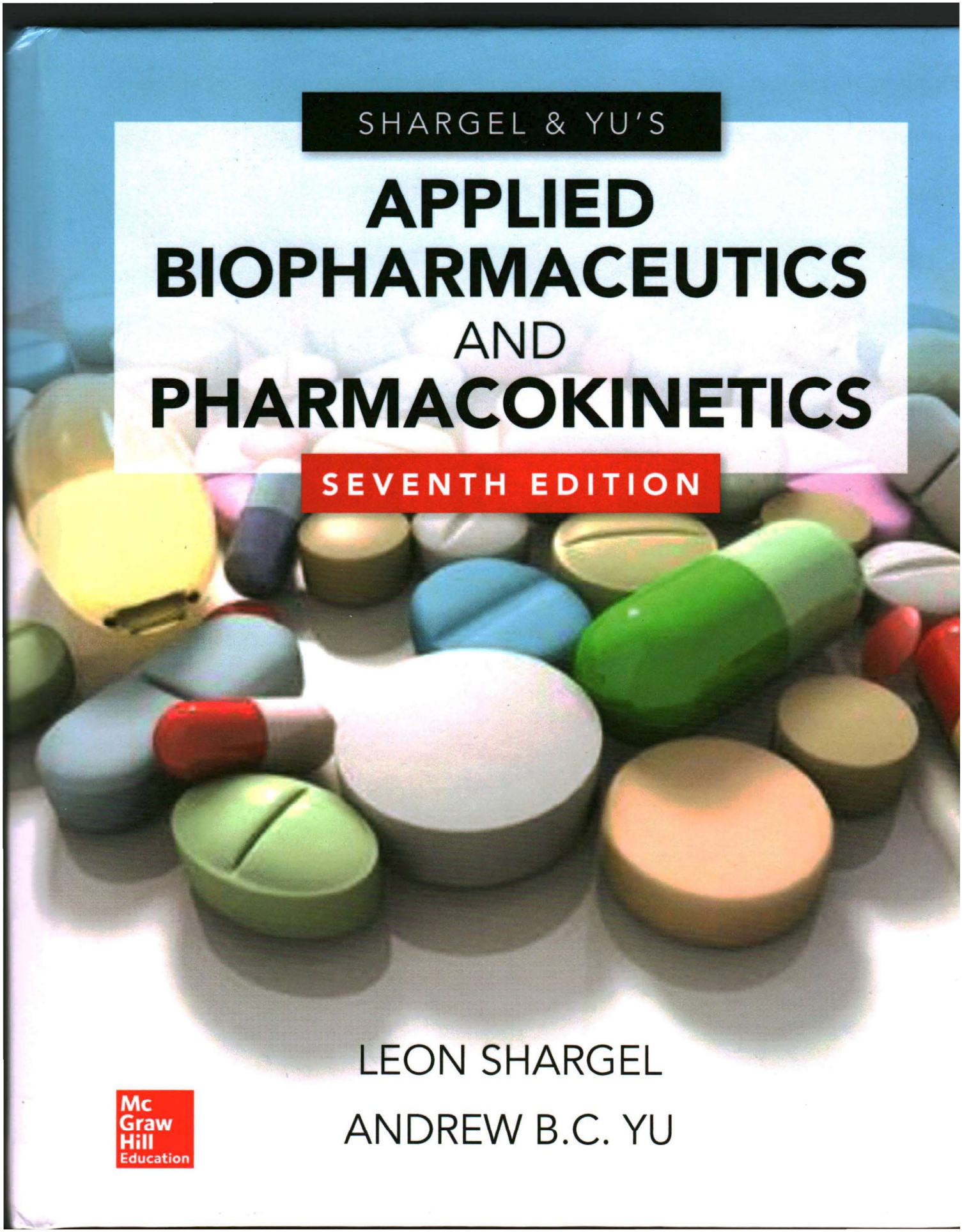
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Applied Biopharmaceutics & Pharmacokinetics

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Contents

9 Multiple-Dosage Regimens

Rodney C. Siwale and Shabnam N. Sani

Chapter Objectives

- Define the index for measuring drug accumulation.
- Define drug accumulation and drug accumulation $t_{1/2}$.
- Explain the principle of superposition and its assumptions in multiple-dose regimens.
- Calculate the steady-state C_{max} and C_{min} after multiple IV bolus dosing of drugs.
- Calculate k and V_D of aminoglycosides in multiple-dose regimens.
- Adjust the steady-state C_{max} and C_{min} in the event the last dose is given too early, too late, or totally missed following multiple IV dosing.

Earlier chapters of this book discussed single-dose drug and constant-rate drug administration. By far though, most drugs are given in several doses, for example, multiple doses to treat chronic disease such as arthritis, hypertension, etc. After single-dose drug administration, the plasma drug level rises above and then falls below the *minimum effective concentration* (MEC), resulting in a decline in therapeutic effect. To treat chronic disease, multiple-dosage or IV infusion regimens are used to maintain the plasma drug levels within the narrow limits of the therapeutic window (eg, plasma drug concentrations above the MEC but below the *minimum toxic concentration* or MTC) to achieve optimal clinical effectiveness. These drugs may include antibacterials, cardiotonics, anticonvulsants, hypoglycemics, antihypertensives, hormones, and others. Ideally, a dosage regimen is established for each drug to provide the correct plasma level without excessive fluctuation and drug accumulation outside the therapeutic window.

For certain drugs, such as antibiotics, a desirable MEC can be determined. For drugs that have a narrow therapeutic range (eg, digoxin and phenytoin), there is a need to define the therapeutic minimum and maximum nontoxic plasma concentrations (MEC and MTC, respectively). In calculating a multiple-dose regimen, the desired or *target* plasma drug concentration must be related to a therapeutic response, and the multiple-dose regimen must be designed to produce plasma concentrations within the therapeutic window.

There are two main parameters that can be adjusted in developing a dosage regimen: (1) the size of the drug dose and (2) τ, the frequency of drug administration (ie, the time interval between doses).

DRUG ACCUMULATION

To calculate a multiple-dose regimen for a patient or patients, pharmacokinetic parameters are first obtained from the plasma level–time curve generated by single-dose drug studies. With these pharmacokinetic parameters and knowledge of the size of the dose and dosage interval (τ), the complete plasma level–time curve or

the plasma level may be predicted at any time after the beginning of the dosage regimen.

For calculation of multiple-dose regimens, it is necessary to decide whether successive doses of drug will have any effect on the previous dose. The principle of *superposition* assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses. Therefore, the blood levels after the second, third, or *n*th dose will overlay or superimpose the blood level attained after the $(n-1)$th dose. In addition, the $\text{AUC} = (\int_0^\infty C_p\,dt)$ for the first dose is equal to the steady-state area between doses, that is, $(\int_{t_1}^{t_2} C_p\,dt)$ as shown in Fig. 9-1.

The principle of *superposition* allows the pharmacokineticist to project the plasma drug concentration–time curve of a drug after multiple consecutive doses based on the plasma drug concentration–time curve obtained after a single dose. The basic assumptions are (1) that the drug is eliminated by first-order kinetics and (2) that the pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses.

The plasma drug concentrations after multiple doses may be predicted from the plasma drug concentrations obtained after a single dose. In Table 9-1, the plasma drug concentrations from 0 to 24 hours are measured after a single dose. A constant dose of drug is given every 4 hours and plasma drug concentrations after each dose are generated using the data after the first dose. Thus, the *predicted* plasma drug concentration in the patient is the total drug concentration obtained by adding the residual drug concentration obtained after each previous dose. The superposition principle may be used to predict drug concentrations after multiple doses of many drugs. Because the superposition principle is an overlay method, it may be used to predict drug concentrations after multiple doses given at either *equal* or *unequal* dosage intervals. For example, the plasma drug concentrations may be predicted after a drug dose is given every 8 hours, or 3 times a day before meals at 8 AM, 12 noon, and 6 PM.

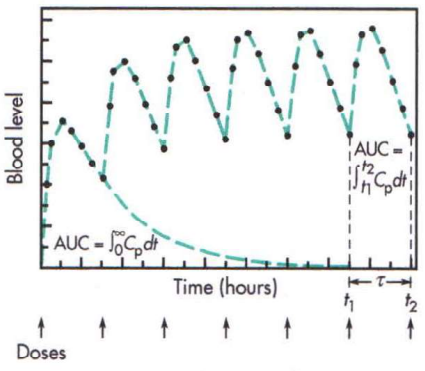

FIGURE 9-1 Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.

There are situations, however, in which the superposition principle does not apply. In these cases, the pharmacokinetics of the drug change after multiple dosing due to various factors, including changing pathophysiology in the patient, saturation of a drug carrier system, enzyme induction, and enzyme inhibition. Drugs that follow nonlinear pharmacokinetics (see Chapter 10) generally do not have predictable plasma drug concentrations after multiple doses using the superposition principle.

If the drug is administered at a fixed dose and a fixed dosage interval, as is the case with many multiple-dose regimens, the amount of drug in the body will increase and then plateau to a mean plasma level higher than the peak C_p obtained from the initial dose (Figs. 9-1 and 9-2). When the second dose is given after a time interval shorter than the time required to "completely" eliminate the previous dose, *drug accumulation* will occur in the body. In other words, the plasma concentrations following the second dose will be higher than corresponding plasma concentrations immediately following the first dose. However, if the second dose is given after a time interval longer than the time required to eliminate the previous dose, drug will not accumulate (see Table 9-1).

As repetitive equal doses are given at a constant frequency, the plasma level–time curve plateaus and a steady state is obtained. At steady state, the plasma drug levels fluctuate between C^{∞}_{max} and C^{∞}_{min}. Once steady state is obtained, C^{∞}_{max} and C^{∞}_{min} are constant and remain unchanged from dose to dose. In addition, the AUC between $(\int_{t_1}^{t_2} C_p\,dt)$ is constant during a dosing interval at steady state (see Fig. 9-1). The C^{∞}_{max} is important in determining drug safety. The C^{∞}_{max} should always remain below the MTC. The C^{∞}_{max}

TABLE 9-1 Predicted Plasma Drug Concentrations for Multiple-Dose Regimen Using the Superposition Principle[a]

Dose Number	Time (h)	Plasma Drug Concentration (μg/mL)						
		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Total
1	0	0						0
	1	21.0						21.0
	2	22.3						22.3
	3	19.8						19.8
2	4	16.9	0					16.9
	5	14.3	21.0					35.3
	6	12.0	22.3					34.3
	7	10.1	19.8					29.9
3	8	8.50	16.9	0				25.4
	9	7.15	14.3	21.0				42.5
	10	6.01	12.0	22.3				40.3
	11	5.06	10.1	19.8				35.0
4	12	4.25	8.50	16.9	0			29.7
	13	3.58	7.15	14.3	21.0			46.0
	14	3.01	6.01	12.0	22.3			43.3
	15	2.53	5.06	10.1	19.8			37.5
5	16	2.13	4.25	8.50	16.9	0		31.8
	17	1.79	3.58	7.15	14.3	21.0		47.8
	18	1.51	3.01	6.01	12.0	22.3		44.8
	19	1.27	2.53	5.06	10.1	19.8		38.8
6	20	1.07	2.13	4.25	8.50	16.9	0	32.9
	21	0.90	1.79	3.58	7.15	14.3	21.0	48.7
	22	0.75	1.51	3.01	6.01	12.0	22.3	45.6
	23	0.63	1.27	2.53	5.06	10.1	19.8	39.4
	24	0.53	1.07	2.13	4.25	8.50	16.9	33.4

[a]A single oral dose of 350 mg was given and the plasma drug concentrations were measured for 0–24 h. The same plasma drug concentrations are assumed to occur after doses 2–6. The total plasma drug concentration is the sum of the plasma drug concentrations due to each dose. For this example, $V_D = 10$ L, $t_{1/2} = 4$ h, and $k_a = 1.5$ h^{-1}. The drug is 100% bioavailable and follows the pharmacokinetics of a one-compartment open model.

is also a good indication of drug accumulation. If a drug produces the same C^{∞}_{max} at steady state, compared with the $(C_{n-1})_{max}$ after the first dose, then there is no drug accumulation. If C^{∞}_{max} is much larger than $(C_{n-1})_{max}$, then there is significant accumulation during the multiple-dose regimen. Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation R is

$$R = \frac{(C^{\infty})_{max}}{(C_{n=1})_{max}} \tag{9.1}$$

Substituting for C_{max} after the first dose and at steady state yields

$$R = \frac{D_0/V_D[1/(1-e^{-k\tau})]}{D_0/V_D} \tag{9.2}$$

$$R = \frac{1}{1-e^{-k\tau}}$$

Equation 9.2 shows that drug accumulation measured with the R index depends on the elimination constant and the dosing interval and is independent of the dose. For a drug given in repetitive oral doses, the time required to reach steady state is dependent on the elimination half-life of the drug and is independent of the size of the dose, the length of the dosing interval, and the number of doses. For example, if the dose or dosage interval of the drug is altered as shown in Fig. 9-2, the time required for the drug to reach steady state is the same, but the final steady-state plasma level changes proportionately.

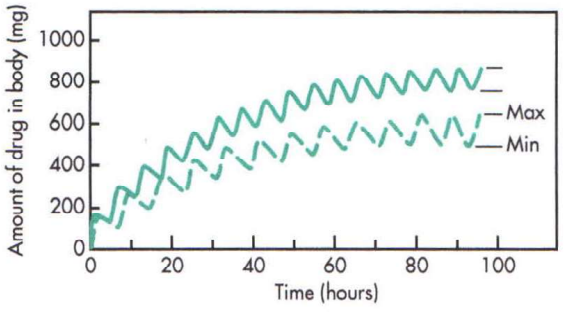

FIGURE 9-2 Amount of drug in the body as a function of time. Equal doses of drug were given every 6 hours (upper curve) and every 8 hours (lower curve). k_a and k remain constant.

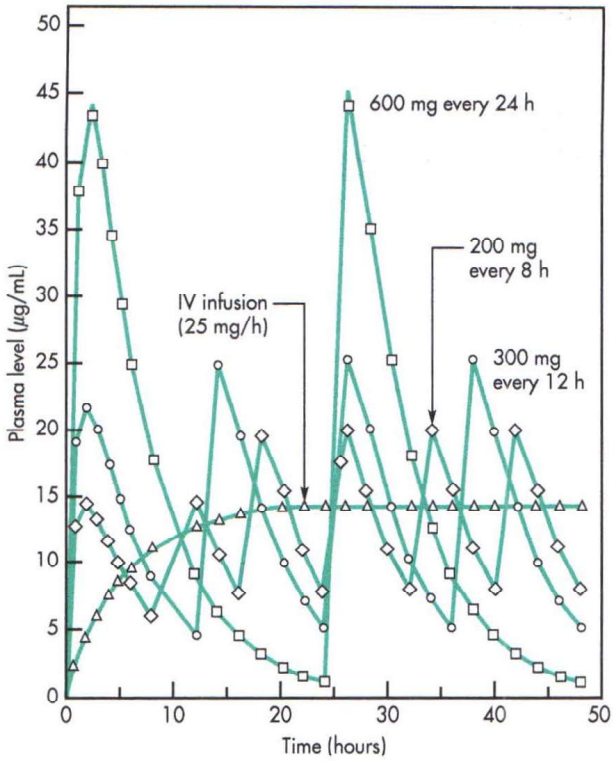

FIGURE 9-3 Simulated plasma drug concentration–time curves after IV infusion and oral multiple doses for a drug with an elimination half-life of 4 hours and apparent V_D of 10 L. IV infusion given at a rate of 25 mg/h, oral multiple doses are 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours.

Furthermore, if the drug is given at the same dosing rate but as an infusion (eg, 25 mg/h), the average plasma drug concentrations will (C^{∞}_{av}) be the same but the fluctuations between C^{∞}_{max} and C^{∞}_{min} will vary (Fig. 9-3). An average steady-state plasma drug concentration is obtained by dividing the area under the curve (AUC) for a dosing period (ie, $\int_{t_1}^{t_2} C_p\, dt$) by the dosing interval τ, at steady state.

An equation for the estimation of the time to reach one-half of the steady-state plasma levels or the accumulation half-life has been described by van Rossum and Tomey (1968).

$$\text{Accumulation } t_{1/2} = t_{1/2}\left(1 + 3.3\log\frac{k_a}{k_a - k}\right) \tag{9.3}$$

For IV administration, k_a is very rapid (approaches ∞); k is very small in comparison to k_a and can be omitted

in the denominator of Equation 9.3. Thus, Equation 9.3 reduces to

$$\text{Accumulation } t_{1/2} = t_{1/2}\left(1+3.3\log\frac{k_a}{k_a}\right) \qquad (9.4)$$

Since $k_a/k_a = 1$ and $\log 1 = 0$, the accumulation $t_{1/2}$ of a drug administered intravenously is the elimination $t_{1/2}$ of the drug. From this relationship, the time to reach 50% steady-state drug concentrations is dependent only on the elimination $t_{1/2}$ and not on the dose or dosage interval.

As shown in Equation 9.4, the accumulation $t_{1/2}$ is directly proportional to the elimination $t_{1/2}$. Table 9-2 gives the accumulation $t_{1/2}$ of drugs with various elimination half-lives given by multiple oral doses (see Table 9-2).

From a clinical viewpoint, the time needed to reach 90% of the steady-state plasma concentration is 3.3 times the elimination half-life, whereas the time required to reach 99% of the steady-state plasma concentration is 6.6 times the elimination half-life (Table 9-3). It should be noted from Table 9-3 that at a constant dose size, the shorter the dosage interval, the larger the dosing rate (mg/h), and the higher the steady-state drug level.

The number of doses for a given drug to reach steady state is dependent on the elimination half-life of the drug and the dosage interval τ (see Table 9-3). If the drug is given at a dosage interval equal to the half-life of the drug, then 6.6 doses are required to reach 99% of the theoretical steady-state plasma drug concentration. The number of doses needed to reach steady state is $6.6t_{1/2}/\tau$, as calculated in the far right column of Table 9-3. As discussed in Chapter 6, Table 6-1, it takes 4.32 half-lives to reach 95% of steady state.

CLINICAL EXAMPLE

Paroxetine (Prozac) is an antidepressant drug with a long elimination half-life of 21 hours. Paroxetine is well absorbed after oral administration and has a t_{max} of about 5 hours, longer than most drugs. Slow elimination may cause the plasma curve to peak slowly. The t_{max} is affected by k and k_a, as discussed in Chapter 8. The C_{max} for paroxetine after multiple dosing of 30 mg of paroxetine for 30 days in one study ranged from 8.6 to 105 ng/mL among 15 subjects. Clinically it is important to achieve a stable steady-state level in multiple dosing that does not "underdose" or overdose the patient. The pharmacist should advise the patient to follow the prescribed dosing interval and dose as accurately as possible. Taking a dose too early or too late contributes to

TABLE 9-2 Effect of Elimination Half-Life and Absorption Rate Constant on Accumulation Half-Life after Oral Administration[a]

Elimination Half-life (h)	Elimination Rate constant (1/h)	Absorption Rate Constant (1/h)	Accumulation Half-life (h)
4	0.173	1.50	4.70
8	0.0866	1.50	8.67
12	0.0578	1.50	12.8
24	0.0289	1.50	24.7
4	0.173	1.00	5.09
8	0.0866	1.00	8.99
12	0.0578	1.00	13.0
24	0.0289	1.00	25.0

[a]Accumulation half-life is calculated by Equation 8.3, and is the half-time for accumulation of the drug to 90% of the steady-state plasma drug concentration.

TABLE 9-3 Interrelation of Elimination Half-Life, Dosage Interval, Maximum Plasma Concentration, and Time to Reach Steady-State Plasma Concentration[a]

Elimination Half-Life (h)	Dosage Interval, τ(h)	C^{∞}_{max} (μg/mL)	Time for $C^{\infty b}_{av}$ (h)	NO. Doses to Reach 99% Steady State
0.5	0.5	200	3.3	6.6
0.5	1.0	133	3.3	3.3
1.0	0.5	341	6.6	13.2
1.0	1.0	200	6.6	6.6
1.0	2.0	133	6.6	3.3
1.0	4.0	107	6.6	1.65
1.0	10.0	100[c]	6.6	0.66
2.0	1.0	341	13.2	13.2
2.0	2.0	200	13.2	6.1

[a]A single dose of 1000 mg of three hypothetical drugs with various elimination half-lives but equal volumes of distribution (V_D = 10 L) were given by multiple IV doses at various dosing intervals. All time values are in hours; C^{∞}_{max} = maximum steady-state concentration; ($C^{\infty b}_{av}$) = average steady-state plasma concentration; the maximum plasma drug concentration after the first dose of the drug is $(C_{n=1})_{max}$ = 100 μg/mL.

[b]Time to reach 99% of steady-state plasma concentration.

[c]Since the dosage interval, τ, is very large compared to the elimination half-life, no accumulation of drug occurs.

variation. Individual variation in metabolism rate can also cause variable blood levels, as discussed later in Chapter 13.

REPETITIVE INTRAVENOUS INJECTIONS

The maximum amount of drug in the body following a single rapid IV injection is equal to the dose of the drug. For a one-compartment open model, the drug will be eliminated according to first-order kinetics.

$$D_B = D_0 e^{-k\tau} \tag{9.5}$$

If τ is equal to the dosage interval (ie, the time between the first dose and the next dose), then the amount of drug remaining in the body after several hours can be determined with

$$D_B = D_0 e^{-k\tau} \tag{9.6}$$

The fraction (f) of the dose remaining in the body is related to the elimination constant (k) and the dosage interval (τ) as follows:

$$f = \frac{D_B}{D_0} = e^{-k\tau} \tag{9.7}$$

With any given dose, f depends on k and τ. If τ is large, f will be smaller because D_B (the amount of drug remaining in the body) is smaller.

EXAMPLES ▶▶▶

1. A patient receives 1000 mg every 6 hours by repetitive IV injection of an antibiotic with an elimination half-life of 3 hours. Assume the drug is distributed according to a one-compartment model and the volume of distribution is 20 L.

a. Find the maximum and minimum amounts of drug in the body.

b. Determine the maximum and minimum plasma concentrations of the drug.

Solution

a. The fraction of drug remaining in the body is estimated by Equation 9.7. The concentration of the drug declines to one-half after 3 hours ($t_{1/2}$ = 3 h), after which the amount of drug will again decline by one-half at the end of the next 3 hours. Therefore, at the end of 6 hours, only one-quarter, or 0.25, of the original dose remains in the body. Thus f is equal to 0.25. To use Equation 9.7, we must first find the value of k from the $t_{1/2}$.

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{3} = 0.231\ h^{-1}$$

The time interval τ is equal to 6 hours. From Equation 9.7,

$$f = e^{-(0.231)(6)}$$

$$f = 0.25$$

In this example, 1000 mg of drug is given intravenously, so the amount of drug in the body is immediately increased by 1000 mg. At the end of the dosage interval (ie, before the next dose), the amount of drug remaining in the body is 25% of the amount of drug present just after the previous dose, because f = 0.25. Thus, if the value of f is known, a table can be constructed relating the fraction of the dose in the body before and after rapid IV injection (Table 9-4).

From Table 9-4 the maximum amount of drug in the body is 1333 mg and the minimum amount of drug in the body is 333 mg. The difference between the maximum and minimum values, D_0, will always equal the injected dose.

$$D_{max} - D_{min} = D_0 \qquad (9.8)$$

In this example,

$$1333 - 333 = 1000\ mg$$

D^{∞}_{max} can also be calculated directly by the relationship

$$D^{\infty}_{max} = \frac{D_0}{1-f} \qquad (9.9)$$

TABLE 9-4 Fraction of the Dose in the Body before and after Intravenous Injections of a 1000-mg Dose[a]

	Amount of Drug in Body	
Number of Doses	Before Dose	After Dose
1	0	1000
2	250	1250
3	312	1312
4	328	1328
5	332	1332
6	333	1333
7	333	1333
∞	333	1333

[a] f = 0.25.

Substituting known data, we obtain

$$D^{\infty}_{max} = \frac{1000}{1-0.25} = 1333\ mg$$

Then, from Equation 9.8,

$$D^{\infty}_{min} = 1333 - 1000 = 333\ mg$$

The average amount of drug in the body at steady state, D^{∞}_{av}, can be found by Equation 9.10 or Equation 9.11. F is the fraction of dose absorbed. For an IV injection, F is equal to 1.0.

$$D^{\infty}_{av} = \frac{FD_0}{k\tau} \qquad (9.10)$$

$$D^{\infty}_{av} = \frac{FD_0 1.44 t_{1/2}}{\tau} \qquad (9.11)$$

Equations 9.10 and 9.11 can be used for repetitive dosing at constant time intervals and for any route of administration as long as elimination occurs from the central compartment. Substitution of values from the example into Equation 9.11 gives

$$D^{\infty}_{av} = \frac{(1)(1000)(1.44)(3)}{6} = 720\ mg$$

Since the drug in the body declines exponentially (ie, first-order drug elimination), the value D^{∞}_{av} is not the arithmetic mean of D^{∞}_{max} and D^{∞}_{min}. The limitation

of using D^{∞}_{av} is that the fluctuations of D^{∞}_{max} and D^{∞}_{min} are not known.

b. To determine the concentration of drug in the body after multiple doses, divide the amount of drug in the body by the volume in which it is dissolved. For a one-compartment model, the maximum, minimum, and steady-state concentrations of drug in the plasma are found by the following equations:

$$C^{\infty}_{max} = \frac{D^{\infty}_{max}}{V_D} \tag{9.12}$$

$$C^{\infty}_{min} = \frac{D^{\infty}_{min}}{V_D} \tag{9.13}$$

$$C^{\infty}_{av} = \frac{D^{\infty}_{av}}{V_D} \tag{9.14}$$

A more direct approach to finding C^{∞}_{max}, and C^{∞}_{min}, is C^{∞}_{av}:

$$C^{\infty}_{max} = \frac{C^0_p}{1-e^{-k\tau}} \tag{9.15}$$

where C^0_p is equal to D_0/V_D.

$$C^{\infty}_{min} = \frac{C^0_p e^{-k\tau}}{1-e^{-k\tau}} \tag{9.16}$$

$$C^{\infty}_{av} = \frac{FD_0}{V_D k\tau} \tag{9.17}$$

For this example, the values for C^{∞}_{max}, C^{∞}_{min}, and C^{∞}_{av} are 66.7, 16.7, and 36.1 μg/mL, respectively.

As mentioned, C^{∞}_{av} is not the arithmetic mean of C^{∞}_{max} and C^{∞}_{min} because plasma drug concentration declines exponentially. The C^{∞}_{av} is equal to $[AUC]^{t_2}_{t_1}$ or $(\int^{t_2}_{t_1} C_p\, dt)$ for a dosage interval at steady state divided by the dosage interval τ.

$$C^{\infty}_{av} = \frac{[AUC]^{t_2}_{t_1}}{\tau} \tag{9.18}$$

C^{∞}_{av} gives an estimate of the mean plasma drug concentration at steady state. The C^{∞}_{av} is often the target drug concentration for optimal therapeutic effect and gives an indication as to how long this plasma drug concentration is maintained during the dosing interval (between doses). The C^{∞}_{av} is dependent on both AUC and τ. The C^{∞}_{av} reflects drug exposure after multiple doses. Drug exposure is often related to drug safety and efficacy as discussed later in Chapter 21. For example, drug exposure is closely monitored when a cytotoxic or immunosuppressive, anticancer drug is administered during therapy. AUC may be estimated by sampling several plasma drug concentrations over time. Theoretically, AUC is superior to sampling just the C_{max} or C_{min}. For example, when cyclosporine dosing is clinically evaluated using AUC, the AUC is approximately estimated by two or three points. Dosing error is less than using AUC compared to the trough method alone (Primmett et al, 1998). In general, C_{min} or trough level is more frequently used than C^{∞}_{max}. C_{min} is the drug concentration just before the next dose is given and is less variable than peak drug concentration, C^{∞}_{max}. The sample time for C^{∞}_{max} is approximated and the true C^{∞}_{max} may not be accurately estimated. In some cases, the plasma trough level, C^{∞}_{min} is considered by some investigators as a more reliable sample since the drug is equilibrated with the surrounding tissues, although this may also depend on other factors.

The AUC is related to the amount of drug absorbed divided by total body clearance (Cl), as shown in the following equation:

$$[AUC]^{t_2}_{t_1} = \frac{FD_0}{Cl} = \frac{FD_0}{kV_D} \tag{9.19}$$

Substitution of FD_0/kV_D for AUC in Equation 9.18 gives Equation 9.17. Equation 9.17 or 9.18 can be used to obtain C^{∞}_{av} after a multiple-dose regimen regardless of the route of administration.

It is sometimes desirable to know the plasma drug concentration at any time after the administration of n doses of drug. The general expression for calculating this plasma drug concentration is

$$C_p = \frac{D_0}{V_D}\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kt} \tag{9.20}$$

where n is the number of doses given and t is the time after the nth dose.

At steady state, $e^{-nk\tau}$ approaches zero and Equation 9.20 reduces to

$$C_p^{\infty} = \frac{D_0}{V_D}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt} \qquad (9.21)$$

where C_p^{∞} is the steady-state drug concentration at time t after the dose.

2. The patient in the previous example received 1000 mg of an antibiotic every 6 hours by repetitive IV injection. The drug has an apparent volume of distribution of 20 L and elimination half-life of 3 hours. Calculate **(a)** the plasma drug concentration, C_p at 3 hours after the second dose, **(b)** the steady-state plasma drug concentration, C_p^{∞} at 3 hours after the last dose, **(c)** C_{max}^{∞}, **(d)** C_{min}^{∞}, and **(e)** C_{SS}.

Solution

a. The C_p at 3 hours after the second dose—use Equation 9.20 and let $n = 2$, $t = 3$ hours, and make other appropriate substitutions.

$$C_p = \frac{1000}{20}\left(\frac{1-e^{-(2)(0.231)(6)}}{1-e^{-(0.231)(6)}}\right)e^{-0.231(3)}$$

$$C_p = 31.3 \text{ mg/L}$$

b. The C_p^{∞} at 3 hours after the last dose—because steady state is reached, use Equation 9.21 and perform the following calculation:

$$C_p^{\infty} = \frac{1000}{20}\left(\frac{1}{1-e^{-0.231(6)}}\right)e^{-0.231(3)}$$

$$C_p^{\infty} = 33.3 \text{ mg/L}$$

c. The C_{max}^{∞} is calculated from Equation 9.15.

$$C_{max}^{\infty} = \frac{1000/20}{1-e^{-(0.231)(6)}} = 66.7 \text{ mg/L}$$

d. The C_{min}^{∞} may be estimated as the drug concentration after the dosage interval τ, or just before the next dose.

$$C_{min}^{\infty} = C_{max}^{\infty}e^{-kt} = 66.7e^{-(0.231)(6)} = 16.7 \text{ mg/L}$$

e. The C_{av}^{∞} is estimated by Equation 9.17—because the drug is given by IV bolus injections, $F = 1$.

$$C_{av}^{\infty} = \frac{1000}{(0.231)(20)(6)} = 36.1 \text{ mg/L}$$

C_{av}^{∞} is represented as C_{SS} in some references.

Problem of a Missed Dose

Equation 9.22 describes the plasma drug concentration t hours after the nth dose is administered; the doses are administered τ hours apart according to a multiple-dose regimen:

$$C_p = \frac{D_0}{V_D}\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kt} \qquad (9.22)$$

Concentration contributed by the missing dose is

$$C_p' = \frac{D_0}{V_D}e^{-kt_{miss}} \qquad (9.23)$$

in which t_{miss} = time elapsed since the scheduled dose was missed. Subtracting Equation 9.23 from Equation 9.20 corrects for the missing dose as shown in Equation 9.24.

$$C_p = \frac{D_0}{V_D}\left[\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kt} - e^{-kt_{miss}}\right] \qquad (9.24)$$

Note: If steady state is reached (ie, either n = large or after many doses), the equation simplifies to Equation 9.25. Equation 9.25 is useful when steady state is reached.

$$C_p = \frac{D_0}{V_D}\left(\frac{e^{-kt}}{1-e^{-kt}}\right) - e^{-kt_{miss}} \qquad (9.25)$$

Generally, if the missing dose is recent, it will affect the present drug level more. If the missing dose is several half-lives later ($>5t_{1/2}$), the missing dose may be omitted because it will be very small. Equation 9.24 accounts for one missing dose, but several missing doses can be subtracted in a similar way if necessary.

EXAMPLE ▶▶▶

A cephalosporin ($k = 0.2$ h^{-1}, $V_D = 10$ L) was administered by IV multiple dosing; 100 mg was injected every 6 hours for 6 doses. What was the plasma drug concentration 4 hours after the sixth dose (ie, 40 hours later) if **(a)** the fifth dose was omitted, **(b)** the sixth dose was omitted, and **(c)** the fourth dose was omitted?

Solution

Substitute $k = 0.2\ h^{-1}$, $V_D = 10$ L, $D = 100$ mg, $n = 6$, $t = 4$ hours, and $\tau = 6$ hours into Equation 9.20 and evaluate:

$$C_p = 6.425 \text{ mg/L}$$

If no dose was omitted, then 4 hours after the sixth injection, C_p would be 6.425 mg/L.

a. Missing the fifth dose, its contribution must be subtracted off, $t_{miss} = 6 + 4 = 10$ hours (the time elapsed since missing the dose) using the steady-state equation:

$$C_p' = \frac{D_0}{V_D} e^{-kt_{miss}} = \frac{100}{10} e^{-(0.2\times10)}$$

Drug concentration correcting for the missing dose = 6.425 – 1.353 = 5.072 mg/L.

b. If the sixth dose is missing, $t_{miss} = 4$ hours:

$$C_p' = \frac{D_0}{V_D} e^{-kt_{miss}} = \frac{100}{10} e^{-(0.2\times4)} = 4.493 \text{ mg/L}$$

Drug concentration correcting for the missing dose = 6.425 – 4.493 = 1.932 mg/L.

c. If the fourth dose is missing, $t_{miss} = 12 + 4 = 16$ hours:

$$C_p' = \frac{D_0}{V_D} e^{-kt_{miss}} = \frac{100}{10} e^{-(0.2\times16)} = 0.408 \text{ mg/L}$$

The drug concentration corrected for the missing dose = 6.425 – 0.408 = 6.017 mg/L.

Note: The effect of a missing dose becomes less pronounced at a later time. A strict dose regimen compliance is advised for all drugs. With some drugs, missing a dose can have a serious effect on therapy. For example, compliance is important for the anti-HIV1 drugs such as the protease inhibitors.

Early or Late Dose Administration during Multiple Dosing

When one of the drug doses is taken earlier or later than scheduled, the resulting plasma drug concentration can still be calculated based on the principle of superposition. The dose can be treated as missing, with the late or early dose added back to take into account the actual time of dosing, using Equation 9.26.

$$C_p = \frac{D_0}{V_D}\left(\frac{1-e^{-nkt}}{1-e^{-kt}} e^{-kt} - e^{-kt_{miss}} + e^{-kt_{actual}}\right) \quad (9.26)$$

in which t_{miss} = time elapsed since the dose (late or early) is scheduled, and t_{actual} = time elapsed since the dose (late or early) is actually taken. Using a similar approach, a second missed dose can be subtracted from Equation 9.20. Similarly, a second late/early dose may be corrected by subtracting the scheduled dose followed by adding the actual dose. Similarly, if a different dose is given, the regular dose may be subtracted and the new dose added back.

EXAMPLE ▶▶▶

Assume the same drug as above (ie, $k = 0.2\ h^{-1}$, $V_D = 10$ L) was given by multiple IV bolus injections and that at a dose of 100 mg every 6 hours for 6 doses. What is the plasma drug concentration 4 hours after the sixth dose, if the fifth dose were given an hour late?

Substitute into Equation 9.26 for all unknowns: $k = 0.2\ h^{-1}$, $V_D = 10$ L, $D = 100$ mg, $n = 6$, $\tau = 4$ h, $\tau = 6$ h, $t_{miss} = 6 + 4 = 10$ hours, $t_{actual} = 9$ hours (taken 1 hour late, ie, 5 hours before the sixth dose).

$$C_p = \frac{D_0}{V_D}\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} e^{-k\tau} - e^{-kt_{miss}} + e^{-kt_{actual}}\right)$$

$$C_p = 6.425 - 1.353 + 1.653 = 6.725 \text{ mg/L}$$

Note: 1.353 mg/L was subtracted and 1.653 mg/mL was added because the fifth dose was not given as planned, but was given 1 hour later.

INTERMITTENT INTRAVENOUS INFUSION

Intermittent IV infusion is a method of successive short IV drug infusions in which the drug is given by IV infusion for a short period of time followed by a drug elimination period, then followed by another

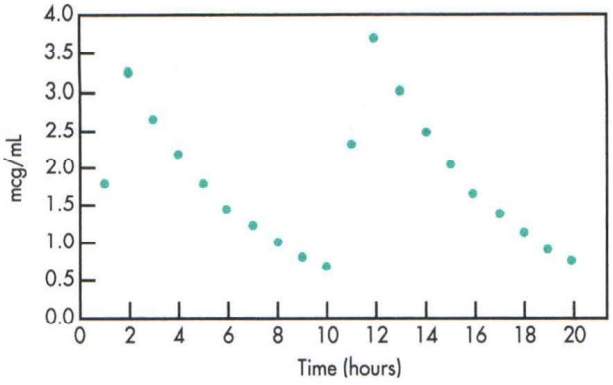

FIGURE 9-4 Plasma drug concentration after two doses by IV infusion. Data from Table 9-5.

short IV infusion (Fig. 9-4). In drug regimens involving short IV infusion, the drug may not reach steady state. The rationale for intermittent IV infusion is to prevent transient high drug concentrations and accompanying side effects. Many drugs are better tolerated when infused slowly over time compared to IV bolus dosing.

Administering One or More Doses by Constant Infusion: Superposition of Several IV Infusion Doses

For a continuous IV infusion (see Chapter 7):

$$C_p = \frac{R}{Cl}(1-e^{-kt}) = \frac{R}{kV_D}(1-e^{-kt}) \qquad (9.27)$$

Equation 9.27 may be modified to determine drug concentration after one or more short IV infusions for a specified time period (Equation 9.28).

$$C_p = \frac{D}{t_{inf}V_D k}(1-e^{-kt}) \qquad (9.28)$$

where R = rate of infusion = D/t_{inf}, D = size of infusion dose, and t_{inf} = infusion period.

After the infusion is stopped, the drug concentration post-IV infusion is obtained using the first-order equation for drug elimination:

$$C_p = C_{stop}e^{-kt} \qquad (9.29)$$

where C_{stop} = concentration when infusion stops, and t = time elapsed since infusion stopped.

EXAMPLE ▶▶▶

An antibiotic was infused with a 40-mg IV dose over 2 hours. Ten hours later, a second dose of 40 mg was infused, again over 2 hours. **(a)** What is the plasma drug concentration 2 hours after the start of the first infusion? **(b)** What is the plasma drug concentration 5 hours after the second dose infusion was started? Assume $k = 0.2\ h^{-1}$ and V_D = 10 L for the antibiotic.

Solution

The predicted plasma drug concentrations after the first and second IV infusions are shown in Table 9-5. Using the principle of superposition, the total plasma drug concentration is the sum of the residual drug concentrations due to the first IV infusion (column 3) and the drug concentrations due to the second IV infusion (column 4). A graphical representation of these data is shown in Fig. 9-4.

a. The plasma drug concentration at 2 hours after the first IV infusion starts is calculated from Equation 9.28.

$$C_p = \frac{40/2}{10\times 0.2}(1-e^{-0.2/2}) = 3.30\ \text{mg/L}$$

b. From Table 9-5, the plasma drug concentration at 15 hours (ie, 5 hours after the start of the second IV infusion) is 2.06 μg/mL. At 5 hours after the second IV infusion starts, the plasma drug concentration is the sum of the residual plasma drug concentrations from the first 2-hour infusion according to first-order elimination and the residual plasma drug concentrations from the second 2-hour IV infusion as shown in the following scheme:

← 10 hours →		← 10 hours →	
First infusion for 2 hours	Stopped (no infusion for 8 hours)	Second infusion for 2 hours	Stopped (no infusion for 8 hours)

The plasma drug concentration is calculated using the first-order elimination equation, where C_{stop} is the plasma drug concentration at the stop of the 2-hour IV infusion.

TABLE 9-5 Drug Concentration after Two Intravenous Infusions[a]

	Time(h)	Plasma Drug Concentration after Infusion 1	Plasma Drug Concentration after Infusion 2	Total Plasma Drug Concentration
Infusion 1 begins	0	0		0
	1	1.81		1.81
Infusion 1 stopped	2	3.30		3.30
	3	2.70		2.70
	4	2.21		2.21
	5	1.81		1.81
	6	1.48		1.48
	7	1.21		1.21
	8	0.99		0.99
	9	0.81		0.81
Infusion 2 begins	10	0.67	0	0.67
	11	0.55	1.81	2.36
Infusion 2 stopped	12	0.45	3.30	3.74
	13	0.37	2.70	3.07
	14	0.30	2.21	2.51
	15	0.25	1.81	2.06

[a]Drug is given by a 2-hour infusion separated by a 10-hour drug elimination interval. All drug concentrations are in μg/mL. The declining drug concentration after the first infusion dose and the drug concentration after the second infusion dose give the total plasma drug concentration.

The plasma drug concentration after the completion of the first IV infusion when $t = 15$ hours is

$$C_p = C_{stop}e^{-kt} = 3.30e^{-0.2\times15} = 0.25\ \mu g/L$$

The plasma drug concentration 5 hours after the second IV infusion is

$$C_p = C_{stop}e^{-kt} = 3.30e^{-0.2\times3} = 1.81\ \mu g/mL$$

The total plasma drug concentration 5 hours after the start of the second IV infusion is

$$0.25\ mg/L + 1.81\ mg/L = 2.06\ mg/L.$$

CLINICAL EXAMPLE

Gentamicin sulfate was given to an adult male patient (57 years old, 70 kg) by intermittent IV infusions. One-hour IV infusions of 90 mg of gentamicin was given at 8-hour intervals. Gentamicin clearance is similar to creatinine clearance and was estimated as 7.2 L/h with an elimination half-life of 3 hours.

a. What is the plasma drug concentration after the first IV infusion?

b. What is the peak plasma drug concentration, C_{max}, and the trough plasma drug concentration, C_{min}, at steady state?

Solution

a. The plasma drug concentration directly after the first infusion is calculated from Equation 9.27, where $R = 90$ mg/h, $Cl = 7.2$ L/h, and $k = 0.231$ h^{-1}. The time for infusion, t_{int}, is 1 hour.

$$C_p = \frac{90}{7.2}(1 - e^{-(0.231)(1)}) = 2.58 \text{ mg/L}$$

b. The C^{∞}_{max} at steady state may be obtained from Equation 9.30.

$$C^{\infty}_{max} = \frac{R(1 - e^{-kt_{inf}})}{Cl} \frac{1}{(1 - e^{-kt})} \qquad (9.30)$$

where C_{max} is the peak drug concentration following the nth infusion, at steady state, t_{inf} is the time period of infusion, and τ is the dosage interval. The term $1/(1 - e^{-k\tau})$ is the accumulation factor for repeated drug administration. Substitution in Equation 9.30 gives

$$C^{\infty}_{max} = \frac{90(1 - e^{-(0.231)(1)})}{7.2} \times \frac{1}{(1 - e^{-(0.231)(8)})}$$

$$= 3.06 \text{ mg/L}$$

The plasma drug concentration C^{∞}_{p} at any time t after the last infusion ends when steady state is obtained by Equation 9.31 and assumes that plasma drug concentrations decline according to first-order elimination kinetics.

$$C^{\infty}_{p} = \frac{R(1 - e^{-kt_{inf}})}{Cl} \times \frac{1}{(1 - e^{-kt})} \times e^{-k(t)} \qquad (9.31)$$

where t_{inf} is the time for infusion and t is the time period after the end of the infusion.

The trough plasma drug concentration, C^{∞}_{min}, at steady state is the drug concentration just before the start of the next IV infusion or after a dosage interval equal to 8 hours after the last infusion stopped. Equation 9.31 can be used to determine the plasma drug concentration at any time after the last infusion is stopped (after steady state has been reached).

$$C^{\infty}_{min} = \frac{90(1 - e^{-(0.231)(1)})}{7.2} \times \frac{e^{-(0.231)(8)}}{(1 - e^{-(0.231)(8)})}$$

$$= 0.48 \text{ mg/L}$$

ESTIMATION OF k AND V_D OF AMINOGLYCOSIDES IN CLINICAL SITUATIONS

As illustrated above, antibiotics are often infused intravenously by multiple doses, so it is desirable to adjust the recommended starting dose based on the patient's individual k and V_D values. According to Sawchuk and Zaske (1976), individual parameters for aminoglycoside pharmacokinetics may be determined in a patient by using a limited number of plasma drug samples taken at appropriate time intervals. The equation was simplified by replacing an elaborate model with the one-compartment model to describe drug elimination and appropriately avoiding the distributive phase. The plasma sample should be collected 15–30 minutes postinfusion (with infusion lasting about 60 minutes) and, in patients with poor renal function, 1–2 hours postinfusion, to allow adequate tissue distribution. The second and third blood samples should be collected about 2–3 half-lives later, in order to get a good estimation of the slope. The data may be determined graphically or by regression analysis using a scientific calculator or computer program.

$$V_D = \frac{R(1 - e^{-kt_{inf}})}{[C^{\infty}_{max} - C^{\infty}_{min} e^{-kt_{inf}}} \qquad (9.32)$$

The dose of aminoglycoside is generally fixed by the desirable peak, C^{∞}_{max}, and trough plasma concentration, C^{∞}_{min}. For example, C^{∞}_{max} for gentamicin may be set at 6–10 μg/mL with the steady-state trough level, C^{∞}_{min}, generally about 0.5–2 μg/mL, depending on the severity of the infection and renal considerations. The upper range is used only for life-threatening infections. The infusion rate for any desired peak drug concentration may be calculated using Equation 9.33.

$$R = \frac{V_D k C^{\infty}_{max}(1 - e^{-k\tau})}{(1 - e^{-kt_{inf}})} \qquad (9.33)$$

The dosing interval τ between infusions may be adjusted to obtain a desired concentration.

Frequently Asked Questions

- *Is the drug accumulation index* (R) *applicable to any drug given by multiple doses or only to drugs that are eliminated slowly from the body?*
- *What are the advantages/disadvantages for giving a drug by a constant IV infusion, intermittent IV infusion, or multiple IV bolus injections? What drugs would most likely be given by each route of administration? Why?*
- *Why is the accumulation index,* R, *not affected by the dose or clearance of a drug? Would it be possible for a drug with a short half-life to have* R *much greater than 1?*

MULTIPLE-ORAL-DOSE REGIMEN

Figures 9-1 and 9-2 present typical cumulation curves for the concentration of drug in the body after multiple oral doses given at a constant dosage interval. The plasma concentration at any time during an oral or extravascular multiple-dose regimen, assuming a one-compartment model and constant doses and dose interval, can be determined as follows:

$$C_p = \frac{Fk_aD_0}{V_D(k-k_a)}\left[\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_at} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kt}\right]$$

where n = number of doses, τ = dosage interval, F = fraction of dose absorbed, and t = time after administration of n doses.

The mean plasma level at steady state, C_{av}^{∞}, is determined by a similar method to that employed for repeat IV injections. Equation 9.17 can be used for finding C_{av}^{∞} for any route of administration.

$$C_{av}^{\infty} = \frac{FD_0}{V_Dk\tau} \tag{9.17}$$

Because proper evaluation of F and V_D requires IV data, the AUC of a dosing interval at steady state may be substituted in Equation 9.17 to obtain

$$C_{av}^{\infty} = \frac{\int_0^{\infty} C_p\,dt}{\tau} = \frac{[AUC]_0^{\infty}}{\tau} \tag{9.35}$$

One can see from Equation 9.17 that the magnitude of C_{av}^{∞} is directly proportional to the size of the dose and the extent of drug absorbed. Furthermore, if the dosage interval (τ) is shortened, then the value for C_{av}^{∞} will increase. The C_{av}^{∞} will be predictably higher for drugs distributed in a small V_D (eg, plasma water) or that have long elimination half-lives than for drugs distributed in a large V_D (eg, total body water) or that have very short elimination half-lives. Because body clearance (Cl_T) is equal to kV_D, substitution into Equation 9.17 yields

$$C_{av}^{\infty} = \frac{FD_0}{Cl_T\tau} \tag{9.36}$$

Thus, if Cl_T decreases, C_{av}^{∞} will increase.

The C_{av}^{∞} does not give information concerning the fluctuations in plasma concentration (C_{max}^{∞} and C_{min}^{∞}). In multiple-dose regimens, C_p at any time can be obtained using Equation 9.34, where n = nth dose. At steady state, the drug concentration can be determined by letting n equal infinity. Therefore, $e^{-nk\tau}$ becomes approximately equal to zero and Equation 9.22 becomes

$$C_p^{\infty} = \frac{k_aFD_0}{V_D(k_a-k)}\left[\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt} - \left(\frac{1}{1-e^{k_a\tau}}\right)e^{-k_at}\right] \tag{9.37}$$

The maximum and minimum drug concentrations (C_{max}^{∞} and C_{min}^{∞}) can be obtained with the following equations:

$$C_{max}^{\infty} = \frac{FD_0}{V_D}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt_p} \tag{9.38}$$

$$C_{min}^{\infty} = \frac{k_aFD_0}{V_D(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau} \tag{9.39}$$

The time at which maximum (peak) plasma concentration (or t_{max}) occurs following a single oral dose is

$$t_{max} = \frac{2.3}{k_a-k}\log\frac{k_a}{k} \tag{9.40}$$

whereas the peak plasma concentration, t_p, following multiple doses is given by Equation 9.41.

$$t_p = \frac{1}{k_a-k}\ln\left[\frac{k_a(1-e^{-k\tau})}{k(1-e^{-k_a\tau})}\right] \tag{9.41}$$

Large fluctuations between C_{max}^{∞} and C_{min}^{∞} can be hazardous, particularly with drugs that have a narrow therapeutic index. The larger the number of divided doses, the smaller the fluctuations in the plasma drug concentrations. For example, a 500-mg dose of drug

given every 6 hours will produce the same C_{av}^{∞} value as a 250-mg dose of the same drug given every 3 hours, while the C_{max}^{∞} and C_{min}^{∞} fluctuations for the latter dose will be decreased by one-half (see Fig. 9-3). With drugs that have a narrow therapeutic index, the dosage interval should not be longer than the elimination half-life.

EXAMPLE ▶▶▶

An adult male patient (46 years old, 81 kg) was given 250 mg of tetracycline hydrochloride orally every 8 hours for 2 weeks. From the literature, tetracycline hydrochloride is about 75% bioavailable and has an apparent volume of distribution of 1.5 L/kg. The elimination half-life is about 10 hours. The absorption rate constant is 0.9 h^{-1}. From this information, calculate **(a)** C_{max} after the first dose, **(b)** C_{min} after the first dose, **(c)** plasma drug concentration C_p at 4 hours after the seventh dose, **(d)** maximum plasma drug concentration at steady state, C_{max}^{∞}, **(e)** minimum plasma drug concentration at steady state, C_{min}^{∞}, and **(f)** average plasma drug concentration at steady state, C_{av}^{∞}.

Solution

a. C_{max} after the first dose occurs at t_{max}—therefore, using Equation 9.40,

$$t_{max} = \frac{2.3}{0.9-0.07}\log\left(\frac{0.9}{0.07}\right)$$

$$t_{max} = 3.07$$

Then substitute t_{max} into the following equation for a single oral dose (one-compartment model) to obtain C_{max}.

$$C_{max} = \frac{FD_0k_a}{V_D(k_a-k)}(e^{-kt_{max}} - e^{-k_at_{max}})$$

$$C_{max} = \frac{(0.75)(250)(0.9)}{(121.5)(0.9-0.07)}(e^{-0.07(3.07)} - e^{-0.9(3.07)})$$

$$C_{max} = 1.28 \text{ mg/L}$$

b. C_{min} after the first dose occurs just before the administration of the next dose of drug—therefore, set $t = 8$ hours and solve for C_{min}.

$$C_{min} = \frac{(0.75)(250)(0.9)}{(121.5)(0.9-0.07)}(e^{-0.07(8)} - e^{-0.9(8)})$$

$$C_{min} = 0.95 \text{ mg/L}$$

c. C_p at 4 hours after the seventh dose may be calculated using Equation 9.34, letting $n = 7$, $t = 4$, $\tau = 8$, and making the appropriate substitutions.

$$C_p = \frac{(0.75)(250)(0.9)}{(121.5)(0.07-0.9)} \times \left[\left(\frac{1-e^{-(7)(0.9)(8)}}{1-e^{-0.9(8)}}\right)e^{-0.9(4)} - \left(\frac{1-e^{-(7)(0.07)(8)}}{1-e^{-(0.07)(8)}}\right)e^{-0.07(4)}\right]$$

$$C_p = 2.86 \text{ mg/L}$$

d. C_{max}^{∞} at steady state: t_p at steady state is obtained from Equation 9.41.

$$t_p = \frac{1}{k_a-k}\ln\left[\frac{k_a(1-e^{-k\tau})}{k(1-e^{-k_a\tau})}\right]$$

$$t_p = \frac{1}{0.9-0.07}\ln\left[\frac{0.9(1-e^{-(0.07)(8)})}{0.07(1-e^{-(0.9)(8)})}\right]$$

$$t_p = 2.05 \text{ hours}$$

Then C_{max}^{∞} is obtained using Equation 9.38.

$$C_{max}^{\infty} = \frac{0.75(250)}{121.5}\left(\frac{1}{1-e^{-0.07(8)}}\right)e^{-0.07(2.05)}$$

$$C_{min}^{\infty} = 3.12 \text{ mg/L}$$

e. C_{min}^{∞} at steady state is calculated from Equation 9.39.

$$C_{min}^{\infty} = \frac{(0.9)(0.75)(250)}{(121.5)(0.9-0.07)}\left(\frac{1}{1-e^{-0.07(8)}}\right)e^{-(0.7)(8)}$$

$$C_{max}^{\infty} = 2.23 \text{ mg/L}$$

f. C_{av}^{∞} at steady state is calculated from Equation 9.17.

$$C_{av}^{\infty} = \frac{(0.75)(250)}{(121.5)(0.07)(8)}$$

$$C_{av}^{\infty} = 2.76 \text{ mg/L}$$

LOADING DOSE

Since extravascular doses require time for absorption into the plasma to occur, therapeutic effects are delayed until sufficient plasma concentrations are achieved. To reduce the onset time of the drug—that is,

the time it takes to achieve the minimum effective concentration (assumed to be equivalent to the C_{av}^{∞})—a loading (priming) or initial dose of drug is given. The main objective of the loading dose is to achieve desired plasma concentrations, C_{av}^{∞}, as quickly as possible. If the drug follows one-compartment pharmacokinetics, then in theory, steady state is also achieved immediately following the loading dose. Thereafter, a maintenance dose is given to maintain C_{av}^{∞} and steady state so that the therapeutic effect is also maintained. In practice, a loading dose may be given as a bolus dose or a short-term loading IV infusion.

As discussed earlier, the time required for the drug to accumulate to a steady-state plasma level is dependent mainly on its elimination half-life. The time needed to reach 90% of C_{av}^{∞} is approximately 3.3 half-lives, and the time required to reach 99% of C_{av}^{∞} is equal to approximately 6.6 half-lives. For a drug with a half-life of 4 hours, it will take approximately 13 and 26 hours to reach 90% and 99% of C_{av}^{∞}, respectively.

For drugs absorbed rapidly in relation to elimination ($k_a >> k$) and that are distributed rapidly, the loading dose D_L can be calculated as follows:

$$\frac{D_L}{D_0} = \frac{1}{(1-e^{-k_a\tau})(1-e^{-k\tau})} \qquad (9.42)$$

For extremely rapid absorption, as when the product of $k_a\tau$ is large or in the case of IV infusion, $e^{-k_a\tau}$ becomes approximately zero and Equation 9.42 reduces to

$$\frac{D_L}{D_0} = \frac{1}{1-e^{-k\tau}} \qquad (9.43)$$

The loading dose should approximate the amount of drug contained in the body at steady state. The dose ratio is equal to the loading dose divided by the maintenance dose.

$$\text{Dose ratio} = \frac{D_L}{D_0} \qquad (9.44)$$

As a general rule of thumb, if the selected dosage interval is equal to the drug's elimination half-life, then the dose ratio calculated from Equation 9.44 should be equal to 2.0. In other words, the loading dose will be equal to double the initial drug dose. Figure 9-5 shows the plasma level–time curve for dosage regimens with equal maintenance doses but different loading doses. A rapid approximation of loading dose, D_L, may be estimated from

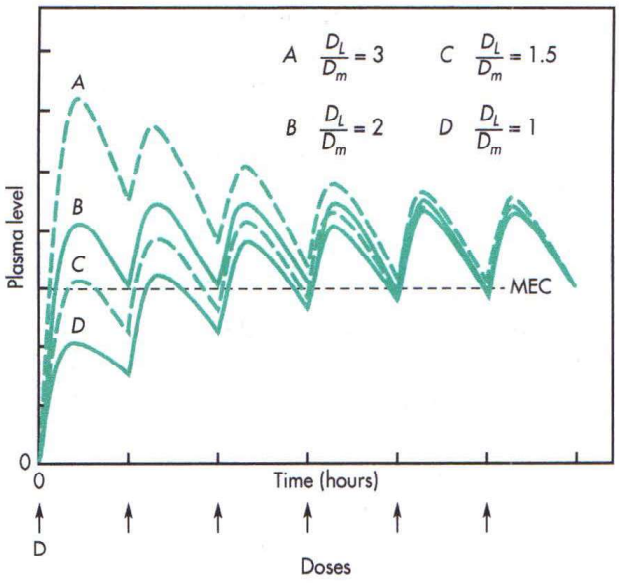

FIGURE 9-5 Concentration curves for dosage regimens with equal maintenance doses (D) and dosage intervals (τ) and different dose ratios. (From Kruger-Thiemer, 1968, with permission.)

$$D_L = \frac{V_D C_{av}^{\infty}}{(S)(F)} \qquad (9.45)$$

where C_{av}^{∞} is the desired plasma drug concentration, S is the salt form of the drug, and F is the fraction of drug bioavailability.

Equation 9.45 assumes very rapid drug absorption from an immediate-release dosage form. The D_L calculated by this method has been used in clinical situations for which only an approximation of the D_L is needed.

These calculations for loading doses are not applicable to drugs that demonstrate multicompartment kinetics. Such drugs distribute slowly into extravascular tissues, and drug equilibration and steady state may not occur until after the apparent plateau is reached in the vascular (central) compartment.

DOSAGE REGIMEN SCHEDULES

Predictions of steady-state plasma drug concentrations usually assume the drug is given at a constant dosage interval throughout a 24-hour day. Very often,

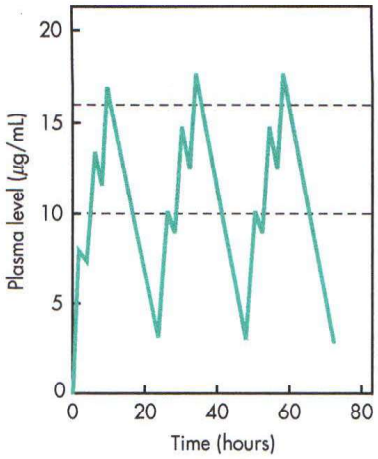

FIGURE 9-6 Plasma level–time curve for theophylline given in doses of 160 mg 3 times a day. Dashed lines indicate the therapeutic range. (From Niebergall et al, 1974, with permission.)

however, the drug is given only during the waking hours (Fig. 9-6). Niebergall et al (1974) discussed the problem of scheduling dosage regimens and particularly warned against improper timing of the drug dosage. For drugs with a narrow therapeutic index such as theophylline (Fig. 9-6), large fluctuation between the maximum and minimum plasma levels are undesirable and may lead to subtherapeutic plasma drug concentrations and/or to high, possibly toxic, drug concentrations. These wide fluctuations occur if larger doses are given at wider dosage intervals (see Fig. 9-3). For example, Fig. 9-7 shows

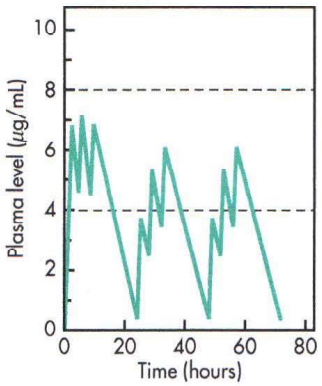

FIGURE 9-7 Plasma level–time curve for procainamide given in an initial dose of 1.0 g followed by doses of 0.5 g 4 times a day. Dashed lines indicate the therapeutic range. (From Niebergall et al, 1974, with permission.)

procainamide given with a 1.0-g loading dose on the first day followed by maintainence doses of 0.5-g four times a day. On the second, third, and subsequent days, the procainamide plasma levels did not reach the therapeutic range until after the second dose of drug.

Ideally, drug doses should be given at evenly spaced intervals. However, to improve patient compliance, dosage regimens may be designed to fit with the lifestyle of the patient. For example, the patient is directed to take a drug such as amoxicillin four times a day (QID), before meals and at bedtime, for a systemic infection. This dosage regimen will produce unequal dosage intervals during the day, because the patient takes the drug before breakfast, at 0800 hours (8 AM); before lunch, at 1200 hours (12 noon); before dinner, at 1800 hours (6 PM); and before bedtime, at 2300 hours (11 PM). For these drugs, evenly spaced dosage intervals are not that critical to the effectiveness of the antibiotic as long as the plasma drug concentrations are maintained above the *minimum inhibitory concentration* (MIC) for the microorganism. In some cases, a drug may be given at a larger dose allowing for a longer duration above MIC if fluctuation is less critical. In Augmentin Bid-875 (amoxicillin/clavulanate tablets), the amoxicillin/clavulanate tablet is administered twice daily.

Patient compliance with multiple-dose regimens may be a problem for the patient in following the prescribed dosage regimen. Occasionally, a patient may miss taking the drug dose at the prescribed dosage interval. For drugs with long elimination half-lives (eg, levothyroxine sodium or oral contraceptives), the consequences of one missed dose are minimal, since only a small fraction of drug is lost between daily dosing intervals. The patient should either take the next drug dose as soon as the patient remembers or continue the dosing schedule starting at the next prescribed dosing period. If it is almost time for the next dose, then the skipped dose should not be taken and the regular dosing schedule should be maintained. Generally, the patient should not double the dose of the medication. For specific drug information on missed doses, USP DI II, *Advice for the Patient*, published annually by the United States Pharmacopeia, is a good source of information.

The problems of widely fluctuating plasma drug concentrations may be prevented by using a controlled-release formulation of the drug, or a drug in

the same therapeutic class that has a long elimination half-life. The use of extended-release dosage forms allows for less frequent dosing and prevents undermedication between the last evening dose and the first morning dose. Extended-release drug products may improve patient compliance by decreasing the number of doses within a 24-hour period that the patient needs to take. Patients generally show better compliance with a twice-a-day (BID) dosage regimen compared to a three-times-a-day (TID) dosage schedule.

CLINICAL EXAMPLE

Bupropion hydrochloride (Wellbutrin) is a noradrenergic/dopaminergic antidepressant. Jefferson et al, 2005, have reviewed the pharmacokinetic properties of bupropion and its various various formulations and clinical applications, the goal of which is optimization of major depressive disorder treatment. Bupropion hydrochloride is available in three oral formulations. The immediate-release (IR) tablet is given three times a day, the sustained-release tablet (Wellbutrin SR) is given twice a day, and the extended-release tablet (Wellbutrin XL) is given once a day.

The total daily dose was 300 mg bupropion HCl. The area under the curve, AUC, for each dose treatment was similar showing that the formulations were bioequivalent based on extent of absorption. The fluctuations between peak and trough levels were greatest for the IR product given three times a day and least for the once-a-day XL product. According to the manufacturer, all three dosage regimens provide equivalent clinical efficacy. The advantage of the extended-release product is that the patient needs only to take the drug once a day. Often, immediate-release drug products are less expensive compared to an extended-release drug product. In this case, the fluctuating plasma drug levels for buproprion IR tablet given three times a day are not a safety issue and the tablet is equally efficacious as the 150-mg SR tablet given twice a day or the 300-mg XL tablet given once a day. The patient may also consider the cost of the medication.

PRACTICE PROBLEMS

1. Patient C.S. is a 35-year-old man weighing 76.6 kg. The patient is to be given multiple IV bolus injections of an antibiotic every 6 hours. The effective concentration of this drug is 15 μg/mL. After the patient is given a single IV dose, the elimination half-life for the drug is determined to be 3.0 hours and the apparent V_D is 196 mL/kg. Determine a multiple IV dose regimen for this drug (assume drug is given every 6 hours).

Solution

$$C_{av}^{\infty} = \frac{FD_0}{V_D k\tau}$$

For IV dose, $F = 1$,

$$D_0 = (15\ \mu g/mL)\left(\frac{0.693}{3\ h}\right)(196\ mL/kg)(6\ h)$$

$$D_0 = 4.07\ mg/kg \text{ every } 6 \text{ hours}$$

Since patient C.S. weighs 76.6 kg, the dose should be as shown:

$$D_0 = (4.07\ mg/kg)(76.6\ kg)$$
$$D_0 = 312\ mg \text{ every } 6 \text{ hours}$$

After the condition of this patient has stabilized, the patient is to be given the drug orally for convenience of drug administration. The objective is to design an oral dosage regimen that will produce the same steady-state blood level as the multiple IV doses. The drug dose will depend on the bioavailability of the drug from the drug product, the desired therapeutic drug level, and the dosage interval chosen. Assume that the antibiotic is 90% bioavailable and that the physician would like to continue oral medication every 6 hours.

The average or steady-state plasma drug level is given by

$$C_{av}^{\infty} = \frac{FD_0}{V_D k\tau}$$

$$D_0 = \frac{(15\ \mu g/mL)(193\ mL/kg)(0.693)(6\ h)}{(0.9)(3\ h)}$$

$$D_0 = 454\ mg/kg$$

Because patient C.S. weighs 76.6 kg, he should be given the following dose:

$$D_0 = (4.54\ mg/kg)(76.6\ kg)$$
$$D_0 = 348\ mg \text{ every } 6 \text{ hours}$$

For drugs with equal absorption but slower absorption rates (F is the same but k_a is smaller), the initial dosing period may show a lower blood level; however, the steady-state blood level will be unchanged.

2. In practice, drug products are usually commercially available in certain specified strengths. Using the information provided in the preceding problem, assume that the antibiotic is available in 125-, 250-, and 500-mg tablets. Therefore, the pharmacist or prescriber must now decide which tablets are to be given to the patient. In this case, it may be possible to give the patient 375 mg (eg, one 125-mg tablet and one 250-mg tablet) every 6 hours. However, the C_{av}^{∞} should be calculated to determine if the plasma level is approaching a toxic value. Alternatively, a new dosage interval might be appropriate for the patient. It is very important to design the dosage interval and the dose to be as simple as possible, so that the patient will not be confused and will be able to comply with the medication program properly.
   a. What is the new C_{av}^{∞} if the patient is given 375 mg every 6 hours?

Solution

$$C_{av}^{\infty} = \frac{(0.9)(375{,}000)(3)}{(196)(76.6)(6)(0.693)}$$

$$C_{av}^{\infty} = 16.2\ \mu g/mL$$

Because the therapeutic objective was to achieve a minimum effective concentration (MEC) of 15 μg/mL, a value of 16.2 μg/mL is reasonable.

   b. The patient has difficulty in distinguishing tablets of different strengths. Can the patient take a 500-mg dose (eg, two 250-mg tablets)?

Solution

The dosage interval (τ) for the 500-mg tablet would have to be calculated as follows:

$$\tau = \frac{(0.9)(500{,}000)(3)}{(196)(76.6)(15)(0.693)}$$

$$\tau = 8.63\ h$$

   c. A dosage interval of 8.63 hours is difficult to remember. Is a dosage regimen of 500 mg every 8 hours reasonable?

Solution

$$C_{av}^{\infty} = \frac{(0.9)(500{,}000)(3)}{(196)(76.6)(8)(0.693)}$$

$$C_{av}^{\infty} = 16.2\ \mu g/mL$$

Notice that a larger dose is necessary if the drug is given at longer intervals.

In designing a dosage regimen, one should consider a regimen that is practical and convenient for the patient. For example, for good compliance, the dosage interval should be spaced conveniently for the patient. In addition, one should consider the commercially available dosage strengths of the prescribed drug product.

The use of Equation 9.17 to estimate a dosage regimen initially has wide utility. The C_{av}^{∞} is equal to the dosing rate divided by the total body clearance of the drug in the patient:

$$C_{av}^{\infty} = \frac{FD_0}{\tau}\frac{1}{Cl_T} \qquad (9.47)$$

where FD_0/τ is equal to the dosing rate R, and $1/Cl_T$ is equal to $1/kV_D$.

In designing dosage regimens, the dosing rate D_0/τ is adjusted for the patient's drug clearance to obtain the desired C_{av}^{∞}. For an IV infusion, the zero-order rate of infusion (R) is used to obtain the desired steady-state plasma drug concentration C_{SS}. If R is substituted for FD_0/τ in Equation 9.47, then the following equation for estimating C_{SS} after an IV infusion is obtained:

$$C_{ss} = \frac{R}{Cl_T} \qquad (9.48)$$

From Equations 9.47 and 9.48, all dosage schedules having the same dosing rate D_0/τ, or R, will have the same C_{av}^{∞} or C_{SS}, whether the drug is given by multiple doses or by IV infusion. For example, dosage schedules of 100 mg every 4 hours, 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours will yield the same C_{av}^{∞} in the patient. An IV infusion rate of 25 mg/h in the same patient will give a C_{SS} equal to the C_{av}^{∞} obtained with the multiple-dose schedule (see Fig. 9-3; Table 9-6).

TABLE 9-6 Effect of Dosing Schedule on Predicted Steady-State Plasma Drug Concentrations[a]

Dosing Schedule			Steady-State Drug Concentration (μg/mL)		
Dose (mg)	1 (h)	Dosing Rate, D_0/τ (mg/h)	C^{∞}_{max}	C^{∞}_{av}	C^{∞}_{min}
—	—	25[b]	14.5	14.5	14.5
100	4	25	16.2	14.5	11.6
200	8	25	20.2	14.5	7.81
300	12	25	25.3	14.5	5.03
600	24	25	44.1	14.5	1.12
400	8	50	40.4	28.9	15.6
600	8	75	60.6	43.4	23.4

[a]Drug has an elimination half-life of 4 hours and an apparent V_D of 10 L.

[b]Drug given by IV infusion. The first-order absorption rate constant k_a is 1.2 h^{-1} and the drug follows a one-compartment open model.

Frequently Asked Questions

▶ *Why is the steady-state peak plasma drug concentration measured sometime after an IV dose is given in a clinical situation?*

▶ *Why is the C_{min} value at steady state less variable than the C_{max} value at steady state?*

▶ *Is it possible to take a single blood sample to measure the C_{av} value at steady state?*

CHAPTER SUMMARY

The purpose of giving a loading dose is to achieve desired (therapeutic) plasma concentrations as quickly as possible. For a drug with long elimination half-life, it may take a long time (several half-lives) to achieve steady-state levels. The loading dose must be calculated appropriately based on pharmacokinetic parameters to avoid overdosing. When several doses are administered for a drug with linear kinetics, drug accumulation may occur according to the principle of superposition. Superposition allows the derivation of equations that predict the plasma drug peak and trough concentrations of a drug at steady state and the theoretical drug concentrations at any time after the dose is given. The principle of superposition is used to examine the effect of an early, late, or missing dose on steady-state drug concentration.

C^{∞}_{max}, C^{∞}_{min}, and C^{∞}_{av} are useful parameters for monitoring the safety and efficacy of a drug during multiple dosing. A clinical example of multiple dosing using short, intermittent intravenous infusions has been applied to the aminoglycosides and is based on pharmacokinetics and clinical factors for safer dosing. The index for measuring drug accumulation during multiple dosing, R, is related to the dosing interval and the half-life of the drug, but not the dose. This parameter compares the steady-state concentration with drug concentration after the initial dose. The plasma concentration at any time during an oral or extravascular multiple-dose regimen, for a one-compartment model and constant doses and dose interval, is dependent on n = number of doses, τ = dosage interval, F = fraction of dose absorbed, and t = time after administration of n doses.

$$C_p = \frac{Fk_aD_0}{V_D(k-k_a)}\left[\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_a\tau} - \left(\frac{1-e^{-nk_a\tau}}{1-e^{-k\tau}}\right)e^{-kt}\right]$$

The trough steady-state concentration after multiple oral dosing is

$$C_{\text{min}}^{\infty} = \frac{k_a F D_0}{V_D(k_a - k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

The relationship between average steady-state concentration, the AUC, and dosing interval is

$$C_{\text{av}}^{\infty} = \frac{\int_0^{\infty} C_p\, dt}{\tau} = \frac{[\text{AUC}]_0^{\infty}}{\tau}$$

This parameter is a good measure of drug exposure.

LEARNING QUESTIONS

1. Gentamicin has an average elimination half-life of approximately 2 hours and an apparent volume of distribution of 20% of body weight. It is necessary to give gentamicin, 1 mg/kg every 8 hours by multiple IV injections, to a 50-kg woman with normal renal function. Calculate **(a)** C_{max}, **(b)** C_{min}, and **(c)** C_{av}^{∞}.
2. A physician wants to give theophylline to a young male asthmatic patient (age 29 years, 80 kg). According to the literature, the elimination half-life for theophylline is 5 hours and the apparent V_D is equal to 50% of the body weight. The plasma level of theophylline required to provide adequate airway ventilation is approximately 10 μg/mL.
   a. The physician wants the patient to take medication every 6 hours around the clock. What dose of theophylline would you recommend (assume theophylline is 100% bioavailable)?
   b. If you were to find that theophylline is available to you only in 225-mg capsules, what dosage regimen would you recommend?
3. What pharmacokinetic parameter is most important in determining the time at which the steady-state plasma drug level (C_{av}^{∞}) is reached?
4. Name two ways in which the fluctuations of plasma concentrations (between C_{max}^{∞} and C_{min}^{∞}) can be minimized for a person on a multiple-dose drug regimen without altering the C_{av}^{∞}.
5. What is the purpose of giving a loading dose?
6. What is the loading dose for an antibiotic (k = 0.23 h^{-1}) with a maintenance dose of 200 mg every 3 hours?
7. What is the main advantage of giving a potent drug by IV infusion as opposed to multiple IV injections?
8. A drug has an elimination half-life of 2 hours and a volume of distribution of 40 L. The drug is given at a dose of 200 mg every 4 hours by multiple IV bolus injections. Predict the plasma drug concentration at 1 hour after the third dose.
9. The elimination half-life of an antibiotic is 3 hours and the apparent volume of distribution is 20% of the body weight. The therapeutic window for this drug is from 2 to 10 μg/mL. Adverse toxicity is often observed at drug concentrations above 15 μg/mL. The drug will be given by multiple IV bolus injections.
   a. Calculate the dose for an adult male patient (68 years old, 82 kg) with normal renal function to be given every 8 hours.
   b. Calculate the anticipated C_{max}^{∞} and C_{min}^{∞} values.
   c. Calculate the C_{av}^{∞} value.
   d. Comment on the adequacy of your dosage regimen.
10. Tetracycline hydrochloride (Achromycin V, Lederle) is prescribed for a young adult male patient (28 years old, 78 kg) suffering from gonorrhea. According to the literature, tetracycline HCl is 77% orally absorbed, is 65% bound to plasma proteins, has an apparent volume of distribution of 0.5 L/kg, has an elimination half-life of 10.6 hours, and is 58% excreted unchanged in the urine. The minimum inhibitory drug concentration (MIC) for gonorrhea is 25–30 μg/mL.
    a. Calculate an *exact* maintenance dose for this patient to be given every 6 hours around the clock.
    b. Achromycin V is available in 250- and 500-mg capsules. How many capsules (state dose) should the patient take every 6 hours?
    c. What loading dose using the above capsules would you recommend for this patient?

11. The body clearance of sumatriptan (Imitrex) is 250 mL/min. The drug is about 14% bioavailable. What would be the average plasma drug concentration after 5 doses of 100 mg PO every 8 hours in a patient? (Assume steady state was reached.)

12. Cefotaxime has a volume of distribution of 0.17 L/kg and an elimination half-life of 1.5 hours. What is the peak plasma drug concentration in a patient weighing 75 kg after receiving 1 g IV of the drug 3 times daily for 3 days?

ANSWERS

Frequently Asked Questions

*Is the drug accumulation index (*R*) applicable to any drug given by multiple doses or only to drugs that are eliminated slowly from the body?*

- *Accumulation index*, R, is a ratio that indicates steady-state drug concentration to the drug concentration after the first dose. The accumulation index does not measure the absolute size of overdosing; it measures the amount of drug cumulation that can occur due to frequent drug administration. Factors that affect R are the elimination rate constant, k, and the dosing interval, τ. If the first dose is not chosen appropriately, the steady-state level may still be incorrect. Therefore, the first dose and the dosing interval must be determined correctly to avoid any significant drug accumulation. The accumulation index is a good indication of accumulation due to frequent drug dosing, applicable to any drug, regardless of whether the drug is bound to tissues.

What are the advantages/disadvantages for giving a drug by constant IV infusion, intermittent IV infusion, or multiple IV bolus injections? What drugs would most likely be given by each route of administration? Why?

- Some of the advantages of administering a drug by constant IV infusion include the following: (1) A drug may be infused continuously for many hours without disturbing the patient. (2) Constant infusion provides a stable blood drug level for drugs that have a narrow therapeutic index. (3) Some drugs are better tolerated when infused slowly. (4) Some drugs may be infused simultaneously with electrolytes or other infusion media in an acute-care setting. Disadvantages of administering a drug by constant IV infusion include the following: (1) Some drugs are more suitable to be administered as an IV bolus injection. For example, some reports show that an aminoglycoside given once daily resulted in fewer side effects compared with dividing the dose into two or three doses daily. Due to drug accumulation in the kidney and adverse toxicity, aminoglycosides are generally not given by prolonged IV infusions. In contrast, a prolonged period of low drug level for penicillins and tetracyclines may not be so efficacious and may result in a longer cure time for an infection. The pharmacodynamics of the individual drug must be studied to determine the best course of action. (2) Drugs such as nitroglycerin are less likely to produce tolerance when administered intermittently versus continuously.

Why is the steady-state peak plasma drug concentration often measured sometime after an IV dose is given in a clinical situation?

- After an IV bolus drug injection, the drug is well distributed within a few minutes. In practice, however, an IV bolus dose may be administered slowly over several minutes or the drug may have a slow distribution phase. Therefore, clinicians often prefer to take a blood sample 15 minutes or 30 minutes after IV bolus injection and refer to that drug concentration as the peak concentration. In some cases, a blood sample is taken an hour later to avoid the fluctuating concentration in the distributive phase. The error due to changing sampling time can be large for a drug with a short elimination half-life.

Is a loading dose always necessary when placing a patient on a multiple-dose regimen? What are the determining factors?

- A loading or priming dose is used to rapidly raise the plasma drug concentration to therapeutic drug

levels to obtain a more rapid pharmacodynamic response. In addition, the loading dose along with the maintenance dose allows the drug to reach steady-state concentration quickly, particularly for drugs with long elimination half-lives.

An alternative way of explaining the loading dose is based on clearance. After multiple IV dosing, the maintenance dose required is based on Cl, C_{ss}, and τ.

$$C_{ss} = \frac{\text{Dose}}{\tau Cl}$$

$$\text{Dose} = C_{ss}\tau Cl$$

If C_{ss} and τ are fixed, a drug with a smaller clearance requires a smaller maintenance dose. In practice, the dosing interval is adjustable and may be longer for drugs with a small Cl if the drug does not need to be dosed frequently. The steady-state drug level is generally determined by the desired therapeutic drug.

Does a loading dose significantly affect the steady-state concentration of a drug given by a constant multiple-dose regimen?

- The loading dose will affect only the initial drug concentrations in the body. Steady-state drug levels are obtained after several elimination half-lives (eg, $4.32t_{1/2}$ for 95% steady-state level). Only 5% of the drug contributed by the loading dose will remain at 95% steady state. At 99% steady-state level, only 1% of the loading dose will remain.

Learning Questions

1. $V_D = 0.20(50\text{ kg}) = 10{,}000\text{ mL}$

a. $D_{max} = \dfrac{D_0}{1-f} = \dfrac{50\text{ mg}}{1-e^{-(0.693/2)(8)}} = 53.3\text{ mg}$

$$C_{max} = \frac{D_{max}}{V_D} = \frac{53.3\text{ mg}}{10{,}000\text{ mL}} = 5.33\ \mu\text{g/mL}$$

b. $D_{min} = 53.3 - 50 = 3.3\text{ mg}$

$$C_{min} = \frac{3.3\text{ mg}}{10{,}000\text{ mL}} = 0.33\ \mu\text{g/mL}$$

c. $C_{av}^{\infty} = \dfrac{FD_0 1.44t_{1/2}}{V_D\tau}$

$$= \frac{(50)(1.44)(2)}{(10{,}000)(8)} = 1.8\ \mu\text{g/mL}$$

2. a. $D_0 = \dfrac{C_{av}^{\infty} V_D \tau}{1.44t_{1/2}}$

$$= \frac{(10)(40{,}000)(6)}{(1.44)(5)}$$

$$= 333\text{ mg every 6 h}$$

b. $\tau = \dfrac{FD_0 1.44t_{1/2}}{V_D C_{av}^{\infty}}$

$$= \frac{(225{,}000)(1.44)(5)}{(40{,}000)(10)} = 4.05\text{ h}$$

6. Dose the patient with 200 mg every 3 hours.

$$D_L = \frac{D_0}{1-e^{-k\tau}} = \frac{200}{1-e^{-(0.23)(3)}} = 400\text{ mg}$$

Notice that D_L is twice the maintenance dose, because the drug is given at a dosage interval equal approximately to the $t_{1/2}$ of 3 hours.

8. The plasma drug concentration, C_p, may be calculated at any time after n doses by Equation 9.21 and proper substitution.

$$C_p = \frac{D_0}{V_D}\left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right)e^{-kt}$$

$$C_p = \frac{200}{40}\left(\frac{1-e^{-(3)(0.347)(4)}}{1-e^{-(0.347)(4)}}\right)e^{-(0.347)(1)}$$

$$= 4.63\text{ mg/L}$$

Alternatively, one may conclude that for a drug whose elimination $t_{1/2}$ is 2 hours, the predicted plasma drug concentration is approximately at steady state after 3 doses or 12 hours. Therefore, the above calculation may be simplified to the following:

$$C_p = \frac{D_0}{V_D}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

$$C_p = \left(\frac{200}{40}\right)\left(\frac{1}{1-e^{-(0.347)(4)}}\right)e^{-(0.347)(1)}$$

$$= 4.71\text{ mg/L}$$

9. $C^{\infty}_{max} = \dfrac{D_0/V_D}{1-e^{-k\tau}}$

where

$V_D = 20\%$ of 82 kg $= (0.2)(82) = 16.4$ L

$k = (0.693/3) = 0.231\ h^{-1}$

$D_0 = V_D C^{\infty}_{max}(1-e^{-k\tau}) = (16.4)(10)(1-e^{-(0.231)(8)})$

a. $D_0 = 138.16$ mg to be given every 8 hours

b. $C^{\infty}_{min} = C^{\infty}_{max}(e^{-k\tau}) = (10)(e^{-(0.231)(8)})$

$= 1.58$ mg/L

c. $C^{\infty}_{av} = \dfrac{D_0}{kV_D\tau} = \dfrac{138.16}{(0.231)(16.4)(8)}$

$= 4.56$ mg/L

d. In the above dosage regimen, the C^{∞}_{min} of 1.59 mg/L is below the desired C^{∞}_{min} of 2 mg/L. Alternatively, the dosage interval, τ, could be changed to 6 hours.

$D_0 = V_D C^{\infty}_{max}(1-e^{-k\tau}) = (16.4)(10)(1-e^{-(0.231)(6)})$

$D_0 = 123$ mg to be given every 6 h

$C^{\infty}_{min} = C^{\infty}_{max}(e^{-k\tau}) = (10)(e^{-(0.231)(6)}) = 2.5$ mg/L

$C^{\infty}_{av} = \dfrac{D_0}{kV_D\tau} = \dfrac{123}{(0.231)(16.4)(6)} = 5.41$ mg/L

10. a. $C^{\infty}_{av} = \dfrac{FD_0}{kV_D\tau}$

Let $C^{\infty}_{av} = 27.5$ mg/L

$D_0 = \dfrac{C^{\infty}_{av}kV_D\tau}{F} = \dfrac{(27.5)(0.693/10.6)(0.5)(78)(6)}{0.77}$

$= 546.3$ mg

$D_0 = 546.3$ mg every 6 h

b. If a 500-mg capsule is given every 6 hours,

$C^{\infty}_{av} = \dfrac{FD_0}{kV_D\tau} = \dfrac{(0.77)(500)}{(0.693/10.6)(0.5)(78)(6)}$

$= 25.2$ mg/L

c. $D_L = \dfrac{D_M}{1-e^{-k\tau}} = \dfrac{500}{1-e^{(0.654)(6)}} = 1543$ mg

$D_L = 3 \times 500$ mg capsules $= 1500$ mg

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