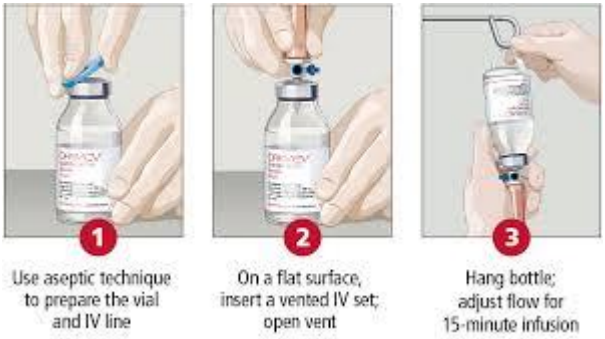


Chapter 5
INTRAVENOUS INFUSION: INTRODUCTION

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.

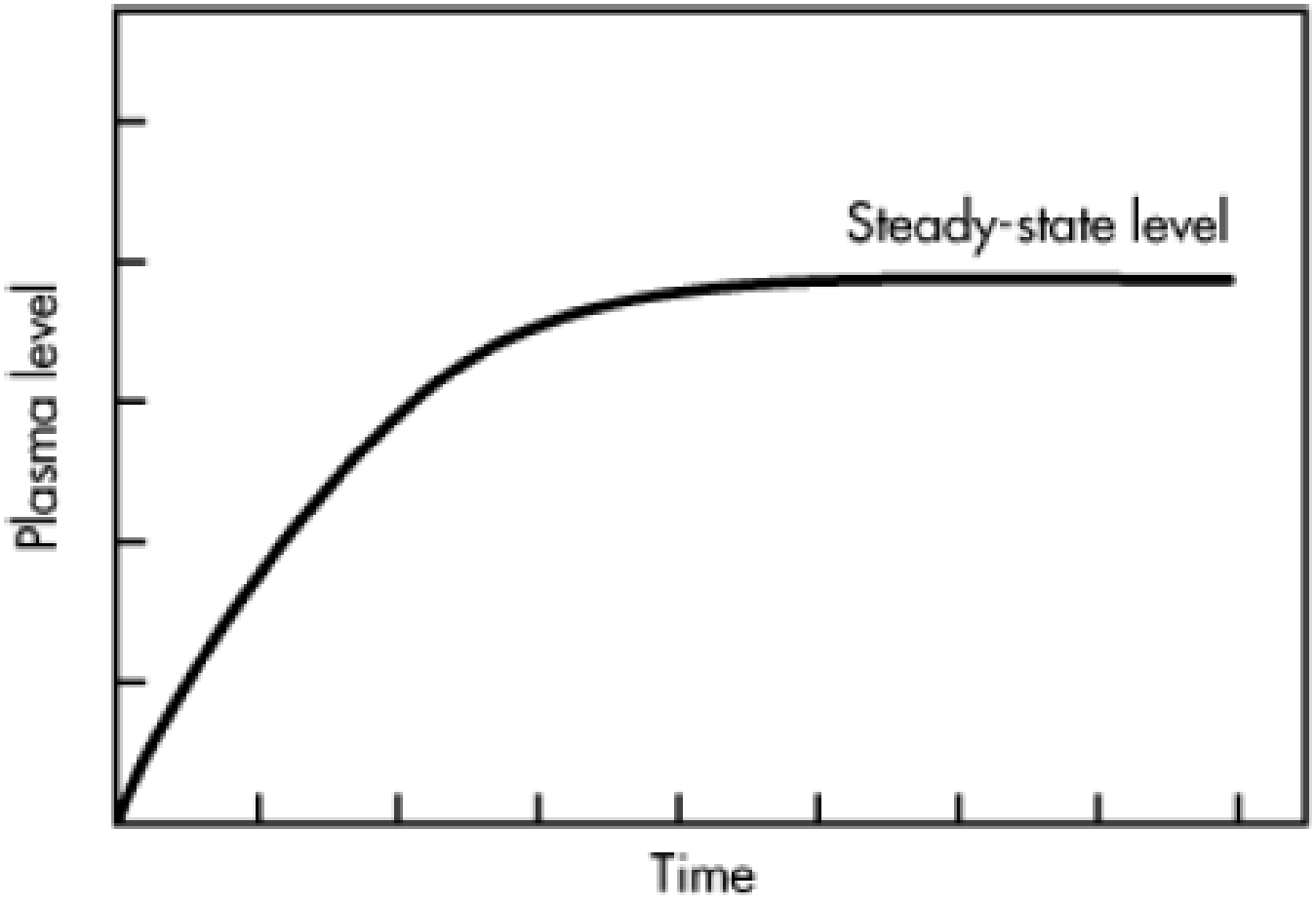
Intravenous (IV) drug solutions may be given either as a bolus dose (injected all at once) or infused slowly through a vein into the plasma at a constant or zero-order rate. **The main advantage for giving a drug by IV infusion is that IV infusion allows precise control of plasma drug concentrations 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.



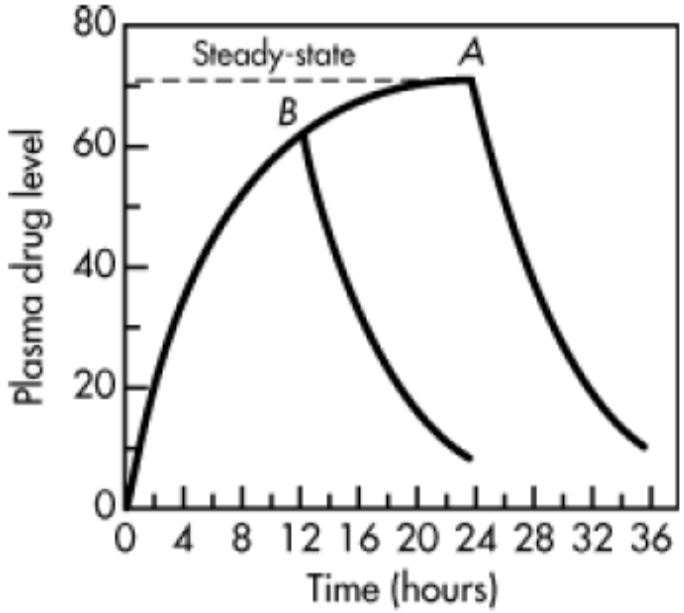
Based on this simple mass balance relationship, a pharmacokinetic equation for infusion may be derived depending on whether the drug follows one- or two-compartment kinetics.

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.



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.**

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.**

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 steadystate 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.

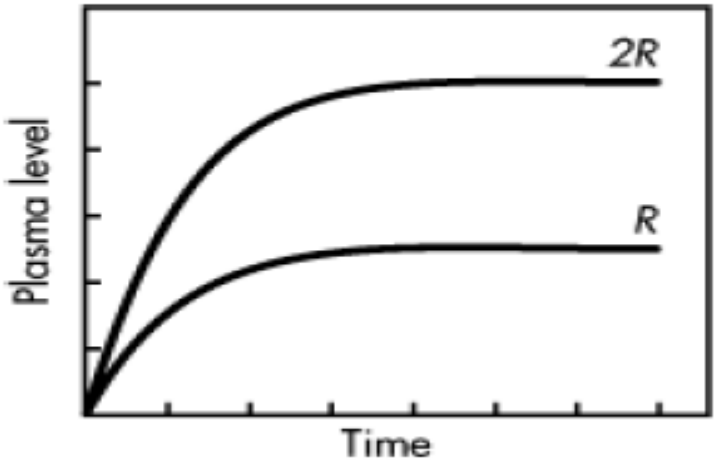
Table 5.1 Number of $t_{1/2}$ to Reach a Fraction of C_{SS}

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,

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

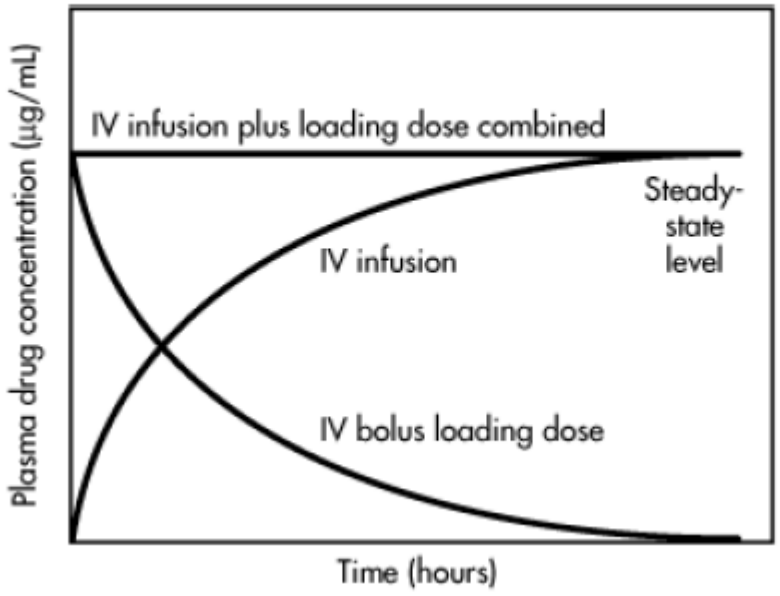
Substituting $D_L = R/k$ in Equation 5.11 makes the expression in parentheses in Equation 5.11 cancel out. Equation 5.11 reduces to Equation 5.13, which is the same expression for C_{SS} or steady-state plasma concentration:

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

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

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.**

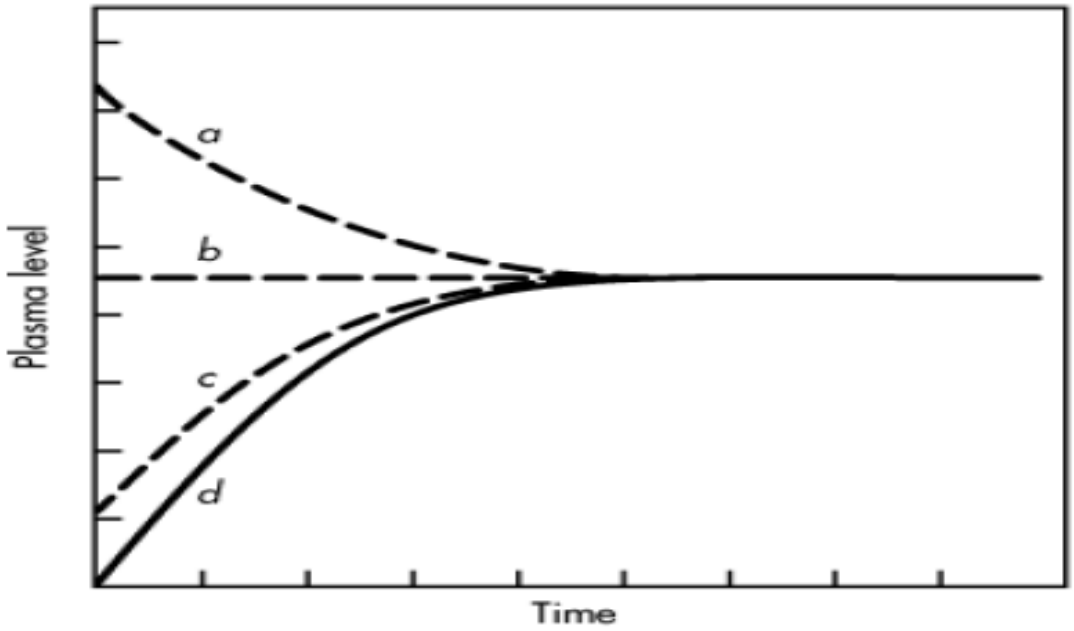
In order to maintain **instant steady-state level [(*dC* p/*dt*) = 0], the loading dose should be equal to *R/k*.**

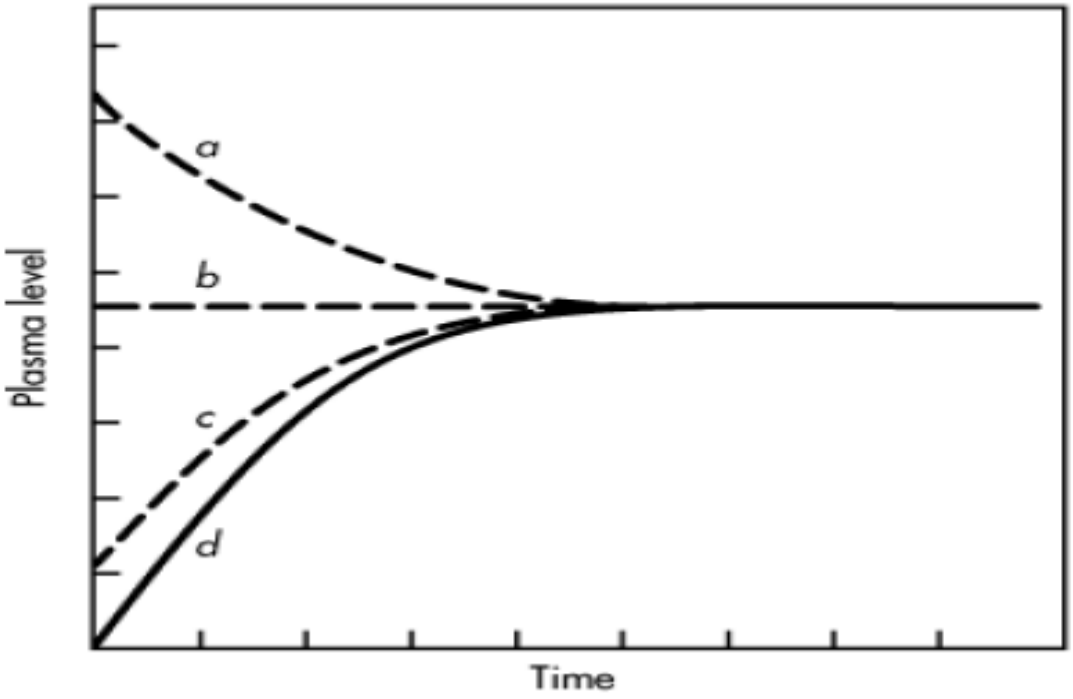
For a one-compartment drug, **if the *D*L and infusion rate are calculated such that *C*0 and *C* SS are the same and both *D*L and infusion are started concurrently, then steady state and *C* SS will be achieved immediately after the loading dose is administered** . Similarly, curve *b* shows the blood 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.

ESTIMATION OF DRUG CLEARANCE AND *V* D FROM INFUSION DATA

The plasma concentration of a drug during constant infusion was described in terms of volume of distribution and elimination constant *k* in Equation 5.2. Alternatively, the equation may be described in terms of clearance by substituting for *k* into Equation 5.2 with *k* = *Cl*/*V* D:

$$C_P = \frac{R}{Cl}(1 - e^{-(Cl/V_D)t}) \qquad (5.21) \qquad C_P = \frac{R}{V_D k}(1 - e^{-kt}) \qquad (5.2)$$

The drug concentration in this physiologic model is described in terms of volume of distribution of *V*D and total body clearance (*Cl*). The independent parameters are clearance and volume of distribution; *k* is viewed as a dependent variable that depends on *Cl* and *V*D. In this model, the time to reach steady state and the resulting steady-state concentration will be dependent on both clearance and volume of distribution. When a constant volume of distribution is evident, the time to reach steady state is then inversely related to clearance. Thus, drugs with small clearance will take a long time to reach steady state. Although this newer approach is preferred by some clinical pharmacists, the alternative approach to parameter estimation was known for some time in classical pharmacokinetics. Equation 5.21 has been applied in population pharmacokinetics to estimate both *Cl* and *V*D in individual patients with one or more data points. However, clearance in patients may differ greatly from subjects in the population, especially subjects with different renal functions.

Unfortunately, the plasma samples taken at time equivalent to less than one half-life after infusion was started may not be very discriminating, due to the small change in the drug concentration. **Blood samples taken at 3-4 half-lives later are much more reflective of the difference in clearance.**

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.**

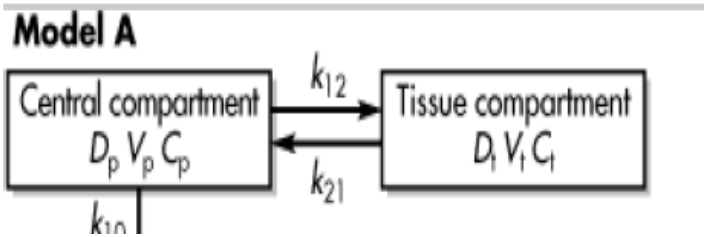
The time needed to reach a steady-state blood level depends entirely on the distribution half-life of the drug.

The equation describing plasma drug concentration as a function of time is as follows:

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

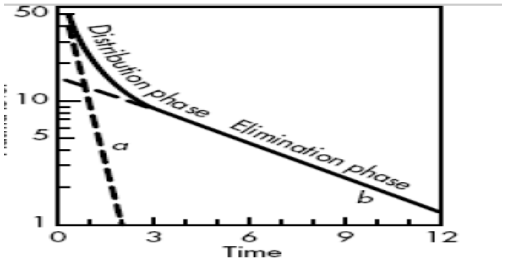
$$C_p = Ae^{-at} + Be^{-bt} \qquad (4.12)$$

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



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

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



$$C_{SS} = \frac{R}{V_p k} \qquad (5.23)$$

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

$$R = C_{SS} V_p k \qquad (5.24)$$

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.**