INTRAVENOUS INFUSION:

IV solutions may be given either as a **bolus dose** or **infused slowly** through a vein into the plasma at a constant or **zero-order rate**.

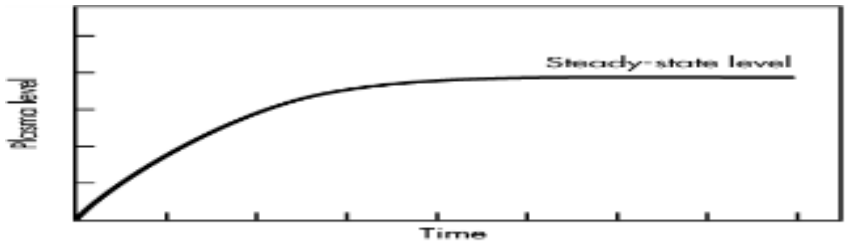
The main advantage for IV infusion is that:

1- IV infusion **allows precise control of plasma drug concentrations to fit the individual needs** of the patient.
2- For drugs with a narrow therapeutic window (eg, heparin), IV infusion maintains an effective constant plasma drug concentration by eliminating wide fluctuations between maximum and minimum plasma concentration.
3- The IV infusion of drugs, such as antibiotics, may be given with IV fluids that include electrolytes and nutrients.
4- 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, **at steady state**, the rate of change in the plasma drug concentration, $dC_p/dt = 0$,

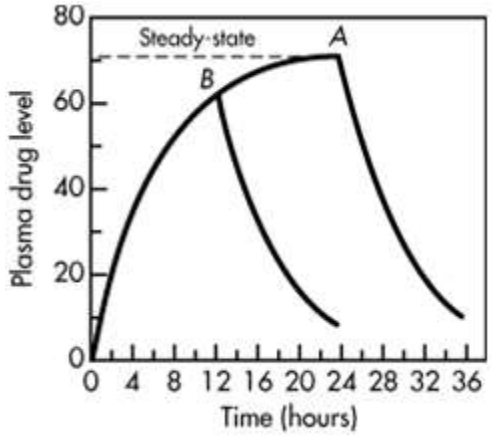
$$\underset{\text{(infusion rate)}}{\text{Rate of drug input}} = \underset{\text{(elimination rate)}}{\text{rate of drug output}}$$



ONE-COMPARTMENT MODEL DRUGS

The pharmacokinetics of a drug given by IV infusion follows **zero-order** input in which the drug 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.

In 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.



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

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

At infinite time, $t = \infty$, e^{-kt} approaches zero

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

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

Steady-State Drug Concentration (C_{SS}) and Time Needed to Reach C_{SS}

The rate of drug leaving the body is equal to the rate of drug entering the body (infusion rate) at steady state.

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 $-k/2.3$.

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.

During 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. 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

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.

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

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

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

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

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

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 k =0.2 hr^{-1}.A steady-state plasma concentration of 10 g/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows.

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

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

$$R = 20\ mg/hr$$

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 mg/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

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

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

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

Take the natural logarithm on both sides: -kt=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 steadystate 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

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:*

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

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

$$C_p = C_{SS}(1 - e^{-kt})$$

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

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.

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 + C2

, 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,

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

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

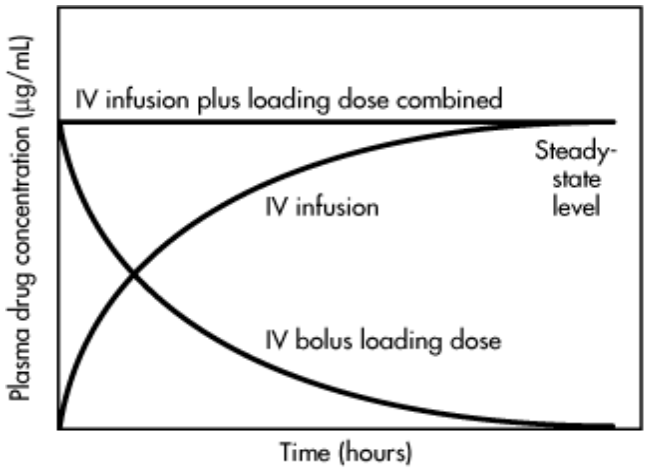
Substituting $D_L = R/k$ in Equation 5.11 makes the expression in parentheses in Equation 5.11 cancel out. Equation 5.11 reduces to Equation 5.13, which is the same expression for C_{SS} or steady-state plasma concentration:

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

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

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 ($R = dD_B/dt$).



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

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

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

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

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 g/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 post infusion), 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:

$$C'_{\mathrm{P}} = \frac{R}{V_{\mathrm{D}}k}(1 - e^{-kt})$$

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

$$C = C'_{\mathrm{P}} e^{-0.01(2)}$$

$$C = 1.14\ \mu\mathrm{g/mL}$$

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 g/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 g/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 g/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.

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

$$D_L = 184\ \text{mg aminophylline}$$

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

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

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

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

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

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

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}.

$$R = C_{SS} k V_D$$
$$R = (14 \text{ mg/L})(0.693/2 \text{ hr})(1.5 \text{ L/kg})(80 \text{ kg})$$
$$R = 485.1 \text{ mg/hr}$$

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) Cp (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.

$$C_{\mathrm{p}} = \frac{R}{Cl}\left(1 - e^{-(Cl/V_{\mathrm{D}})t}\right)$$

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?

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 g/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.