IV Infusion

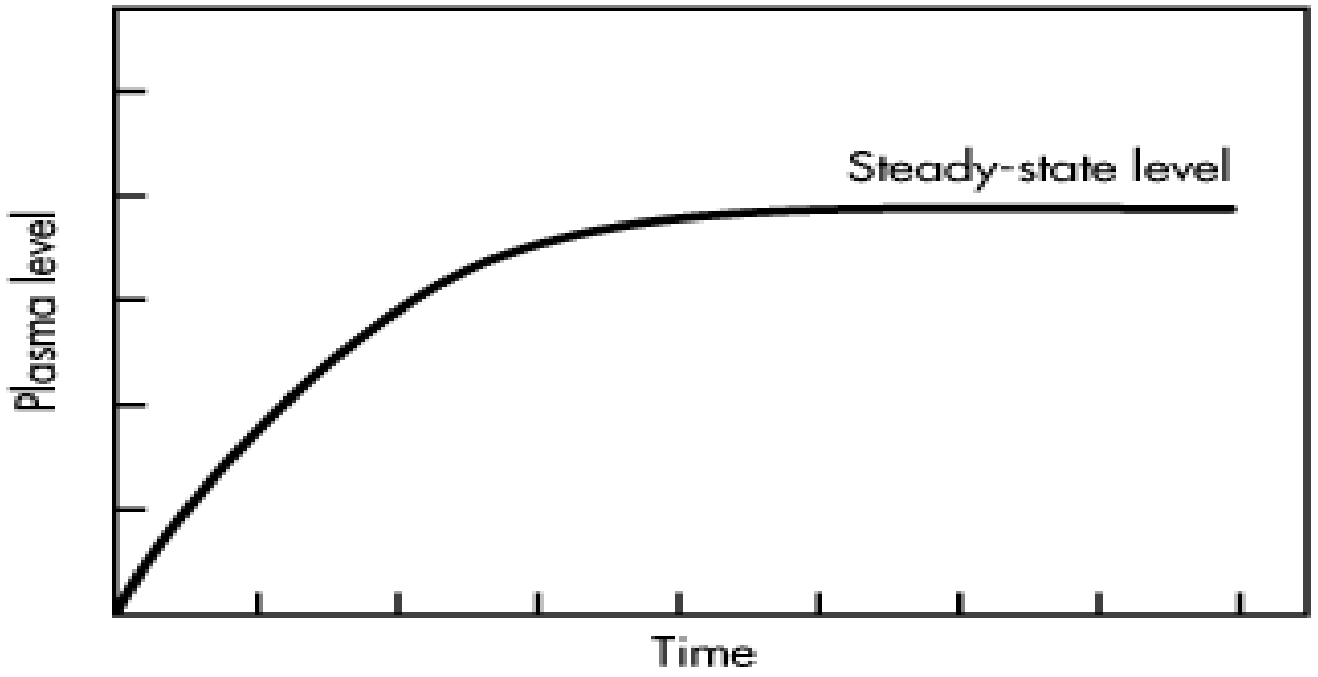
IV solutions

- **Dose infused slowly** through vein into plasma at **zero-order rate**.
- At steady state, **rate of drug leaving** body = **rate of drug (infusion rate) entering** body.
- **at steady state**, rate change in plasma drug conc, $dC_p/dt = 0$.

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

advantage for IV infusion

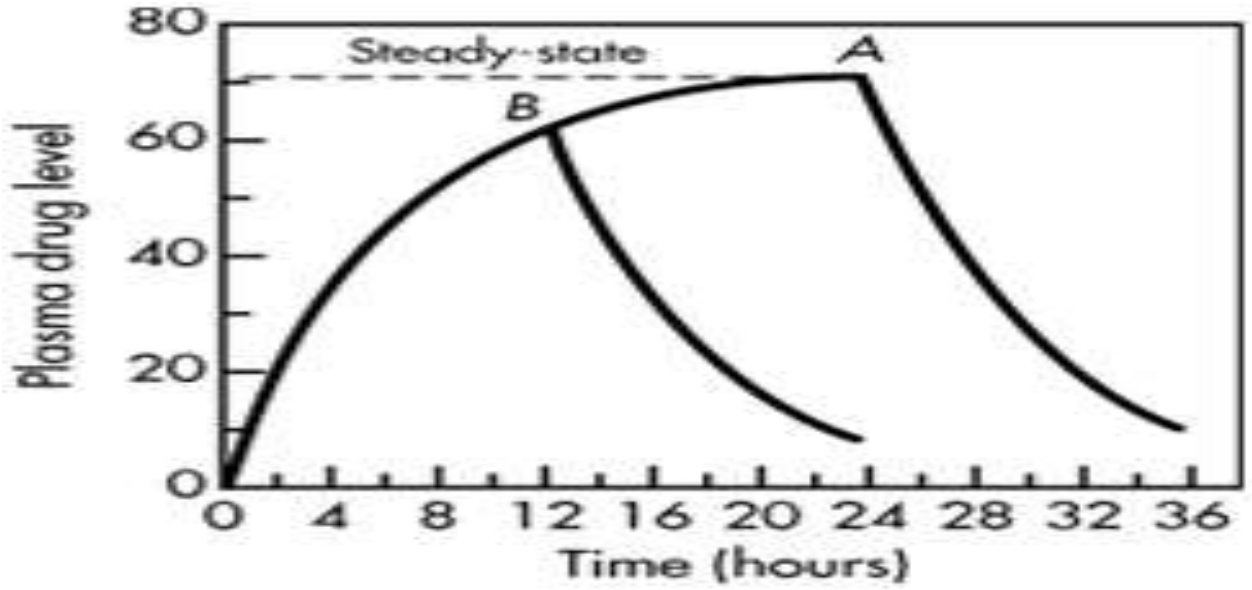
1. P**recise control of plasma conc.**
2. Narrow therapeutic index (heparin) maintains constant plasma drug conc by eliminating wide fluctuations between Cmax and Cmin.
3. Antibiotics, given with IV fluids.
4. The duration of drug therapy maintained as needed.



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

ONE-COMPARTMENT MODEL DRUGS

- 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: rate input –rate output.



$$\frac{dD_B}{dt} = R - kD_B \qquad (5.1)$$

$D_B = C_p V_D$

zero order – First order

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

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

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

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

- **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 $-k/2.3$.

- The time required to reach Css in plasma depend on Ke of drug for constant Vd.

- During IV infusion, the drug concentration increases in the plasma and the rate of drug elimination increases because rate of elimination is concentration dependent.
- ***C* p keeps increasing until** Css.
- C_{SS} is related to rate of infusion and inversely related to body clearance of drug.

- During IV infusion, the drug concentration increases in the plasma and the rate of drug elimination increases because rate of elimination is concentration dependent.

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

- increase in the infusion rate will not shorten the time to reach the steady-state 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

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

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

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

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

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

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

1. the volume of distribution,
2. the elimination rate constant, and
3. 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 g/mL, we must determine a new rate of infusion as follows.

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

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

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

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

- **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.

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

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

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

- **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.

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

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

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

- **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? From above

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

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

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

LOADING DOSE PLUS IV INFUSION

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,

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

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

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

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

- **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?

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

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

- **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)?

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

$$C_{\text{P}} = \frac{D_{\text{L}}}{V_{\text{D}}} e^{-kt} - \frac{R}{V_{\text{D}} k} \left(1 - e^{-kt}\right)$$

$$C_{\text{P}} = \frac{10{,}000}{10{,}000}\, e^{-(0.693/3)(6)} - \frac{2{,}000}{(10{,}000)\,(0.693/3)} \left(1 - e^{-(0.693/3)(6)}\right)$$

$$C_{\text{P}} = 0.90\ \mu\text{g/mL}$$

where b = length of time of infusion period, t = total time (infusion and post infusion), and $t - b$ =

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

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

- **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?

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

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

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

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

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

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

- **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?

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

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

$$D_L = 184\ mg\ aminophylline$$

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

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

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

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

- **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.

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

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

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

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

Thus, R = 3.23 mL/hr.