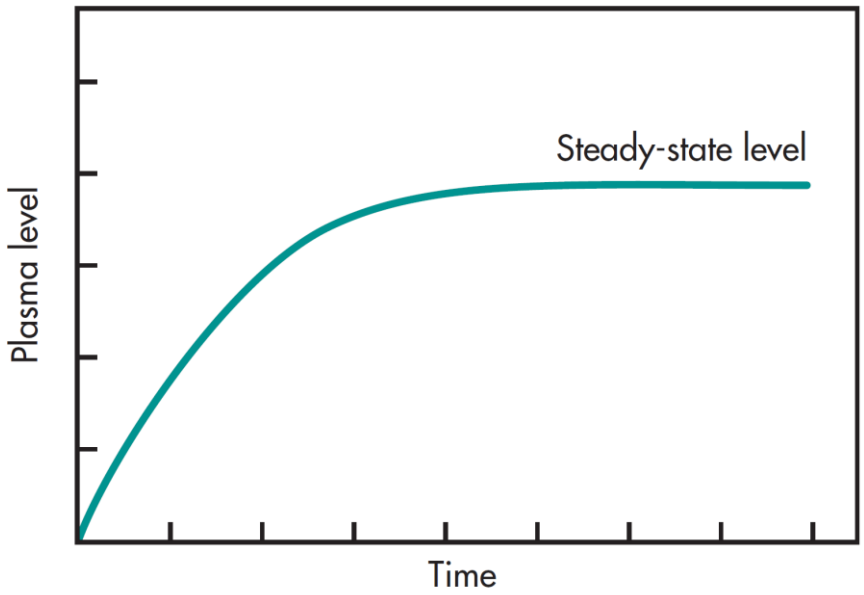
Intravenous Infusion

Parenteral routes of administration include intravenous, subcutaneous, and intramuscular. Intravenous (IV) drug solutions may be either injected as a bolus dose (all at once) or infused slowly through a vein into the plasma at a constant rate (zero order).

The advantages for giving a drug by IV infusion include:

1. Precise control of plasma drug concentrations to fit the individual needs of the patient. This is important for drugs with narrow therapeutic window (eg, heparin).
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.



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 $dC_p/dt = 0$,

Rate of drug input (infusion rate) = rate of drug output (elimination rate)

IV Infusion of Drugs that follow one-compartment model

The input of drug to the body is determined by the infusion rate (zero order) and the elimination from the body is, in most cases, first-order process.

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.

$$\boldsymbol{dD_B/dt = R - kD_B}$$

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).

Since $D_B = C_p V_D$, then

$$\boldsymbol{C_p = \frac{R}{V_D K}\left(1 - e^{-kt}\right)}$$

Where C_p is plasma concentration at any time during infusion (before reaching steady state concentration, C_{ss})
When C_{ss} is reached t = ∞ and the value of e^{-kt} approaches zero. Therefore:

$$\boldsymbol{C_{ss} = \frac{R}{V_D K} = \frac{R}{Cl}}$$

The time required to reach 99% of C_{ss} is 6.6 half-life

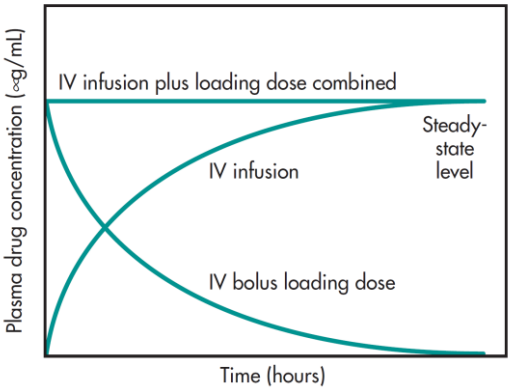
Note: for zero-order elimination processes, if rate of input is greater than rate of elimination, plasma drug concentrations will keep increasing and no steady state will be reached. This is a potentially dangerous situation that will occur when saturation of metabolic process occurs.

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 calculation of loading dose (IV bolus) required to instantly achieve C_{ss} can be calculated from the following equation assuming that both loading dose and infusion are started concurrently.

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



PRACTICE PROBLEMS

1. A physician wants to administer an anesthetic agent at a rate of 2 mg/h by IV infusion. The elimination rate constant is 0.1 h^{-1} and the volume of distribution (one compartment) is 10 L. How much is the drug plasma concentration at the steady state? What loading dose should be recommended to reach steady state immediately?

Solution

$$C_{ss} = \frac{R}{V_D K} = \frac{2}{10 \times 0.1} = 2 \text{ mg/L } (\mu g/mL)$$

To reach C_{ss} instantly,

$$D_L = \frac{R}{k} = \frac{2}{0.1} 20\, mg$$

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

Solution

In this question we don't know if the administered loading dose is enough to reach the Css instantly. Therefore, the concentration in plasma will equal to the summation of concentrations from loading dose and the infusion of the drug.

$$C_p = C_p^0 e^{-kt} + \frac{R}{V_D K} (1 - e^{-kt})$$

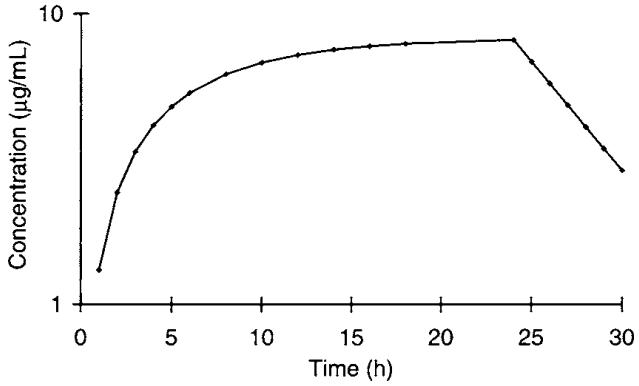
$$C_p^0 = \frac{D}{Vd}, \quad k = \frac{0.693}{t_{1/2}}$$

$$C_p = \frac{10}{10} e^{-0.231 \times 6} + \frac{2}{10 \times 0.231} (1 - e^{-0.231 \times 6}) = 0.9 \text{ mg/L}$$

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

Solution

If we calculate $t_{1/2}$ the value will be 69.3 h which means that Css has not been achieved following the infusion of the drug for 6 h. In this case we should calculate the concertation of the drug at the end of the infusion time then calculating the decrease in plasma concentration following the cessation of infusion.



Following the cessation of infusion, the decline in plasma concentration for a drug that follows one-compartment model can be calculated from the equation:

$C_p = C_{end}\, e^{-kt}$, where C_{end} in this case is the concentration at the end of infusion and t is the time after the infusion has been stopped.

To solve the above question, we should calculate the concentration at the end of infusion

$$\boldsymbol{C_{end} = \frac{R}{V_D K}\left(1 - e^{-kt}\right) = \frac{2}{10 \times 0.01}\left(1 - e^{-0.01 \times 6}\right) = 1.165\ mg/L}$$

$C_p = C_{end}\, e^{-kt}$ = 1.165 $e^{-0.01 \times 2}$ = 1.14 mg/L the concentration following 2 h after the end of infusion.