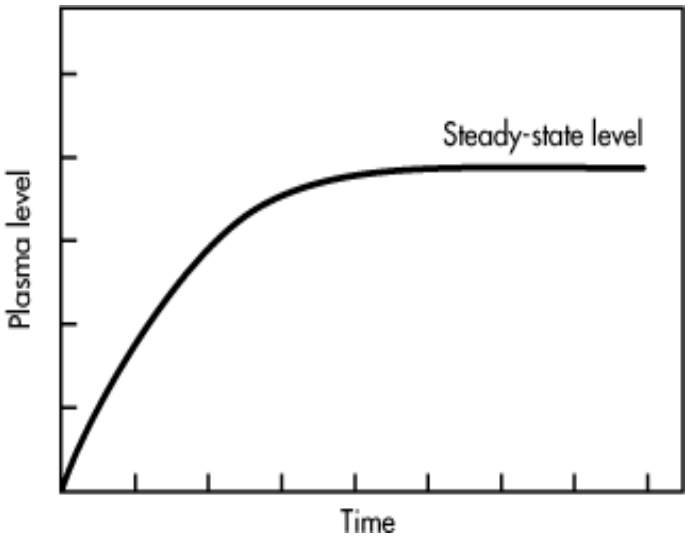
Pharmacokinetics of Intravenous Infusion

*Intravenous (IV) drug solutions may be given either as a bolus dose (injected all at once) that produce the desired therapeutic concentration immediately or infused slowly through a vein into the plasma at a constant or zero-order rate.

*The main advantage for giving a drug by IV infusion is that IV infusion allows precise control of plasma drug concentrations by maintaining drug concentration within the therapeutic range for a longer duration 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.

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



*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 = 0

* Duration of drug therapy may be maintained or terminated as needed using I.V. infusion

One-Compartment Model Drugs

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 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), and k is the elimination rate constant (first order).

By integration and substitution of $D_B = C_p V_D$ gives:

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

- The amount of drug in blood will be influenced by the chosen infusion rate and the duration of infusion.

The infusion rate (R) of a drug is controlled by:

- The flow rate (e.g. mL/h)
- Concentration (mg/mL or % w/v) of the drug in solution.

Example / 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?

- R= 1x75=75/ 60= 1.25 mg/min

  R= flow rate x concentration

1.25mg/min=25mg/ml x flow rate

- Flow rate= 1.25 mg/min / 25 mg/ml = **0.05 ml/min**

Steady State Concentration (Css) and Time Needed to Reach Css

*Mathematically, the time to reach true steady-state concentration, *Css*, would take an infinite time. The time required to reach the Css in the plasma is dependent on the elimination rate constant of the drug for a constant volume of distribution.

*For a zero-order elimination process, if the rate of input is greater than the rate of elimination, plasma drug concentration 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.

*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 5 $t_{1/2}$, or 5 x 6 hours = 30 hours.

*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. So doubling the infusion rate will not allow the steady-state condition to be achieved faster but the steady-state plasma concentration will also double.

* The true steady-state plasma concentration which will be attained only at time infinity.

– When t = ∞ Cp = (Cp)ss **WHY**

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

*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 C_{SS}.

* If a patient exhibits renal impairment (indicated by lowered creatinine clearance), this will be reflected in lower systemic clearance of a drug undergoing elimination via the kidneys. Therefore the same infusion rate will yield a higher, and perhaps toxic, plasma concentration of the drug, **so the infusion rate of a drug is reduced.**

Examples

1. An antibiotic has a volume of distribution of 10 L and *k* of 0.2 1/hr. A steady-state plasma concentration of 10 µg/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows.

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

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

$$R = 20\ mg/hr$$

2. 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 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

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

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

Rearranging and taking the log on both sides

$$\log\left(\frac{C_{SS} - C_P}{C_{SS}}\right) = -\frac{kt}{2.3}$$

Examples

3-An antibiotic has an elimination half-life of 3- 5 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 drug half-life in this patient?

Because the second plasma sample was taken at 24 hours, or 24/5 ≈ 5 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 = 5 hours.

$$\log\left(\frac{C_{SS}-C_P}{C_{SS}}\right) = -\frac{kt}{2.3}$$

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

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

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

4- If the desired therapeutic plasma concentration is 8 mg/L for the above patient, what is a suitable infusion rate for the patient?

From last example, 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:

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

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

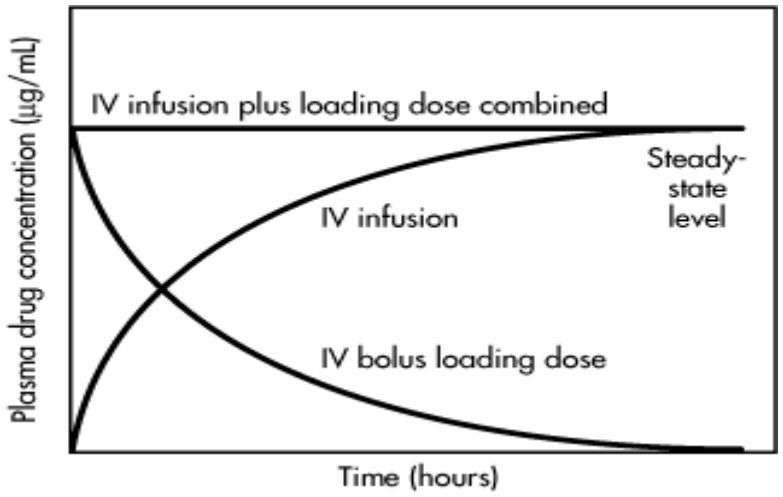
The new infusion rate should be

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

Loading Dose plus IV Infusion: One-Compartment Model

Life-threatening situations in the hospital setting will often demand that the desired plasma concentration of the drug (of course, always within its therapeutic range) is attained instantaneously and then is maintained for a long duration.

This may be accomplished by administering a loading intravenous bolus dose (D_L) concomitant with the commencement of the infusion rate.



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.

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

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

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 $C1 + C2$, due to the sum contributions of bolus and infusion

$$C_P = C_1 + C_2$$

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

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

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

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

$$D_L = C_{SS} V_D$$

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

By substitution in the main equation:

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

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

Therefore, if an IV loading dose is given followed by an IV infusion, steady-state plasma drug concentrations are obtained **immediately and maintained.**

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 1/hr, 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 µg/mL immediately?

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

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 2.0 mg/hr (the drug has $t_{1/2}$ of 3 hr and a volume of distribution of 10 L)?

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

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

$$C_P = \frac{10{,}000}{10{,}000} e^{-(0.693/3)(6)} + \frac{2{,}000}{(10{,}000)(0.693/3)}(1 - e^{-(0.693/3)(6)})$$

$$C_P = 0.86\ \mu g/mL$$

Calculation the drug concentration in the blood after infusion has been stopped:

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

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.

3. 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?

$$C_P = \frac{2000}{(0.01)(10{,}000)}(1-e^{-0.01(6)})e^{-0.01(8-6)}$$

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

Special Case

4. A 78 kg adult male asthmatic patient with a history of heavy smoking was given an IV infusion of aminophylline at a rate of 0.6 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 µg/mL of theophylline. The apparent V D for theophylline is 0.45 L/kg. Aminophylline is the 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 µg/mL. What dosage recommendation would you give the physician? Would you recommend another loading dose?

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 5 $t_{1/2}$ to reach 95% of Css. Therefore, a second loading dose should be recommended to rapidly increase the plasma theophylline conc. to 10 µg/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.

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

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.

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

$$D_L = 184\ mg\ aminophylline$$

The maintenance IV infusion rate may be calculated after estimation of the patient's clearance, Cl_T.

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

$$Cl_T = 8.07\ L/hr$$

The new IV infusion rate, R', is calculated by

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

$$R' = 10\ mg/L\ .\ 8.07 L/hr \quad = 80.7\ mg/hr$$