Note: Large images and tables on this page may necessitate printing in landscape mode.

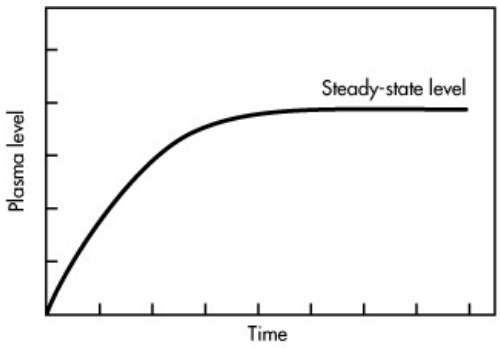
INTRAVENOUS INFUSION: INTRODUCTION

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.

The plasma drug concentration-versus-time curve of a drug given by constant IV infusion is shown in . 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, at 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.



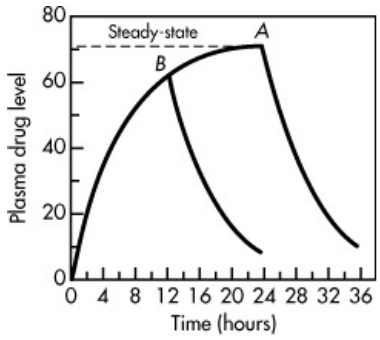
Plasma level–time curve for constant IV infusion.

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. The graph of Equation 5.2 appears in and . 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, $t = \infty$, 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.

In clinical practice, a plasma drug concentration prior to, but asymptotically approaching, the theoretical steady state is considered the steady-state plasma drug concentration (C_{SS}). In a constant IV infusion, drug solution is infused at a constant or zero-order rate, R. 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 = kC_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% ($4.32t_{1/2}$) and 99% ($6.65t_{1/2}$)

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 $5t_{1/2}$, or 5 x 6 hours = 30 hours. The calculation of the values in is given in the example that follows.

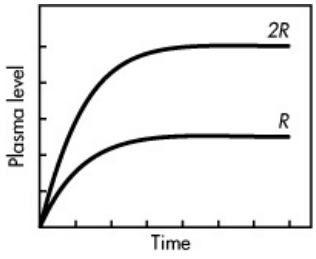
Table 5.1 Number of $t_{1/2}$ to Reach a Fraction of C_{SS}

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 $2R$, respectively.

$$\frac{dC_P}{dt} = 0$$

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

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

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

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

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.

Examples

1. An antibiotic has a volume of distribution of 10 L and a k of 0.2 hr^{-1}. A steady-state plasma concentration of 10 µg/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows.

Equation 5.6 can be rewritten as

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

$$R = (10\ \mu g/mL)(10)(1000\ mL)(0.2\ hr^{-1})$$

$$R = 20\ mg/hr$$

Assume the patient has a uremic condition and the elimination rate constant has decreased to 0.1 hr^{-1}. To maintain the steady-state concentration of 10 µg/mL, we must determine a new rate of infusion as follows.

$$R = (10\ \mu g/mL)(10)(1000\ mL)(0.1\ hr^{-1}) = 10\ mg/hr$$

When the elimination rate constant decreases, the infusion rate must decrease proportionately to maintain the same C_{SS}. However, because the elimination rate constant is smaller (ie, the elimination $t_{1/2}$ is longer), the time to reach C_{SS} will be longer.

2. An infinitely long period of time is needed to reach steady-state drug levels. However, in practice it is quite acceptable to reach 99% C_{SS} (ie, 99% steady-state level). Using Equation 5.6, we know that the steady state level is

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

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.

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

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

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

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 $V_D k$,

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

3. A patient was given an antibiotic ($t_{1/2}$ = 6 hr) by constant IV infusion at a rate of 2 mg/hr. At the end of 2 days, the serum drug concentration was 10 mg/L. Calculate the total body clearance Cl_T for this antibiotic.

The total body clearance may be estimated from Equation 5.7. The serum sample was taken after 2 days or 48 hours of infusion, which time represents 8 x $t_{1/2}$, therefore, this serum drug concentration approximates the C_{SS}.

$$Cl_T = \frac{R}{C_{SS}} = \frac{2\ mg/hr}{10\ mg/L} = 200\ mL/hr$$

INFUSION METHOD FOR CALCULATING PATIENT ELIMINATION HALF-LIFE

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.

Example 1

An antibiotic has an elimination half-life of 3–6 hours in the general population. A patient was given an IV infusion of an antibiotic at an infusion rate of 15 mg/hr. Blood samples were taken at 8 and at 24 hours and plasma drug concentrations were 5.5 and 6.5 mg/L, respectively. Estimate the elimination half-life of the drug in this patient.

Solution

Because the second plasma sample was taken at 24 hours, or 24/6 = 4 half-lives after infusion, the plasma drug concentration in this sample is approaching 95% of the true plasma steady-state drug concentration assuming the extreme case of $t_{1/2}$ = 6 hours.

By substitution into Equation 5.8,

$$\log\left(\frac{6.5 - 5.5}{6.5}\right) = -\frac{k(8)}{2.3}$$

$$k = 0.234 \text{ hr}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.234} = 2.96 \text{ hr}$$

The elimination half-life calculated in this manner is not as accurate as the calculation of $t_{1/2}$ using multiple plasma drug concentration time points after a single IV bolus dose or after stopping the IV infusion. However, this method may be sufficient in clinical practice. As the second blood sample is taken closer to the time for steady state, the accuracy of this method improves. At the 30th hour, for example, the plasma concentration would be 99% of the true steady-state value (corresponding to 30/6 or 5 elimination half-lives), and less error would result in applying Equation 5.8.

When Equation 5.8 was used as in the example above to calculate the drug $t_{1/2}$ of the patient, the second plasma drug concentration was assumed to be the theoretical C_{SS}. As demonstrated below, when $t_{1/2}$ and the corresponding values are substituted,

$$\log\left(\frac{C_{SS} - 5.5}{C_{SS}}\right) = -\frac{(0.231)(8)}{2.3}$$

$$\frac{C_{SS} - 5.5}{C_{SS}} = 0.157$$

$$C_{SS} = 6.5 \text{ mg/L}$$

(Note that C_{SS} is in fact the same as the concentration at 24 hours in the example above.)

In practice, before starting an IV infusion, an appropriate infusion rate (R) is generally calculated from Equation 5.8 using literature values for C_{SS}, k, and V_D or Cl_T. Two plasma samples are taken and the sampling times recorded. The second sample should be taken near the theoretical time for steady state. Equation 5.8 would then be used to calculate a $t_{1/2}$. If the elimination half-life calculated confirms that the second sample was taken at steady state, the plasma concentration is simply assumed as the steady-state concentration and a new infusion rate may be calculated.

Example 2

If the desired therapeutic plasma concentration is 8 mg/L for the above patient (), what is a suitable infusion rate for the patient?

Solution

From Example 1, the trial infusion rate was 15 mg/hr. Assuming the second blood sample is the steady-state level, 6.5 mg/mL, the clearance of the patient is

$$C_{SS} = \frac{R}{Cl}$$

$$Cl = \frac{R}{C_{SS}} = 15/6.5 = 2.31 \text{ L/hr}$$

The new infusion rate should be

$$R = C_{SS} \times Cl = 8 \times 2.31 = 18.48 \text{ mg/hr}$$

In this example, the $t_{1/2}$ of this patient is a little shorter, about 3 hours, compared to 3–6 hours reported for the general population. Therefore, the infusion rate should be a little greater in order to maintain the desired steady-state level of 15 mg/L.

Equation 5.7 or the steady-state clearance method has been applied to the clinical infusion of drugs. The method was regarded as simple and accurate compared with other methods, including the two-point method ().

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

$$C_P = C_1 + C_2$$

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

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

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

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,

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

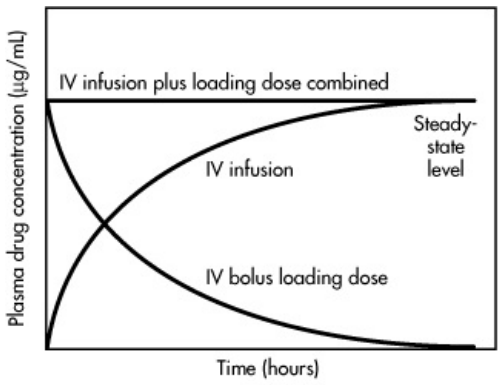
Substituting $D_L = R/k$ in Equation 5.11 makes the expression in parentheses in Equation 5.11 cancel out. Equation 5.11 reduces to Equation 5.13, which is the same expression for C_{SS} or steady-state plasma concentration:

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

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

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.

The loading dose needed to get immediate steady-state drug levels can also be found by the following approach.

Loading dose equation:

$$C_1 = \frac{D_L}{V_D} e^{-kt}$$

Infusion equation:

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

Adding up the two equations yields Equation 5.15, an equation describing simultaneous infusion after a loading dose:

$$C_2 = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k}(1 - e^{-kt}) \qquad (5.15)$$

By differentiating this equation at steady state, we obtain

$$\frac{dC_p}{dt} = 0 = \frac{-D_L k}{V_D} e^{-kt} + \frac{Rk}{V_D k} e^{-kt} \qquad (5.16)$$

$$0 = e^{-kt}\left(\frac{-D_L k}{V_D} + \frac{R}{V_D}\right)$$

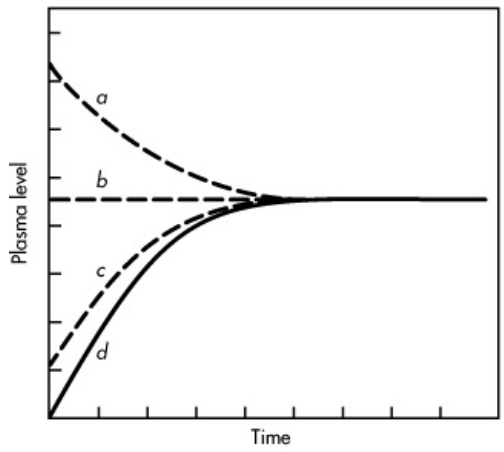
$$\frac{D_L k}{V_D} = \frac{R}{V_D} \qquad (5.17)$$

$$D_L = \frac{R}{k} = \text{loading dose}$$

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, in , 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.

Figure 5-5.



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.

Practice Problems

1. A physician wants to administer an anesthetic agent at a rate of 2 mg/hr by IV infusion. The elimination rate constant is 0.1 hr^{-1}, and the volume of distribution (one compartment) is 10 L. What loading dose should be recommended if the doctor wants the drug level to reach 2 µg/mL immediately?

Solution

$$C_{SS} = \frac{R}{V_D k} = \frac{2000}{(10 \times 10^3)(0.1)} = 2\ \mu g/mL$$

To reach C_{SS} instantly,

$$D_L = \frac{R}{k} = \frac{2\ mg/hr}{0.1/hr} \qquad D_L = 20\ mg$$

2. What is the concentration of a drug 6 hours after administration of a loading dose of 10 mg and simultaneous infusion at 2 mg/hr (the drug has a $t_{1/2}$ of 3 hr and a volume of distribution of 10 L)?

Solution

$$k = \frac{0.693}{3\ hr}$$

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

$$C_p = \frac{10{,}000}{10{,}000}e^{-(0.693/3)(6)} - \frac{2{,}000}{(10{,}000)(0.693/3)}(1 - e^{-(0.693/3)(6)})$$

$$C_p = 0.90\ \mu g/mL$$

3. Calculate the drug concentration in the blood after infusion has been stopped.

Solution

This concentration can be calculated in two parts (see , point A). First, calculate the concentration of drug during infusion; and second, calculate the final infusion concentration, C_0. Then use the IV bolus dose equation ($C = C_0 e^{-kt}$) for calculations for any further point in time. For convenience, the two equations can be combined as follows.

$$C_p = \frac{R}{V_D k}(1 - e^{-kb})e^{-k(t-b)} \qquad (5.19)$$

where b = length of time of infusion period, t = total time (infusion and postinfusion), and $t - b$ = length of time after infusion has stopped.

4. A patient was infused for 6 hours with a drug (k = 0.01 hr^{-1}; V_D = 10 L) at a rate of 2 mg/hr. What is the concentration of the drug in the body 2 hours after cessation of the infusion?

Solution

Using Equation 5.19,

$$C_p = \frac{200}{(0.01)(10{,}000)}(1-e^{-0.01(6)})e^{-0.01(8-6)}$$

$$C_p = 1.14\ \mu g/mL$$

Alternatively, when infusion stops, C'_p is calculated:

$$C'_p = \frac{R}{V_D k}(1-e^{-kt})$$

$$C'_p = \frac{2{,}000}{0.01 \times 10{,}000}(1-e^{-0.01(6)})$$

$$C = C'_p e^{-0.01(2)}$$

$$C = 1.14\ \mu g/mL$$

The two approaches should give the same answer.

5. An adult male asthmatic patient (78 kg, 48 years old) with a history of heavy smoking was given an IV infusion of aminophylline at a rate of 0.5 mg/kg per hr. A loading dose of 6 mg/kg was given by IV bolus injection just prior to the start of the infusion. At 2 hours after the start of the IV infusion, the plasma theophylline concentration was measured and found to contain 5.8 µg/mL of theophylline. The apparent V_D for theophylline is 0.45 L/kg. Aminophylline is the ethylenediamine salt of theophylline and contains 80% of theophylline base.

Because the patient was responding poorly to the aminophylline therapy, the physician wanted to increase the plasma theophylline concentration in the patient to 10 µg/mL. What dosage recommendation would you give the physician? Would you recommend another loading dose?

Solution

If no loading dose is given and the IV infusion rate is increased, the time to reach steady-state plasma drug concentrations will be about 4 to 5 $t_{1/2}$ to reach 95% of C_{SS}. Therefore, a second loading dose should be recommended to rapidly increase the plasma theophylline concentration to 10 µg/mL. The infusion rate must also be increased to maintain this desired C_{SS}.

The calculation of loading dose D_L must consider the present plasma theophylline concentration.

$$D_L = \frac{V_D(C_{p,desired} - C_{p,present})}{(S)(F)} \qquad (5.20)$$

where S is the salt form of the drug and F is the fraction of drug bioavailable. For aminophylline, S is equal to 0.80, and for an IV bolus injection, F is equal to 1.

$$D_L = \frac{(0.45\ L/kg)(78\ kg)(10 - 5.8\ mg/L)}{(0.8)(1)}$$

$$D_L = 184\ mg\ aminophylline$$

The maintenance IV infusion rate may be calculated after estimation of the patient's clearance, Cl_T. Because a loading dose and an IV infusion of 0.5 mg/hr per kilogram was given to the patient, the plasma theophylline concentration of 5.8 mg/L is at steady-state C_{SS}. Total clearance may be estimated by

$$Cl_T = \frac{R}{C_{SS,present}} = \frac{(0.6\ mg/hr\ kg)(78\ kg)}{5.8\ mg/L}$$

$$Cl_T = 8.07\ L/hr \quad or \quad 1.72\ mL/min\ per\ kg$$

The usual Cl_T for adult, nonsmoking patients with uncomplicated asthma is approximately 0.65 mL/min per kilogram. Heavy smoking is known to increase Cl_T for theophylline.

The new IV infusion rate, R', is calculated by

$$R' = C_{SS,desired}\ Cl_T$$

$$R' = \text{mg/L} \times 8.07\ \text{L/hr} = 80.7\ \text{mg/hr}\ \ \text{or}\ \ 1.03\ \text{mg/hr per kg}$$

6. An adult male patient (43 years old, 80 kg) is to be given an antibiotic by IV infusion. According to the literature, the antibiotic has an elimination $t_{1/2}$ of 2 hours, a V_D of 1.25 L/kg, and is effective at a plasma drug concentration of 14 mg/L. The drug is supplied in 5-mL ampuls containing 150 mg/mL.

a. Recommend a starting infusion rate in milligrams per hour and liters per hour.

Solution

Assume the effective plasma drug concentration is the target drug concentration or C_{SS}.

$$R = C_{SS}kV_D$$

$$R = (14\ \text{mg/L})(0.693/2\ \text{hr})(1.5\ \text{L/kg})(80\ \text{kg})$$

$$R = 485.1\ \text{mg/hr}$$

Because the drug is supplied at a concentration of 150 mg/mL,

$$(485.1\ \text{mg})(\text{mL}/150\ \text{mg}) = 3.23\ \text{mL}$$

Thus, R = 3.23 mL/hr.

b. Blood samples were taken from the patient at 12, 16, and 24 hours after the start of the infusion. Plasma drug concentrations were as shown below:

t (hr)	C_p (mg/L)
12	16.1
16	16.3
24	16.5

From this additional data, calculate the total body clearance Cl_T for the drug in this patient.

Solution

Because the plasma drug concentrations at 12, 16, and 24 hours were similar, steady state has essentially been reached. (Note: The continuous increase in plasma drug concentrations could be caused by drug accumulation due to a second tissue compartment, or could be due to variation in the drug assay.) Assuming a C_{SS} of 16.3 mg/mL, Cl_T is calculated.

$$Cl_T = \frac{R}{C_{SS}} = \frac{485.1\ \text{mg/hr}}{16.3\ \text{mg/L}} = 29.8\ \text{L/hr}$$

c. From the above data, estimate the elimination half-life for the antibiotic in this patient.

Solution

Generally, the apparent volume of distribution (V_D) is less variable than $t_{1/2}$. Assuming that the literature value for V_D is 1.25 L/kg, then $t_{1/2}$ may be estimated from the Cl_T.

$$Cl_T = kV_D$$

$$k = \frac{Cl_T}{V_D} = \frac{29.9\ \text{L/hr}}{(1.25\ \text{L/kg})\,(80\ \text{kg})} = 0.299\ \text{hr}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.299\ \text{hr}^{-1}} = 2.32\ \text{hr}$$

Thus the $t_{1/2}$ for the antibiotic in this patient is 2.32 hours, which is in good agreement with the literature value of 2 hours.

d. After reviewing pharmacokinetics of the antibiotic in this patient, should the infusion rate for the antibiotic be changed?

Solution

To decide whether the infusion rate should be changed, the clinical pharmacist must consider the pharmacodynamics and toxicity of the drug. Assuming the drug has a wide therapeutic window and shows no sign of adverse drug toxicity, the infusion rate of 485.1 mg/hr, calculated according to pharmacokinetic literature values for the drug, appears to be correct.

$$C_p = \frac{R}{Cl}(1 - e^{-(Cl/V_D)t})$$

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 $k = Cl/V_D$:

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

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 open 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:

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

where a and b are hybrid rate constants and R is the rate of infusion. At steady state (ie, $t = \infty$), Equation 5.22 reduces to

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

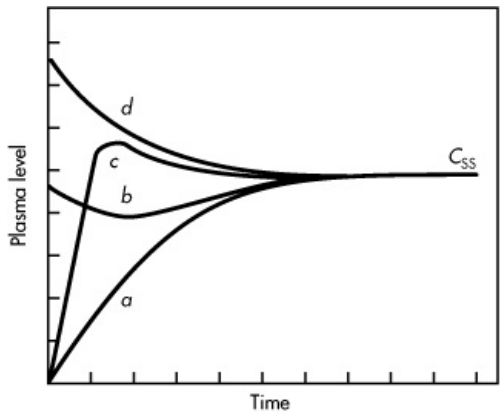
By rearranging this equation, the infusion rate for a desired steady-state plasma drug concentration may be calculated.

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

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. The plasma drug concentration of a drug that follows a two-compartment model after various loading doses is shown in . 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 (see).

Figure 5-6.



Plasma drug level after various loading doses and rates of infusion for a drug that follows a two-compartment model: *a*, no loading dose; *b*, loading dose = *R*/*k* (rapid infusion); *c*, loading dose = *R*/*b* (slow infusion); and *d*, loading dose = *R*/*b* (rapid infusion).

Apparent Volume of Distribution at Steady State, Two-Compartment Model

After administration of any drug that follows two-compartment kinetics, plasma drug levels will decline due to elimination, and some redistribution will occur as drug in tissue diffuses back into the plasma fluid. The volume of distribution at steady state, $(V_D)_{SS}$, is the "hypothetical space" in which the drug is assumed to be distributed. The product of the plasma drug concentration with $(V_D)_{SS}$ will give the total amount of drug in the body at that time period, such that $C_{pSS} \times (V_D)_{SS}$ = amount of drug in the body at steady state. At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment. These rates of drug transfer are described by the following expressions:

$$D_t k_{21} = D_p k_{12} \qquad (5.25)$$

$$D_t = \frac{k_{12} D_p}{k_{12}} \qquad (5.26)$$

where D_t is the amount of drug in the tissue compartment. Because the amount of drug in the central compartment, D_p, is equal to $V_p C_p$, by substitution in the above equation,

$$D_t = \frac{k_{12} C_p V_p}{k_{21}} \qquad (5.27)$$

The total amount of drug in the body at steady state is equal to the sum of the amount of drug in the tissue compartment, D_t, and the amount of drug in the central compartment, D_p. Therefore, the apparent volume of drug at steady state $(V_D)_{SS}$ may be calculated by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady state:

$$(V_D)_{SS} = \frac{D_p + D_t}{C_p} \qquad (5.28)$$

By substitution of Equation 5.27 into Equation 5.28, and by expressing D_p as $V_p C_p$, a more useful equation for the calculation of $(V_D)_{SS}$ is obtained:

$$(V_D)_{SS} = \frac{C_p V_p + k_{12} V_p C_p / k_{21}}{C_p} \qquad (5.29)$$

which reduces to

$$(V_D)_{SS} = V_p + \frac{k_{12}}{k_{21}} V_p \qquad (5.30)$$

In practice, Equation 5.30 is used to calculate $(V_D)_{SS}$. The $(V_D)_{SS}$ is a function of the transfer constants, k_{12} and k_{21}, which represent the rate constants of drug going into and out of the tissue compartment, respectively. The magnitude of $(V_D)_{SS}$ is dependent on the hemodynamic factors responsible for drug distribution and on the physical properties of the drug, properties which, in turn, determine the relative amount of intra- and extravascular drug.

Another volume term used in two-compartment modeling is $(V_D)_b$ (see). $(V_D)_b$ is often calculated from total body clearance divided by *b*. Unlike the steady-state volume of distribution, $(V_D)_{SS}$, $(V_D)_b$ is influenced by drug elimination in the beta "b"

phase. Reduced drug clearance from the body may increase the area under the curve, AUC, such that $(V_D)_b$ is either reduced or unchanged, depending on the value of *b* as shown in Equation 4.30 (see):

$$(V_D)_b = (V_D)_{area} = \frac{D_0}{b[AUC]_0^\infty} \qquad (4.30)$$

Unlike $(V_D)_b$, $(V_D)_{SS}$ is not affected by changes in drug elimination. $(V_D)_{SS}$ reflects the true distributional volume occupied by the plasma and the tissue pool when steady state is reached. Although this volume is not useful in calculating the amount of drug in the body during pre-steady state, $(V_D)_{SS}$ multiplied by the steady-state plasma drug concentration, C_{SS}, yields the amount of drug in the body. This volume is often used to determine the loading drug dose necessary to upload the body to a desired plasma drug concentration. As shown by Equation 4.30, $(V_D)_{SS}$ is several times greater than V_p, which represents the volume of the plasma compartment, but differs somewhat in value depending on the transfer constants.

Practical Focus

Questions

1. Do you agree with the following statements for a drug that is described by a two-compartment pharmacokinetic model? At steady state, the drug is well equilibrated between the plasma and the tissue compartment, $C_p = C_t$, and the rates of drug diffusion into and from the plasma compartment are equal. The steady-state volume of distribution is much larger than the initial volume, V_i, or the original plasma volume, V_p, of the central compartment. The loading dose is often calculated using the $(V_D)_{SS}$ instead of V_p.

2. Azithromycin may be described by a plasma and a tissue compartment model (refer to).

3. "Rapid distribution of azithromycin into cells causes higher concentration in the tissues than in the plasma. . . ." Does this statement conflict with the steady-state concept?

4. Why is a loading dose used?

Solutions

1. For a drug that follows a multiple-compartment model, the rates of drug diffusion into the tissues from the plasma and from the tissues into the plasma are equal at steady state. However, the tissue drug concentration is generally not equal to the plasma drug concentration.

2. When plasma drug concentration data are used alone to describe the disposition of the drug, no information on tissue drug concentration is known, and no model will predict actual tissue drug concentrations. To account for the mass balance (drug mass/volume = body drug concentration) of drug present in the body (tissue and plasma pool) at any time after dosing, the body drug concentration is assumed to be the plasma drug concentration. In reality, azithromycin tissue concentration is much higher. Therefore, the calculated volume of the tissue compartment is much bigger (31.1 L/kg) than its actual volume.

The product of the steady-state apparent $(V_D)_{SS}$ and the steady-state plasma drug concentration (C_{SS}) estimates the amount of drug present in the body. The amount of drug present in the body may be important information for toxicity considerations, but may be used as a therapeutic end point. In most cases, the therapeutic drug at the site of action accounts for only a small fraction of total drug in the tissue compartment. The pharmacodynamic profile may be described as a separate compartment (see effect compartment in). Based on pharmacokinetic and biopharmaceutic studies, the factors that account for high tissue concentrations include diffusion constant, lipid solubility, and tissue binding to cell components. A ratio measuring the relative drug concentration in tissue and plasma is the partition coefficient, which is helpful in predicting the distribution of a drug into tissues. Ultimately, studies of tissue drug distribution using radiolabeled drug are much more useful.

The real tissue drug level will differ from the plasma drug concentration depending on the partitioning of drug in tissues and plasma. $(V_D)_b$ is a volume of distribution often calculated because it is easier to calculate than $(V_D)_{SS}$. This volume of distribution, $(V_D)_b$, allows the area under the curve to be calculated, an area that has been related to toxicities associated with many cancer chemotherapy agents. Many values for apparent volumes of distribution reported in the clinical literature are obtained using the area equation. Some early pharmacokinetic literature includes only the steady-state volume of distribution, which approximates the $(V_D)_b$ but is substantially smaller in many cases. In general, both volume terms reflect extravascular drug distribution. $(V_D)_b$ appears to be much more affected by the dynamics of drug disposition in the beta phase, whereas $(V_D)_{SS}$ reflects more accurately the inherent distribution of the drug.

3. When drugs are given in a multiple-dose regimen, a loading dose may be given to achieve steady-state drug concentrations more rapidly.

FREQUENTLY ASKED QUESTIONS

1. What is the main reason for giving a drug by slow IV infusion?

2. Why do we use a loading dose to rapidly achieve therapeutic concentration for a drug with a long elimination half-life, instead of increasing the rate of drug infusion or increasing the size of the infusion dose?

3. What are some of the complications involved with IV infusion?

LEARNING QUESTIONS

1. A female patient (35 years old, 65 kg) with normal renal function is to be given a drug by IV infusion. According to the literature, the elimination half-life of this drug is 7 hours and the apparent V_D is 23.1% of body weight. The pharmacokinetics of this drug assumes a first-order process. The desired steady-state plasma level for this antibiotic is 10 μg/mL.

a. Assuming no loading dose, how long after the start of the IV infusion would it take to reach 95% of the C_{SS}?

b. What is the proper loading dose for this antibiotic?

c. What is the proper infusion rate for this drug?

d. What is the total body clearance?

e. If the patient suddenly develops partial renal failure, how long would it take for a new steady-state plasma level to be established (assume that 95% of the C_{SS} is a reasonable approximation)?

f. If the total body clearance declined 50% due to partial renal failure, what new infusion rate would you recommend to maintain the desired steady-state plasma level of 10 µg/mL?

2. An anticonvulsant drug was given as (**a**) a single IV dose and (**b**) a constant IV infusion. The serum drug concentrations are as presented in .

Table 5.2 Serum Drug Concentrations for a Hypothetical Anticonvulsant Drug

	Concentration in Plasma (µg/mL)	
Time (hr)	**Single IV Dose (1 mg/kg)**	**Constant IV Infusion (0.2 mg/kg per hr)**
0	10.0	0
2	6.7	3.3
4	4.5	5.5
6	3.0	7.0
8	2.0	8.0
10	1.35	8.6
12		9.1
18		9.7
24		9.9

a. What is the steady-state plasma drug level?

b. What is the time for 95% steady-state plasma drug level?

c. What is the drug clearance?

d. What is the plasma concentration of the drug 4 hours after stopping infusion? (Infusion was stopped after 24 hours.)

e. What is the infusion rate for a patient weighing 75 kg to maintain a steady-state drug level of 10 µg/mL?

f. What is the plasma drug concentration 4 hours after an IV dose of 1 mg/kg followed by a constant infusion of 0.2 mg/kg per hour?

3. An antibiotic is to be given by IV infusion. How many milliliters per minute should a sterile drug solution containing 25 mg/mL be given to a 75-kg adult male patient to achieve an infusion rate of 1 mg/kg per hour?

4. An antibiotic drug is to be given to an adult male patient (75 kg, 58 years old) by IV infusion. The drug is supplied in sterile vials containing 30 mL of the antibiotic solution at a concentration of 125 mg/mL. What rate in milliliters per hour would you infuse this patient to obtain a steady-state concentration of 20 µg/mL? What loading dose would you suggest? Assume the drug follows the pharmacokinetics of a one-compartment open model. The apparent volume of distribution of this drug is 0.5 L/kg, and the elimination half-life is 3 hours.

5. According to the manufacturer, a steady-state serum concentration of 17 µg/mL was measured when the antibiotic cephradine (Velosef, Bristol-Meyers, Squibb) was given by IV infusion to 9 adult male volunteers (average weight, 71.7 kg) at a rate of 5.3 mg/kg hr for 4 hours.

a. Calculate the total body clearance for this drug.

b. When the IV infusion was discontinued, the cephradine serum concentration decreased exponentially, declining to 1.5 µg/mL at 6.5 hours after the start of the infusion. Calculate the elimination half-life.

c. From the information above, calculate the apparent volume of distribution.

d. Cephradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cephradine concentration. What is the probable mechanism for this interaction of probenecid with cephradine?

6. Calculate the excretion rate at steady state for a drug given by IV infusion at a rate of 30 mg/hr. The C_{SS} is 20 µg/mL. If the rate of infusion were increased to 40 mg/hr, what would be the new steady-state drug concentration, C_{SS}? Would the excretion rate for the drug at the new steady state be the same? Assume first-order elimination kinetics and a one-compartment model.

7. An antibiotic is to be given to an adult male patient (58 years old, 75 kg) by IV infusion. The elimination half-life is 8 hours and the apparent volume of distribution is 1.5 L/kg. The drug is supplied in 60-mL ampules at a drug concentration of 15 mg/mL. The desired steady-state drug concentration is 20 µg/mL.

a. What infusion rate, in milliliters per hour, would you recommend for this patient?

b. What loading dose would you recommend for this patient? By what route of administration would you give the loading dose? When?

c. Why should a loading dose be recommended?

d. According to the manufacturer, the recommended starting infusion rate is 15 mL/hr. Do you agree with this recommended infusion rate for your patient? Give a reason for your answer.

e. If you were to monitor the patient's serum drug concentration, when would you request a blood sample? Give a reason for your answer.

f. The observed serum drug concentration is higher than anticipated. Give two possible reasons based on sound pharmacokinetic principles that would account for this observation.

8. Which of the following statements **(a–e)** is/are true regarding the time to reach steady state for the three drugs below.

	Drug A	**Drug B**	**Drug C**
Rate of infusion (mg/hr)	10	20	15
k (hr^{-1})	0.5	0.1	0.05
Cl (L/hr)	5	20	5

a. Drug A takes the longest time to reach steady state.

b. Drug B takes the longest time to reach steady state.

c. Drug C takes the longest time to reach steady state.

d. Drug A takes 6.9 hours to reach steady state.

e. None of the above is true.

9. The steady-state drug concentration of a cephalosporin after constant infusion of 250 mg/hr is 45 µg/mL. What is the drug clearance of this cephalosporin?

10. Some clinical pharmacists assumed that, at steady state when equilibration is reached between the plasma and the tissue, the tissue drug concentration would be the same as the plasma. Do you agree?

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