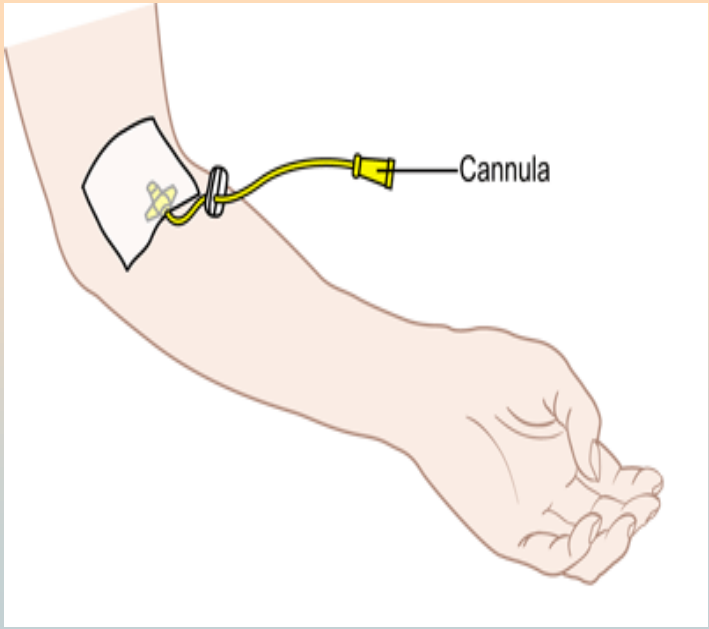
Intravenous Infusion:

Introduction



Intravenous Infusion

- Parenteral routes of administration include:
  - **Intravenous (IV).**
  - **Subcutaneous (SC).**
  - **intramuscular (IM).**

- Intravenous (IV) drug solutions may be given either as:
  I. **A bolus dose** (injected all at once).
  II. **Infused slowly** through a vein into the plasma at a constant or zero-order rate.

Intravenous Infusion

- The main advantage for giving a drug by IV infusion is that:

1) 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.

Intravenous Infusion

2) The IV infusion of drugs, such as antibiotics, may be given with IV fluids that include electrolytes and nutrients.

3) The duration of drug therapy may be maintained or terminated as needed using IV infusion.

Intravenous Infusion

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

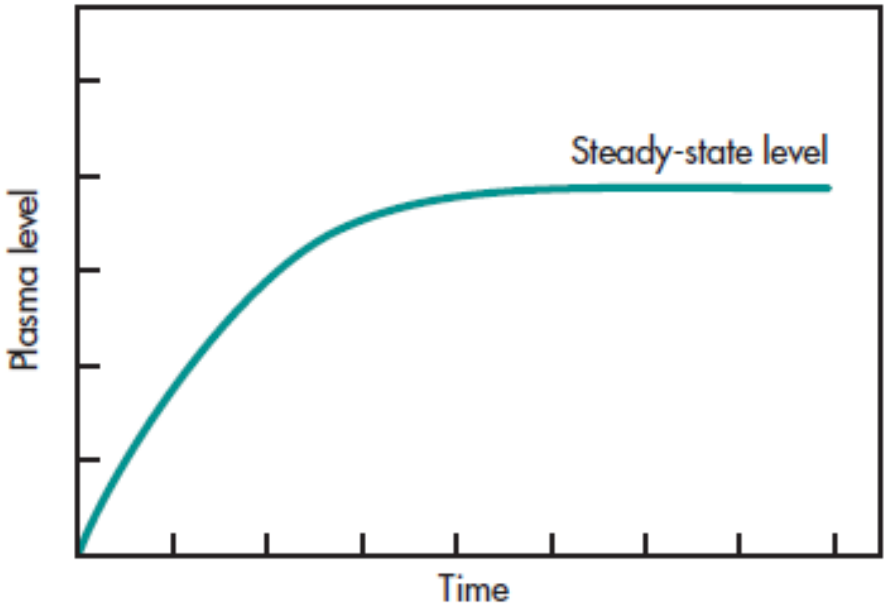


FIGURE 6-1 Plasma level–time curve for constant IV infusion.

- Drug level rises from zero drug concentration and gradually becomes constant when a ***plateau*** or ***steady-state*** drug concentration is reached.

Intravenous Infusion

- At steady state, the rate of drug leaving the body is equal to the rate of drug (infusion rate) entering the body.

- At steady state, the rate of change in the plasma drug concentration, $dC_p/dt = 0$, and

$$\text{Rate of drug input} = \text{Rate of drug output}$$

$$(\text{infusion rate}) = (\text{elimination rate})$$

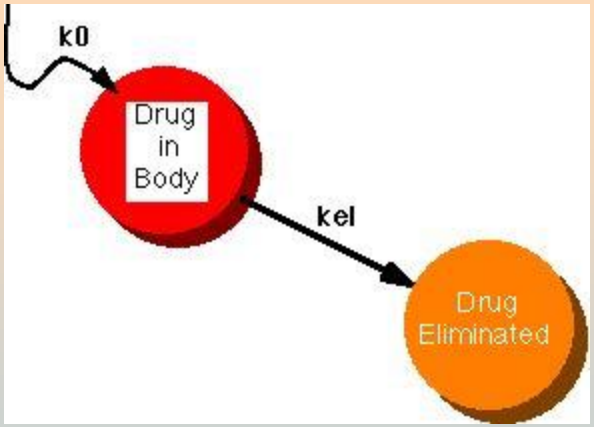
Intravenous Infusion One-Compartment Model

- 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.

$$\frac{dD_B}{dt} = R - kD_B$$

Where: D_B is the amount of drug in the body.
R is the infusion rate (zero order).
k is the elimination rate constant (first order).



Scheme for one compartment Intravenous Infusion

Intravenous Infusion One-Compartment Model

$$\frac{dD_B}{dt} = R - kD_B$$

$$D_B = C_P V_D$$

$$\frac{d(C_P V_D)}{dt} = R - kD_B$$

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

integrating the above equation gives:

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

Intravenous Infusion One-Compartment Model

- As the drug is infused, the value for time (t) increases in Equation. At infinite time (steady state), $t = \infty$, e^{-kt} approaches zero, and the equation reduces to:

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

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

$$C_{ss} = \frac{R}{V_D k} = \frac{R}{Cl}$$

Steady-State Drug Concentration (C_{ss})

- At steady state, the rate of drug leaving the body is equal to the rate of drug entering the body (infusion rate).
  - 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.

Intravenous Infusion One-Compartment Model

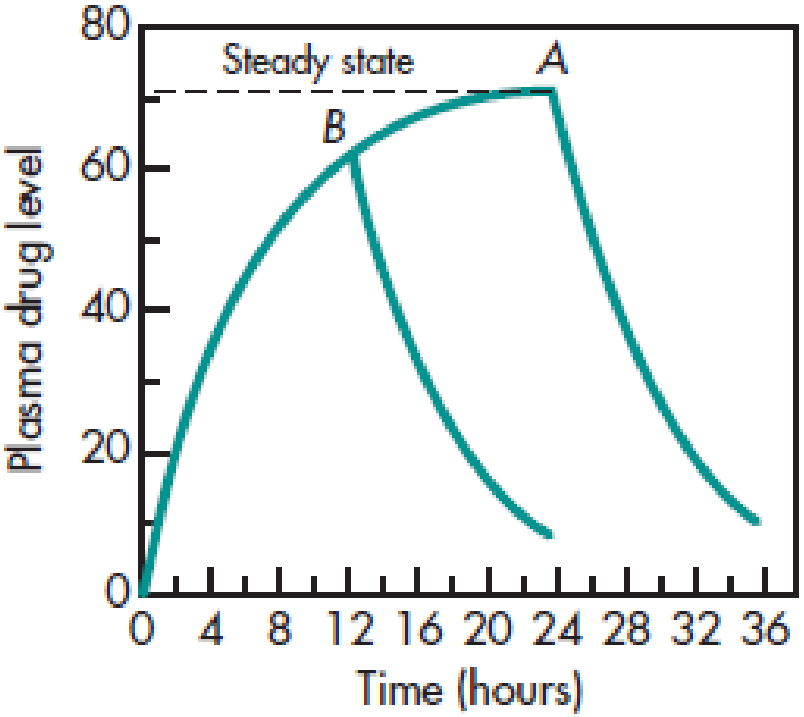


FIGURE 6-2 Plasma drug concentration–time profiles after IV infusion. IV infusion is stopped at steady state (*A*) or prior to steady state (*B*). In both cases, plasma drug concentrations decline exponentially (first order) according to a similar slope.

Steady-State Drug Concentration (C_{ss})

- In 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.
- 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.

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

Steady-State Drug Concentration (C_{ss})

- The time to reach a certain % of the steady-state drug concentration in the plasma can be calculated:

$$t_{1/2} = \frac{0.693}{k}$$

$$C_P = \frac{R}{V_D k}\left(1 - e^{-0.693}\right) = 0.5\frac{R}{V_D k} = 50\% C_{SS}$$

$$C_P = \frac{R}{V_D k}\left(1 - e^{-0.693\times 2}\right) = 75\% C_{SS}$$

$$C_P = \frac{R}{V_D k}\left(1 - e^{-0.693\times 3}\right) = 88\% C_{SS}$$

$$C_P = \frac{R}{V_D k}\left(1 - e^{-0.693\times 4}\right) = 94\% C_{SS}$$

$$C_P = \frac{R}{V_D k}\left(1 - e^{-0.693\times 5}\right) = 97\% C_{SS}$$

Steady-State Drug Concentration (C_{ss})

- 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.
- 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.

Steady-State Drug Concentration (C_{ss})

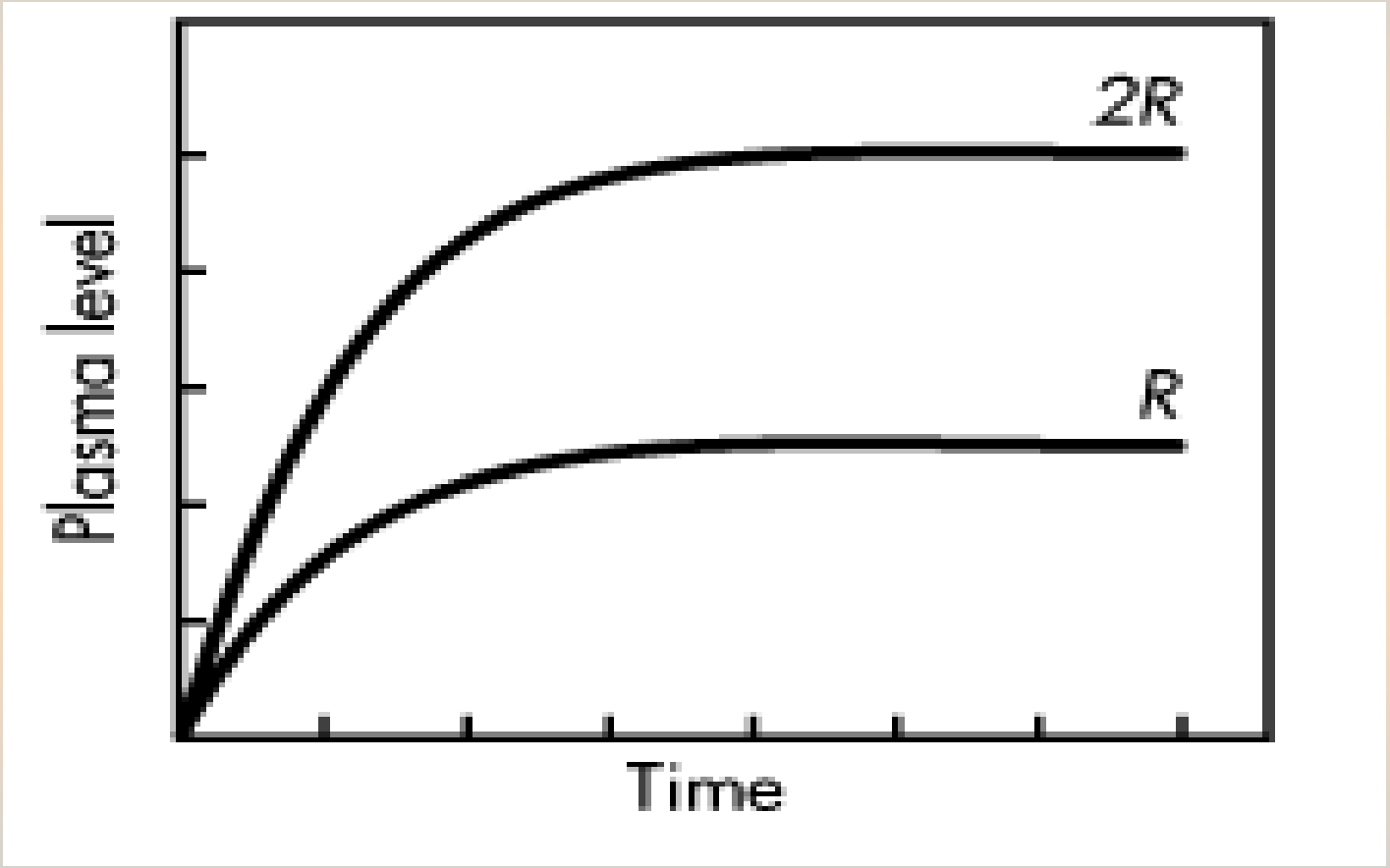
Number of $t_{1/2}$ to Reach a Fraction of C_{ss}	
Percent of C_{ss} Reached[a]	Number of Half-Lives
90	3.32
95	4.32
99	6.65

- 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.

Steady-State Drug Concentration (C_{ss})

- 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.
- 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.

Steady-State Drug Concentration (C_{ss})



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

Steady-State Drug Concentration (C_{ss})

- C_{ss} can also obtained as follows, because at C_{ss} the net change in the plasma drug concentration is equal to zero.

the steady-state concentration (C_{SS}) is dependent on:

- ✓The volume of distribution.
- ✓The elimination rate constant.
- ✓The infusion rate.

Altering any one of these factors can affect steady-state concentration.

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

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

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

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

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

Example

- An antibiotic has a volume of distribution of 10L and a *k* of 0.2 hr^{-1}. A steady-state plasma concentration of 10 µg/ml is desired.

  I. Determine the infusion rate needed to maintain this concentration.

  II. Assume the patient has a uremic condition and the elimination rate constant has decreased to 0.1 hr^{-1}., Determine a new rate of infusion to maintain the steady-state concentration of 10 µg/ml.

  III. Detrmine the time needed for a drug to reach 99% C_{SS}.

Solution

I.

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

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

$$R = 20 mg / hr$$

II.

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

$$R = 10 mg / hr$$

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.

Solution

III. $C_{SS} = \frac{R}{V_D k}$ and 99% steady-state level is

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

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

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

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

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

Solution

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:
The time needed to reach steady state is not dependent on the rate of infusion, but only on the elimination half-life.

Intravenous Infusion One-Compartment Model

- Intravenous infusion may be used to determine total body clearance if the infusion rate and steady-state level are known.

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

$$C_{ss} = \frac{R}{V_D k} = \frac{R}{Cl_T}$$

$$Cl_T = \frac{R}{C_{ss}}$$

Example

- 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.

$$Cl_T = \frac{R}{C_{ss}} = \frac{2mg/hr}{10mg/l} = 200ml/hr$$

  - 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}.

Infusion Method for Calculating Patient Elimination Half-Life

- An IV infusion Eq. may be used to calculate *k*, or indirectly the elimination half-life of the drug in a patient.

$$C_P = \frac{R}{V_D k}\left(1 - e^{-kt}\right) \quad \text{since,} \quad C_{ss} = \frac{R}{V_D k}$$

$$C_P = C_{ss}\left(1 - e^{-kt}\right)$$

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

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 hrs

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

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

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

✓The $t_{1/2}$ 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 IV infusion.

✓This method may be sufficient in clinical practice.

✓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 .

Example # 2

- If the desired therapeutic plasma concentration is 8 mg/L for the previous 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:

$$Cl_T = \frac{R}{C_{ss}} = \frac{15mg/hr}{6.5mg/l} = 2.31l/hr$$

Solution

- The new infusion rate should be:

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

- 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:

$$C_1 = C_0 e^{-kt} = \frac{D_L}{V_D} e^{-kt}$$

- and concentration by infusion at the rate *R* is:

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

Loading Dose Plus IV Infusion: One-Compartment Model

- 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

$$C_P = C_1 + C_2$$

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

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

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

Loading Dose Plus IV Infusion: One-Compartment Model

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

$$D_L = C_{SS} V_D \rightarrow C_{SS} V_D = R / k$$

$$D_L = \frac{R}{k}$$

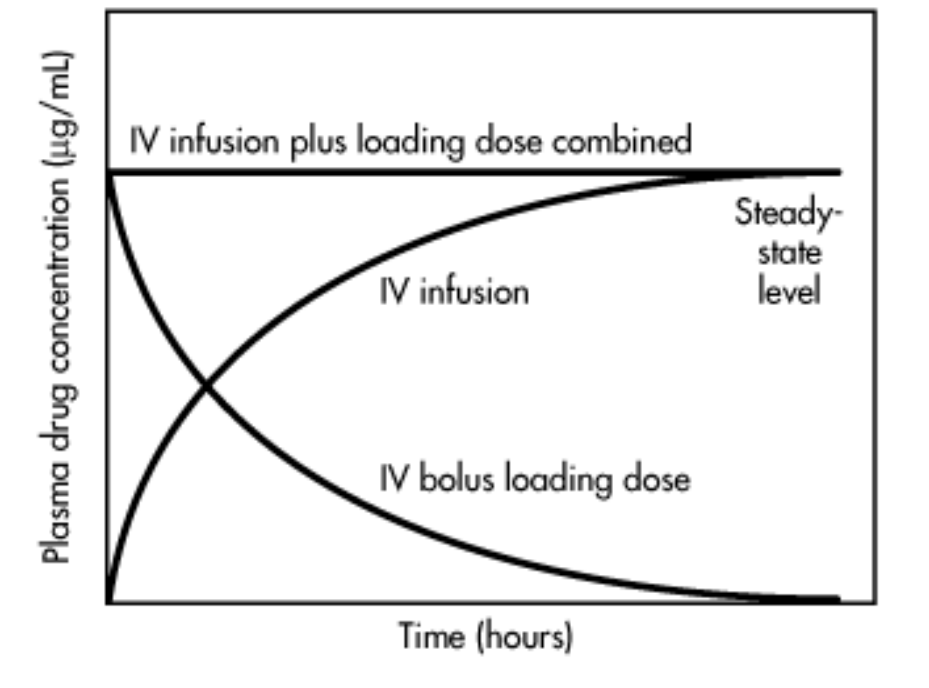
- C_P is the same as steady state,

$$C_P = \frac{R}{V_D k}$$

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

Loading Dose Plus IV Infusion:

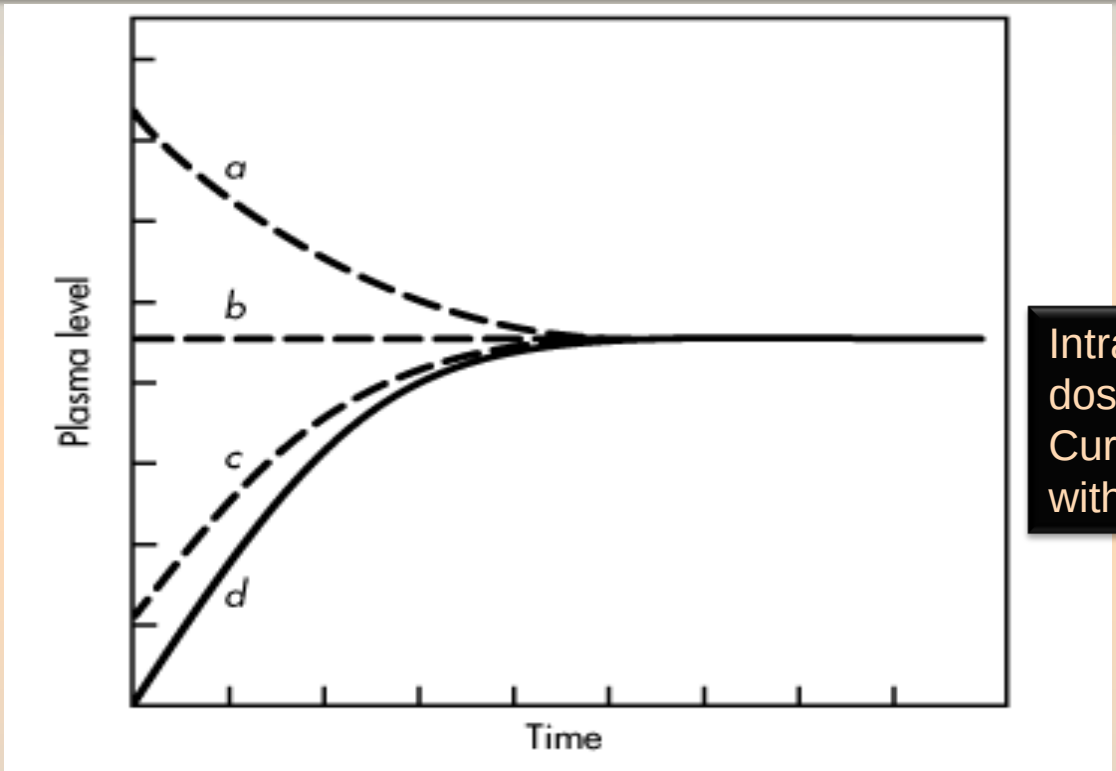
One-Compartment Model



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.

Loading Dose Plus IV Infusion: One-Compartment Model

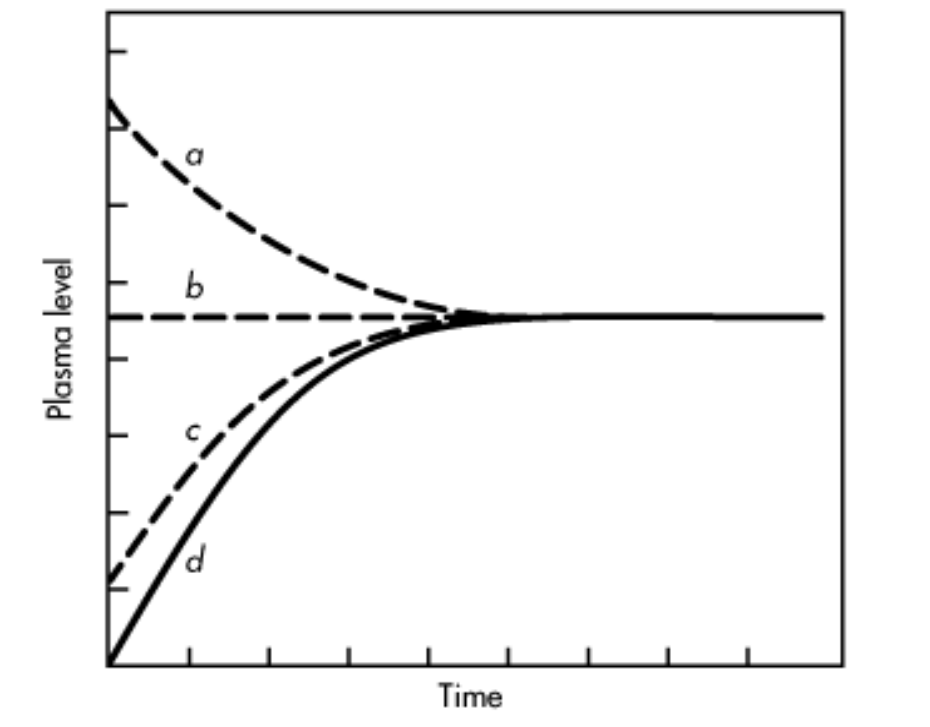


Intravenous infusion with loading doses *a*, *b*, and *c*.
Curve *d* represents an IV infusion without a loading dose.

- 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.

Loading Dose Plus IV Infusion:

One-Compartment Model



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

- 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.

Example # 1

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

Solution

$$k = \frac{0.693}{3} = 0.231 hr^{-1}$$

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

$$C_P = \frac{10000 \mu g}{10000 ml} e^{-0.231 \times 6} + \frac{2000 \mu g / hr}{10000 ml \times 0.231 hr^{-1}}\left(1 - e^{-0.231 \times 6}\right)$$

$$C_P = 0.90 \mu g / ml$$

Example # 2

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

Solution

$$C_P = \frac{R}{V_D k}\left(1 - e^{-kb}\right)e^{-k(t-b)}$$

$$C_P = \frac{200}{(0.01)(10{,}000)}\left(1 - e^{-0.1\times 6}\right)e^{-0.01(8-6)}$$

$$C_P = 1.14\,\mu g / ml$$

Where:

b = length of time of infusion period.

t = total time (infusion and post-infusion).

$t - b$ = length of time after infusion has stopped.

Solution

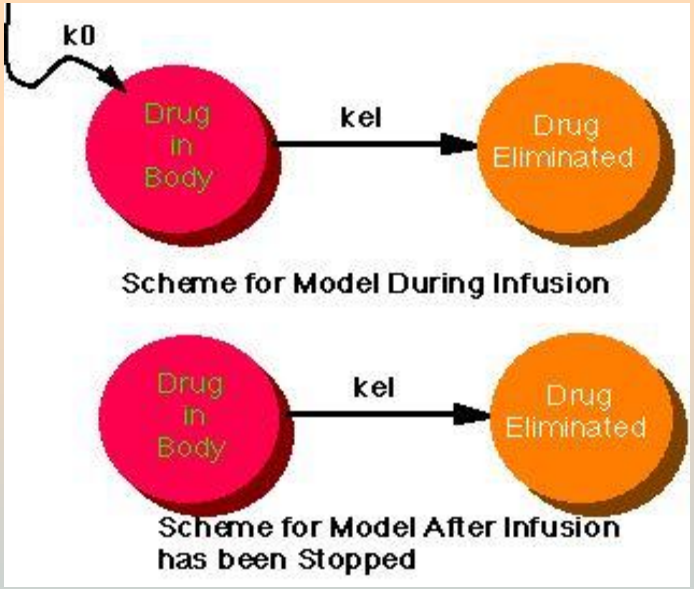
Alternatively, when infusion stops, C'_p is calculated:

$$C_P' = \frac{R}{V_D k}\left(1 - e^{-kt}\right)$$

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

$$C = C_P' e^{-0.01\times 2}$$

$$C_P = 1.14 \mu g / ml$$



During and After an IV Infusion - One Compartment Model

Example # 3

- 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 1.25L/kg, and is effective at a plasma drug concentration of 14mg/L. The drug is supplied in 5-mL ampuls containing 150 mg/mL.

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}.

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

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

$$(485.1 mg)(ml/150 mg) = 3.23 ml$$
$$Thus,\ R = 3.23 ml/hr$$

Estimation of Drug Clearance and V_D from Infusion Data

- The drug concentration in this model can be described in terms of volume of distribution (V_D) and total body clearance (Cl)

$$k = Cl / V_D$$

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

- 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.