Intravenous Bolus Dose

Outline

• Different compartmental models for Pharmacokinetic analysis
• IV bolus administration
  – Volume of distribution
  – Drug concentration and drug amount changes over time
  – Elimination rate constant and half life
  – Fraction of drug remaining in the body
  – Total clearance
  – Better ways to calculate clearance and volume of distribution

Intravascular Administration

• Bolus injection
• IV infusion
  – More in practice
• Intra-arterial administration
  – Directly inject to target
  – Less used

1. Different Compartmental Models
1.1. One Compartmental Model

- Assume distribution is rapid

\[ C = C(0) \cdot e^{-kt} \]

1.2. Two Compartmental Model

- Distribution faster than elimination
- Need two exponential terms

\[ C = C_1 \cdot e^{-k_1t} + C_2 \cdot e^{-k_2t} \]
Disposition From Plasma

- Concentration (C) vs. time curve
  - Dose: IV 500 mg, theophylline
  - fast early exponential decline
    - From 29 to 18 mg/ml, takes 30 min
  - Slower exponential decline
    - From 19 to 8 mg/ml, takes 4 hrs

- Log concentration (Log C) vs. time curve
  - Rapid fall to 16 mg/ml, within 1 hr
  - Then slow linear decline

Distribution Phase

- Dose = 500 mg
- Within 5 min
  - C = 33mg/L
  - Vp = 3 L
  - Amount in plasma (A) = 3 x 33 = 99 mg
- Other 401 mg
  - Must be in other tissues----- distribution

Elimination Phase

- The time for plasma concentration (C) or amount of drug in the body (A) to fall by 50%
  - Theophylline, from 16 to 8 mg/ml, it takes 5 hrs
  - From 12 to 6 mg/ml, it takes 5 hrs
  - T_{1/2} is independent of amount of drug in the body

1.3. Three Compartmental Model

![Diagram of three compartmental model with input, slow distribution, fast distribution, peripheral compartment, central compartment, and elimination rate constant (k).]
Three Compartmental Model

- Central compartment
  - Assume elimination from central compartment
- Fast distribution compartment
- Slow distribution compartment
- Need three exponential terms to define C

1.4. Physiologically Based Pharmacokinetic Model (PBPK)

2. IV Bolus Administration

One Compartment Model as An Example
One Compartment Model

2.1. Volume of Distribution (V, V_d)
- One compartment model as an example
  - Hypothetical body distribution volume
  - Distribution equilibrium has to be reached before first data for V calculation
  - No drug has been eliminated yet at time 0
    - A: Dose of injection
    - Plasma concentration C(0) at time 0

\[
V = \frac{A}{C}
\]

Volume of Distribution
- One compartmental model
- \( V = \text{Dose} / C(0) \)
- Dose = \( V \cdot C(0) \)
- How to get \( C(0) \):
  \[
  \ln C = \ln C(0) - k t
  \]
  - \( k \) is slope of the decline
  - \( C(0) \) is the extrapolated value from this equation
  - Negative sign indicate decline

2.2. Amount of Drug in the Body
- \( A = V \cdot C(t) \),
  - at any given time \( t \)
  - \( V \) is volume of distribution (or other related volumes)
  - \( C \) is after distribution equilibrium
Example

- Theophyline Dose = 500 mg
- C(0) = 18 mg/L
- V = 500 / 18 = 28 L
- How much drug in the body when plasma C is 5 mg/L?
  - A = VC = 28 x 5 = 140 mg
- How much drug in the plasma when plasma C is 5 mg/L
  - A = VC/5 x 5 mg/L = 15 mg

2.3. Plasma Drug Concentration Changes with Time

\[ \ln C = \ln C(0) - kt \]

\[ C = C(0) \cdot e^{-kt} \]

Multiply each side by V

\[ A = Dose \cdot e^{-kt} \]

These two equations can estimate drug concentration and amount of drug in the body at any given time.

2.4. Amount of Drug in the Body Changing with Time

\[ A = Dose \cdot e^{-kt} \]

\[ \frac{dA}{dt} = -k \cdot Dose \cdot e^{-kt} \]

\[ \frac{dA}{dt} = -k \cdot A \]

\[ LnA = LnA(0) - k \cdot t \]

- First order elimination process
- K: first order rate constant

First order vs. Zero Order Kinetics

\[ \frac{dA}{dt} = -k \cdot A \]

\[ \frac{dA}{dt} = -k \cdot A^0 \]

Divide both side by V

\[ \frac{dC}{dt} = -k \cdot C \]

\[ \frac{dC}{dt} = -k \cdot C^0 \]

First order

Zero order
2.5. Elimination Rate Constant

\[ k = - \frac{dA}{dt} / A \]

- \( k \) = rate of elimination / amount in body

2.6. Half Life \( (t_{1/2}) \)

- At one half life, \( C = \frac{1}{2} C(0) \)

\[ C = C(0) \cdot e^{-kt} \quad 0.5 = e^{-kt_{1/2}} \]

\[ e^{kt_{1/2}} = 2 \]

\[ kt_{1/2} = \text{Ln}2 = 0.693 \]

\[ t_{1/2} = \frac{0.693}{k} \]

Calculation of Half Life \( (t_{1/2}) \)
Example-Theophyline IV (500mg)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>( C_p ) (mg/ml)</th>
<th>( \text{Ln} \ C_p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16</td>
<td>2.77</td>
</tr>
<tr>
<td>3</td>
<td>13.9</td>
<td>2.63</td>
</tr>
<tr>
<td>4</td>
<td>12.2</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>10.6</td>
<td>2.36</td>
</tr>
<tr>
<td>6</td>
<td>9.2</td>
<td>2.22</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>2.08</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>1.94</td>
</tr>
</tbody>
</table>

C ~ T, and Ln C ~ T

- Graphs showing concentration over time and log scale.
Calculation of Half Life (t_{1/2})

- Elimination rate constant $K = \text{slope of Ln } C\text{-}t$ curve
  - $K = 0.1386 \text{ hr}^{-1}$
  - $T_{1/2} = 0.693 / K = 0.693 / 0.1386 = 5 \text{ hrs}$

2.8. Fraction of Dose Remaining in the Body

- Fraction of dose remaining at any given time
  
  \[ A = \text{Dose} \cdot e^{-kt} \]

  \[
  \text{Fraction of dose remaining} = \frac{A}{\text{Dose}} = e^{-kt}
  \]

- Define $n$ is number of half-lives

  \[
  n = \frac{t}{t_{1/2}} \quad k = \frac{0.693}{t_{1/2}}
  \]

2.8. Fraction of Dose Remaining in the Body

- Then

  \[
  \text{Fraction of dose remaining} = e^{-kt} = e^{-0.693n}
  \]

  \[
  e^{-0.693} = \frac{1}{2}
  \]

  \[
  \text{Fraction of dose remaining} = \left(\frac{1}{2}\right)^n
  \]

<table>
<thead>
<tr>
<th>Number of half lives $n$</th>
<th>Fraction of dose remaining $e^{kt}$</th>
<th>Fraction of dose loss $1-e^{-kt}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>0.125</td>
<td>0.875</td>
</tr>
<tr>
<td>4</td>
<td>0.0625</td>
<td>0.9375</td>
</tr>
<tr>
<td>5</td>
<td>0.03</td>
<td>0.97</td>
</tr>
</tbody>
</table>
2.9. Total Clearance

- Rate of elimination = CL. C
  \[
  \frac{dA}{dt} = -k \cdot A = -k \cdot V \cdot C
  \]
- \( A = V \cdot C \)
- Clearance \( CL = k \cdot V \)

Relationship among CL, V, k, and \( t_{1/2} \)

\[
CL = k \cdot V
\]
\[
k = \frac{0.693}{t_{1/2}}
\]
\[
t_{1/2} = \frac{0.693 \cdot V}{CL}
\]
- Two independent parameters (V, CL) controls \( t_{1/2} \)

Examples

- Creatinine
  - MW 113
  - CL = 7.2 L/hr
  - V = 42 L (total body water)
  - \( T_{1/2} = ? \)
- Inulin
  - MW 5000
  - CL = 7.2 L/hr
  - V = 15 L
  - \( T_{1/2} = ? \)

2.10. Calculate CL using AUC and Dose

- Rate of elimination = CL. C
  \[
  \frac{dA}{dt} = CL \cdot C \quad dA = CL \cdot C \cdot dt
  \]
- Amount eliminated in interval \( dt \), \( dA = CL \cdot C \cdot dt \)
  - C. dt: small area under C-time curve within time interval \( dt \)
  - Amount of drug eliminated from time 0 to infinity = adding up or integrating amount eliminated in each interval = Dose
  - AUC: adding up or integrating small area in each time interval

\[
Dose = CL \cdot AUC \quad CL = \frac{Dose}{AUC}
\]
Advantage to Use AUC for Calculation of CL

\[ \text{Dose} = CL \cdot AUC \]

- No need to know \( t_{1/2} \)
- No need to know \( V \)
- Independent of shape of C-t curve
- Appendix A

- Amount eliminated up to time \( t \),
  \[ A_t = CL \cdot AUC(0, t) \]
- Fraction of drug eliminated up to time \( t \),
  \[ F_t = \frac{AUC(0, t)}{AUC(0, \infty)} \]
- Fraction of drug remaining up to time \( t \),
  \[ A_{\text{remaining}} = 1 - \frac{AUC(0, t)}{AUC(0, \infty)} \]

Example

- Theophylline
  - Dose 500 mg
  - At 3.6 hrs, AUC (0, 3.6) = 40% of total AUC
  - At 3.6 hrs, 40% dose has been eliminated (200 mg)
  - At 3.6 hrs, 300 mg dose remains in the body

2.11. Better Method to Calculate \( V \)

- Extrapolation
  - \( V = \frac{\text{Dose}}{C(0)} \)
  - It is not suitable when extensive elimination during distribution phase

- Using CL and \( K \)
  - No need \( C(0) \)
  - Can be used in both IV and infusion

\[ V = \frac{CL}{K} = \frac{\text{Dose}}{AUC \cdot K} \]
Summary

• Different compartmental models
• IV bolus (one compartmental model)
  – Volume distribution calculation using Dose and C(0)
  – Concentration and amount of drug change with time
  – Elimination rate constant and half life
  – Fraction of dose remaining in the body
  – Clearance and relationship among CL, V, K
  – Calculate CL using AUC and dose
  – Better method to calculate V

Summary

• Pharmacokinetic parameter calculation after IV bolus (one compartmental model)
  – \( t_{1/2} = \frac{0.693}{k} \)
  – \( CL = \frac{Dose}{AUC} \)
  – \( V = \frac{CL}{K} = \frac{Dose}{AUC \cdot K} \)
  – Other method to calculate V
  – \( V = \frac{Dose}{C(0)} \)

Example

• A 45 year male hospitalized and has concurrently developed an infection in urine and blood (resistant to penicillin). Doctor has decided to use vancomycin.
• The patient was loaded with vancomycin (1 gram) IV on 9/14 at 12 noon. Drug levels in plasma are determined below.
  – Vancomycin 9/16: 08:00am: 22 ug/mL
  – Vancomycin 9/17: 08:00am: 20 ug/mL
• If pharmacokinetic of vancomycin follows one compartment model, and if the desired effective vancomycin concentration is 15 ug/mL (assume that the second dose has to be given when vancomycin concentration is below 15 ug/mL):
  – When should the vancomycin be re-dosed?
  – What is the volume of distribution and clearance of vancomycin? (MD may not be interested in these numbers, but you may need them for dose calculations)
  – What dose regimen (time and dose) do you recommend? (you may not be able to do the second question yet)