Calculation of Bioavailability Parameters

Objectives

• Determine $k_a$ using the
  – Method of Residuals
  – Wagner-Nelson Method
  – Method of Inspection
    • as appropriate to calculate $k_a$
• Calculate $F$ using Plasma or Urine Data
• Understand the difference between absolute and relative bioavailability
• Fit IV and Oral Data Simultaneously

Determine of $k_a$

• Estimation
  – Method of Residuals
  – Wagner-Nelson Method
  – Method of Inspection
• Fitting using non-linear regression analysis
Method of Residuals

• Starting with the Equation for \( C_p \)
  \[
  C_p = \frac{F \cdot \text{Dose} \cdot k_a}{V} \cdot (ka - kel) \cdot \left[ e^{-kel} - e^{-ka} \right]
  \]
  which can be written as
  \[
  C_p = A \cdot e^{-kel} - A \cdot e^{-ka}
  \]
  where
  \[
  A = \frac{F \cdot \text{Dose} \cdot k_a}{V} \cdot (ka - kel)
  \]

Method of Residuals

• IF
  – \( ka/kel \) or \( kel/ka > 5 \)
  AND
  – Both \( ka \) and \( kel \) are first order

\[
C_p = \frac{F \cdot \text{Dose} \cdot k_a}{V \cdot (ka - kel)} \cdot \left[ e^{-kel} - e^{-ka} \right]
\]

Cp at Later Times

• At later time the exponential with the faster rate constant approaches zero more quickly

\[
0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1
\]

0 6 12 18 24

e (-k'•t)

Time (hr)

Slower exponential
Faster exponential
Difference

IF \( ka > kel \)
\[
e^{-ka} \rightarrow 0
\]
and
\[
C_p^{\infty} = A \cdot e^{-ka}
\]
Semi-log Plot of $C_p$ versus Time

\[ \text{Intercept} = C_p \cdot \text{Dose} \cdot k_a \]

\[ C_p = \text{late} \]

\[ k_a \text{ (from slope)} \]

The Next Step

• Once we determine $C_p^{\text{late}}$ from the terminal slope

\[ C_p = A \cdot e^{-k_e t} - A \cdot e^{-k_a t} \]

since $C_p^{\text{late}} = A \cdot e^{-k_e t}$

\[ C_p = C_p^{\text{late}} - A \cdot e^{-k_a t} \]

or

\[ C_p^{\text{late}} - C_p = A \cdot e^{-k_a t} \]

Residual

Plot Residual versus Time

Plot of Residual versus Time

"Feathering"
Requirements for the Method of Residuals

- One Rate Constant at least five times greater than the other
- Both Absorption and Elimination are first Order Processes

Example Data Set

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Plasma Concentration (mg/L)</th>
<th>Cp (late) (mg/L)</th>
<th>Residual (Col 3 - Col 2) (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>1.91</td>
<td>5.23</td>
<td>3.32</td>
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<tr>
<td>0.5</td>
<td>2.98</td>
<td>4.98</td>
<td>2.00</td>
</tr>
<tr>
<td>0.75</td>
<td>3.63</td>
<td>4.73</td>
<td>1.10</td>
</tr>
<tr>
<td>1.0</td>
<td>3.84</td>
<td>4.60</td>
<td>0.76</td>
</tr>
<tr>
<td>1.5</td>
<td>3.84</td>
<td>4.00</td>
<td>0.24</td>
</tr>
<tr>
<td>2</td>
<td>3.62</td>
<td>3.80</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>3.44</td>
<td>3.60</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>3.00</td>
<td>3.40</td>
<td>0.00</td>
</tr>
<tr>
<td>5</td>
<td>2.68</td>
<td>3.20</td>
<td>0.00</td>
</tr>
<tr>
<td>6</td>
<td>2.49</td>
<td>3.00</td>
<td>0.00</td>
</tr>
<tr>
<td>7</td>
<td>2.37</td>
<td>2.80</td>
<td>0.00</td>
</tr>
</tbody>
</table>

\[
Cp \text{ (late)} = 5.5 \times e^{-0.2t}
\]

\[
\text{Residual} = 5.5 \times e^{-2.05t}
\]

Semi-log Plot
Wagner-Nelson Method

- Advantages:
  - Absorption and Elimination can be quite similar in value
  - Absorption doesn’t need to be first order
- Disadvantages
  - Need to have a value for kel - from IV Data
  - Calculations are more involved


Theory ...

Working Equation

\[
\frac{dA}{dt} = \frac{dX}{dt} + \frac{dU}{dt}
\]

Differentiating each term gives

\[
\frac{dA}{dt} = \frac{dX}{dt} + \frac{dU}{dt}
\]

or

\[
\frac{dA}{dt} = V\cdot dCp + V\cdot kel\cdot Cp
\]

Theory … (contd)

\[
dA = V\cdot dCp + kel\cdot V\cdot Cp\cdot dt
\]

Integrating gives:

\[
A = V\cdot Cp + kel\cdot \int Cp\cdot dt
\]

or

\[
\frac{A}{V} = Cp + kel\cdot \int Cp\cdot dt
\]
Theory ... (contd)²

\[ \frac{\Delta}{V} = C_p + \text{kel} \int_0^t C_p \cdot dt \]

Amount absorbed
Up to time \( t \)
Divided by \( V \)

\[ \text{kel} \times \text{AUC} \]
from \( t = 0 \) to \( t = t \)

At \( t = \infty \), \( C_p = 0 \)

\[ \frac{\Delta_{\text{max}}}{V} = \text{kel} \int_0^\infty C_p \cdot dt = \text{kel} \cdot \text{AUC}_\infty \]

If Absorption is First Order

• \( (\Delta_{\text{max}}/A) \) is the Amount Remaining to be Absorbed

\[ \frac{\Delta_{\text{max}}}{V} \cdot \frac{A}{V} \cdot \frac{X_g}{V} = \frac{X_g}{V} \cdot e^{-\text{ka} \cdot t} = \frac{F \cdot \text{Dose}}{V} \cdot e^{-\text{ka} \cdot t} \]

Plot \( \ln(\Delta_{\text{max}}/A)/V \) versus Time

Example Data - W-N Method

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Concentration (mg/L)</th>
<th>Est 3 AUC</th>
<th>Est 4 AUC</th>
<th>Est 5 AUC</th>
<th>A/V</th>
<th>(Amax-A)/V</th>
<th>( \text{Kel} = 0.2 ) hr⁻¹ from IV data</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>4.9</td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
<td>0.6</td>
<td>0.4</td>
<td>0.6</td>
<td>1.02</td>
<td>1.52</td>
<td>5.58</td>
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<tr>
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<td>1.6</td>
<td>1.5</td>
<td>2.1</td>
<td>0.42</td>
<td>2.25</td>
<td>2.94</td>
<td>2.64</td>
</tr>
<tr>
<td>3</td>
<td>2.1</td>
<td>1.05</td>
<td>3.05</td>
<td>2.01</td>
<td>2.94</td>
<td>1.99</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>2.15</td>
<td>0.2</td>
<td>1.24</td>
<td>3.44</td>
<td>1.46</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.2</td>
<td>2.2</td>
<td>0.4</td>
<td>1.68</td>
<td>3.09</td>
<td>1.52</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>2.1</td>
<td>0.5</td>
<td>2.1</td>
<td>4.1</td>
<td>0.0</td>
<td></td>
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<tr>
<td>8</td>
<td>1.3</td>
<td>2.7</td>
<td>14.2</td>
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<td>10</td>
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<td>0.16</td>
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<td>19.5</td>
<td>0.8</td>
<td>4.8</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>0.5</td>
<td>5.0</td>
<td>24.5</td>
<td>4.9</td>
<td>4.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
The Plot - Semi-log

\[ ka = 0.3056 \text{ hr}^{-1} \]

The Plot - Linear

![Linear Plot]

By Inspection

- Assuming \( ka \) somewhat larger than \( kel \) (>5 times)
- Assuming absorption complete (> 95%) at time of peak concentration
- Determine \( t_{\text{peak}} = 5 \times t_{1/2 \text{ (absorption)}} \)
- That is, \( t_{1/2 \text{ (absorption)}} = t_{\text{peak}}/5 \)
Example

\[ t_{\text{peak}} \approx 1.5 \text{ hour} \]

\[ t_{\frac{1}{2} \text{ (absorption)}} \approx 0.3 \text{ hour} \]

\[ k_a \approx 2.3 \text{ hr}^{-1} \]

\[ \text{Actual value } 2 \text{ hr}^{-1} \]

Example …

\[ t_{\text{peak}} = 1.5 \text{ hour} \]

\[ t_{\frac{1}{2} \text{ (absorption)}} = 0.3 \text{ hour} \]

\[ k_a = 2.3 \text{ hr}^{-1} \]

\[ \text{Actual value } 2 \text{ hr}^{-1} \]

Calculation of F

\[ \frac{F}{V} \text{ from only Oral Data} \]

\[ \text{Need to have Reference Data} \]

– Absolute Bioavailability
– Relative Bioavailability

\[ \text{Using Plasma Data} \]

\[ \text{Using Urine Data} \]
F - Bioavailability, Fraction Absorbed

\[ C_P = \frac{F \times \text{Dose} \times ka}{V \times (ka - kel)} \times [e^{-kel \times t} - e^{-ka \times t}] \]

- From Oral Data Alone
  - Can calculate kel and ka
  - Know Dose
  - Cannot separate F from V
    - We get V/F or F/V

Bioavailability (F)

- Absolute Bioavailability
  - Comparison with IV Dose
- Relative Bioavailability
  - Comparison with another Extravascular Dosage form
- Bioavailability Study may use IV, Solution or Innovator’s Product as Reference

Using Plasma Data

- Equation for \( A_{\text{max}} \) from Wagner-Nelson Derivation

\[ A_{\text{max}} = F \times \text{Dose} = \text{kel} \times V \times \text{AUC} \]

Therefore

\[ F = \frac{\text{kel} \times V \times \text{AUC}}{\text{Dose}} \]
Comparing Two Dosage Forms

Since we don’t know \( V \) unless we have prior information

\[
F^a = \frac{\text{Dose}^a \cdot \text{AUC}^a}{\text{Dose}^b \cdot \text{AUC}^b}
\]

If \( \text{Dose}^a = \text{Dose}^b \) and we can assume that \( \text{kel}^a = \text{kel}^b \) and \( V^a = V^b \)

\[
F = \frac{F^a}{F^b} = \frac{\text{AUC}^a}{\text{AUC}^b}
\]

Example Calculation

- Data: \( \text{AUC}^a = 12.4 \text{ mg.hr/L} \); \( \text{Dose}^a = 250 \text{ mg} \); \( \text{AUC}^b = 14.1 \text{ mg/L} \); and \( \text{Dose}^b = 200 \text{ mg} \)
- Question: Calculate \( F \)
- Equation: \( F = \frac{\text{AUC}^a \cdot \text{Dose}^a}{\text{Dose}^b \cdot \text{AUC}^b} \)
- Result: \( F = \frac{12.4}{250} \cdot \frac{200}{14.1} = 0.70 \)

Using Urine Data

- Starting with the equation for \( fe \) (last semester)

\[
fe = \frac{U^a}{Xg} = \frac{U^a}{F \cdot \text{Dose}}
\]

\[
F = \frac{U^a}{fe \cdot \text{Dose}}
\]

\[
F^a = \frac{U^a}{fe^a \cdot \text{Dose}^a}
\]

\[
F^b = \frac{U^b}{fe^b \cdot \text{Dose}^b}
\]
Using Urine Data …

\[
\frac{F^A}{F^B} = \frac{U^{\infty}_A}{fe^A \cdot \text{Dose}^A} \cdot \frac{fe^B \cdot \text{Dose}^B}{U^{\infty}_B}
\]

- If Dose^A = Dose^B and fe^A = fe^B

\[
F = \frac{F^A}{F^B} = \frac{U^{\infty}_A}{U^{\infty}_B}
\]

Example Calculation

- Data: Dose = 250 mg; U^A = 175 mg; U^B = 183 mg
- Question: What is F
- Equation:

\[
F = \frac{U^{\infty}_A}{U^{\infty}_B}
\]

- Results:

\[
F = \frac{175}{183} = 0.96
\]

Data Analysis using Boomer

- Draw the Model - Numbering Components and Data Sets
- Create Table of Parameters and Constants
- Start the Program
The Model

Drug in G-I Tract

Drug in Body

ka

kel

Parameter Values

• From Earlier - Method of Residuals
  – $ka = 2.05 \text{ hr}^{-1}$
  – $kel = 0.2 \text{ hr}^{-1}$
  – $A = 5.5 \text{ mg/L} = \frac{F \cdot \text{Dose} \cdot ka}{V \cdot ka - kel}$
    \[
    5.5 = \frac{250 \cdot 2.05}{V \cdot (2.05 - 0.2)}
    \]
    \[
    V = \frac{250 \cdot 2.05}{5.5 \cdot 1.85} = 50.4 \text{ L}
    \]

Create the Parameter Table

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Value</th>
<th>To</th>
<th>Name</th>
<th>From</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1</td>
<td>250</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ka</td>
<td>2</td>
<td>2.05</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>kel</td>
<td>2</td>
<td>0.2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>V/F</td>
<td>18</td>
<td>50.4</td>
<td>1</td>
<td>Cp</td>
<td>2</td>
</tr>
</tbody>
</table>
Fitting Oral Data Alone Using Boomer

Open the .BAT file

Using the SAAM II

Start SAAM II
Load Program File

Fitting Oral and IV Data Together
Simultaneous Fit to IV and Oral data

Objectives

• Determine $ka$ using the
  – Method of Residuals
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  – Method of Inspection
  • as Appropriate to calculate $ka$
• Calculate $F$ using Plasma or Urine Data
• Understand the difference between absolute and relative bioavailability
• Fit IV and Oral Data Simultaneously