Biopharmaceutics

4th Stage

College of Pharmacy

Lecture 4: INTRAVENOUS INFUSION

By : Dr. Nizar Awish Jassem

Ph.D in Pharmaceutics

2026 -2027

Semester: 1st

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 advantages for IV infusion :

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.

Steady-State Plasma Drug Concentration During Constant IV Infusion

- Plasma drug concentration increases progressively from zero and eventually reaches a plateau known as the **steady state**.
- At steady state, the **rate of drug infusion (entering) equals the rate of drug elimination**.
- Consequently, at steady state, plasma drug concentration remains constant over time, with $dC_p/dt=0$.

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

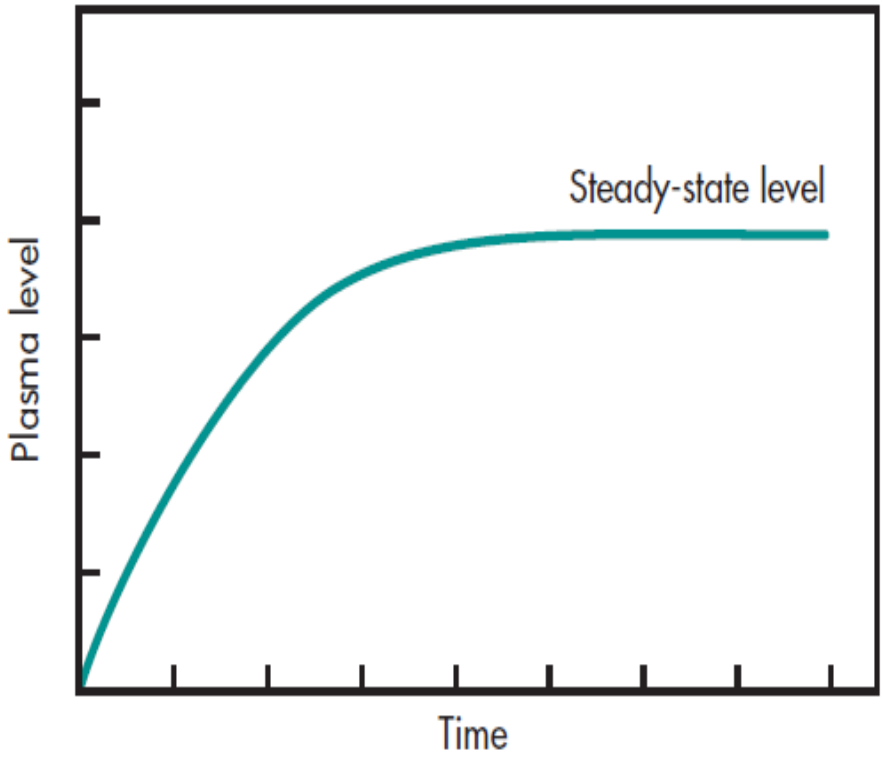


FIGURE: Plasma level-time curve for constant IV infusion.

ONE-COMPARTMENT MODEL DRUGS - INTRAVENOUS 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.**

$$\frac{dD_B}{dt} = R - kD_B \qquad (6.1)$$

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 6.1 and substitution of $D_B = C_p V_D$ gives

$$C_p = \frac{R}{V_D k}(1 - e^{-kt}) \qquad (6.2)$$

Equation 6.2 gives the **plasma drug concentration at any time during the IV infusion**, where *t* is the time for infusion.

At infinite time $t = \infty$, e^{-kt} approaches zero, and Equation 6.2 reduces to Equation 6.4, as the steady-state drug concentration (*C*ss).

$$C_p = \frac{R}{V_D k}(1 - e^{-\infty}) \qquad (6.3)$$

$$C_{ss} = \frac{R}{V_D k} \qquad (6.4)$$

The body clearance, ***Cl***, is equal to $\boldsymbol{V_D k}$, therefore:

$$C_{ss} = \frac{R}{V_D k} = \frac{R}{Cl} \qquad (6.5)$$

Steady-State Drug Concentration (*Css*) and Time Needed to Reach *Css*

- 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***.
- 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 = $k\ C_p$).
- 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 dr***ug, as shown in Equation 6.6.

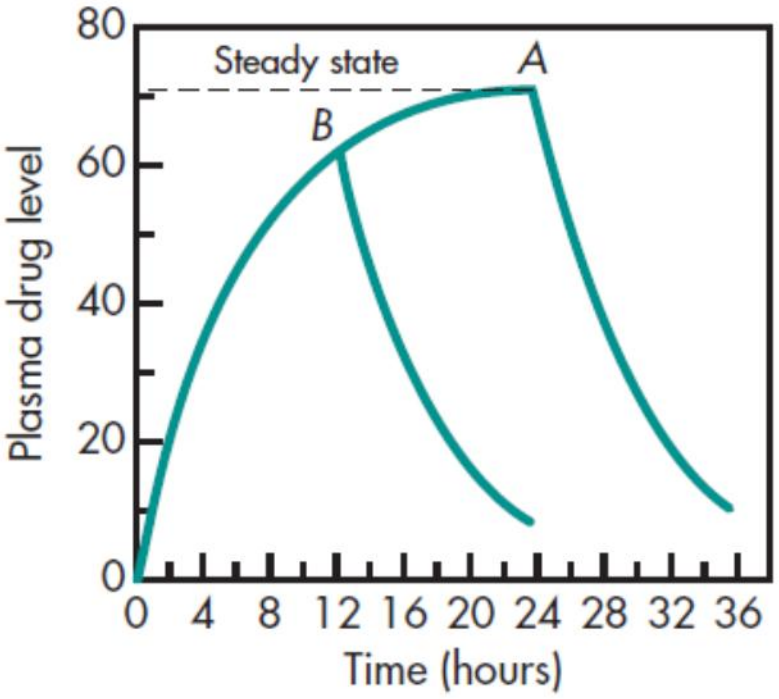
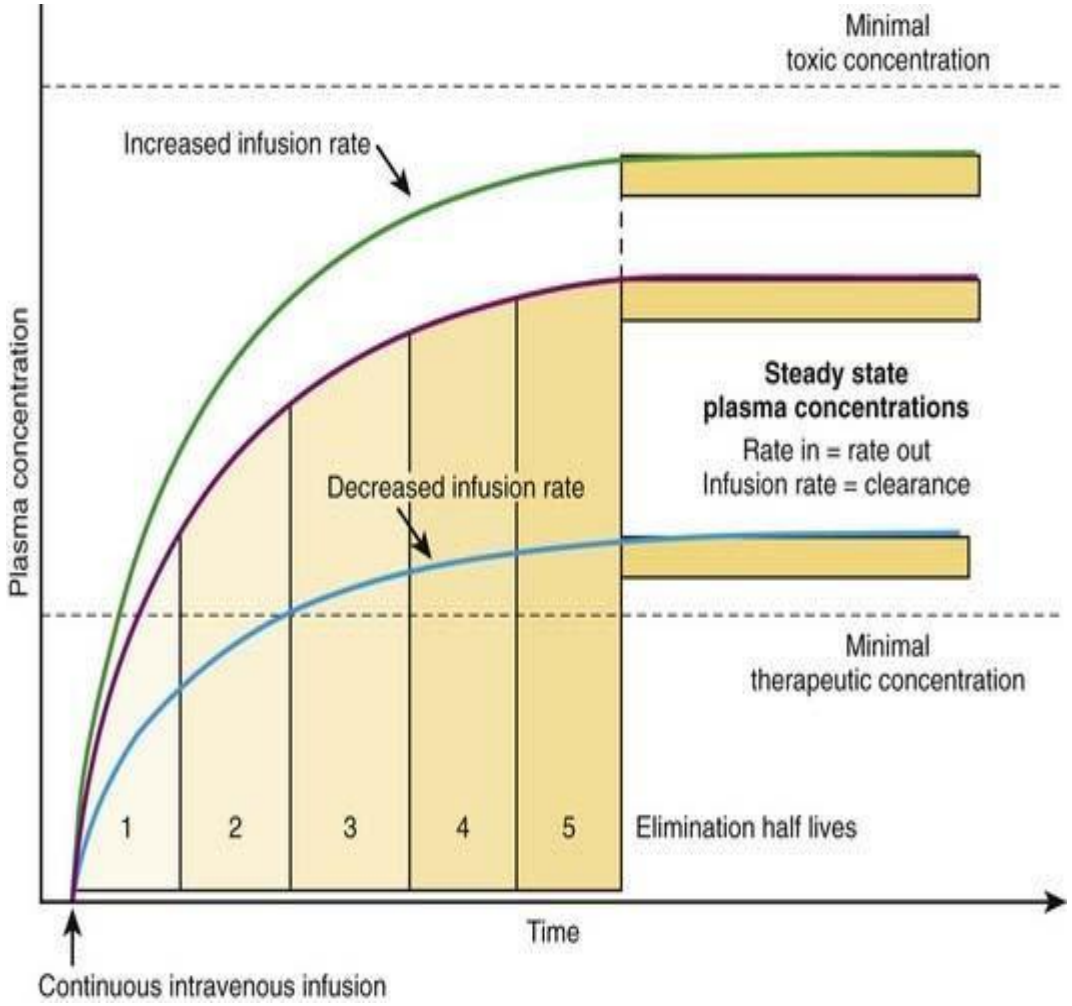


FIGURE: Plasma drug concentration-time profiles after IV infusion. IV infusion is stopped at steady state (*A*) or prior to steady state (*B*). In both cases, plasma drug concentrations decline exponentially (first order) according to a similar slope.

- 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**.
- i.e. Increasing the infusion rate increases the steady-state concentration, but it does not change the time required to reach steady state, provided the drug follows linear, first-order pharmacokinetics.



Equation for steady-state concentration

- 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.
- Equation 6.6 shows that the steady-state concentration (C_{ss}) is dependent on the volume of distribution, the elimination rate constant, and the infusion rate.

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

$$\frac{dC_p}{dt} = \frac{R}{V_D} - kC_p = 0$$

$$(\text{Rate}_{in}) - (\text{Rate}_{out}) = 0$$

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

$$C_{ss} = \frac{R}{V_D k} \qquad (6.6)$$

The time required to reach steady state depends mainly on the drug's elimination half-life $t_{1/2}$

- It generally takes about **4–5 half-lives to reach approximately 94–97% of steady state**.

Example

- A drug has an elimination half-life of 6 hours. How long will it take to reach approximately 95%of steady state?
- Therefore,

$$\text{Time} = 4.32 \times t_{1/2}$$

$$= 4.32 \times 6 = \boxed{25.92 \text{ hours}}$$

Therefore, it takes approximately **26 hours**.

- The calculation of the values in is given in the example that follows

Percentage of C_{ss} reached	Number of half-lives
50%	1
75%	2
87.5%	3
90%	3.32
95%	4.32
97%	5
99%	6.65

Parameters affects steady-state concentration

Parameter increases	Effect on C_{ss}
Infusion rate (R_0)	Increases
Clearance (CL)	Decreases
Elimination rate constant (k), with fixed V_d	Decreases
Volume of distribution (V_d), with fixed k	Decreases

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 ug/mL is desired. what is The **infusion rate** needed to maintain this concentration?

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

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

$$= 20\ mg/h$$

- IV infusion may be used to determine **total body clearance** if the infusion rate and the steady-state level are known, as with Equation 6.6 repeated here:

$$C_{ss} = \frac{R}{V_D k} \qquad (6.6)$$

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

Because total body clearance, Cl_T, is equal to $V_D k$,

$$Cl_T = \frac{R}{C_{ss}} \qquad (6.7)$$

Example

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

Solution

The total body clearance may be estimated from Equation 6.7. The serum sample was taken after 2 days or 48 hours of infusion, which time represents 8 × $t_{1/2}$; therefore, this serum drug concentration approximates the *C*ss.

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

INFUSION METHOD FOR CALCULATING PATIENT ELIMINATION HALF-LIFE

- The C_p-versus-time relationship that occurs during an IV infusion (Equation 6.2) may be used to calculate *k*, or indirectly the elimination half-life of the drug in a patient.
- To simplify calculation, Equation 6.2 is arranged to solve for *k*:

$$C_p = \frac{R}{V_D k}(1 - e^{-kt}) \qquad (6.2)$$

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

substituting into Equation 6.2:

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

Rearranging and taking the log on both sides:

$$\log\left(\frac{C_{ss} - C_p}{C_{ss}}\right) = -\frac{kt}{2.3}$$

$$k = \frac{-2.3}{t}\log\left(\frac{C_{ss} - C_p}{C_{ss}}\right) \qquad (6.8)$$

where C_p is the plasma drug concentration taken at time *t*, and **Css** 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

2nd plasma sample was taken at 24 hours, or 24/6 = 4 half-lives after infusion, which approaching 95% of the plasma **steady-state drug** concentration assuming the extreme case of $t_{1/2}$ = 6 hours. By substitution into Equation 5.8,

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

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

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

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

$$C_{ss} = R/Cl$$

$$Cl = R/C_{ss} = 15/6.5 = 2.31\ \text{L/h}$$

The new infusion rate should be

$$R = C_{ss} \times Cl = 8 \times 2.31 = 18.48\ \text{mg/h}$$

- 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.
- 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 6.4, $C_{ss}V_D = R/k$. Therefore,

$$D_L = R/k \qquad (6.12)$$

- expression for Css or steady-state plasma concentrations (Equation 6.14 is identical to Equation 6.6):

$$C_p = \frac{R}{V_D k} \qquad (6.13)$$

$$C_{ss} = \frac{R}{V_D k} \qquad (6.14)$$

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

$$\frac{D_L k}{V_D} = \frac{R}{V_D} \qquad (6.17)$$

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

- Another method for the calculation of loading dose *D*L is based on knowledge of the desired steady-state drug concentration ***Css*** and the apparent volume of distribution V_D for the drug, as shown in Equation 6.18.

$$D_L = C_{ss} V_D \qquad (6.18)$$

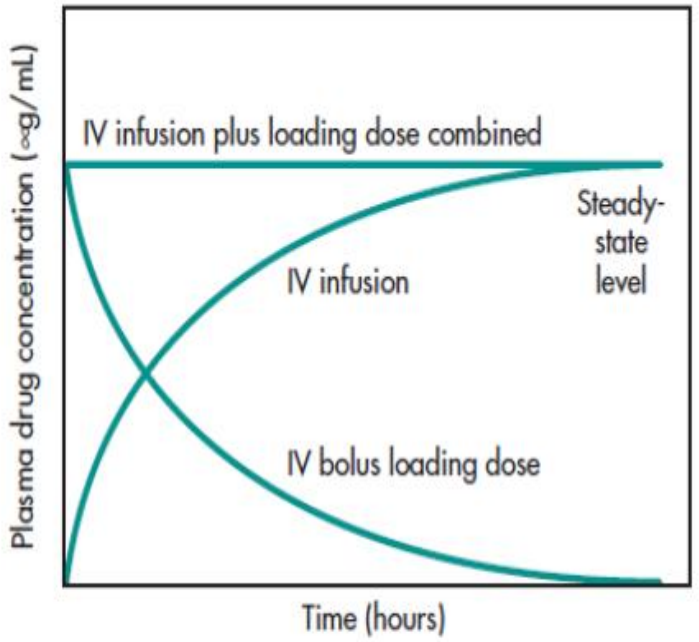


FIGURE 6-4 IV infusion with loading dose D_L. The loading dose is given by IV bolus injection at the start of the infusion. Plasma drug concentrations decline exponentially after D_L whereas they increase exponentially during the infusion. The resulting plasma drug concentration–time curve is a straight line due to the summation of the two curves.

Adding up the two equations yields Equation 6.15, an equation describing **simultaneous infusion after a loading dose**.

$$C_p = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k}(1 - e^{-kt}) \qquad (6.15)$$

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.

1. How much is the drug plasma concentration at the steady state?
2. What loading dose should be recommended to reach steady state 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,

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

Practice Problems 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)?

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

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

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

$$+ \frac{2000}{(10{,}000)(0.693/3)}(1 - e^{-(0.693/3)(6)})$$

$$C_p = 0.90\ \mu\text{g/mL}$$

Estimation of Drug Clearance (CL) and Volume of Distribution V D from Infusion Data

- During a constant-rate intravenous infusion, the plasma drug concentration increases until it reaches a steady-state concentration Css.
- Two important pharmacokinetic parameters can be estimated from infusion data:
  - Clearance (CL): the volume of plasma cleared of drug per unit time.
  - Volume of distribution VD: a theoretical volume that relates the amount of drug in the body to its plasma concentration.

Main equation

- The plasma concentration during constant-rate infusion is:

$$C_p = \frac{R}{Cl}(1 - e^{-(Cl/V_D)t}) \qquad (6.21)$$

Important relationships

$$k = \frac{CL}{V_D}$$

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

- In this model, the time for steady state and the resulting steady-state concentration will be dependent on both clearance and volume of distribution.

Home work

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 ($\boldsymbol{C_{ss}}$) for this antibiotic is 10 *u*g/mL.

a. Assuming no loading dose, how long after the start of the IV infusion would it take to reach 95% of the $\boldsymbol{C_{ss}}$?
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 $\boldsymbol{C_{ss}}$ 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 *u*g/mL.