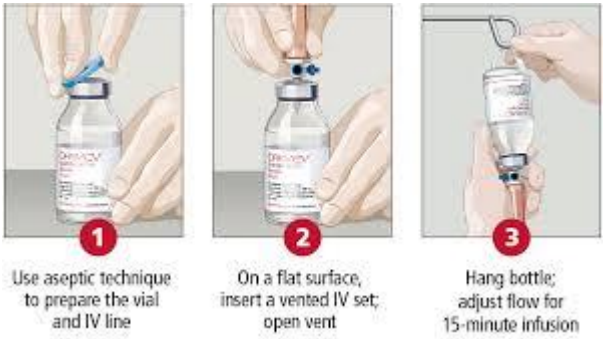


Chapter 5
INTRAVENOUS INFUSION: INTRODUCTION







Drugs may be administered to patients by one of several routes, including oral, topical, or parenteral routes of administration. Examples of parenteral routes of administration include intravenous, subcutaneous, and intramuscular.

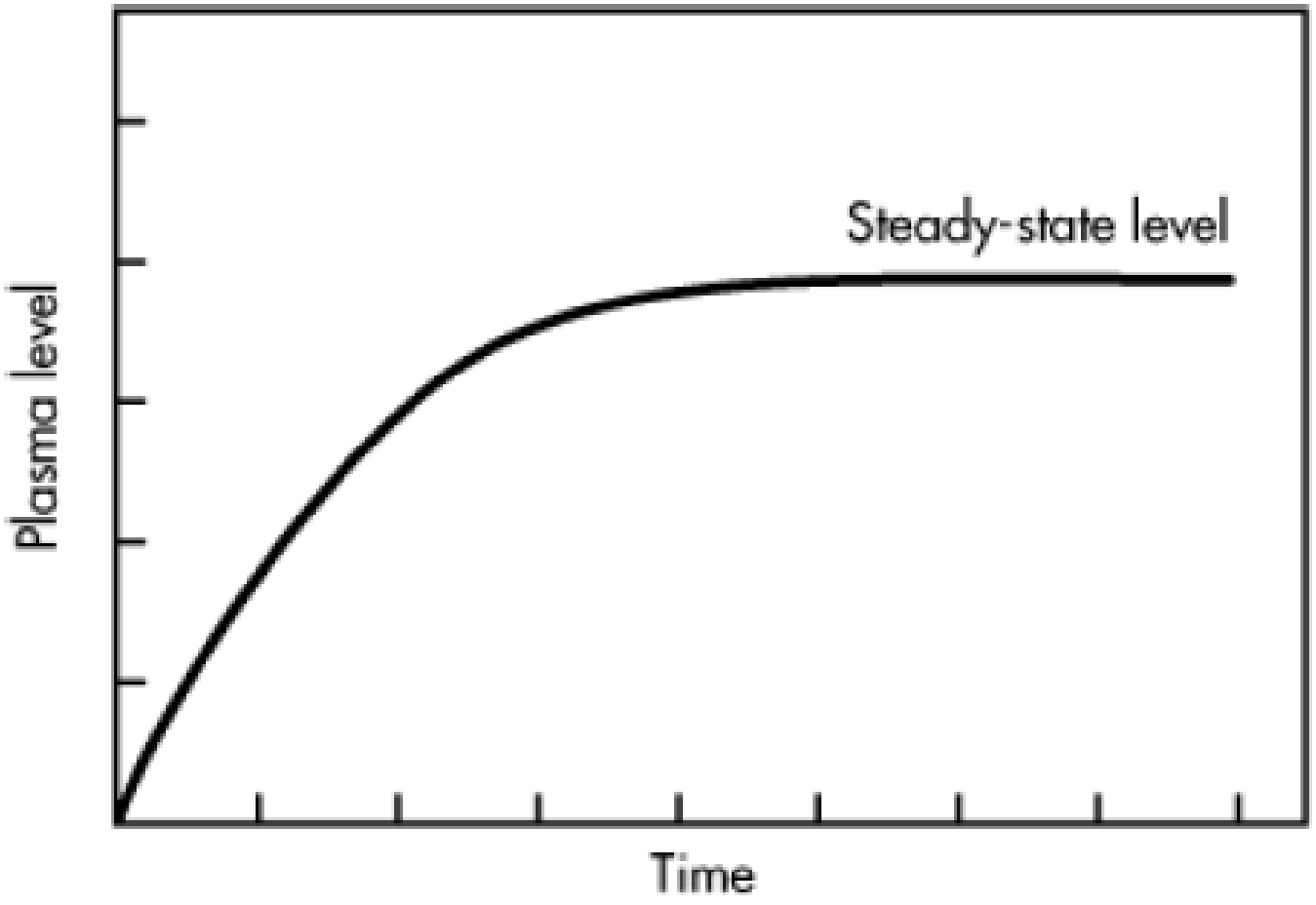
Intravenous (IV) drug solutions may be given either as a bolus dose (injected all at once) or infused slowly through a vein into the plasma at a constant or zero-order rate. **The main advantage for giving a drug by IV infusion is that IV infusion allows precise control of plasma drug concentrations to fit the individual needs of the patient**. For drugs with a narrow therapeutic window (eg, heparin), IV infusion maintains an effective constant plasma drug concentration by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug concentration.

Moreover, the IV infusion of drugs, such as antibiotics, may be given with IV fluids that include electrolytes and nutrients. Furthermore, the duration of drug therapy may be maintained or terminated as needed using IV infusion.

Because no drug was present in the body at zero time, drug level rises from zero drug concentration and gradually becomes constant when a *plateau* or *steady-state* drug concentration is reached. At steady state, the rate of drug leaving the body is equal to the rate of drug (infusion rate) entering the body. Therefore, a**t steady state, the rate of change in the plasma drug concentration, *dC* p/*dt* = 0, and**

$$\underset{\text{(infusion rate)}}{\text{Rate of drug input}} = \underset{\text{(elimination rate)}}{\text{rate of drug output}}$$

Figure 5-1.



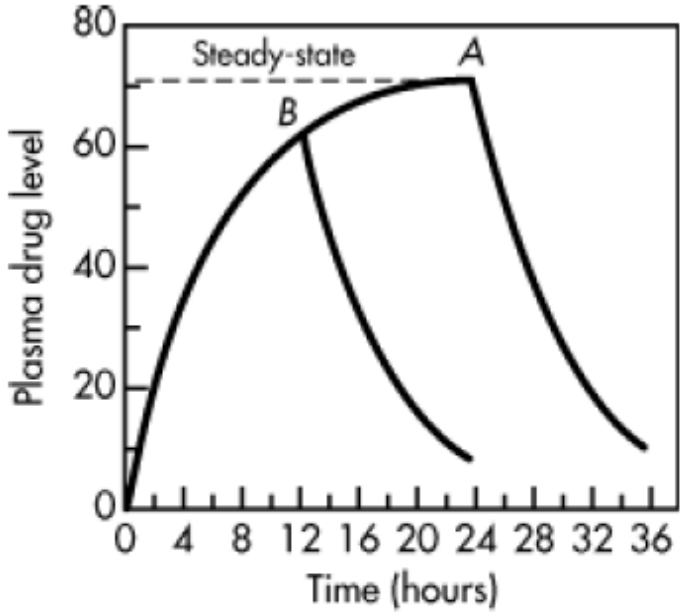
Based on this simple mass balance relationship, a pharmacokinetic equation for infusion may be derived depending on whether the drug follows one- or two-compartment kinetics.

ONE-COMPARTMENT MODEL DRUGS

The pharmacokinetics of a drug given by constant IV infusion **follows a zero-order input** process in which the drug is infused directly into the systemic blood circulation**. Equation 5.2, below, gives the plasma drug concentration at any time during the IV infusion, where *t* is the time for infusion.**

For most drugs, elimination of drug from the plasma is a first-order process. Therefore, in this one-compartment model, the infused drug follows zero-order input and first-order output. **The change in the amount of drug in the body at any time (*dD* B/*dt*) during the infusion is the rate of input minus the rate of output.**

Figure 5-2.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

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Plasma drug concentrations versus time profiles after IV infusion. IV infusion is stopped at steady state (*A*) or prior to steady state (*B*). In both cases, plasma drug concentrations decline exponentially (first order) according to a similar slope.

$$\frac{dD_B}{dt} = R - kD_B \qquad (5.1)$$

where *D*B is the amount of drug in the body, *R* is the infusion rate (zero order), and *k* is the elimination rate constant (first order).
Integration of Equation 5.1 and substitution of *D*B = *C*p *V*D gives

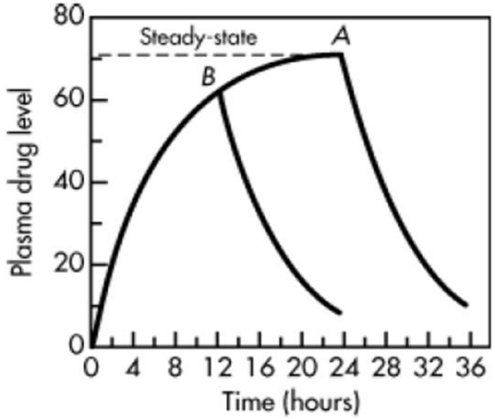
$$C_P = \frac{R}{V_D k}(1 - e^{-kt}) \qquad (5.2)$$

As the drug is infused, the value for time (*t*) increases in Equation 5.2. **At infinite time, *t* = ∞ , e^{-kt} approaches zero, and Equation 5.2 reduces to Equation 5.4.**

$$C_P = \frac{R}{V_D k}(1 - e^{-\infty}) \qquad (5.3)$$

$$C_{SS} = \frac{R}{V_D k} \qquad (5.4)$$

$$C_{SS} = \frac{R}{V_D k} = \frac{R}{Cl} \qquad (5.5)$$



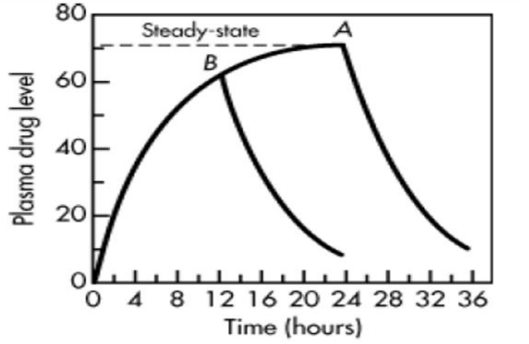
Steady-State Drug Concentration (*C* SS) and Time Needed to Reach *C* SS

As stated earlier, the rate of drug leaving the body is equal to the rate of drug entering the body (infusion rate) at steady state. In other words, there is no *net* change in the amount of drug in the body, *D*B, as a function of time during steady state. Drug elimination occurs according to first-order elimination rate.

Whenever the infusion stops either at steady state or before steady state is reached, the log drug concentration declines according to first-order kinetics with **the slope of the elimination curve equal to - *k*/2.3**. **If the infusion is stopped before steady state is reached, the slope of the elimination curve remains the same**.

Mathematically, the time to reach true steady-state drug concentration, *C* SS, would take an infinite time. The time required to reach the steady state drug concentration in the plasma **is dependent on the elimination rate constant of the drug for a constant volume of distribution, as shown in Equation 5.4. Because drug elimination is exponential (first order), the plasma drug concentration becomes asymptotic to the theoretical steady-state plasma drug concentration. For a zero-order elimination process, if the rate of input is greater than the rate of elimination, plasma drug concentration will keep increasing and no steady state will be reached. This is a potentially dangerous situation that will occur when saturation of metabolic process occurs.**

$$C_{SS} = \frac{R}{V_D k} \qquad (5.4)$$



During the IV infusion, the drug concentration increases in the plasma and the rate of drug elimination increases because rate of elimination is concentration dependent (ie, rate of drug elimination = *k C*p). ***C*p keeps increasing until steady state is reached, at which time the rate of drug input (IV infusion rate) equals the rate of drug output (elimination rate). The resulting plasma drug concentration at steady state (*C* SS) is related to the rate of infusion and inversely related to the body clearance of the drug, as shown in Equation 5.5.**

$$C_{SS} = \frac{R}{V_D k} = \frac{R}{Cl} \qquad (5.5)$$

In clinical practice, **the activity** of the drug will be observed when the drug concentration is close to the desired plasma drug concentration, which is usually **the *target* or *desired* steady-state** drug concentration.

The time to reach 90%, 95%, and 99% of the steady-state drug concentration, *C* SS, may be calculated.

For therapeutic purposes, the time for the plasma drug concentration to reach more than 95% of the steady state drug concentration in the plasma is often estimated. As detailed in , after IV infusion of the drug for 5 half-lives, the plasma drug concentration will be between 95% (4.32*t* 1/2) and 99% (6.65*t* 1/2) of the steady state drug concentration. Thus, the time for a drug whose *t*1/2 is 6 hours to reach at least 95% of the steady state plasma drug concentration will be 5 *t*1/2, or 5 x 6 hours = 30 hours.

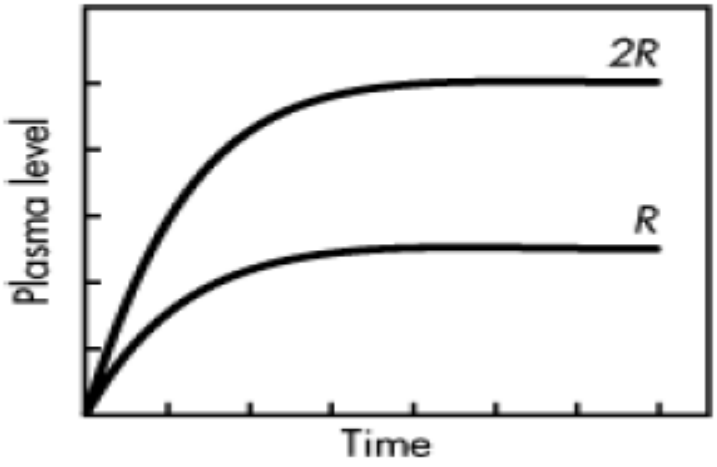
Table 5.1 Number of $t_{1/2}$ to Reach a Fraction of C_{SS}

Percent of C_{SS} Reached[a]	Number of Half-Lives
90	3.32
95	4.32
99	6.65

[a]C_{ss} is the steady-state drug concentration in plasma.

An increase in the infusion rate will not shorten the time to reach the steady-state drug concentration. If the drug is given at a more rapid infusion rate, a higher steady-state drug level will be obtained, but the time to reach steady state is the same. This equation may also be obtained with the following approach. At steady state, the rate of infusion equals the rate of elimination. Therefore, the rate of change in the plasma drug concentration is equal to zero.

Figure 5-3.



Plasma level-time curve for IV infusions given at rates of *R* and 2*R*, respectively.

$$\frac{dC_P}{dt} = 0 \qquad \frac{dD_B}{dt} = R - kD_B \qquad (5.1)$$

$$\frac{dC_P}{dt} = \frac{R}{V_D} - kC_P = 0$$

$$(Rate_{in}) - (rate_{out}) = 0$$

$$\frac{R}{V_D} = kC_P$$

$$C_{SS} = \frac{R}{V_D k} \qquad (5.6)$$

Equation 5.6 shows that the steady-state concentration (*C* SS) is dependent on the volume of distribution, the elimination rate constant, and the infusion rate. Altering any one of these factors can affect steady-state concentration

$$C_{SS} = \frac{R}{V_D k}$$

and 99% steady-state level is

$$99\% \ \frac{R}{V_D k}$$

Substituting into Equation 5.2 for C_p, we can find the time needed to reach steady state by solving for t.

$$99\% \ \frac{R}{V_D k} = \frac{R}{V_D k}(1 - e^{-kt})$$

$$99\% = 1 - e^{-kt}$$

$$e^{-kt} = 1\%$$

$$C_P = \frac{R}{V_D k}(1 - e^{-kt}) \qquad (5.2)$$

Take the natural logarithm on both sides:

$$-kt = \ln 0.01$$

$$t_{99\%SS} = \frac{\ln 0.01}{-k} = \frac{-4.61}{-k} = \frac{4.61}{k}$$

substituting $(0.693/t_{1/2})$ for k,

$$t_{99\%SS} = \frac{4.61}{(0.693/t_{1/2})} = \frac{4.61}{0.693} t_{1/2}$$

$$t_{99\%SS} = 6.65\, t_{1/2}$$

Notice that in the equation directly above, the time needed to reach steady state is not dependent on the rate of infusion, but only on the elimination half-life. Using similar calculations, the time needed to reach any percentage of the steady-state drug concentration may be obtained.

Intravenous infusion may be used to determine total body clearance if the infusion rate and steady-state level are known, as with Equation 5.6 repeated here:

$$C_{SS} = \frac{R}{V_D k} \qquad (5.6)$$

$$V_D k = \frac{R}{C_{SS}}$$

because total body clearance, Cl_T, is equal to $V_D k$,

$$Cl_T = \frac{R}{C_{SS}} \qquad (5.7)$$

INFUSION METHOD FOR CALCULATING PATIENT ELIMINATION HALFLIFE

The *C*p-versus-time relationship that occurs during an IV infusion (Eq. 5.2) may be used to **calculate *k*, or indirectly the elimination half-life of the drug in a patient.** Some information about the elimination half-life of the drug in the population must be known, and one or two plasma samples must be taken at a known time after infusion. **Knowing the half-life in the general population helps to determine if the sample is taken at steady state in the patient. To simplify calculation, Equation 5.2 is arranged to solve for *k:***

$$C_P = \frac{R}{V_D k}(1-e^{-kt}) \qquad (5.2)$$

Since

$$C_{SS} = \frac{R}{V_D K}$$

Substituting into Equation 5.2;

$$C_P = C_{SS}\,(1-e^{-kt})$$

Rearranging and taking the log on both sides,

$$\log\left(\frac{C_{SS}-C_P}{C_{SS}}\right) = -\frac{kt}{2.3} \quad \text{and} \quad k = \frac{-2.3}{t}\log\left(\frac{C_{SS}-C_P}{C_{SS}}\right) \qquad (5.8)$$

where C_p is the plasma drug concentration taken at time t; C_{SS} is the approximate steady-state plasma drug concentration in the patient.

LOADING DOSE PLUS IV INFUSION: ONE-COMPARTMENT MODEL

The *loading dose*, *D*L, or initial bolus dose of a drug, is used to obtain desired concentrations as rapidly as possible. The concentration of drug in the body for a one-compartment model after an **IV bolus dose** is described by

$$C_1 = C_0 e^{-kt} = \frac{D_L}{V_D} e^{-kt} \qquad (5.9)$$

and concentration by infusion at the rate *R* is

$$C_2 = \frac{R}{V_D k} = (1 - e^{-kt}) \qquad (5.10)$$

Assume that an IV bolus dose *D*L of the drug is given and that an IV infusion is started at the same time. The total concentration *C*p at *t* hours after the start of infusion is *C* 1 + *C* 2, due to the sum contributions of bolus and infusion, or



$$C_P = C_1 + C_2$$

$$C_P = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k}(1 - e^{-kt})$$

$$C_P = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k} - \frac{R}{V_D k} e^{-kt}$$

$$C_P = \frac{R}{V_D k} + \left(\frac{D_L}{V_D} e^{-kt} - \frac{R}{V_D k} e^{-kt} \right) \qquad (5.11)$$

$$C_P = \frac{R}{V_D k} (1 - e^{-\infty}) \qquad (5.3)$$

$$C_{SS} = \frac{R}{V_D k} \qquad (5.4)$$

$$C_{SS} = \frac{R}{V_D k} = \frac{R}{Cl} \qquad (5.5)$$

Let the loading dose (D_L) equal the amount of drug in the body at steady state:

$$D_L = C_{SS} V_D$$

From Equation 5.4, $C_{SS} V_D = R/k$. Therefore,

$$D_L = \frac{R}{k} \qquad (5.12)$$

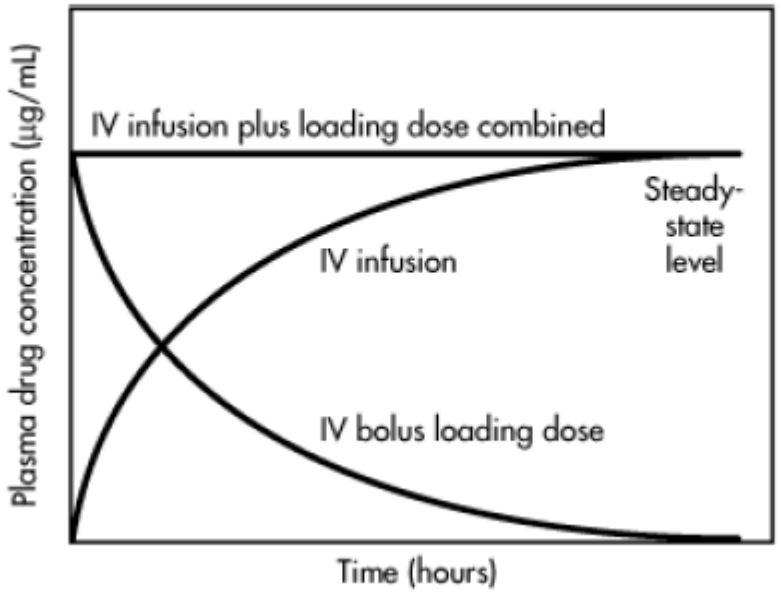
Substituting $D_L = R/k$ in Equation 5.11 makes the expression in parentheses in Equation 5.11 cancel out. Equation 5.11 reduces to Equation 5.13, which is the same expression for C_{SS} or steady-state plasma concentration:

$$C_P = \frac{R}{V_D k} \qquad (5.13)$$

$$C_{SS} = \frac{R}{V_D k} \qquad (5.14)$$

Therefore, **if an IV loading dose of *R/k* is given,** followed by an IV infusion, **steady-state plasma drug concentrations are obtained immediately and maintained**. In this situation, steady state is also achieved in a one-compartment model, since rate in = rate out ($R = dD\ B/dt$).

Figure 5-4.



IV Infusion with loading dose *D*L. The loading dose is given by IV bolus injection at the start of the infusion. Plasma drug concentrations decline exponentially after *D* L whereas they increase exponentially during the infusion. **The resulting plasma drug concentration-versus-time curve is a straight line due to the summation of the two curves.**

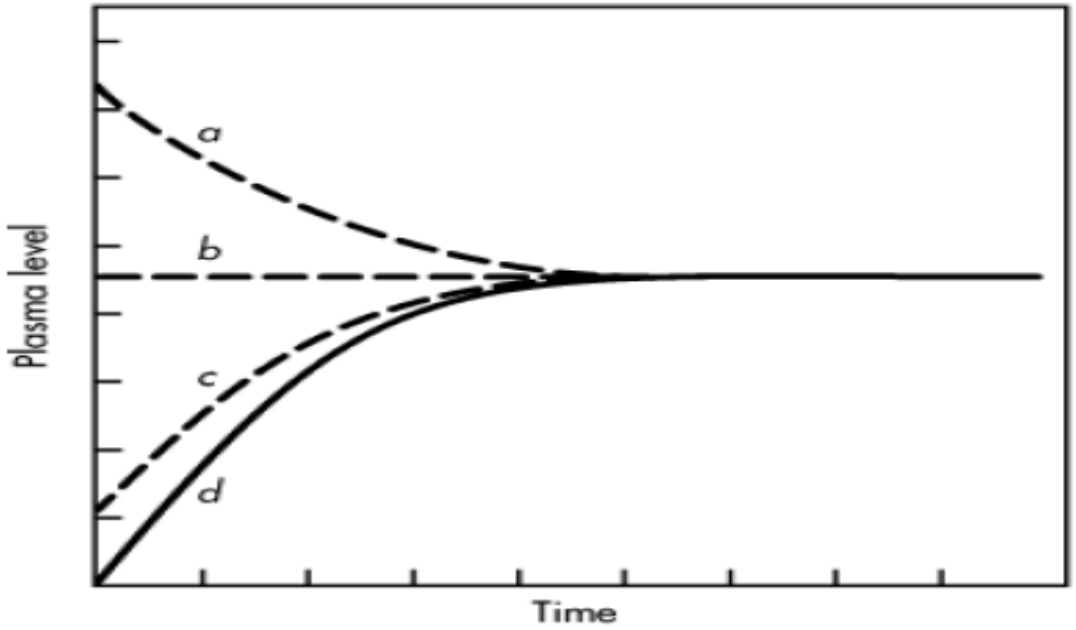
In order to maintain **instant steady-state level** **[(*dC* p/*dt*) = 0], the loading dose should be equal to *R/k*.**

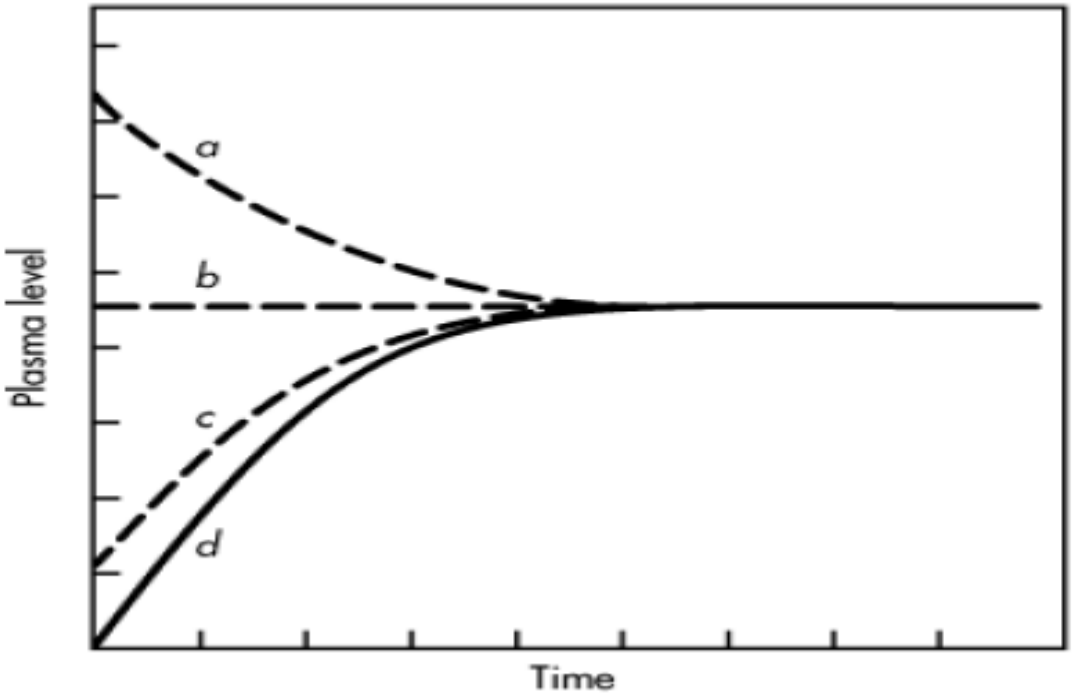
For a one-compartment drug, **if the *D*L and infusion rate are calculated such that *C*0 and *C* SS are the same and both *D*L and infusion are started concurrently, then steady state and *C* SS will be achieved immediately after the loading dose is administered** . Similarly, curve *b* shows the blood level after a single loading dose of *R/k* plus infusion from which the concentration desired at steady state is obtained.

If the *D* L is not equal to *R/k*, then steady state will not occur immediately.

If the loading dose given is larger than *R/k*, the plasma drug concentration takes longer to decline to the concentration desired at steady state (curve *a*).

If the loading dose is lower than *R/k*, the plasma drug concentrations will increase slowly to desired drug levels (curve *c*), but more quickly than without any loading dose.





Intravenous infusion with loading doses *a*, *b*, and *c*. Curve *d* represents an IV infusion without a loading dose.

Another method for the calculation of loading dose *D* L is based on knowledge of the desired steady-state drug concentration *C* SS and the apparent volume of distribution *V*D for the drug, as shown in Equation 5.18.

$$D_L = C_{SS} V_D \qquad (5.18)$$

For many drugs, **the desired *C* SS is reported in the literature as the effective therapeutic drug concentration.**

The *V*D and the elimination half-life are also available for these drugs.

INTRAVENOUS INFUSION OF TWO-COMPARTMENT MODEL DRUGS

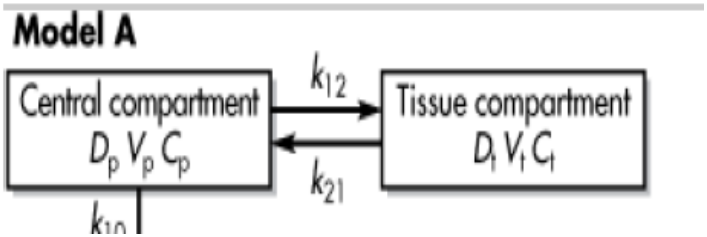
Many drugs given by **IV infusion follow two-compartment kinetics**. **For example, the respective distributions of theophylline and lidocaine in humans are described by the two-compartment model**. With two compartment model drugs, IV infusion requires a **distribution and equilibration of the drug before a stable blood level is reached**. **During a constant IV infusion, drug in the tissue compartment is in distribution equilibrium with the plasma; thus, constant *C* SS levels also result in constant drug concentrations in the tissue**; ie, no *net* change in the amount of drug in the tissue occurs at steady state. Although some clinicians assume that tissue and plasma concentrations are equal when fully equilibrated, kinetic models predict only that the rates of drug transfer into and out of the compartments are equal at steady state. **In other words, drug concentrations in the tissue are also constant, but may differ from plasma concentrations.**

The time needed to reach a steady-state blood level depends entirely on the distribution half-life of the drug.

$$C_p = \frac{R}{V_p k}\left[1 - \left(\frac{k-b}{a-b}\right)e^{-at} - \left(\frac{a-k}{a-b}\right)e^{-bt}\right] \qquad (5.22)$$

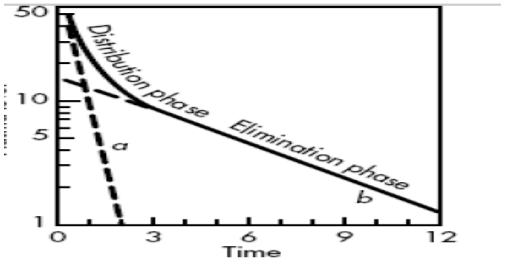
$$C_p = Ae^{-at} + Be^{-bt} \qquad (4.12)$$

By rearranging this equation, the infusion rate for a desired steady-state plasma drug concentration may be calculated



$$A = \frac{D_0(a - k_{21})}{V_p(a - b)} \qquad (4.13)$$

$$B = \frac{D_0(k_{21} - b)}{V_p(a - b)} \qquad (4.14)$$



LOADING DOSE PLUS IV INFUSION: TWO-COMPARTMENT MODEL

Drugs with **long** half-lives require a loading dose to more rapidly attain steady-state plasma drug levels. It is clinically desirable to achieve rapid therapeutic drug levels by using a loading dose. **However, for drugs that follow the two-compartment pharmacokinetic model, the drug distributes slowly into extravascular tissues (compartment 2). Thus, drug equilibrium is not immediate. If a loading dose is given too rapidly, the drug may initially give excessively high concentrations in the plasma (central compartment), which then decreases as drug equilibrium is reached**. **It is not possible to maintain an instantaneous, stable steady-state blood level for a two compartment model drug with a zero-order rate of infusion**. Therefore, a loading dose produces an initial blood level either slightly higher or lower than the steady-state blood level. **To overcome this problem, several IV bolus injections given as short intermittent IV infusions may be used as a method for administering a loading dose to the patient.**

Chapter 8
MULTIPLE-DOSAGE REGIMENS
Introduction

In earlier chapters of this book we have discussed single-dose drug administration. 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 maintain prolonged therapeutic activity, many drugs are given in a multiple-dosage regimen.** The plasma levels of drugs given in multiple doses must be maintained 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. Among these drugs are **antibacterials, cardiotonics, anticonvulsants, and hormones**. 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. Some drugs that have a narrow therapeutic range (eg, digoxin and phenytoin) require definition of 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.**

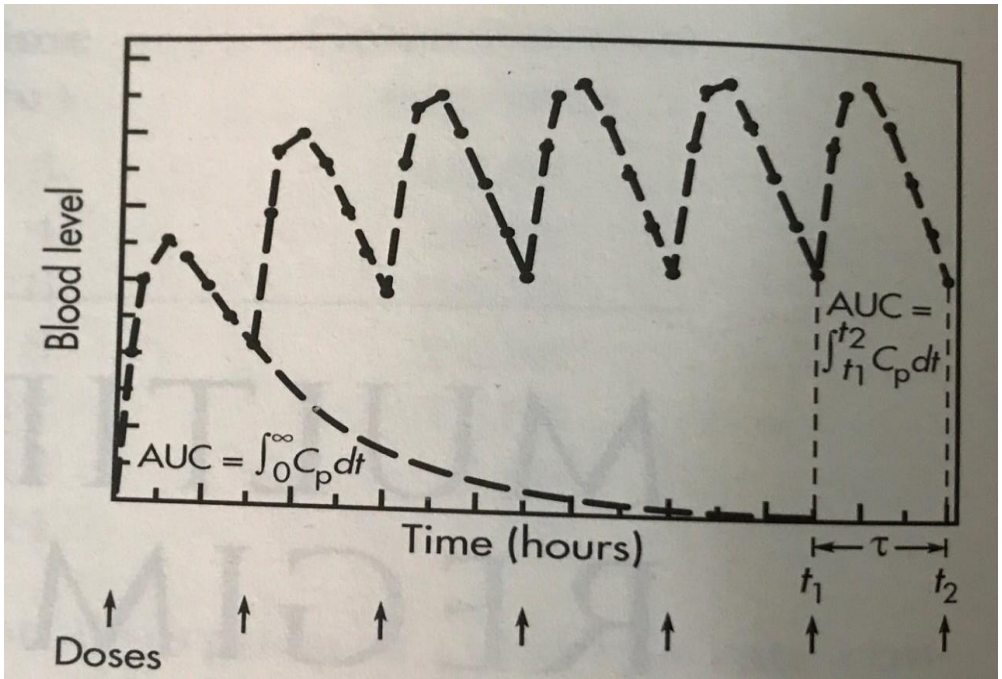
There are two main parameters that can be adjusted in developing a dosage regimen: (1) the size of the drug dose and (2) , the frequency of drug administration (ie, the time interval between doses).

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 , the complete plasma level-time curve or the plasma level may be predicted at any time after the beginning of the dosage regimen.

To calculate **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 AUC ($\int_0^\infty C_p\,dt$) following the administration of a single dose equals the AUC($\int_{t1}^{t2} C_p\,dt$) during a dosing interval at steady state .**

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



The principle of ***superposition*** allows one 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 that the drug is eliminated by first-order kinetics and 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. 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**. As shown in table below. 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.

		Plasma Drug Concentration (μg/mL)						
Dose Number	Time (hr)	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

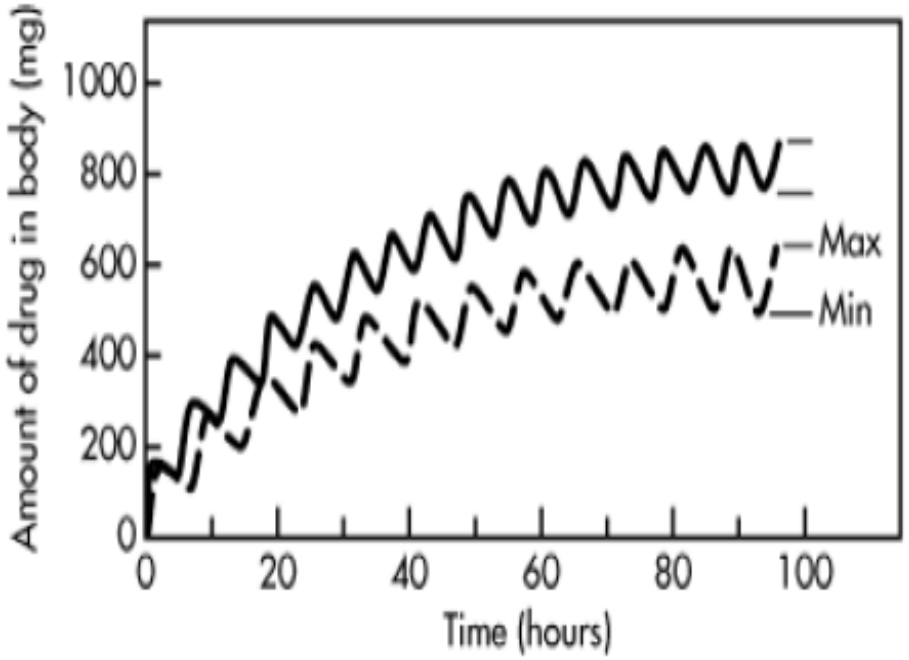
A single oral dose of 350 mg was given and the plasma drug concentrations were measured for 0-24 hr. The same plasma drug concentrations are assumed to occur after doses 2-6. The total plasma drug concentration is the sum of the plasma drug concentrations due to each dose. For this example, V D = 10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

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, 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 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 . **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.

Figure 8-2.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

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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.

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.

1-The C^{∞}_{max} is important in determining drug **safety.** The C^{∞}_{max} should always remain **below the minimum toxic concentration**. **2-**The C^{∞}_{max} 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.

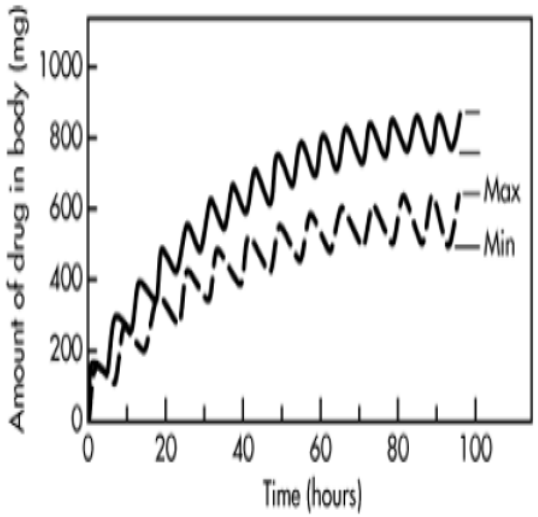
Accumulation is affected by the 1-elimination half-life of the drug and 2-the dosing interval. The index for measuring drug accumulation *R* is

$$R = \frac{(C^{\infty})_{max}}{(C_{n=1})_{max}} \qquad (8.1)$$

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

$$R = \frac{D_0/V_D[1/(1 - e^{-k\tau})]}{D_0/V_D} \qquad (8.2)$$

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

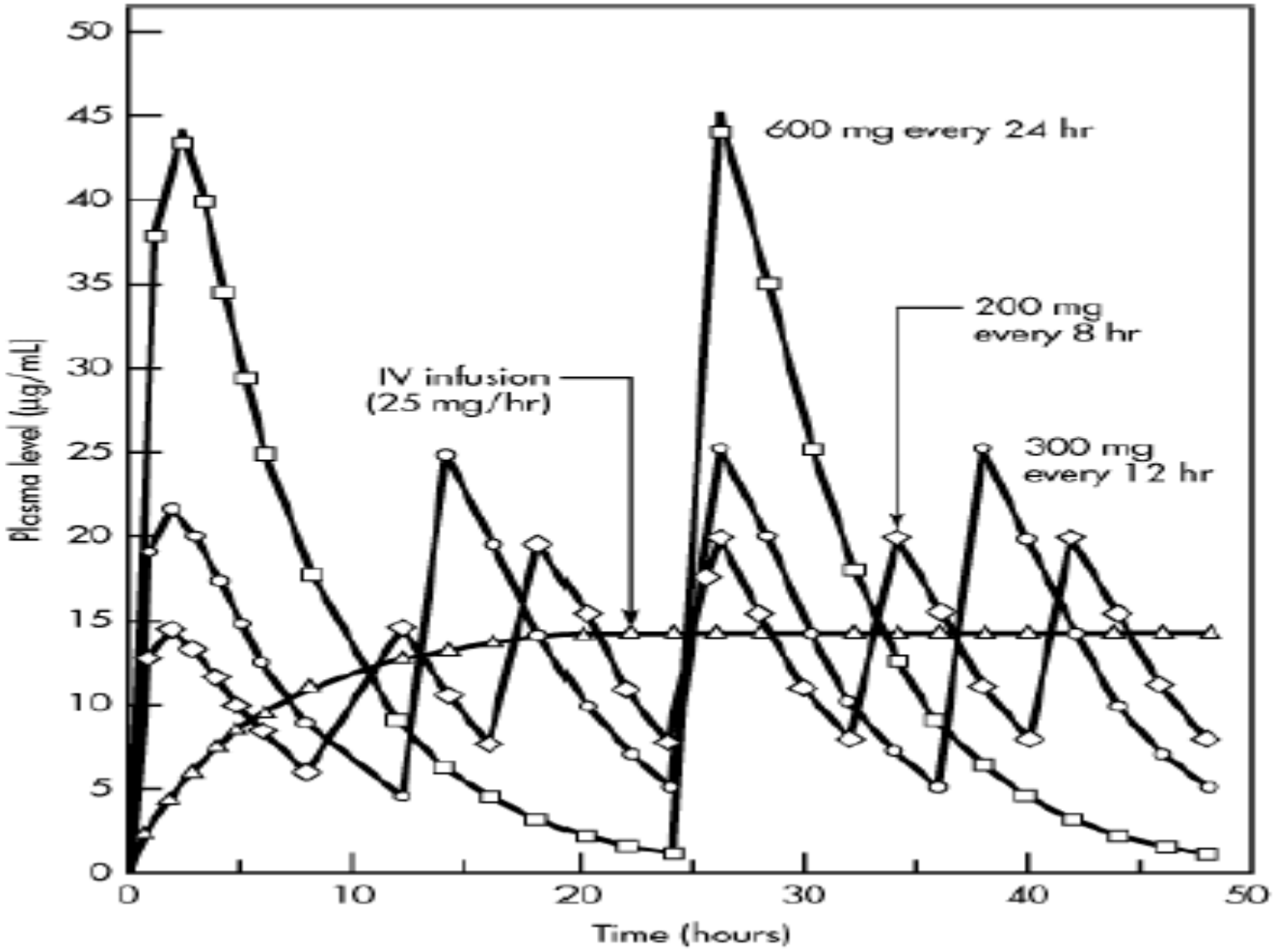


$$R = \frac{1}{1 - e^{-k\tau}}$$

Equation 8.2 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 **1- dose or 2-dosage interval of the drug is altered as shown below , the time required for the drug to reach steady state is the same**, **but the final steady- state plasma level changes proportionately.** Furthermore, if the drug is given at the same dosing rate but as an infusion (eg, 25 mg/hr), the average plasma drug concentrations (C^{∞}_{av}) will be the same but the fluctuations between C^{∞}_{max} and C^{∞}_{min} will vary . **An average steady-state plasma drug concentration is obtained by dividing the area under the curve (AUC) for a dosing period ($\int^{t2}_{t1} C_p\, dt$) by the dosing interval , at steady state.**



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/hr, oral multiple doses are 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours.

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 .**

$$\text{Accumulation } t_{1/2} = t_{1/2}\left(1 + 3.3 \log \frac{k_a}{k_a - k}\right) \qquad (8.3)$$

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 8.3. Thus, Equation 8.3 reduces to

$$\text{Accumulation } t_{1/2} = t_{1/2}\left(1 + 3.3 \log \frac{k_a}{k_a}\right) \qquad (8.4)$$

Because *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 on the elimination *t* 1/2 and not on the dose or dosage interval.

As shown in Equation 8.4, the accumulation *t* 1/2 is directly proportional to the elimination *t* 1/2.

Table 8.2 Effect of Elimination Half-Life and Absorption Rate Constant on Accumulation Half-Life after Oral Administration[a]

Elimination Half-Life (hr)	Elimination Rate Constant (1/hr)	Absorption Rate Constant (1/hr)	Accumulation Half-Life (hr)
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.

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. It should be noted from that at a constant dose size, the shorter the dosage interval, the larger the dosing rate (mg/hr), and the higher the steady-state drug level.

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.

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

If T 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

$$D_B = D_0 e^{-k\tau} \qquad (8.6)$$

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

$$f = \frac{D_B}{D_0} = e^{-k\tau} \qquad (8.7)$$

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

a. The fraction of drug remaining in the body is estimated by Equation 8.7. The concentration of the drug declines to one-half after 3 hours ($t_{1/2}$ = 3 hr), 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 8.7, we must first find the value of *k* from the $t_{1/2}$.

$$f = \frac{D_B}{D_0} = e^{-k\tau} \qquad (8.7)$$

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

The time interval τ is equal to 6 hours. From Equation 8.7,

$$f = e^{-(0.231)(6)}$$
$$f = 0.25$$

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

Number of Doses	Amount of Drug in Body	
	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
âˆ	333	1333

[a] $f = 0.25$.

From 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.

$$D_{\max} - D_{\min} = D_0 \qquad (8.8)$$

In this example,

$$1333 - 333 = 1000 \text{ mg}$$

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

$$D^{\infty}_{\max} = \frac{D_0}{1 - f} \qquad (8.9)$$

Substituting known data, we obtain

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

then, from Equation 8.8,

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

The average amount of drug in the body at steady state, D^{∞}_{av} , can be found by Equation 8.10 or Equation 8.11. *F* is the fraction of dose absorbed. For an IV injection, *F* is equal to 1.0.

$$D^{\infty}_{\text{av}} = \frac{FD_0}{k\tau} \qquad (8.10)$$

$$D^{\infty}_{\text{av}} = \frac{FD_0 1.44 t_{1/2}}{\tau} \qquad (8.11)$$

Equations 8.10 and 8.11 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.**

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:**

$$C_{\max}^{\infty} = \frac{D_{\max}^{\infty}}{V_{\mathrm{D}}} \qquad (8.12)$$

$$C_{\min}^{\infty} = \frac{D_{\min}^{\infty}}{V_{\mathrm{D}}} \qquad (8.13)$$

$$C_{\mathrm{av}}^{\infty} = \frac{D_{\mathrm{av}}^{\infty}}{V_{\mathrm{D}}} \qquad (8.14)$$

$$C_{\max}^{\infty} = \frac{C_{\mathrm{p}}^{0}}{1 - e^{-k\tau}} \qquad (8.15)$$

$$C_{\min}^{\infty} = \frac{C_{\mathrm{p}}^{0} e^{-k\tau}}{1 - e^{-k\tau}} \qquad (8.16)$$

$$C_{\mathrm{av}}^{\infty} = \frac{FD_0}{V_{\mathrm{D}} k\tau} \qquad (8.17)$$

$$D_{\mathrm{av}}^{\infty} = \frac{FD_0}{k\tau} \qquad (8.10)$$

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 the AUC $\int^{t2}_{t1} C_p\, dt$ for a dosage interval at steady state divided by the dosage interval .

$$C_{av}^{\infty} = \frac{[\mathrm{AUC}]_{t_1}^{t_2}}{\tau} \qquad (8.18)$$

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

$$[\mathrm{AUC}]_{t_1}^{t_2} = \frac{FD_0}{Cl_\tau} = \frac{FD_0}{kV_\mathrm{D}} \qquad (8.19)$$

Substitution of *FD*o/*kV*D for AUC in Equation 8.18 gives Equation 8.17. Equation 8.17 or 8.18 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

$$C_\mathrm{P} = \frac{D_0}{V_\mathrm{D}}\left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}}\right)e^{-kt} \qquad (8.20)$$

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

At steady state, $e^{-nk\tau}$ approaches zero and Equation 8.20 reduces to

$$C_P^{\infty} = \frac{D_0}{V_D}\left(\frac{1}{1 - e^{-k\tau}}\right)e^{-kt} \qquad (8.21)$$

MULTIPLE-ORAL-DOSE REGIMEN

and 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 multipledose regimen, **assuming a one-compartment model and constant doses and dose interval, can be determined as follows**:

$$C_P = \frac{Fk_aD_0}{V_D(k - k_a)}\left[\left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_at} - \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}}\right)e^{-kt}\right] \qquad (8.34)$$

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

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, 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 halflife 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 are distributed rapidly, the loading dose DL can be calculated as follows:

$$\frac{D_L}{D_0} = \frac{1}{(1 - e^{-k_a \tau})(1 - e^{-k\tau})} \qquad (8.42)$$

For extremely rapid absorption, as when the product of *k*aT is large or in the case of IV infusion, e^{-kaT} becomes approximately zero and Equation 8.42 reduces to

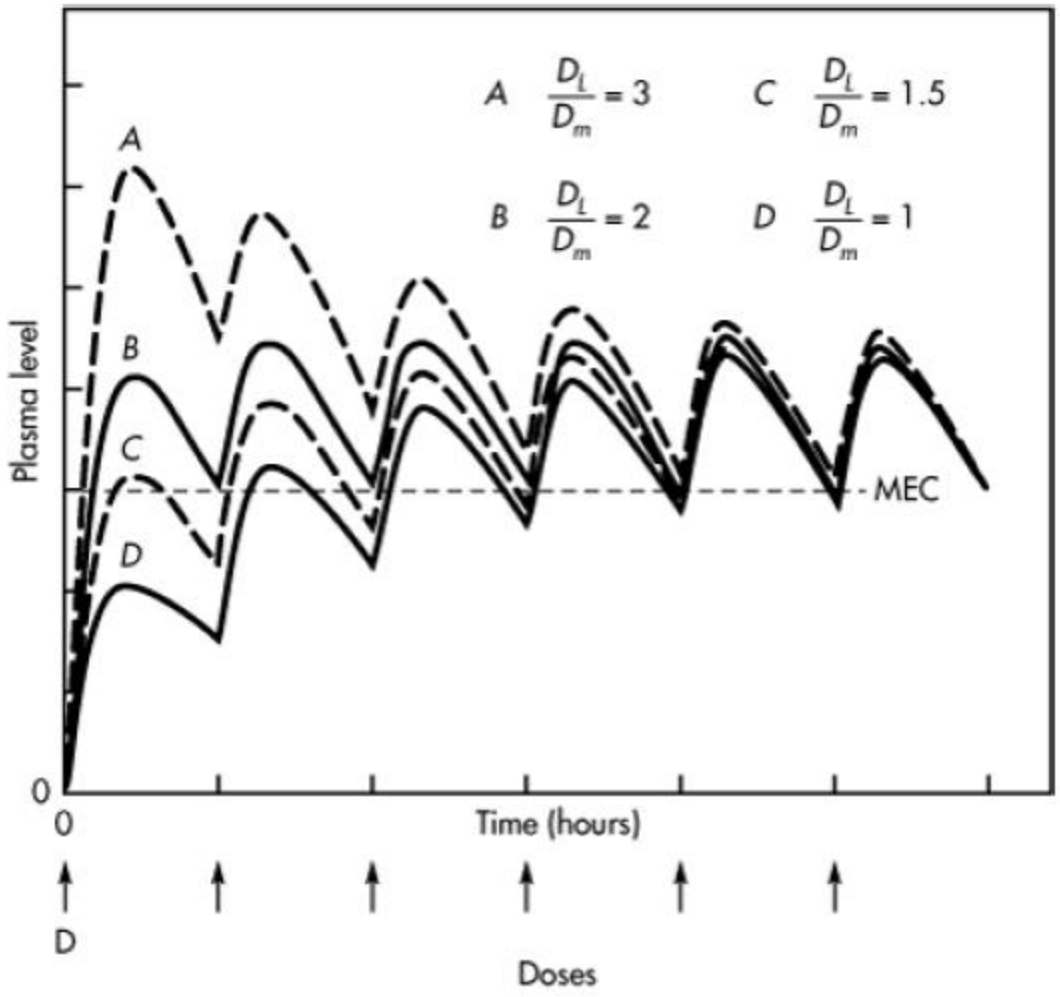
$$\frac{D_L}{D_0} = \frac{1}{1 - e^{-k\tau}} \qquad (8.43)$$

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.

$$\text{Dose ratio} = \frac{D_L}{D_0} \qquad (8.44)$$

As a general rule, **the dose ratio should be equal to 2.0 if the selected dosage interval is equal to the elimination half-life.**

Figure 8-5.


A $\frac{D_L}{D_m} = 3$
B $\frac{D_L}{D_m} = 2$
C $\frac{D_L}{D_m} = 1.5$
D $\frac{D_L}{D_m} = 1$
A
B
C
D
MEC
Plasma level
0
0
Time (hours)
D
Doses