2

CLINICAL PHARMACOKINETIC EQUATIONS AND CALCULATIONS

INTRODUCTION

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

When medications are administered to humans, the body acts as if it is a series of compartments[1] (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.[2,3] 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

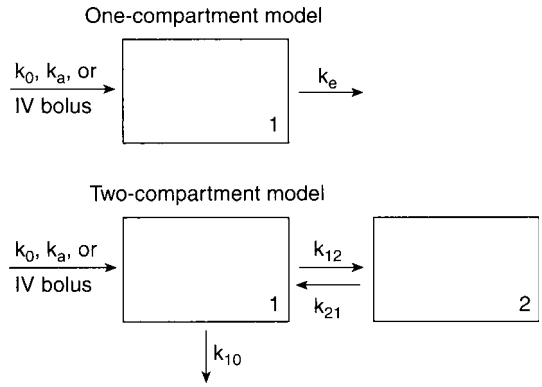

FIGURE 2-1 Using compartment models, the body can be represented as a series of discrete sections. The simplest model is the one-compartment model which depicts the body as one large container where drug distribution between blood and tissues occurs instantaneously. Drug is introduced into the compartment by infusion (k_o), 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.[4,5] 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 h^{-1}, and the half-life ($t_{1/2}$) is 6 hours ($t_{1/2} = 0.693/k_e = 0.693/0.115\ h^{-1} = 6$ h). To compute the expected theophylline concentration 4 hours after the dose was given, a one-compartment model intravenous bolus equation can be used: $C = (D/V)e^{-k_e t} = (400\ mg/30\ L)e^{-(0.115\ h^{-1})(4\ h)} = 8.4$ mg/L.

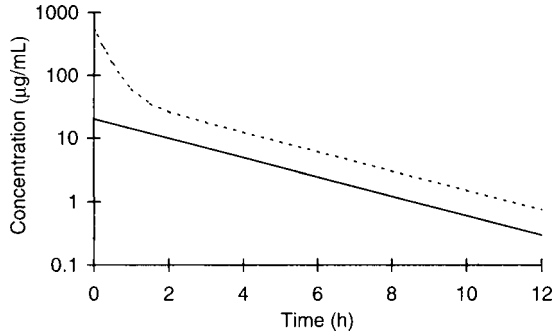

FIGURE 2-2 The *solid line* shows the serum concentration/time graph for a drug that follows one-compartment model pharmacokinetics after intravenous bolus administration. Drug distribution occurs instantaneously, and serum concentrations decline in a straight line on semilogarithmic axes. The *dashed 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.[6] 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 h^{-1}, and the half-life equals 9 h ($t_{1/2}$ = $0.693/k_e$ = $0.693/0.077\ h^{-1}$ = 9 h). To calculate the expected vancomycin concentration 12 hours after the dose was given, a one compartment model intravenous bolus equation can be used: $C = (D/V)e^{-k_e t} = (1000\ mg/50\ L)e^{-(0.077\ h^{-1})(12\ h)} = 7.9\ mg/L$.

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

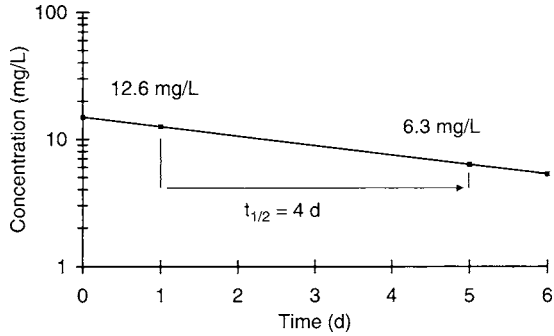

FIGURE 2-3 Phenobarbital concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life *($t_{1/2}$)* is determined by measuring the time needed for serum concentrations to decline by $^1/_2$ (i.e., from 12.6 mg/L to 6.3 mg/L), and is converted to the elimination rate constant ($k_e = 0.693/t_{1/2} = 0.693/4d = 0.173d^{-1}$). The concentration/time line can be extrapolated to the concentration axis to derive the concentration at time zero (C_0 = 15 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: $k_e = 0.693/t_{1/2} = 0.693/4$ d = 0.173 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 mg/L in this case) can be used to calculate the volume of distribution (Figure 2-4): $V = D/C_0$ = 600 mg/(15 mg/L) = 40 L.

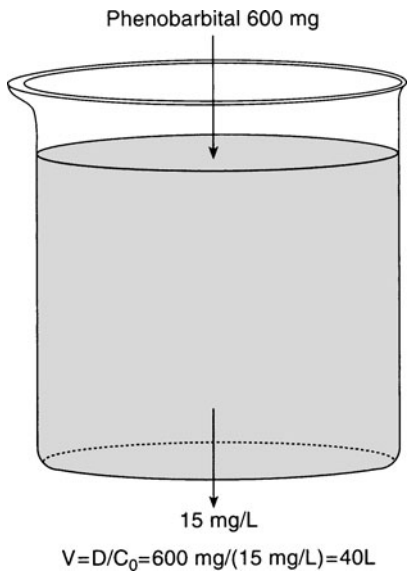

FIGURE 2-4 For a one-compartment model, the body can be thought of as a beaker containing fluid. If 600 mg of phenobarbital is added to a beaker of unknown volume and the resulting concentration is 15 mg/L, the volume can be computed by taking the quotient of the amount placed into the beaker and the concentration: $V = D/C_0$ = 600 mg/(15 mg/L) = 40 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: $t_{1/2} = 0.693/k_e = 0.693/0.173 \text{ d}^{-1} = 4$ 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): $C_0 = C/e^{-k_e t} = (12.6 \text{ mg/L})/e^{-(0.173 \text{ d}^{-1})(1 \text{ d})} = 15.0$ mg/L. The volume of distribution (V) is then computed: $V = D/C_0 = 600 \text{ mg}/(15 \text{ mg/L}) = 40$ 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 μg/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 (Css) can be calculated easily: $Css = k_0/Cl = k_0/(k_e V)$.

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

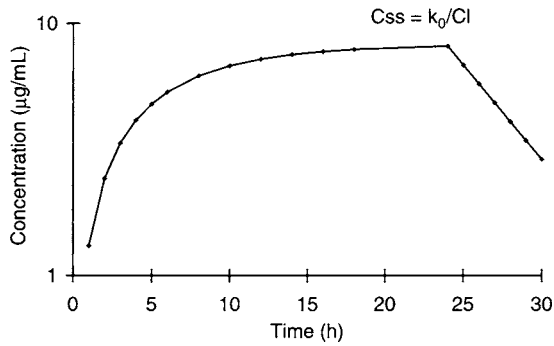

FIGURE 2-5 If a drug is given as a continuous intravenous infusion, serum concentrations increase until a steady-state concentration *(Css)* is achieved in 5–7 half-lives. The steady-state concentration is determined by the quotient of the infusion rate *(k_0)* and drug clearance *(Cl):* $Css = k_0/Cl$. 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: slope = $-k_e/2.303$.

equation in the preceding paragraph, and the following equation: $C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}}$, where k_e is the elimination rate constant and $t_{postinfusion}$ is the postinfusion time ($t_{postinfusion} = 0$ 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 $k_e = 0.139\ h^{-1}$. The serum concentration of theophylline in this patient after receiving the drug for 8 hours and at steady state can be calculated: $C = [k_0/(k_eV)](1 - e^{-k_e t}) = [(60\ mg/h)/(0.139\ h^{-1} \cdot 40\ L)](1 - e^{-(0.139\ h^{-1})(8\ h)}) = 7.2$ mg/L; $Css = k_0/(k_eV) = (60\ mg/h)/(0.139\ h^{-1} \cdot 40\ L) = 10.8$ 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: $C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}} = (7.2\ mg/L)e^{-(0.139\ h^{-1})(6\ h)} = 3.1$ mg/L. If the infusion ran until steady state was achieved, the serum concentration 6 hours after the infusion ended would be: $C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}} = (10.8\ mg/L)e^{-(0.139\ h^{-1})(6\ h)} = 4.7$ 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.[4, 5] 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 $0.231\ h^{-1}$, and the half-life equals 3 h ($t_{1/2} = 0.693/k_e = 0.693/0.231\ h^{-1} = 3$ h). To compute the gentamicin concentration at the end of infusion, a one compartment model intravenous infusion equation can be employed: $C = [k_0/(k_eV)](1 - e^{-k_e t}) = [(100\ mg/1\ h)/(0.231\ h^{-1} \cdot 20\ L)](1 - e^{-(0.231\ h^{-1})(1\ h)}) = 4.5$ 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: $Cl = k_0/Css$. 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: $Cl = k_0/Css = (5\ mg/min)/(8\ mg/L) = 0.625$ 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:

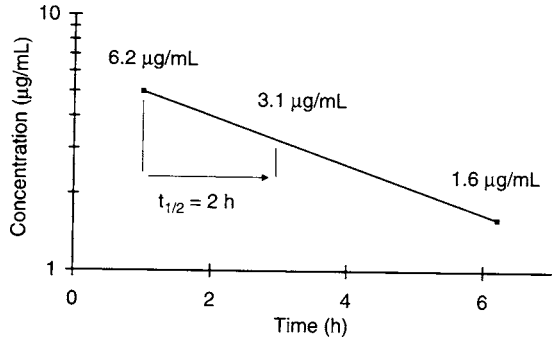

FIGURE 2-6 Tobramycin concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life ($t_{1/2}$) is determined by measuring the time needed for serum concentrations to decline by $^1/_2$ (i.e., from 6.2 mg/L to 3.1 mg/L), and is converted to the elimination rate constant ($k_e = 0.693/t_{1/2} = 0.693/2$ h $= 0.347$ h^{-1}). Volume of distribution is computed using the equation given in the text.

$k_e = 0.693/t_{1/2} = 0.693/2$ h $= 0.347$ 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; $k_e = -[\ln (6.2 \text{ mg/L}) - \ln (1.6 \text{ mg/L})]/(1 \text{ h} - 5 \text{ h}) = 0.339$ 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: $t_{1/2} = 0.693/k_e = 0.693/0.339$ h$^{-1} = 2$ h.

The volume of distribution (V) can be computed using the following equation[4]:

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

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 $C_{predose}$ 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: $C = \{(Fk_aD)/[V(k_a - k_e)]\}(e^{-k_e t} - e^{-k_a t})$, 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

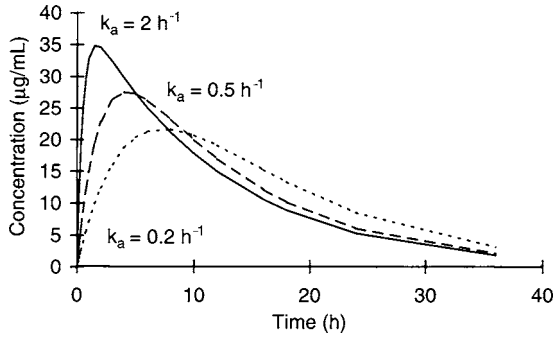

FIGURE 2-7 Serum concentration/time curves for extravascular drug administration for agents following a one-compartment pharmacokinetics. The absorption rate constant *(k_a)* controls how quickly the drug enters the body. A large absorption rate constant allows drug to enter the body quickly while a 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 h^{-1}. The *dashed* and *dotted lines* depict serum concentration/time plots for elimination rate constants of 0.5 h^{-1} and 0.2 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 h^{-1} ($k_e = 0.693/t_{1/2} = 0.693/4$ h = 0.173 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 h^{-1}, and an oral bioavailability fraction of 0.85. The procainamide serum concentration 4 hours after a single dose would be equal to:

$$C = \frac{Fk_aD}{V(k_a - k_e)}(e^{-k_et} - e^{-k_at})$$

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

$$C = 1.3\ mg/L$$

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: $C = [(FD)/V]e^{-k_et}$, 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 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: $C = [(FD)/V]e^{-k_e t} = [(0.90 \cdot 24 \text{ mEq})/60 \text{ L}]$ $e^{-(0.058 \text{ h}^{-1})(12 \text{ h})} = 0.18$ 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 ($C_0 = 70$ mg/L) is used to estimate the hybrid volume of distribution/bioavailability (V/F) parameter: $V/F = D/C_0 = 750 \text{ mg}/70 \text{ L} = 10.7$ 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

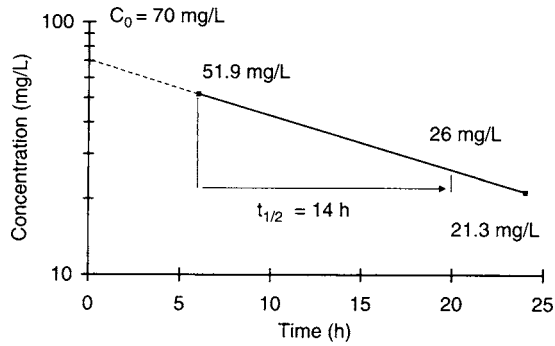

FIGURE 2-8 Valproic acid concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life *($t_{1/2}$)* is determined by measuring the time needed for serum concentrations to decline by $^1/_2$ (i.e., from 51.9 mg/L to 26 mg/L), and is converted 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 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: $t_{1/2} = 0.693/k_e = 0.693/0.0495 \text{ h}^{-1} = 14$ 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): $C_0 = C/e^{-k_e t} = (21.3 \text{ mg/L})/e^{-(0.0495 \text{ h}^{-1})(24 \text{ h})} = 70$ mg/L. The hybrid volume of distribution/bioavailability constant (V/F) is then computed: $V/F = D/C_0 = 750 \text{ mg}/(70 \text{ mg/L}) = 10.7$ 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.[7] 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 τ 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 τ 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 τ 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	$Css = k_0/Cl = k_0/(k_e V)$
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	$Css = [F(D/\tau)]/Cl$

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, τ is the dosage interval, k_0 is the infusion rate, Cl is clearance, t' is infusion time, N/A is not applicable.

Intravenous bolus. A patient with tonic-clonic seizures is given phenobarbital 100 mg intravenously daily until steady-state occurs. Pharmacokinetic constants for phenobarbital in the patient are: $k_e = 0.116\ d^{-1}$, V = 75 L. The steady-state concentration 23 hours [(23 h)/(24 h/d) = 0.96 d] after the last dose equals: $C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})] = (100\ mg/75\ L)[e^{-(0.116\ d^{-1})(0.96\ d)}/(1 - e^{-(0.116\ d^{-1})(1\ d)})] = 10.9$ mg/L.

Intermittent intravenous infusion. A patient with gram-negative pneumonia is administered tobramycin 140 mg every 8 hours until steady state is achieved. Pharmacokinetic parameters for tobramycin in the patient are: V = 16 L, $k_e = 0.30\ h^{-1}$. The steady-state concentration immediately after a 1 hour infusion equals: $C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e \tau})] = [(140\ mg/h)/(0.30\ h^{-1} \cdot 16\ L)][(1 - e^{(-0.30\ h^{-1} \cdot 1\ h)})/(1 - e^{(-0.30\ h^{-1} \cdot 8\ h)})] = 8.3$ mg/L.

Extravascular. A patient with an arrhythmia is administered 250 mg of quinidine orally (as 300 mg quinidine sulfate tablets) every six hours until steady state occurs. Pharmacokinetic constants for quinidine in the patient are: V = 180 L, $k_e = 0.0693\ h^{-1}$, F = 0.7. The postabsorption, postdistribution steady-state concentration just before the next dose (t = 6 h) equals: $C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e \tau})] = [(0.7 \cdot 250\ mg)/180\ L][e^{(-0.0693\ h^{-1} \cdot 6\ h)}/(1 - e^{(-0.0693\ h^{-1} \cdot 6\ h)})] = 1.9$ mg/L.

It is also possible to compute pharmacokinetic parameters under multiple dose and steady-state conditions. Table 2-2 lists the methods to compute pharmacokinetic constants using a one compartment model for different routes of administration under single-dose, multiple-dose, and steady-state conditions. The main difference between single-dose and multiple-dose calculations is in the computation of the volume of distribution. When a single dose of medication is given, the predose concentration is assumed to be zero. However, when multiple doses are given, the predose concentration is not usually zero, and the volume of distribution equation (V) needs to have the baseline, predose concentration ($C_{predose}$) subtracted from the extrapolated drug concentration at time = 0 (C_0) for the intravenous bolus ($V = D/[C_0 - C_{predose}]$, where D is dose) and extravascular ($V/F = D/[C_0 - C_{predose}]$, where F is the bioavailability fraction and D is dose) cases. In the case of intermittent intravenous infusions, the volume of distribution equation already has a parameter for the predose concentration in it[4]:

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

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 $C_{predose}$ is the predose concentration. For each route of administration, the elimination rate constant (k_e) is computed using the same equation as the single dose situation: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$, where C_1 is the first concentration at time = t_1, and C_2 is the second concentration at time = t_2.

The following are examples of multiple dose and steady-state computations of pharmacokinetic parameters using a one compartment model for intravenous, intermittent intravenous infusions, and extravascular routes of administration:

Intravenous bolus. A patient receiving theophylline 300 mg intravenously every 6 hours has a predose concentration equal to 2.5 mg/L and postdose concentrations of 9.2 mg/L one hour and 4.5 mg/L five hours after the second dose is given. The patient has an elimination rate constant (k_e) equal to: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 9.2\ mg/L) - (\ln 4.5\ mg/L)]/(1\ h - 5\ h) = 0.179\ h^{-1}$. The volume of distribution (V) of theophylline for

TABLE 2-2 Single-Dose, Multiple-Dose, and Steady-State Pharmacokinetic Constant Computations Utilizing a One Compartment Model

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/C_0$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_eV$
Continuous intravenous infusion	N/A	N/A	$Cl = k_0/Css$
Intermittent intravenous infusion	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_et'})]/\{k_e[C_{max} - (C_{predose}e^{-k_et'})]\}$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_et'})]/\{k_e[C_{max} - (C_{predose}e^{-k_et'})]\}$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_et'})]/\{k_e[C_{max} - (C_{predose}e^{-k_et'})]\}$ $Cl = k_eV$
Extravascular (postabsorption, postdistribution)	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/C_0$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$
Average steady-state concentration (any route of administration)	N/A	N/A	$Cl/F = (D/\tau)/Css$

Symbol key: C_1 is drug serum concentration at time $= t_1$, C_2 is drug serum concentration at time $= t_2$, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, k_0 is the continuous infusion rate, t′ is the infusion time, V/F is the hybrid constant volume of distribution/bioavailability fraction, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, Cl/F is the hybrid constant clearance/bioavailability fraction, $C_{predose}$ is the predose concentration, Css is the steady-state concentration, N/A is not applicable.

the patient is: $C_0 = C/e^{-k_e t} = (9.2 \text{ mg/L})/e^{(-0.179 \text{ h}^{-1})(1 \text{ h})} = 11.0$ mg/L and $V = D/[C_0 - C_{predose}] = (300 \text{ mg})/(11.0 \text{ mg/L} - 2.5 \text{ mg/L}) = 35.3$ L.

Intermittent intravenous infusion. A patient is prescribed gentamicin 100 mg infused over 60 minutes every 12 hours. A predose steady-state concentration ($C_{predose}$) is drawn and equals 2.5 mg/L. After the 1-hour infusion, a steady-state maximum concentration (C_{max}) is obtained and equals 7.9 mg/L. Since the patient is at steady state, it can be assumed that all predose steady-state concentrations are equal. Because of this the predose steady-state concentration 12 hours after the dose can also be considered equal to 2.5 mg/L and used to compute the elimination rate constant (k_e) of gentamicin for the patient: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 7.9 \text{ mg/L}) - (\ln 2.5 \text{ mg/L})]/(1 \text{ h} - 12 \text{ h}) = 0.105 \text{ h}^{-1}$. The volume of distribution (V) of gentamicin for the patient is:

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

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 $C_{predose}$ is the predose concentration. In this example, volume of distribution is:

$$V = \frac{(100 \text{ mg/1 h})(1 - e^{-(0.105 \text{h}^{-1})(1 \text{ h})})}{0.105 \text{h}^{-1}[(7.9 \text{ mg/L}) - (2.5 \text{ mg/L} \cdot e^{-(0.105 \text{ h}^{-1})(1 \text{ h})})]} = 16.8 \text{ L}$$

Extravascular. A patient is given procainamide capsules 750 mg every 6 hours. The following concentrations are obtained before and after the second dose: $C_{predose} = 1.1$ mg/L, concentrations 2 hours and 6 hours postdose equal 4.6 mg/L and 2.9 mg/L. The patient has an elimination rate constant (k_e) equal to: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 4.6 \text{ mg/L}) - (\ln 2.9 \text{ mg/L})]/(2 \text{ h} - 6 \text{ h}) = 0.115 \text{ h}^{-1}$. The hybrid volume of distribution/bioavailability constant (V/F) of procainamide for the patient is: $C_0 = C/e^{-k_e t} = (2.9 \text{ mg/L})/e^{(-0.115 \text{ h}^{-1})(6 \text{ h})} = 5.8$ mg/L and $V/F = D/[C_0 - C_{predose}] = (750 \text{ mg})/(5.8 \text{ mg/L} - 1.1 \text{ mg/L}) = 160$ L.

Average Steady-State Concentration Equation

A very useful and easy equation can be used to compute the average steady-state concentration (Css) of a drug: $Css = [F(D/\tau)]/Cl$, where F is the bioavailability fraction, D is the dose, τ is the dosage interval, and Cl is the drug clearance.[8] This equation works for any single or multiple compartment model, and because of this it is deemed a model-independent equation. The steady-state concentration computed by this equation is the concentration that would have occurred if the dose, adjusted for bioavailability, was given as a continuous intravenous infusion. For example, 600 mg of theophylline tablets given orally every 12 hours (F = 1.0) would be equivalent to a 50 mg/h (600 mg/12 h = 50 mg/h) continuous intravenous infusion of theophylline. The average steady-state concentration equation is very useful when the half-life of the drug is long compared to the dosage interval or if a sustained-release dosage form is used. Examples of both situations follow:

Long half-life compared to dosage interval. A patient is administered 250 µg of digoxin tablets daily for heart failure until steady state. The pharmacokinetic constants for digoxin in the patient are: F = 0.7, Cl = 120 L/d. The average steady-state concentration would equal: $Css = [F(D/\tau)]/Cl = [0.7(250 \text{ µg/d})]/(120 \text{ L/d}) = 1.5$ µg/L.

Sustained-release dosage form. A patient is given 1500 mg of procainamide sustained-release tablets every 12 hours until steady state for the treatment of an arrhythmia. The pharmacokinetic parameters for procainamide in the patient are: F = 0.85, Cl = 30 L/h. The average steady-state concentration would be: Css = [F(D/τ)]/Cl = [0.85(1500 mg/12 h)] / (30 L/h) = 3.5 mg/L.

If an average steady-state concentration (Css) is known for a drug, the hybrid pharmacokinetic constant clearance/bioavailability (Cl/F) can be computed: Cl/F = (D/τ)/Css, where D is dose and τ is the dosage interval. For example, a patient receiving 600 mg of sustained-release theophylline every 12 hours has a steady-state concentration equal to 11.2 mg/L. The clearance/bioavailability constant for theophylline in this patient would equal: Cl/F = (D/τ) / Css = (600 mg/12 h) / 11.2 mg/L = 4.5 L/h.

DESIGNING INDIVIDUALIZED DOSAGE REGIMENS USING ONE COMPARTMENT MODEL EQUATIONS

The goal of therapeutic drug monitoring is to customize medication doses that provide the optimal drug efficacy without adverse reactions. One compartment model equations can be used to compute initial drug doses employing population pharmacokinetic parameters that estimate the constants for a patient.[4, 5, 9] The patient's own, unique pharmacokinetic parameters can be computed once doses have been administered and drug serum concentrations measured. At that time, individualized dosage regimens at steady state can be designed for a patient. Table 2-3 lists the equations used to customize doses for the various routes of administration.

TABLE 2-3 Equations to Compute Individualized Dosage Regimens for Various Routes of Administration

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR k_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$
Continuous intravenous infusion	$k_0 = Css\ Cl = Css\ k_eV$ $LD = CssV$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau}) / (1 - e^{-k_et'})]$ $LD = k_0/(1 - e^{-k_e\tau})$
Extravascular (postabsorption, postdistribution)	$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$ $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_eT_{max}}]$ $LD = (Css_{max}V)/F$
Average steady-state concentration (any route of administration)	$D = (Css\ Cl\ \tau)/F = (Css\ k_eV\tau)/F$ $LD = (CssV)/F$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, Css is the steady-state concentration, k_0 is the continuous infusion rate, t' is the infusion time, T_{max} is the time that Css_{max} occurs, F is the bioavailability fraction.

Intravenous Bolus

If the volume of distribution and elimination rate constant can be estimated for a patient, a loading dose and initial maintenance dose can be computed. To design these doses, estimates of pharmacokinetic constants are obtained using patient characteristics such as weight, age, gender, renal and liver function, and other disease states and conditions that are known to effect the disposition and elimination of the drug. When the actual elimination rate constant and volume of distribution are measured for the medication, a maintenance dose to achieve any target steady-state concentrations can be designed.

Desired maximum and minimum steady-state concentrations are chosen for the patient. If the patient has never received the drug before, the therapeutic range can be used to choose starting concentrations. If the patient has taken the drug on previous occasions, safe and effective concentrations may be known. The dosage interval (τ) can be computed using the desired maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations: $\tau = (\ln Css_{max} - \ln Css_{min})/k_e$, where k_e is the elimination rate constant. The maintenance dose is then computed using the one compartment model equation for intravenous bolus administration at the time Css_{max} occurs (t = 0 hour after the bolus is given) solved for dose: $D = [Css_{max}\ V(1 - e^{-k_e\tau})] / e^{-k_e(0\ h)} = Css_{max}\ V(1 - e^{-k_e\tau})$. If a loading dose (LD) is necessary, it is computed using the following equation: $LD = Css_{max}\ V$.

An example of this approach is a patient that needs to be treated for complex partial seizures with intravenous phenobarbital. An initial dosage regimen is designed using population pharmacokinetic parameters ($k_e = 0.139\ d^{-1}$, V = 50 L) to achieve maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations equal to 30 mg/L and 25 mg/L, respectively: $\tau = (\ln Css_{max} - \ln Css_{min})/k_e = [\ln (30\ mg/L) - \ln (25\ mg/L)] / 0.139\ d^{-1} = 1.3$ d, round to a practical dosage interval of 1 d; $D = Css_{max}\ V(1 - e^{-k_e\tau}) = (30\ mg/L \cdot 50\ L)(1 - e^{(-0.139\ d^{-1})(1\ d)}) = 195$ mg, round to a practical dose of 200 mg. The patient would be prescribed intravenous phenobarbital 200 mg daily.

Continuous and Intermittent Intravenous Infusion

The dosage regimen for a continuous intravenous infusion is computed using the following equation: $k_0 = Css\ Cl = Css\ k_eV$, where k_0 is the infusion rate, Css is the steady-state drug concentration, Cl is the drug clearance, k_e is the elimination rate constant, and V is the volume of distribution. A loading dose (LD) is computed using the following expression: LD = CssV. An example using this method is a patient with a ventricular arrhythmia after a myocardial infarction needing treatment with lidocaine at a Css of 3.0 mg/L (population pharmacokinetic parameters used: V = 50 L, Cl = 1.0 L/min) : LD = CssV = (3 mg/L)(50 L) = 150 mg; k_0 = CssCl = (3 mg/L)(1.0 L/min) = 3 mg/min. The patient would be prescribed lidocaine 150 mg intravenously followed by a 3 mg/min continuous infusion.

For intermittent intravenous infusions, the dosage interval (τ) is computed by choosing minimum (Css_{min}) and maximum (Css_{max}) steady-state concentrations: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t'$, where k_e is the elimination rate constant, and t' is the infusion time. The maintenance dose is calculated using the one compartment model equation for intermittent intravenous infusions at the time Css_{max} occurs solved for infusion rate (k_0): $k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau}) / (1 - e^{-k_et'})]$, where k_e is the elimination rate constant, and V is the volume of distribution. A loading dose (LD) can be calculated using the following

formula which takes into account the amount of drug eliminated during the infusion time: $LD = k_0/(1 - e^{-k_e\tau})$.

An example using these techniques is a patient receiving tobramycin for the treatment of intraabdominal sepsis. Using pharmacokinetic parameters (V = 20 L, $k_e = 0.087\ h^{-1}$) previously measured in the patient using serum concentrations, compute a tobramycin dose (infused over 1 hour) that would provide maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations of 6 mg/L and 1 mg/L, respectively: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 6\ mg/L - \ln 1\ mg/L)/0.087\ h^{-1}] + 1\ h = 22$ h, round to practical dosage interval of 24 h; $k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau})/(1 - e^{-k_et'})] = [(6\ mg/L)(0.087\ h^{-1})(20\ L)]\ [(1 - e^{(-0.087\ h^{-1})(24\ h)})/(1 - e^{(-0.087\ h^{-1})(1\ h)})] = 110$ mg. The patient would be prescribed tobramycin 110 mg infused over 1 hour every 24 hours.

Extravascular

The dosage regimen for extravascular doses is determined by choosing maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$, where k_e is the elimination rate constant and T_{max} is the time that the maximum concentration occurs. The maintenance dose is computed employing the one compartment model equation for extravascular doses at the time Css_{max} occurs ($t = T_{max}$) solved for dose (D): $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_eT_{max}}]$ where V is the volume of distribution and F is the bioavailability fraction. A loading dose (LD) can be computed using the following equation: $LD = (Css_{max}V)/F$.

An example of these computations is a patient with simple partial seizures that needs to receive valproic acid capsules (population pharmacokinetic parameters are V = 12 L, $k_e = 0.05\ h^{-1}$, $T_{max} = 3$ h, F = 1.0) and maintain steady-state maximum (Css_{max}) and minimum (Css_{min}) concentrations of 80 mg/L and 50 mg/L, respectively: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max} = [(\ln 80\ mg/L - \ln 50\ mg/L)/0.05\ h^{-1}] + 3\ h = 12.4$ h, round to practical dosage interval of 12 h; $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_eT_{max}}] = [(80\ mg/L \cdot 12\ L)/1.0)][(1 - e^{(-0.05\ h^{-1})(12\ h)})/e^{(-0.05\ h^{-1})(3\ h)}] = 503$ mg, round to practical dose of 500 mg. The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.

Average Steady-State Concentration

If the drug is administered as a sustained-release dosage form or the half-life is long compared to the dosage interval, it is possible to use the average steady-state concentration equation to individualize doses. The dosage regimen is computed using the following equation: $D = (Css\ Cl\ \tau)/F = (Css\ k_eV\tau)/F$, where D is the dose, Css is the steady-state drug concentration, Cl is the drug clearance, τ is the dosage interval, k_e is the elimination rate constant, and V is the volume of distribution. A loading dose (LD) is computed using the following expression: $LD = (CssV)/F$.

An example of this technique is a patient with an atrial arrhythmia needing treatment with procainamide sustained-release tablets (clearance equals 24 L/h based on current procainamide continuous infusion; F = 0.85, $\tau = 12$ h for sustained-release tablet) and an average steady-state procainamide concentration equal to 5 mg/L: $D = (Css\ Cl\ \tau)/F = (5\ mg/L \cdot 24\ L/h \cdot 12\ h)/0.85 = 1694$ mg, round to a practical dose of 1500 mg. The patient would be prescribed procainamide sustained-release tablets 1500 mg orally every 12 hours.

MULTICOMPARTMENT MODELS

When serum concentrations decrease in a rapid fashion initially and then decline at a slower rate later (Figure 2-2), a multicompartment model can be used to describe the serum concentration/time curve[1] (Figure 2-1). The reason serum concentrations drop so rapidly after the dose is given is that all of the drug is in the bloodstream initially, and drug is leaving the vascular system by distribution to tissues and by hepatic metabolism and/or renal elimination. This portion of the curve is called the *distribution phase*. After this phase of the curve is finished, drug distribution is nearly complete and a psuedoequilibrium is established between the blood and tissues. During the final part of the curve, serum concentrations drop more slowly since only metabolism and/or elimination are taking place. This portion of the curve is called the *elimination phase*, and the elimination half-life of the drug is measured in this part of the serum concentration/time graph. Digoxin, vancomycin, and lidocaine are examples of drugs that follow multicompartment pharmacokinetics.

A two compartment model is the simplest of the multicompartment models. The equation that describes a two compartment model after an intravenous bolus is: $C = \{[D(\alpha - k_{21})]/[V_1(\alpha - \beta)]\}e^{-\alpha t} + \{[D(k_{21} - \beta)]/[V_1(\alpha - \beta)]\}e^{-\beta t}$, where C is the drug serum concentration, D is the intravenous bolus dose, k_{21} is the rate constant that describes the transfer of drug from compartment 2 to compartment 1, α is the distribution rate constant, β is the elimination rate constant, V_1 is the volume of distribution for compartment 1, and t is the time after the dose was administered. Similar equations for a two compartment model are available for intravenous infusions and extravascular doses. In order to get accurate values for the pharmacokinetic constants in the equation, 3–5 serum concentrations for each phase of the curve need to be obtained after a dose is given to a patient. Because of the cost and time involved to collect 6–10 serum concentrations after a dose, multicompartment models are rarely used in patient care situations. If a drug follows multicompartment pharmacokinetics, serum concentrations are usually not drawn for clinical use until the distribution phase is over and the elimination phase has been established. In these cases, it is possible to use simpler one compartment model equations to compute doses with an acceptable degree of accuracy.

MICHAELIS-MENTEN EQUATIONS FOR SATURABLE PHARMACOKINETICS

When the dose of a drug is increased and steady-state serum concentrations do not increase in a proportional fashion, but instead increase more than expected, Michaelis-Menten or saturable pharmacokinetics may be taking place. This situation occurs when the serum concentration of the drug approaches or exceeds the Km value for the enzyme system that is responsible for its metabolism. The Michaelis-Menten expression describes the dose required to attain a given steady-state drug concentration: $D = (V_{max} \cdot Css)/(Km + Css)$, where D is the dose, Css is the steady-state drug concentration, V_{max} is the maximum rate of drug metabolism, and Km is the concentration where the rate of metabolism equals $V_{max}/2$. Phenytoin is an example of a drug that follows saturable pharmacokinetics.[10]

Computing the Michaelis-Menten constants for a drug is not as straightforward as the calculation of pharmacokinetic parameters for a one-compartment linear pharmacokinetic model. The calculation of V_{max} and Km requires a graphical solution.[10]

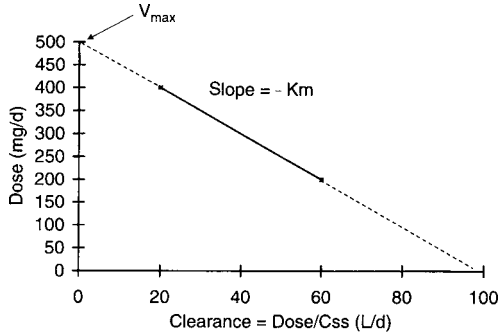

FIGURE 2-9 Michaelis-Menten plot for phenytoin. Dose (D) is plotted versus the ratio of dose and steady-state concentration *(D/Css)* for 2 or more different doses, and a straight line is drawn connecting the points. The slope of the line is –Km , and the y-intercept is V_{max}. The Michaelis-Menten constants are then used to compute the dose needed to achieve a new desired steady-state concentration.

The Michaelis-Menten equation is rearranged to the following formula: $D = V_{max} - [Km (D/Css)]$. This version of the function takes the form of the equation of a straight line: y = y-intercept + [(slope)*x*]. A plot of dose (D) versus dose divided by the steady-state concentration (D/Css) will yield a straight line with a slope equal to –Km and a y-intercept of V_{max}. In order to use this approach, a patient is placed on an initial dose (D_1) of the medication, a steady-state concentration is obtained (Css_1), and the dose/steady-state concentration ratio determined (D_1/Css_1). The dose of the medication is changed (D_2), a second steady-state concentration is measured (Css_2), and the new dose/steady-state concentration ratio is computed (D_2/Css_2). The dose and dose/steady-state concentration pairs are plotted on a graph so that V_{max} (the y-intercept) and Km (the -slope) can be determined (Figure 2-9). If additional doses are administered until steady state has been achieved, they can also be added to the same plot and the best straight line computed using linear regression. Once V_{max} and Km are known, the Michaelis-Menten expression can be used to compute a dose to reach any steady-state concentration.

An example is a patient receiving phenytoin for the treatment of tonic-clonic seizures. The patient received a dose of 300 mg/d with a steady-state concentration of 8 mg/L and a dose of 500 mg/d with a steady-state concentration equal to 22 mg/L. The dose/steady-state concentration ratios are 37.5 L/d and 22.7 L/d for the first and second doses, respectively ([300 mg/d] / 8 mg/L = 37.5 L/d; [500 mg/d] / 22 mg/L = 22.7 L/d). A plot of this data yields a V_{max} = 807 mg/d and a Km = 13.5 mg/L (Figure 2-9). The phenytoin dose to reach a steady-state concentration equal to 13 mg/L is: $D = (V_{max} \cdot Css) / (Km + Css)$ = (807 mg/d · 13 mg/L) / (13.5 mg/L + 13 mg/L) = 396 mg/d, rounded to a practical dose of 400 mg/d.

CALCULATION OF CLEARANCE, VOLUME OF DISTRIBUTION, AND HALF-LIFE IN PHARMACOKINETIC RESEARCH STUDIES

It is important to understand the methods used to compute the three principle pharmacokinetic parameters in research studies since these will be used by clinicians to determine population pharmacokinetic parameters for initial dosage regimen design.[11] The typical

pharmacokinetic research study administers a single dose of the medication and measures 10–15 serum concentrations for an estimated 3–5 half-lives or gives the drug until steady state is achieved and obtains 10–15 serum concentrations over a dosage interval. In either case, the serum concentration/time plot is used to compute the area under the serum concentration/ time curve (AUC). For drugs that follow linear pharmacokinetics, the AUC extrapolated to infinity after a single dose equals the AUC over the dosage interval at steady state for a dose of the same size so either can be used to compute pharmacokinetic constants.

Clearance (Cl) is computed by taking the ratio of the dose (D) and area under the serum concentration/time curve (AUC) for a drug that is administered intravenously: $Cl = D/AUC$. If the dose is administered extravascularly, the bioavailability fraction (F) must be included to compensate for drug that does not reach the systemic vascular system: $Cl = (FD)/AUC$.

Of the three volumes of distribution typically computed in a pharmacokinetic experiment, the one most useful in clinical situations is the volume of distribution (V) calculated using the area under the serum concentration/time curve (AUC): $V = D/(k_eAUC)$, where k_e is the elimination rate constant. For doses administered extravascularly, the bioavailability fraction (F) must be included to compensate for drug that does not reach the systemic vascular system: $V = (FD)/(k_eAUC)$.

Half-life is determined by plotting the serum concentration/time curve and computing the time it takes for serum concentrations to decrease by one-half in the postabsorption, postdistribution phase of the graph. In order to get the most accurate measurement of half-life, 5–7 serum concentrations are usually measured during the terminal portion of the curve, and nonlinear regression is used to compute the best value for the parameter. Alternatively, the data can be plotted on semilogarithmic axes and linear regression utilized to compute the terminal half-life.

PROBLEMS

1. PZ is a 35-year-old, 60-kg female with a *Staphylococcus aureus* wound infection. While receiving vancomycin 1 g every 12 hours (infused over one hour), the steady-state peak concentration (obtained one-half hour after the end of infusion) was 35 mg/L, and the steady-state trough concentration (obtained immediately predose) was 15 mg/L. (A) Using one compartment IV bolus equations, compute the pharmacokinetic parameters for this patient. (B) Using the patient-specific pharmacokinetic parameters calculated in part A, compute a new vancomycin dose that would achieve $Css_{max} = 30$ mg/L and $Css_{min} = 7.5$ mg/L.

2. Negamycin is a new antibiotic with an average volume of distribution of 0.35 L/kg and a half-life of 2 hours in patients with cystic fibrosis. Compute a dosage regimen for JM, a 22-year-old, 45-kg female cystic fibrosis patient with *Pseudomonas aeruginosa* in her sputum, that will achieve steady-state peak concentrations of 10 mg/L and trough concentrations of 0.6 mg/L using one-compartment model IV bolus equations (assume that the drug is given as an IV bolus).

3. KL is a 65-year-old, 60-kg female being treated for septic shock. Among other antibiotics, she is being treated with tobramycin 60 mg every 8 hours (infused over 1 hour). Steady-state serum concentrations are: Css_{max} = 7.1 mg/L, Css_{min} = 3.1 mg/L. Using one compartment intermittent intravenous infusion equations, compute the pharmacokinetic parameters for this patient and use them to individualize the tobramycin dose to achieve Css_{max} = 8 mg/L and Css_{min} = 1.0 mg/L.

4. JB is a 52-year-old, 72-kg male being treated for gram-negative pneumonia. Assuming a V = 18 L and a $t_{1/2}$ = 8 h, design a gentamicin dosage (infused over 1 hour) to achieve Css_{max} = 10 mg/L and Css_{min} = 1.2 mg/L using one compartment intermittent intravenous infusion equations.

5. EV is a 42-year-old, 84-kg male suffering from an acute asthmatic attack. Using one-compartment model equations, compute a theophylline IV bolus loading dose (to be administered over 20 minutes) and continuous infusion to achieve a Css = 12 mg/L. Assume a V = 40 L and $t_{1/2}$ = 5 h.

6. BJ is a 62-year-old, 70-kg female with a ventricular arrhythmia. Assuming a V = 33 L and Cl = 0.5 L/min, use one-compartment model equations to compute a lidocaine IV bolus loading dose (to be administered over 1–2 minutes) and continuous infusion to achieve a Css = 3 mg/L.

7. MM is a 54-year-old, 68-kg male being treated with procainamide 750-mg regular release capsules every 6 hours for an arrhythmia. The following steady-state concentration is available: Css_{min} = 1.5 mg/L (obtained immediately predose). Calculate a dose that will achieve a Css_{min} = 2.5 mg/L.

8. LM is a 59-year-old, 85-kg male needing treatment with oral quinidine for an arrhythmia. Assuming F = 0.7, T_{max} = 2 h, V = 200 L, and $t_{1/2}$ = 8 h, compute Css_{min} for a dose of oral quinidine 400 mg every 6 hours.

9. JB is a 78-year-old, 100-kg male being treated with digoxin for heart failure. While receiving digoxin tablets 125 μg daily, a steady-state digoxin concentration equal to 0.6 μg/L is obtained. (A) Assuming F = 0.7, compute digoxin clearance for the patient using the average steady-state concentration equation. (B) Compute a new digoxin tablet dose for the patient that will achieve Css = 1.2 μg/L.

10. QJ is a 67-year-old, 80-kg male being treated for chronic obstructive pulmonary disease. Sustained-release oral theophylline is being added to his drug regimen. Assuming F = 1.0, V = 40 L, and $t_{1/2}$ = 5 hours, compute an oral theophylline dose to be administered every 12 hours that would achieve a Css = 8 mg/L using the average steady-state concentration equation.

11. TD is a 32-year-old, 70-kg male with generalized tonic-clonic seizures. Assuming Michaelis-Menten parameters of V_{max} = 500 mg/d and Km = 4 mg/L, calculate a dose of phenytoin that will achieve Css = 15 mg/L.

12. OP is a 28-year-old, 55-kg female with complex partial seizures. She has the following information available: Css = 8 mg/L while receiving phenytoin 300 mg at bedtime and Css = 22 mg/L while receiving phenytoin 400 mg at bedtime. Compute the patient's Michaelis-Menten parameters for phenytoin, and the phenytoin dose that would achieve Css = 15 mg/L.