INTRAVENTOUS INFUSION

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

1. The IV infusion allows precise control of plasma drug concentrations to fit the individual needs of the patient.
2. Drugs with a narrow therapeutic window (e.g., heparin), IV infusion maintains an effective constant plasma drug concentration by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug 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.

The plasma drug concentration-versus-time curve of a drug given by constant IV infusion is shown in the figure 1.

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:

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

Rate of drug input (infusion rate) = Rate of drug output (elimination rate)
A pharmacokinetic equation for infusion may be derived depending on whether the drug follows one- or two-compartment kinetics.

**ONE-COMPARTMENT MODEL DRUGS**

The pharmacokinetics of a drug given by constant IV infusion follows a zero-order input process.

The change in the amount of drug in the body at any time \( \frac{dD_B}{dt} \) during the infusion is the rate of input minus the rate of output.

\[
\frac{dD_B}{dt} = R - kD_B \quad \ldots \ldots 1
\]

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 1 and substitution of \( D_B = C_pV_D \) gives:

\[
C_p = \frac{R}{V_D k} \left(1 - e^{-kt}\right) \quad \ldots \ldots 2
\]

As the drug is infused, the value for time (t) increases in Equation 2. At infinite time, \( t = \infty \), \( e^{-kt} \) approaches zero, and Equation 2 reduces to Equation 4

\[
C_p = \frac{R}{V_D k} \left(1 - e^{-\infty}\right) \quad \ldots \ldots 3
\]

\[
C_{ss} = \frac{R}{V_D k} \quad \ldots \ldots 4
\]

\[
C_{ss} = \frac{R}{V_D k} = \frac{R}{cl} \quad \ldots \ldots 5
\]

**Steady-State Drug Concentration (C_{ss}) and Time Needed to Reach C_{ss}**

There is no net change in the amount of drug in the body, \( D_B \), as a function of time during steady state \( i.e. \), 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 the steady-state drug concentration in the plasma is dependent on the elimination rate constant of the drug for a constant volume of distribution, as shown in Equation 4.

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.

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, at which time the rate of drug input (IV infusion rate) equals the rate of drug output (elimination rate).

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 $5 \times 1/2$, or $5 \times 6$ hours = 30 hours.

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.

<table>
<thead>
<tr>
<th>Percent of $C_{ss}$ Reached (a)</th>
<th>Number of Half-Lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>3.32</td>
</tr>
<tr>
<td>95</td>
<td>4.32</td>
</tr>
<tr>
<td>99</td>
<td>6.65</td>
</tr>
</tbody>
</table>

Table 1: number of $t_{1/2}$ s to reach a fraction of $C_{ss}$

Figure 3: Plasma level-time curve for IV infusions given at rates of $R$ and $2R$, respectively.
\[ \frac{dC_p}{dt} = 0 \]
\[ \frac{dC_p}{dt} = \frac{R}{V_D} - kC_p = 0 \]
\[ (\text{Rate in}) - (\text{Rate out}) = 0 \]
\[ \frac{R}{V_D} = kC_p \]
\[ C_{ss} = \frac{R}{V_D k} \]

Equation 6 shows that 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 steady-state concentration.

**Examples 1:** An antibiotic has a volume of distribution of 10 L and a \(k\) of 0.2 hr\(^{-1}\). A steady-state plasma concentration of 10 µg/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows. Equation 6 can be rewritten as

\[ R = C_{ss} V_D k = (10 \text{µg/mL}) (10)(1000\text{mL})(0.2 \text{ hr}^{-1}) = 20 \text{ mg/h} \]

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 µg /mL, we must determine a new rate of infusion as follows.

\[ R = (10 \text{ mg/mL})(10)(1000\text{mL})(0.1 \text{ hr}^{-1}) = 10 \text{ mg/h} \]

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.

**Example 2:** An infinitely long period of time is needed to reach steady-state drug levels. However, in practice it is quite acceptable to reach 99% \(C_{ss}\) (ie, 99% steady-state level). Using Equation 6, we know that the steady state level is

\[ C_{ss} = \frac{R}{V_D k} \] and 99% steady-state level is
Substituting into Equation 2 for $C_p$, we can find the time needed to reach steady state by solving for $t$.  

\[ 99\% \, \frac{R}{V_D k} \]

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 $k$,  

\[ t_{99\%SS} = \frac{4.61}{(0.693/t_{1/2})} = \frac{4.61}{0.693} \cdot t_{1/2} \]

\[ t_{99\%SS} = 6.65 \cdot t_{1/2} \]

Notice that in the equation directly above, the time needed to reach steady state is not dependent on the rate of infusion, but only on the elimination half-life. Using similar calculations, the time needed to reach any percentage of the steady-state drug concentration may be obtained. Table 1.

Intravenous infusion may be used to determine total body clearance if the infusion rate and steady-state level are known, as with Equation 6 repeated here:
because total body clearance, $Cl_T$, is equal to $VDk$,

$$ClT = \frac{R}{CSS} \quad \ldots \ldots 7$$

**Example 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 $ClT$ for this antibiotic.

The total body clearance may be estimated from Equation 7. The serum sample was taken after 2 days or 48 hours of infusion, which time represents $8 \times t_{1/2}$, therefore, this serum drug concentration approximates the $CSS$.

$$ClT = \frac{R}{CSS} = \frac{2\text{mg/hr}}{10\text{mg/L}} = 200 \text{mL/hr}$$

**INFUSION METHOD FOR CALCULATING PATIENT ELIMINATION HALFLIFE**

Equation 2 is arranged to solve for $k$:

$$C_p = \frac{R}{VDk} (1 - e^{-kt}) \quad \ldots \ldots 2 \quad \text{Since } CSS = \frac{R}{VDk}$$

Substituting into Equation 2;

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

Rearranging and taking the log on both sides,
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 $t_{1/2} = 6$ hours.

By substitution into Equation 8,

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

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

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

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

The elimination half-life 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 after stopping the IV infusion.

However, this method may be sufficient in clinical practice. As the second blood sample is taken closer to the time for steady state, the accuracy of this method improves.
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 in applying Equation 8.

When Equation 8 was used as in the example above to calculate the drug $t_{1/2}$ of the patient, the second plasma drug concentration was assumed to be the theoretical $C_{ss}$. As demonstrated below, when $t_{1/2}$ and the corresponding values are substituted,

$$\log \left( \frac{C_{ss} - 5.5}{C_{ss}} \right) = \frac{-(0.231)(8)}{2.3}$$

$$\frac{C_{ss} - 5.5}{C_{ss}} = 0.157$$

$$C_{ss} = 6.5 \text{ mg/L}$$

(Note that $C_{ss}$ is in fact the same as the concentration at 24 hours in the example above.)

**Example 5:**

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

**Solution**

From Example 4, 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

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

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

The new infusion rate should be

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

Equation 7 or the steady-state clearance method has been applied to the clinical infusion of drugs.

**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

$$C1 = C0e^{-kt} = \frac{D_L}{V_D} e^{-kt} \quad \text{.........9}$$

and concentration by infusion at the rate $R$ is

$$C2 = \frac{R}{V_D k} (1 - e^{-kt}) \quad \text{.........10}$$

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

$$C_p = C_1 + C_2$$

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

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

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

\[ \text{.........11} \]

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 4, \( ssVD = \frac{R}{k} \). Therefore,

Substituting \( DL = \frac{R}{k} \) in Equation 11 makes the expression in parentheses in Equation 11 cancel out.

Equation 11 reduces to Equation 13, which is the same expression for \( CSS \) or steady-state plasma concentration:

\[
C_p = \frac{R}{V_p k} \tag{13}
\]

\[
C_{SS} = \frac{R}{V_p k} \tag{14}
\]

Therefore, if an IV loading dose of \( \frac{R}{k} \) is given, followed by an IV infusion, steady-state plasma drug concentrations are obtained immediately and maintained (figure 4). In this situation, steady state is also achieved in a one-compartment model, since rate in = rate out \( (R = dD B/dt) \).

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

Loading dose equation:

\[
C_1 = \frac{D_L}{V_D} e^{-kt}
\]

Infusion equation:

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

Adding up the two equations yields Equation 15, an equation describing simultaneous infusion after a loading dose:

\[
\text{Figure 4: IV Infusion with loading dose } D_L. \text{ The loading dose is given by IV bolus injection at the start of the infusion. Plasma drug concentrations decline exponentially after } D_L \text{ whereas they increase exponentially during the infusion. The resulting plasma drug concentration-versus-time curve is a straight line due to the summation of the two curves.}
\]
By differentiating this equation at steady state, we obtain

\[
\frac{dC_p}{dt} = 0 = \frac{-D_L k}{V_D} e^{-kt} + \frac{R}{V_D} k e^{-kt}
\]  \text{\ldots\ldots16}

\[
0 = e^{-kt} \left( -\frac{D_L k}{V_D} + \frac{R}{V_D} k \right)
\]

\[
\frac{D_L k}{V_D} = \frac{R}{V_D}
\]

\[
D_L = \frac{R}{k} = \text{loading dose}
\]  \text{\ldots\ldots17}

In order to maintain instant steady-state level \([dC_p/dt] = 0\), the loading dose should be equal to \(R/k\).

\text{Figure 5: 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 $DL$ is not equal to $R/k$, then steady state will not occur immediately.

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.

Another method for the calculation of loading dose $DL$ is based on knowledge of the desired steady-state drug concentration $CSS$ and the apparent volume of distribution $VD$ for the drug, as shown in:

$$DL = CSS \times VD \ldots \ldots \text{Equation 18.}$$

**ESTIMATION OF DRUG CLEARANCE AND V D FROM INFUSION DATA:**

The plasma concentration of a drug during constant infusion was described in terms of volume of distribution and elimination constant $k$ in Equation 2. Then Alternatively, the equation may be described in terms of clearance by substituting for $k$ into Equation 2 with $k = Cl/V D$:

$$Cp = \frac{R}{Cl} (1 - e^{-(Cl/V D)t}) \ldots \ldots 19$$

**INTRAVENOUS INFUSION OF TWO-COMPARTMENT MODEL DRUGS**

During a constant IV infusion, drug in the tissue compartment is in distribution equilibrium with the plasma; thus, constant $CSS$ levels also result in constant drug concentrations in the tissue; ie, no net change in the amount of drug in the tissue occurs at steady state. The time needed to reach a steady-state blood level depends entirely on the distribution half-life of the drug.

$$CP = \frac{R}{VPk} \left[ 1 - \left( \frac{k - b}{a - b} \right) e^{-at} - \left( \frac{a - k}{a - b} \right) e^{-bt} \right] \ldots \ldots 20$$
Where \( a \) and \( b \) are hybrid rate constants and \( R \) is the rate of infusion. At steady state (ie, \( t = \infty \)), Equation 20 reduces to

\[
C_{SS} = \frac{R}{V_p k}
\] .....

By rearranging this equation, the infusion rate for a desired steady-state plasma drug concentration may be calculated.

\[
R = C_{ss} VD k \] ........22

**LOADING DOSE PLUS IV INFUSION: TWO-COMPARTMENT MODEL**

The drug distributes slowly into extravascular tissues (compartment 2). Thus, drug equilibrium is not immediate. The plasma drug concentration of a drug that follows a two-compartment model after various loading doses is shown in figure 6.

If a loading dose is given too rapidly, the drug may initially give excessively high concentrations in the plasma (central compartment), which then decreases as drug equilibrium is reached (figure 6). It is not possible to maintain an instantaneous, stable steady-state blood level for a two-compartment model drug with a zero-order rate of infusion.

![Figure 6: Plasma drug level after various loading doses and rates of infusion for a drug that follows a two-compartment model: a, no loading dose; b, loading dose = \( R/k \) (rapid infusion); c, loading dose = \( R/b \) (slow infusion); and d, loading dose = \( R/b \) (rapid infusion).](image)

Figure 6: Plasma drug level after various loading doses and rates of infusion for a drug that follows a two-compartment model: a, no loading dose; b, loading dose = \( R/k \) (rapid infusion); c, loading dose = \( R/b \) (slow infusion); and d, loading dose = \( R/b \) (rapid infusion).
Therefore, a loading dose produces an initial blood level either slightly higher or lower than the steady-state blood level. To overcome this problem, several IV bolus injections given as short intermittent IV infusions may be used as a method for administering a loading dose to the patient.

**Apparent Volume of Distribution at Steady State, Two-Compartment Model**

After administration of any drug that follows two-compartment kinetics, plasma drug levels will decline due to elimination, and some redistribution will occur as drug in tissue diffuses back into the plasma fluid. At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment:

\[ D_{t}k_{21} = D_{p}k_{12} \]  
\[ D_{t} = \frac{k_{12}D_{p}}{k_{12}} \]

\[ \text{\textbf{\ldots\ldots23}} \]

\[ \text{\textbf{\ldots\ldots24}} \]

The apparent volume of drug at steady state \((V_{D})_{SS}\) may be calculated by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady state:

\[ (V_{D})_{SS} = \frac{D_{p} + D_{t}}{C_{p}} \]

\[ \text{\textbf{\ldots\ldots25}} \]

Because the amount of drug in the central compartment, \(D_{p}\), is equal to \(V_{p}C_{p}\), by substitution in the above equation,

\[ D_{t} = \frac{k_{12}C_{p}V_{p}}{k_{21}} \]

\[ \text{\textbf{\ldots\ldots26}} \]
FREQUENTLY ASKED QUESTIONS

1. Do you agree with the following statements for a drug that is described by a two-compartment pharmacokinetic model? At steady state, the drug is well equilibrated between the plasma and the tissue compartment, \( C_p = C_t \), and the rates of drug diffusion into and from the plasma compartment are equal. The steady-state volume of distribution is much larger than the initial volume, \( V_i \), or the original plasma volume, \( V_p \), of the central compartment. The loading dose is often calculated using the \((V_D)_{SS}\) instead of \(V_p\).

**Answer:** For a drug that follows a multiple-compartment model, the rates of drug diffusion into the tissues from the plasma and from the tissues into the plasma are equal at steady state. However, the tissue drug concentration is generally not equal to the plasma drug concentration.

2. Why is a loading dose used?

**Answer:** When drugs are given in a multiple-dose regimen, a loading dose may be given to achieve steady-state drug concentrations more rapidly.

3. What is the main reason for giving a drug by slow IV infusion?

**Answer:** Slow IV infusion may be used to avoid side effects due to rapid drug administration. For example, intravenous immune globulin (human) may cause a rapid fall in blood pressure and possible anaphylactic shock in some patients when infused rapidly. Some antisense drugs also cause a rapid fall in blood pressure when injected rapidly IV into the body. The rate of infusion is particularly important in administering antiarrythmic agents in patients. The rapid IV bolus injection of many drugs (eg, lidocaine) that follow the pharmacokinetics of multiple-compartment models may cause an adverse response due to the initial high drug concentration in the central (plasma) compartment before slow equilibration with the tissues.

4. Why do we use a loading dose to rapidly achieve therapeutic concentration for a drug with a long elimination half-life, instead of increasing the rate of drug infusion or increasing the size of the infusion dose?
**Answer:** The loading drug dose is used to rapidly attain the target drug concentration, which is approximately the steady-state drug concentration. However, the loading dose will not maintain the steady-state level unless an appropriate IV drug infusion rate or maintenance dose is also used. If a larger IV drug infusion rate or maintenance dose is given, the resulting steady-state drug concentration will be much higher and will remain sustained at the higher level. A higher infusion rate may be administered if the initial steady-state drug level is inadequate for the patient.

5. What are some of the complications involved with IV infusion?

**Answer:** The common complications associated with intravenous infusion include phlebitis and infections at the infusion site caused by poor intravenous techniques or indwelling catheters.

6. 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 for this antibiotic is 10 g/mL.
   a. Assuming no loading dose, how long after the start of the IV infusion would it take to reach 95% of the 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 new steady-state plasma level to be established (assume that 95% of the 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 g/mL?

answer:
An anticonvulsant drug was given as (a) a single IV dose and (b) a constant IV infusion. The serum drug concentrations are as presented in the table below. An IV bolus injection may be used at the start of the infusion to quickly achieve the desired steady-state plasma drug concentration. For drug that follow a two-compartment model, multiple small loading dose or intermittent IV infusion may be needed to prevent plasma drug concentration from becoming too high.

Pharmacokinetic parameters may be calculated from samples taken during the IV infusion and after the infusion is stopped, regardless of whether steady-state has been achieved. These calculated pharmacokinetic parameters may then be used to optimize dosing for that patient when population estimates do not provide outcomes suitable for the patient.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Single IV Dose (1 mg/kg)</th>
<th>Constant IV Infusion (0.2 mg/kg per hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
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<td>9.7</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>9.9</td>
</tr>
</tbody>
</table>
a. What is the steady-state plasma drug level?
b. What is the time for 95% steady-state plasma drug level?
c. What is the drug clearance?
d. What is the plasma concentration of the drug 4 hours after stopping infusion? (Infusion was stopped after 24 hours.)
e. What is the infusion rate for a patient weighing 75 kg to maintain a steady-state drug level of 10 g/mL?
f. What is the plasma drug concentration 4 hours after an IV dose of 1 mg/kg followed by a constant infusion of 0.2 mg/kg per hour?

Answer:
a. The steady-state level can be found by plotting the IV infusion data. The plasma drug-time curves plateau at 10 g/mL. Alternatively, V D and k can be found from the single IV dose data:

\[ V_D = 100 \text{ mL/kg} \quad k = 0.2 \text{ hr}^{-1} \]

b. Using equations developed in Example 2 in the first set of examples in:

\[
0.95 \frac{R}{V_D k} = \frac{R}{V_D k} (1 - e^{-kT}) \\
0.95 = 1 - e^{-e^{0.05}} \\
0.05 = e^{-0.2t} \\
t_{95%} = \frac{\ln 0.05}{-0.2} = 15 \text{ hr}
\]

c. \( CL_T = V_d k \)

\[
CL_T = 100 \times 0.2 \quad V_d = \frac{D_0}{C_p^0} \\
V_d = 1000 \times 0.1 = \frac{100 \text{ mL}}{\text{kg}} \\
CL_T = 20 \text{ mL/kg hr}
\]

d. The drug level 4 hours after stopping the IV infusion can be found by considering the drug concentration at the termination of infusion as \( C_0 \). At the termination of the infusion, the drug level will decline by a first-order process.

\[
C_p = C_p^0 e^{-kT} \\
C_p = 9.0e^{-0.2t(t)} \\
C_p = 4.5 \mu\text{g/mL}
\]
8. 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?

**Answer:**

Infusion rate R for a 75-kg patient:

\[ R = (1 \text{ mg/kg hr})(75 \text{ kg}) = 75 \text{ mg/hr} \]

Sterile drug solution contains 25 mg/mL. Therefore, 3 mL contains (3 mL) x (25 mg/mL), or 75 mg. The patient should receive 3 mL (75 mg)/hr by IV infusion.

9. An antibiotic drug is to be given to an adult male patient (75 kg, 58 years old) by IV infusion. The drug is supplied in sterile vials containing 30 mL of the antibiotic solution at a concentration of 125 mg/mL. What rate in milliliters per hour would you infuse this patient to obtain a steady-state concentration of 20 g/mL? What loading dose would you suggest? Assume the drug follows the pharmacokinetics of a one-compartment open model. The apparent volume of distribution of this drug is 0.5 L/kg, and the elimination half-life is 3 hours.

\[ C_{ss} = \frac{R}{V_0k} \quad R = C_{ss}V_0k \]

\[ R = (20 \text{ mg/L})(0.5 \text{ L/kg})(75 \text{ kg})(\frac{0.693}{3 \text{ hr}}) = 173.25 \text{ mg/hr} \]

Drug is supplied as 125 mg/mL. Therefore,

\[ 125 \text{ mg/mL} = \frac{173.25 \text{ mg}}{X} \quad X = 1.386 \text{ mL} \]

\[ R = 1.386 \text{ mL/hr} \]

\[ D_L = C_{ss}V_D = (20 \text{ mg/L})(0.5 \text{ L/kg})(75 \text{ kg}) = 750 \text{ mg} \]
10. According to the manufacturer, a steady-state serum concentration of 17 g/mL was measured when the antibiotic cephradine (Velosef, Bristol-Meyers, Squibb) was given by IV infusion to 9 adult male volunteers (average weight, 71.7 kg) at a rate of 5.3 mg/kg hr for 4 hours.

a. Calculate the total body clearance for this drug.

b. When the IV infusion was discontinued, the cephradine serum concentration decreased exponentially, declining to 1.5 g/mL at 6.5 hours after the start of the infusion. Calculate the elimination half-life.

c. From the information above, calculate the apparent volume of distribution.

d. Cephradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cephradine concentration. What is the probable mechanism for this interaction of probenecid with cephradine?

\[
C_{SS} = \frac{R}{kV_D} = \frac{R}{C_{LT}}
\]

a. \(C_{LT} = \frac{R}{C_{SS}} = \frac{5.3 \text{ mg/kg hr} \times 71.7 \text{ kg}}{17 \text{ mg/L}} = 22.4 \text{ L/hr}
\]

b. At the end of IV infusion, \(C_p = 17 \mu g/mL\). Assuming first-order elimination kinetics:

\[
C_p = C_p^0 e^{-kt}
\]

\[
1.5 = 17e^{-k(25)}
\]

\[
0.0882 = e^{-0.5k}
\]

\[
\ln 0.0882 = -2.5 k
\]

\[
k = 0.971 \text{ hr}^{-1}
\]

\[
t_{1/2} = \frac{0.693}{0.971} = 0.714 \text{ hr}
\]

c. \(C_{LT} = kV_D\), \(V_D = \frac{C_{LT}}{k}\)

\[
V_D = \frac{22.4}{0.971} = 23.1 \text{ L}
\]

d. Probenecid blocks active tubular secretion of cephradine.

11. Calculate the excretion rate at steady state for a drug given by IV infusion at a rate of 30 mg/hr. The C SS is 20 g/mL. If the rate of infusion were increased to 40 mg/hr, what would be the new steady-state drug concentration, C SS? Would the
excretion rate for the drug at the new steady state be the same? Assume first-order elimination kinetics and a one-compartment model.

**Answer:** At steady state, the rate of elimination should equal the rate of absorption. Therefore, the rate of elimination would be 30 mg/hr. The C SS is directly proportional to the rate of infusion R, as shown by

\[
C_{SS} = \frac{R}{kV_D} \quad kV_D = \frac{R}{C_{SS}}
\]

\[
\frac{R_{old}}{C_{SS, old}} = \frac{R_{new}}{C_{SS, new}}
\]

\[
\frac{30 \text{ mg/hr}}{20 \mu g/mL} = \frac{40 \text{ mg/hr}}{C_{SS, new}}
\]

\[
C_{SS, new} = 26.7 \mu g/mL
\]

The new elimination rate will be 40 mg/hr.

12. An antibiotic is to be given to an adult male patient (58 years old, 75 kg) by IV infusion. The elimination half-life is 8 hours and the apparent volume of distribution is 1.5 L/kg. The drug is supplied in 60-mL ampules at a drug concentration of 15 mg/mL. The desired steady-state drug concentration is 20 g/mL.

a. What infusion rate, in milliliters per hour, would you recommend for this patient?
b. What loading dose would you recommend for this patient? By what route of administration would you give the loading dose? When?
c. Why should a loading dose be recommended?
d. According to the manufacturer, the recommended starting infusion rate is 15 mL/hr. Do you agree with this recommended infusion rate for your patient? Give a reason for your answer.
e. If you were to monitor the patient's serum drug concentration, when would you request a blood sample? Give a reason for your answer.
f. The observed serum drug concentration is higher than anticipated. Give two possible reasons based on sound pharmacokinetic principles that would account for this observation.
a. $R = C_{ss}kV_{D}$
   
   $R = (20 \text{ mg/L}) \times (0.693/8 \text{ hr}) \times (1.5 \text{ L/kg}) \times (75 \text{ kg}) = 194.9 \text{ mg/hr}$
   
   $R \approx 195 \text{ mg/hr}$

b. $D_{L} = C_{ss}V_{D} = (20)(1.5)(75) = 2250 \text{ mg given by IV bolus injection}$

c. The loading dose is given to obtain steady-state drug concentrations as rapidly as possible.

d. 15 mL of the antibiotic solution contains 225 mg of drug. Thus, an IV infusion rate of 15 mL/hr is equivalent to 225 mg/hr. The $C_{ss}$ achieved by the manufacturer's recommendation is

   $C_{ss} = \frac{R}{kV_{D}} = \frac{225}{0.0866 \times 112.5} = 23.1 \text{ mg/L}$

The theoretical $C_{ss}$ of 23.1 mg/L is close to the desired $C_{ss}$ of 20 mg/L. Assuming a reasonable therapeutic window, the manufacturer's suggested starting infusion rate is satisfactory.

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