Chapter 15

Intravenous Infusion

Objectives

• To understand the diagrams, schemes, and graphs associated with single and multiple infusion regimens
• To recognize the differential and integrated equations associated with single or multiple infusion regimens
• To use the integrated equations to:
  – Determine kel and V parameter values
  – Develop safe dosage regimens

Intravenous Infusion

• Hospital Setting
• Maintenance therapy
• Stable and compatible drug
• Drugs too toxic for bolus administration
  – E.g. Phenytoin < 50 mg/min
    • Solvent the problem?

Clinical Pharmacology: An Electronic Drug Reference
Scheme

Differential Equation

\[ \frac{V \cdot dC_p}{dt} = k_0 - k_{el} \cdot V \cdot C_p \]

Input +ve
From infusion

Output -ve
By Elimination

Integration

\[ V \cdot s \cdot C_p - C_p(0) = \frac{k_0}{s} - k_{el} \cdot V \cdot C_p \]

\[ V \cdot C_p \cdot (s + k_{el}) = \frac{k_0}{s} \]

\[ C_p = \frac{k_0}{V \cdot s \cdot (s + k_{el})} \]
Back-Transform

Two roots: 0 and -kel

\[ \begin{align*}
C_p &= \frac{k_0}{V \cdot kel} + \frac{k_0}{V \cdot kel} \cdot e^{-kel \cdot t} \\
C_p &= \frac{k_0}{V \cdot kel} \left[1 - e^{-kel \cdot t}\right]
\end{align*} \]

Similar to the Equation for Cumulative Amount Excreted Equation

Continuous Infusion

Approach to Steady State

\[ \begin{align*}
C_p &= \frac{k_0}{kel \cdot V} \left[1 - e^{-kel \cdot t}\right]
\end{align*} \]

When \( t = \infty \) then \( e^{-kel \cdot t} = 0 \)

\[ \frac{V \cdot dC_p}{dt} = k_0 - kel \cdot V \cdot C_p = 0 \]
Example Calculation

- Data: \( t_{1/2} = 4 \text{ hr}; V = 25 \text{ L}; C_{p_{ss}} = 15 \text{ mg/L} \)
- Question: What is the required \( k_0 \)
- \( k_e = 0.693/4 = 0.17 \text{ hr}^{-1} \)
- \( k_0 = k_e \cdot V \cdot C_{p_{ss}} = 0.17 \times 25 \times 15 \)
  \[ = 63.8 \text{ mg/hr} \]
- Using 60 mg/hr
- \( C_{p_{ss}} = 60/(0.17 \times 25) = 14.1 \text{ mg/L} \)

Time to Reach \( C_{p_{ss}} \)

- Time to Reach Effective \( C_p - C_{p_{ss}} \)
  \[ C_p = C_{p_{ss}} \cdot \left[ 1 - e^{-k_e \cdot t_{1/2}} \right] \]
  \[ \frac{1}{2} = 1 - e^{-k_e \cdot t_{1/2}} \]
  \[ \frac{1}{2} = e^{-k_e \cdot t_{1/2}} \text{ or } 2 = e^{k_e \cdot t_{1/2}} \]
  \[ \ln 2 = k_e \cdot t_{1/2} = 0.693 = k_e \cdot t_{1/2} \]
  \[ t_{1/2} = t_{1/2} \text{ That is, the time it takes to get to half } C_{p_{ss}} \text{ is the elimination half-life} \]

Time to Reach \( C_{p_{ss}} \)

- Approach to \( C_{p_{ss}} \) is exponential in nature
- However, speed of approach is controlled by \( k_e \) NOT \( k_0 \)
- And, the value of \( C_{p_{ss}} \) IS controlled or determined by \( k_0 \)
Time to Reach $C_{pss}$

- 50% to steady state in 1 half-life
- 75% to steady state in 2 half-lives
- 86% to steady state in 3 half-lives
- 94% to steady state in 4 half-lives
- If $t_{1/2}$ is 4 hours then it will take 16 hours to reach 94% of the desired $C_{pss}$

Example Calculation

- Data: $k_0 = 60$ mg/hr; $kel = 0.17$ hr$^{-1}$; $C_{p_{reqd}} = 10$ mg/L; $C_{pss} = 14$ mg/L
- Question: How long will it take to reach $C_{p_{reqd}}$

\[
C_p = \frac{k_0}{kel \cdot V} \cdot \left[1 - e^{-kel \cdot t}\right]
\]

\[
10 = \frac{60}{0.17 \times 25} \cdot \left[1 - e^{-0.17 \cdot t}\right]
\]

\[
0.292 = e^{-0.17 \cdot t} \quad \text{OR} \quad t = 7.24 \text{ hr}
\]
Strategies for Faster Approach to $C_p^{ss}$

- Combine Bolus and Infusion Administration
  - When a bolus dose is possible
- Fast then Slow Infusion Regimen

Bolus Dose plus Infusion

- Data: $C_p^{ss} = 14.1$ mg/L; $V = 25$ L; and $k_e = 0.17$ hr$^{-1}$
- Loading Dose
  
  $Dose = V \cdot C_p^{ss} = 25 \times 14.1 = 353$ mg
- Maintenance Dose from before
  
  $k_0 = 60$ mg/hr

Bolus Dose plus Infusion

- Data: $C_p^{ss} = 14.1$ mg/L; $V = 25$ L; and $k_e = 0.17$ hr$^{-1}$
- Loading Dose
  
  $Dose = V \cdot C_p^{ss} = 25 \times 14.1 = 353$ mg
- Maintenance Dose from before
  
  $k_0 = 60$ mg/hr
Fast and Slow Infusion

- Data: \( C_{pss} = 14.1 \text{ mg/L}; \ k_0 = 60 \text{ mg/hr}; \ V = 25 \text{ L}; \) and \( k_{el} = 0.17 \text{ hr}^{-1} \)
- Required Fast Infusion over 30 minutes
  \[
  C_p = \frac{k_0}{k_{el} \cdot V} \left[ 1 - e^{-k_{el} \cdot t} \right]
  \]
  \[
  14.1 = \frac{k_0}{0.17 \times 25} \left[ 1 - e^{-0.17 \times 0.5} \right]
  \]
  \( k_0 = 735 \text{ mg/hr} \)
- Slow Infusion from before
  \( k_0 = 60 \text{ mg/hr} \)

Fast and Slow Infusion

- Dosage Regimen
  \( k_0 = 735 \text{ mg/hr} \) for 30 minutes
  \( k_0 = 60 \text{ mg/hr} \)
- NOTE: \( C_{pss} \) when \( k_0 = 735 \text{ mg/hr} \)
  \[
  C_{pss} = \frac{k_0}{k_{el} \cdot V} = \frac{735}{0.17 \times 25} = 173 \text{ mg/L}
  \]
  Toxic Overdose
Once the Infusion Stops

- Schemes
- Equations
- Figures

Schemes

Equations

- Differential Equation
  \[
  \frac{dC_p}{dt} = -k_e \cdot C_p
  \]
- Laplace Transform
  \[
  s \cdot C_p' = \frac{k_0}{k_e \cdot V} \cdot \left[1 - e^{-k_e \cdot V} \right] = -k_e \cdot C_p
  \]
  \[
  C_p' = \frac{k_0}{k_e \cdot V} \cdot \left[\frac{1 - e^{-k_e \cdot V}}{s + k_e} \right] = \frac{C_p'}{s + k_e}
  \]
Equation (continued)

Take the Back Transform

\[ C_p = C_p^T e^{-k_0 e^{-k_0 t}} - \frac{k_0}{k_c e^V} \left[ 1 - e^{-k_0 e^{-k_0 T}} \right] e^{-k_0 e^{-k_0 t}} \]

For \( t < T \) then \( T = t \)

For \( t > T \) then \( T = T \)

Linear Plot

![Linear Plot](image)

Intercept = Dose/V

Semi-log Plot

![Semi-log Plot](image)

Slope = \(-k_0\)
Example Calculation

Infusion Rate = 100 mg/hr for 2 hours

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Cp (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
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<td>12</td>
<td>5</td>
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<tr>
<td>18</td>
<td>3.9</td>
</tr>
<tr>
<td>24</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Example Calculation

\[ Cp_T = 13.0 \text{ mg/L} \]

Elimination Rate Constant

\[ kel = \frac{\ln(Cp_1) - \ln(Cp_2)}{t_2 - t_1} \]

\[ kel = \frac{\ln 13 - \ln 1.9}{24 - 2} = 0.087 \text{ hr}^{-1} \]
**Apparent Volume of Distribution**

\[ C_pT = \frac{k_0}{k_e}\cdot V\cdot \left[1 - e^{-k_e T}\right] \]

\[ V = 88.4 \cdot 1 - 0.840 = 14.1 \text{ L} \]

**Data Analysis**

- Using Boomer
  - Define Model
  - Enter Data
  - Review Results

**Time Interrupts**
Data Analysis

• Using Boomer
  – Define Model
  – Enter Data
  – Review Results

Data Analysis

• Using SAAM II
  – Define Model
  – Enter Data
  – Review Results
Data Analysis

- Using SAAM II
  - Define Model
  - Enter Data
  - Review Results

Data Analysis

- Using SAAM II
  - Define Model
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HyperCard Stack

- One Compartment IV Infusion
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