATIONS

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### INTRODUCTION

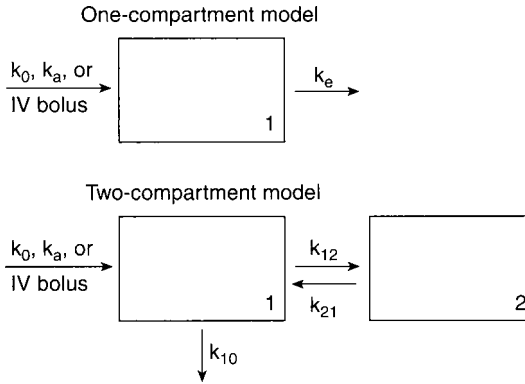
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Clinical pharmacokinetic dosage calculations are conducted using the easiest possible equations and methods. This is because there are usually only a few (sometimes as little as 1–2) drug serum concentrations on which to base the calculations. Drug serum concentrations are expensive (typically \$25–75 each), and obtaining them can cause minor discomfort and trauma to the patient. This situation is much different than that found in pharmacokinetic research studies where there may be 10–15 drug serum concentrations used to calculate pharmacokinetic parameters, and more complex equations can be used to describe the pharmacokinetics of the drug. Since the goal of therapeutic drug monitoring in patients is to individualize the drug dose and serum concentrations in order to produce the desired pharmacological effect and avoid adverse effects, it may not be possible, or even necessary, to compute pharmacokinetic parameters for every patient or clinical situation.

### ONE-COMPARTMENT MODEL EQUATIONS FOR LINEAR PHARMACOKINETICS

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When medications are administered to humans, the body acts as if it is a series of compartments<sup>1</sup> (Figure 2-1). In many cases, the drug distributes from the blood into the tissues quickly, and a pseudoequilibrium of drug movement between blood and tissues is established rapidly. When this occurs, a one-compartment model can be used to describe the serum concentrations of a drug.<sup>2,3</sup> In some clinical situations, it is possible to use a one-compartment model to compute doses for a drug even if drug distribution takes time



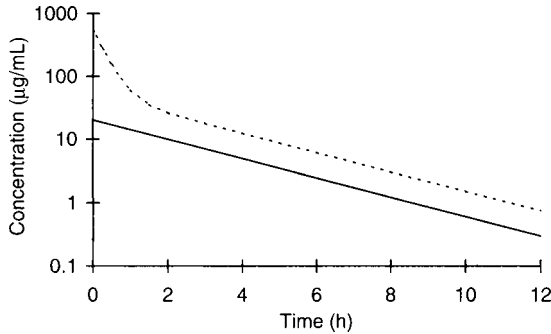
**FIGURE 2-1** Using compartment models, the body can be represented as a series of discrete sections. The simplest model is the one-compartment model which depicts the body as one large container where drug distribution between blood and tissues occurs instantaneously. Drug is introduced into the compartment by infusion ( $k_0$ ), absorption ( $k_a$ ), or IV bolus; distributes immediately into a volume of distribution ( $V$ ); and is removed from the body via metabolism and elimination via the elimination rate constant ( $k_e$ ). The simplest multicompartment model is a two-compartment model which represents the body as a central compartment into which drug is administered and a peripheral compartment into which drug distributes. The central compartment (1) is composed of blood and tissues which equilibrate rapidly with blood. The peripheral compartment (2) represents tissues that equilibrate slowly with blood. Rate constants ( $k_{12}$ ,  $k_{21}$ ) represent the transfer between compartments and elimination from the body ( $k_{10}$ ).

to complete.<sup>4,5</sup> In this case, drug serum concentrations are not obtained in a patient until after the distribution phase is over.

### Intravenous Bolus Equation

When a drug is given as an intravenous bolus and the drug distributes from the blood into the tissues quickly, the serum concentrations often decline in a straight line when plotted on semilogarithmic axes (Figure 2-2). In this case, a one-compartment model intravenous bolus equation can be used:  $C = (D/V)e^{-k_e t}$ , where  $t$  is the time after the intravenous bolus was given ( $t = 0$  at the time the dose was administered),  $C$  is the concentration at time  $t$ ,  $V$  is the volume of distribution, and  $k_e$  is the elimination rate constant. Most drugs given intravenously cannot be given as an actual intravenous bolus because of side effects related to rapid injection. A short infusion of 5–30 minutes can avoid these types of adverse effects, and if the intravenous infusion time is very short compared to the half-life of the drug so that a large amount of drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

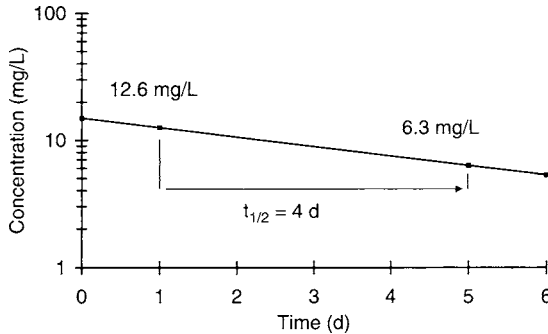
For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes. Because the patient received theophylline during previous hospitalizations, it is known that the volume of distribution is 30 L, the elimination rate constant equals  $0.116 \text{ h}^{-1}$ , and the half-life ( $t_{1/2}$ ) is 6 hours ( $t_{1/2} = 0.693/k_e = 0.693/0.115 \text{ h}^{-1} = 6 \text{ h}$ ). To compute the expected theophylline concentration 4 hours after the dose was given, a one-compartment model intravenous bolus equation can be used:  $C = (D/V)e^{-k_e t} = (400 \text{ mg}/30 \text{ L})e^{-(0.115 \text{ h}^{-1})(4 \text{ h})} = 8.4 \text{ mg/L}$ .



**FIGURE 2-2** The *solid line* shows the serum concentration/time graph for a drug that follows one-compartment model pharmacokinetics after intravenous bolus administration. Drug distribution occurs instantaneously, and serum concentrations decline in a straight line on semilogarithmic axes. The *dashed line* represents the serum concentration/time plot for a drug that follows two-compartment model pharmacokinetics after an intravenous bolus is given. Immediately after the dose is given, serum concentrations decline rapidly. This portion of the curve is known as the distribution phase. During the distribution phase, drug is distributing between blood and tissues and is removed from the body via hepatic metabolism and renal elimination. Later, serum concentrations decline more slowly during the elimination phase. During the elimination phase, drug is primarily being removed from the body.

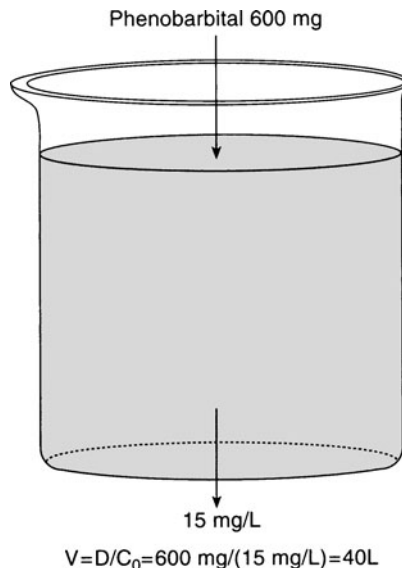
If drug distribution is not rapid, it is still possible to use a one compartment model intravenous bolus equation if the duration of the distribution phase and infusion time is small compared to the half-life of the drug and only a small amount of drug is eliminated during the infusion and distribution phases.<sup>6</sup> The strategy used in this situation is to infuse the medication and wait for the distribution phase to be over before obtaining serum concentrations in the patient. For instance, vancomycin must be infused slowly over 1 hour in order to avoid hypotension and red flushing around the head and neck areas. Additionally, vancomycin distributes slowly to tissues with a  $1/2$ -1 hour distribution phase. Because the half-life of vancomycin in patients with normal renal function is approximately 8 hours, a one compartment model intravenous bolus equation can be used to compute concentrations in the postinfusion, postdistribution phase without a large amount of error. As an example of this approach, a patient is given an intravenous dose of vancomycin 1000 mg. Since the patient has received this drug before, it is known that the volume of distribution equals 50 L, the elimination rate constant is  $0.077 \text{ h}^{-1}$ , and the half-life equals 9 h ( $t_{1/2} = 0.693/k_e = 0.693/0.077 \text{ h}^{-1} = 9 \text{ h}$ ). To calculate the expected vancomycin concentration 12 hours after the dose was given, a one compartment model intravenous bolus equation can be used:  $C = (D/V)e^{-k_e t} = (1000 \text{ mg}/50 \text{ L})e^{-(0.077 \text{ h}^{-1})(12 \text{ h})} = 7.9 \text{ mg/L}$ .

Pharmacokinetic parameters for patients can also be computed for use in the equations. If two or more serum concentrations are obtained after an intravenous bolus dose, the elimination rate constant, half-life and volume of distribution can be calculated (Figure 2-3). For example, a patient was given an intravenous loading dose of phenobarbital 600 mg over a period of about an hour. One day and four days after the dose was administered phenobarbital serum concentrations were 12.6 mg/L and 7.5 mg/L, respectively. By plotting the serum concentration/time data on semilogarithmic axes, the time it takes for serum concentrations to decrease by one-half can be determined and is equal to



**FIGURE 2-3** Phenobarbital concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life ( $t_{1/2}$ ) is determined by measuring the time needed for serum concentrations to decline by  $1/2$  (i.e., from 12.6 mg/L to 6.3 mg/L), and is converted to the elimination rate constant ( $k_e = 0.693/t_{1/2} = 0.693/4\text{d} = 0.173\text{d}^{-1}$ ). The concentration/time line can be extrapolated to the concentration axis to derive the concentration at time zero ( $C_0 = 15\text{ mg/L}$ ) and used to compute the volume of distribution ( $V = D/C_0$ ).

4 days. The elimination rate constant can be computed using the following relationship:  $k_e = 0.693/t_{1/2} = 0.693/4\text{ d} = 0.173\text{ d}^{-1}$ . The concentration/time line can be extrapolated to the y-axis where time = 0. Since this was the first dose of phenobarbital and the predose concentration was zero, the extrapolated concentration at time = 0 ( $C_0 = 15\text{ mg/L}$  in this case) can be used to calculate the volume of distribution (Figure 2-4):  $V = D/C_0 = 600\text{ mg}/(15\text{ mg/L}) = 40\text{ L}$ .



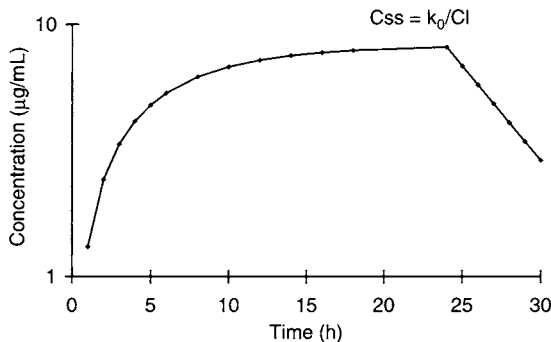
**FIGURE 2-4** For a one-compartment model, the body can be thought of as a beaker containing fluid. If 600 mg of phenobarbital is added to a beaker of unknown volume and the resulting concentration is 15 mg/L, the volume can be computed by taking the quotient of the amount placed into the beaker and the concentration:  $V = D/C_0 = 600\text{ mg}/(15\text{ mg/L}) = 40\text{ L}$ .

Alternatively, these parameters could be obtained by calculation without plotting the concentrations. The elimination rate constant can be computed using the following equation:  $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ , where  $t_1$  and  $C_1$  are the first time/concentration pair and  $t_2$  and  $C_2$  are the second time/concentration pair;  $k_e = -[\ln (12.6 \text{ mg/L}) - \ln (7.5 \text{ mg/L})]/(1 \text{ d} - 4 \text{ d}) = 0.173 \text{ d}^{-1}$ . The elimination rate constant can be converted into the half-life using the following equation:  $t_{1/2} = 0.693/k_e = 0.693/0.173 \text{ d}^{-1} = 4 \text{ d}$ . The volume of distribution can be calculated by dividing the dose by the serum concentration at time = 0. The serum concentration at time = zero ( $C_0$ ) can be computed using a variation of the intravenous bolus equation:  $C_0 = C/e^{-k_e t}$ , where  $t$  and  $C$  are a time/concentration pair that occur after the intravenous bolus dose. Either phenobarbital concentration can be used to compute  $C_0$ . In this case, the time/concentration pair on day 1 will be used (time = 1 d, concentration = 12.6 mg/L):  $C_0 = C/e^{-k_e t} = (12.6 \text{ mg/L})/e^{-(0.173 \text{ d}^{-1})(1 \text{ d})} = 15.0 \text{ mg/L}$ . The volume of distribution ( $V$ ) is then computed:  $V = D/C_0 = 600 \text{ mg}/(15 \text{ mg/L}) = 40 \text{ L}$ .

### Continuous and Intermittent Intravenous Infusion Equations

Some drugs are administered using a continuous intravenous infusion, and if the infusion is discontinued the serum concentration/time profile decreases in a straight line when graphed on a semilogarithmic axes (Figure 2-5). In this case, a one compartment model intravenous infusion equation can be used to compute concentrations ( $C$ ) while the infusion is running:  $C = (k_0/Cl)(1 - e^{-k_e t}) = [k_0/(k_e V)](1 - e^{-k_e t})$ , where  $k_0$  is the drug infusion rate (in amount per unit time, such as mg/h or  $\mu\text{g}/\text{min}$ ),  $Cl$  is the drug clearance (since  $Cl = k_e V$ , this substitution was made in the second version of the equation),  $k_e$  is the elimination rate constant, and  $t$  is the time that the infusion has been running. If the infusion is allowed to continue until steady state is achieved, the steady-state concentration ( $C_{ss}$ ) can be calculated easily:  $C_{ss} = k_0/Cl = k_0/(k_e V)$ .

If the infusion is stopped, postinfusion serum concentrations ( $C_{\text{postinfusion}}$ ) can be computed by calculating the concentration when the infusion ended ( $C_{\text{end}}$ ) using the appropriate



**FIGURE 2-5** If a drug is given as a continuous intravenous infusion, serum concentrations increase until a steady-state concentration ( $C_{ss}$ ) is achieved in 5–7 half-lives. The steady-state concentration is determined by the quotient of the infusion rate ( $k_0$ ) and drug clearance ( $Cl$ ):  $C_{ss} = k_0/Cl$ . When the infusion is discontinued, serum concentrations decline in a straight line if the graph is plotted on semilogarithmic axes. When using  $\log_{10}$  graph paper, the elimination rate constant ( $k_e$ ) can be computed using the following formula:  $\text{slope} = -k_e/2.303$ .

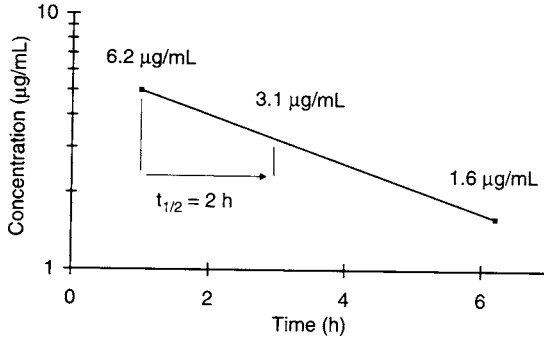
equation in the preceding paragraph, and the following equation:  $C_{\text{postinfusion}} = C_{\text{end}} e^{-k_e t_{\text{postinfusion}}}$ , where  $k_e$  is the elimination rate constant and  $t_{\text{postinfusion}}$  is the postinfusion time ( $t_{\text{postinfusion}} = 0$  at end of infusion and increases from that point).

For example, a patient is administered 60 mg/h of theophylline. It is known from previous hospital admissions that the patient has the following pharmacokinetic parameters for theophylline:  $V = 40$  L and  $k_e = 0.139$  h<sup>-1</sup>. The serum concentration of theophylline in this patient after receiving the drug for 8 hours and at steady state can be calculated:  $C = [k_0/(k_e V)](1 - e^{-k_e t}) = [(60 \text{ mg/h})/(0.139 \text{ h}^{-1} \cdot 40 \text{ L})](1 - e^{-(0.139 \text{ h}^{-1})(8 \text{ h})}) = 7.2$  mg/L;  $C_{\text{ss}} = k_0/(k_e V) = (60 \text{ mg/h})/(0.139 \text{ h}^{-1} \cdot 40 \text{ L}) = 10.8$  mg/L. It is possible to compute the theophylline serum concentration 6 hours after the infusion stopped in either circumstance. If the infusion only ran for 8 hours, the serum concentration 6 hours after the infusion stopped would be:  $C_{\text{postinfusion}} = C_{\text{end}} e^{-k_e t_{\text{postinfusion}}} = (7.2 \text{ mg/L})e^{-(0.139 \text{ h}^{-1})(6 \text{ h})} = 3.1$  mg/L. If the infusion ran until steady state was achieved, the serum concentration 6 hours after the infusion ended would be:  $C_{\text{postinfusion}} = C_{\text{end}} e^{-k_e t_{\text{postinfusion}}} = (10.8 \text{ mg/L})e^{-(0.139 \text{ h}^{-1})(6 \text{ h})} = 4.7$  mg/L.

Even if serum concentrations exhibit a distribution phase after the drug infusion has ended, it is still possible to use one compartment model intravenous infusion equations for the drug without a large amount of error.<sup>4, 5</sup> The strategy used in this instance is to infuse the medication and wait for the distribution phase to be over before measuring serum drug concentrations in the patient. For example, gentamicin, tobramycin, and amikacin are usually infused over one-half hour. When administered this way, these aminoglycoside antibiotics have distribution phases that last about one-half hour. Using this strategy, aminoglycoside serum concentrations are obtained no sooner than one-half hour after a 30-minute infusion in order to avoid the distribution phase. If aminoglycosides are infused over 1 hour, the distribution phase is very short and serum concentrations can be obtained immediately. For example, a patient is given an intravenous infusion of gentamicin 100 mg over 60 minutes. Because the patient received gentamicin before, it is known that the volume of distribution is 20 L, the elimination rate constant equals 0.231 h<sup>-1</sup>, and the half-life equals 3 h ( $t_{1/2} = 0.693/k_e = 0.693/0.231 \text{ h}^{-1} = 3$  h). To compute the gentamicin concentration at the end of infusion, a one compartment model intravenous infusion equation can be employed:  $C = [k_0/(k_e V)](1 - e^{-k_e t}) = [(100 \text{ mg/1 h})/(0.231 \text{ h}^{-1} \cdot 20 \text{ L})](1 - e^{-(0.231 \text{ h}^{-1})(1 \text{ h})}) = 4.5$  mg/L.

Pharmacokinetic constants can also be calculated for use in the equations. If a steady-state concentration is obtained after a continuous intravenous infusion has been running uninterrupted for 3–5 half-lives, the drug clearance (Cl) can be calculated by rearranging the steady-state infusion formula:  $Cl = k_0/C_{\text{ss}}$ . For example, a patient receiving procainamide via intravenous infusion ( $k_0 = 5$  mg/min) has a steady-state procainamide concentration measured as 8 mg/L. Procainamide clearance can be computed using the following expression:  $Cl = k_0/C_{\text{ss}} = (5 \text{ mg/min})/(8 \text{ mg/L}) = 0.625$  L/min.

If the infusion did not run until steady state was achieved, it is still possible to compute pharmacokinetic parameters from postinfusion concentrations. In the following example, a patient was given a single 120-mg dose of tobramycin as a 60-minute infusion, and concentrations at the end of infusion (6.2 mg/L) and 4 hours after the infusion ended (1.6 mg/L) were obtained. By plotting the serum concentration/time information on semilogarithmic axes, the half-life can be determined by measuring the time it takes for serum concentrations to decline by one-half (Figure 2-6), and equals 2 hours in this case. The elimination rate constant ( $k_e$ ) can be calculated using the following formula:



**FIGURE 2-6** Tobramycin concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life ( $t_{1/2}$ ) is determined by measuring the time needed for serum concentrations to decline by  $1/2$  (i.e., from 6.2 mg/L to 3.1 mg/L), and is converted to the elimination rate constant ( $k_e = 0.693/t_{1/2} = 0.693/2 \text{ h} = 0.347 \text{ h}^{-1}$ ). Volume of distribution is computed using the equation given in the text.

$k_e = 0.693/t_{1/2} = 0.693/2 \text{ h} = 0.347 \text{ h}^{-1}$ . Alternatively, the elimination rate constant can be calculated without plotting the concentrations using the following equation:  $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ , where  $t_1$  and  $C_1$  are the first time/concentration pair and  $t_2$  and  $C_2$  are the second time/concentration pair;  $k_e = -[\ln(6.2 \text{ mg/L}) - \ln(1.6 \text{ mg/L})]/(1 \text{ h} - 5 \text{ h}) = 0.339 \text{ h}^{-1}$  (note the slight difference in  $k_e$  is due to rounding errors). The elimination rate constant can be converted into the half-life using the following equation:  $t_{1/2} = 0.693/k_e = 0.693/0.339 \text{ h}^{-1} = 2 \text{ h}$ .

The volume of distribution ( $V$ ) can be computed using the following equation<sup>4</sup>:

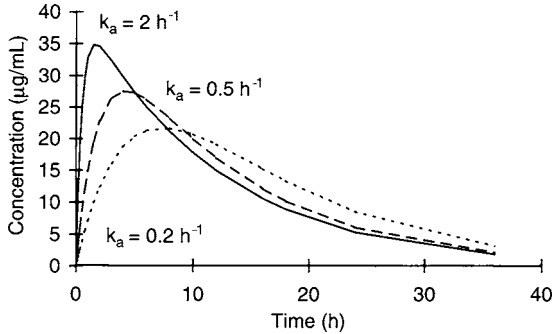
$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e [C_{\max} - (C_{\text{predose}} e^{-k_e t'})]}$$

where  $k_0$  is the infusion rate,  $k_e$  is the elimination rate constant,  $t'$  = infusion time,  $C_{\max}$  is the maximum concentration at the end of infusion, and  $C_{\text{predose}}$  is the predose concentration. In this example, the volume of distribution is:

$$V = \frac{(120 \text{ mg/1 h})(1 - e^{-(0.339 \text{ h}^{-1})(1 \text{ h})})}{0.339 \text{ h}^{-1}[(6.2 \text{ mg/L}) - (0 \text{ mg/L} \cdot e^{-(0.339 \text{ h}^{-1})(1 \text{ h})})]} = 16.4 \text{ L}$$

### Extravascular Equation

When a drug is administered extravascularly (e.g., orally, intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place (Figure 2-7). If serum concentrations decrease in a straight line when plotted on semilogarithmic axes after drug absorption is complete, a one compartment model extravascular equation can be used to describe the serum concentration/time curve:  $C = \{(Fk_a D)/[V(k_a - k_e)]\}(e^{-k_e t} - e^{-k_a t})$ , where  $t$  is the time after the extravascular dose was given ( $t = 0$  at the time the dose was administered),  $C$  is the concentration at time =  $t$ ,  $F$  is the bioavailability fraction,  $k_a$  is the absorption rate constant,  $D$  is the dose,  $V$  is the



**FIGURE 2-7** Serum concentration/time curves for extravascular drug administration for agents following a one-compartment pharmacokinetics. The absorption rate constant ( $k_a$ ) controls how quickly the drug enters the body. A large absorption rate constant allows drug to enter the body quickly while a small elimination rate constant permits drug to enter the body more slowly. The *solid line* shows the concentration/time curve on semilogarithmic axes for an elimination rate constant equal to  $2 \text{ h}^{-1}$ . The *dashed* and *dotted lines* depict serum concentration/time plots for elimination rate constants of  $0.5 \text{ h}^{-1}$  and  $0.2 \text{ h}^{-1}$ , respectively.

volume of distribution, and  $k_e$  is the elimination rate constant. The absorption rate constant describes how quickly drug is absorbed with a large number indicating fast absorption and a small number indicating slow absorption (Figure 2-7).

An example of the use of this equation would be a patient that is administered 500 mg of oral procainamide as a capsule. It is known from prior clinic visits that the patient has a half-life equal to 4 hours, an elimination rate constant of  $0.173 \text{ h}^{-1}$  ( $k_e = 0.693/t_{1/2} = 0.693/4 \text{ h} = 0.173 \text{ h}^{-1}$ ), and a volume of distribution of 175 L. The capsule that is administered to the patient has an absorption rate constant equal to  $2 \text{ h}^{-1}$ , and an oral bioavailability fraction of 0.85. The procainamide serum concentration 4 hours after a single dose would be equal to:

$$C = \frac{Fk_a D}{V(k_a - k_e)} (e^{-k_e t} - e^{-k_a t})$$

$$C = \frac{(0.85)(2 \text{ h}^{-1})(500 \text{ mg})}{(175 \text{ L})(2 \text{ h}^{-1} - 0.173 \text{ h}^{-1})} (e^{-(0.173 \text{ h}^{-1})(4 \text{ h})} - e^{-(2 \text{ h}^{-1})(4 \text{ h})})$$

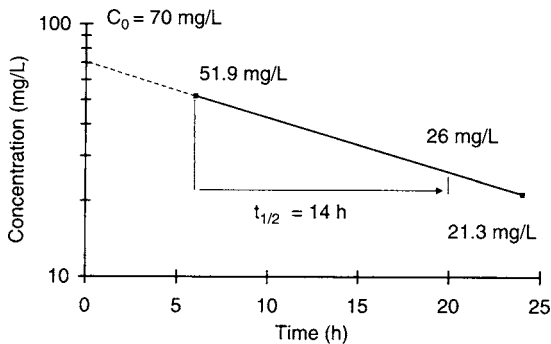
$$C = 1.3 \text{ mg/L}$$

If the serum concentration/time curve displays a distribution phase, it is still possible to use one compartment model equations after an extravascular dose is administered. In order to do this, serum concentrations are obtained only in the postdistribution phase. Since the absorption rate constant is also hard to measure in patients, it is also desirable to avoid drawing drug serum concentrations during the absorption phase in clinical situations. When only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly, the equation simplifies to:  $C = [(FD)/V]e^{-k_e t}$ , where  $C$  is the concentration at any postabsorption, postdistribution time;  $F$  is the

bioavailability fraction;  $D$  is the dose;  $V$  is the volume of distribution;  $k_e$  is the elimination rate constant; and  $t$  is any postabsorption, postdistribution time. This approach works very well when the extravascular dose is rapidly absorbed and not a sustained- or extended-release dosage form. An example would be a patient receiving 24 mEq of lithium ion as lithium carbonate capsules. From previous clinic visits, it is known that the patient has a volume of distribution of 60 L and an elimination rate constant equal to  $0.058 \text{ h}^{-1}$ . The bioavailability of the capsule is known to be 0.90. The serum lithium concentration 12 hours after a single dose would be:  $C = [(FD)/V]e^{-k_e t} = [(0.90 \cdot 24 \text{ mEq})/60 \text{ L}] e^{-(0.058 \text{ h}^{-1})(12 \text{ h})} = 0.18 \text{ mEq/L}$ .

Pharmacokinetic constants can also be calculated and used in these equations. If two or more postabsorption, postdistribution serum concentrations are obtained after an extravascular dose, the volume of distribution, elimination rate constant, and half-life can be computed (Figure 2-8). For example, a patient is given an oral dose of valproic acid 750 mg as capsules. Six and twenty-four hours after the dose, the valproic acid serum concentrations are 51.9 mg/L and 21.3 mg/L, respectively. After graphing the serum concentration/time data on semilogarithmic axes, the time it takes for serum concentrations to decrease by one-half can be measured and equals 14 hours. The elimination rate constant is calculated using the following equation:  $k_e = 0.693/t_{1/2} = 0.693/14 \text{ h} = 0.0495 \text{ h}^{-1}$ . The concentration/time line can be extrapolated to the y-axis where time = 0. Since this was the first dose of valproic acid, the extrapolated concentration at time = 0 ( $C_0 = 70 \text{ mg/L}$ ) is used to estimate the hybrid volume of distribution/bioavailability ( $V/F$ ) parameter:  $V/F = D/C_0 = 750 \text{ mg}/70 \text{ L} = 10.7 \text{ L}$ . Even though the absolute volume of distribution and bioavailability cannot be computed without the administration of intravenous drug, the hybrid constant can be used in extravascular equations in place of  $V/F$ .

An alternative approach is to directly calculate the parameters without plotting the concentrations. The elimination rate constant ( $k_e$ ) is computed using the following



**FIGURE 2-8** Valproic acid concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life ( $t_{1/2}$ ) is determined by measuring the time needed for serum concentrations to decline by  $1/2$  (i.e., from 51.9 mg/L to 26 mg/L), and is converted to the elimination rate constant ( $k_e = 0.693/t_{1/2} = 0.693/14 \text{ h} = 0.0495 \text{ h}^{-1}$ ). The concentration/time line can be extrapolated to the concentration axis to derive the concentration at time zero ( $C_0 = 70 \text{ mg/L}$ ) and used to compute the hybrid constant volume of distribution/bioavailability fraction ( $V/F = D/C_0$ ).

relationship:  $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ , where  $C_1$  is the first concentration at time =  $t_1$ , and  $C_2$  is the second concentration at time =  $t_2$ ;  $k_e = -[\ln(51.9 \text{ mg/L}) - \ln(21.3 \text{ mg/L})]/(6 \text{ h} - 24 \text{ h}) = 0.0495 \text{ h}^{-1}$ . The elimination rate constant can be translated into the half-life using the following equation:  $t_{1/2} = 0.693/k_e = 0.693/0.0495 \text{ h}^{-1} = 14 \text{ h}$ . The hybrid constant volume of distribution/bioavailability ( $V/F$ ) is computed by taking the quotient of the dose and the extrapolated serum concentration at time = 0. The extrapolated serum concentration at time = zero ( $C_0$ ) is calculated using a variation of the intravenous bolus equation:  $C_0 = C/e^{-k_e t}$ , where  $t$  and  $C$  are a time/concentration pair that occur after administration of the extravascular dose in the postabsorption and postdistribution phases. Either valproic acid concentration can be used to compute  $C_0$ . In this situation, the time/concentration pair at 24 hours will be used (time = 24 hours, concentration = 21.3 mg/L):  $C_0 = C/e^{-k_e t} = (21.3 \text{ mg/L})/e^{-(0.0495 \text{ h}^{-1})(24 \text{ h})} = 70 \text{ mg/L}$ . The hybrid volume of distribution/bioavailability constant ( $V/F$ ) is then computed:  $V/F = D/C_0 = 750 \text{ mg}/(70 \text{ mg/L}) = 10.7 \text{ L}$ .

### Multiple-Dose and Steady-State Equations

In most cases, medications are administered to patients as multiple doses, and drug serum concentrations for therapeutic drug monitoring are not obtained until steady state is achieved. For these reasons, multiple dose equations that reflect steady-state conditions are usually more useful in clinical settings than single dose equations. Fortunately, it is simple to convert single dose compartment model equations to their multiple dose and steady-state counterparts.<sup>7</sup> In order to change a single dose equation to the multiple dose version, it is necessary to multiply each exponential term in the equation by the multiple dosing factor:  $(1 - e^{-nk_i\tau})/(1 - e^{-k_i\tau})$ , where  $n$  is the number of doses administered,  $k_i$  is the rate constant found in the exponential of the single dose equation, and  $\tau$  is the dosage interval. At steady state, the number of doses ( $n$ ) is large, the exponential term in the numerator of the multiple dosing factor ( $-nk_i\tau$ ) becomes a large negative number, and the exponent approaches zero. Therefore, the steady-state version of the multiple dosing factor becomes the following:  $1/(1 - e^{-k_i\tau})$  where  $k_i$  is the rate constant found in the exponential of the single dose equation and  $\tau$  is the dosage interval. Whenever the multiple dosing factor is used to change a single dose equation to the multiple dose or steady-state versions, the time variable in the equation resets to zero at the beginning of each dosage interval.

As an example of the conversion of a single dose equation to the steady-state variant, the one compartment model intravenous bolus equation is:  $C = (D/V)e^{-k_e t}$ , where  $C$  is the concentration at time =  $t$ ,  $D$  is the dose,  $V$  is the volume of distribution,  $k_e$  is the elimination rate constant, and  $t$  is time after the dose is administered. Since there is only one exponential in the equation, the multiple dosing factor at steady state is multiplied into the expression at only one place, substituting the elimination rate constant ( $k_e$ ) for the rate constant in the multiple dosing factor:  $C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$ , where  $C$  is the steady-state concentration at any postdose time ( $t$ ) after the dose ( $D$ ) is given,  $V$  is the volume of distribution,  $k_e$  is the elimination rate constant, and  $\tau$  is the dosage interval. Table 2-1 lists the one compartment model equations for the different routes of administration under single dose, multiple dose, and steady-state conditions.

The following are examples of steady-state one compartment model equations for intravenous, intermittent intravenous infusions, and extravascular routes of administration:

**TABLE 2-1 Single-Dose, Multiple-Dose, and Steady-State One-Compartment Model Equations**

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t} [(1 - e^{-nk_e \tau}) / (1 - e^{-k_e \tau})]$	$C = (D/V)[e^{-k_e t} / (1 - e^{-k_e \tau})]$
Continuous intravenous infusion	$C = [k_0 / (k_e V)](1 - e^{-k_e t})$	N/A	$C_{ss} = k_0 / Cl = k_0 / (k_e V)$
Intermittent intravenous infusion	$C = [k_0 / (k_e V)](1 - e^{-k_e t'})$	$C = [k_0 / (k_e V)](1 - e^{-k_e t'}) [(1 - e^{-nk_e \tau}) / (1 - e^{-k_e \tau})]$	$C = [k_0 / (k_e V)][(1 - e^{-k_e t'}) / (1 - e^{-k_e \tau})]$
Extravascular (postabsorption, postdistribution)	$C = [(FD)/V]e^{-k_e t}$	$C = [(FD)/V]e^{-k_e t} [(1 - e^{-nk_e \tau}) / (1 - e^{-k_e \tau})]$	$C = (FD/V)[e^{-k_e t} / (1 - e^{-k_e \tau})]$
Average steady-state concentration (any route of administration)	N/A	N/A	$C_{ss} = [F(D/\tau)] / Cl$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution,  $k_e$  is the elimination rate constant, n is the number of administered doses,  $\tau$  is the dosage interval,  $k_0$  is the infusion rate, Cl is clearance,  $t'$  is infusion time, N/A is not applicable.