Calculation of Bioavailability Parameters

Objectives

- Determine ka using the
  - Method of Residuals
  - Wagner-Nelson Method
  - 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

Determine of ka

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

Method of Residuals

- Starting with the Equation for Cp

$$Cp = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[e^{-kel \cdot t} - e^{-ka \cdot t}\right]$$

which can be written as

$$Cp = A \cdot e^{-kel \cdot t} - A \cdot e^{-ka \cdot t}$$

where

$$A = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)}$$

Method of Residuals

- IF
  - ka/kel or kel/ka > 5

    AND

  - Both ka and kel are first order

$$Cp = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[e^{-kel \cdot t} - e^{-ka \cdot t}\right]$$

Cp at Later Times

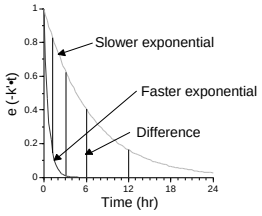
- At later time the exponential with the faster rate constant approaches zero more quickly

IF ka > kel

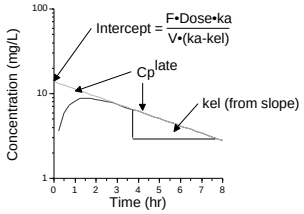
$e^{-ka \cdot t} \rightarrow 0$

and

$Cp^{late} = A \cdot e^{-kel \cdot t}$



Semi-log Plot of Cp versus Time



The Next Step

- Once we determine Cp^{late} from the terminal slope

$$Cp = A \bullet e^{-kel \bullet t} - A \bullet e^{-ka \bullet t}$$

$$\text{since } Cp^{late} = A \bullet e^{-kel \bullet t}$$

$$Cp = Cp^{late} - A \bullet e^{-ka \bullet t}$$

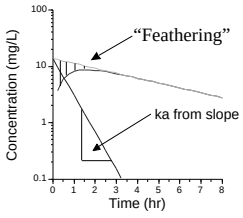
or

$$Cp^{late} - Cp = A \bullet e^{-ka \bullet t}$$

Residual

Plot Residual versus Time

Plot of Residual versus Time



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

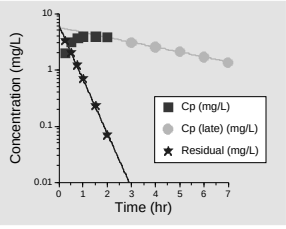
Dose 250 mg

Time (hr)	Plasma Concentration (mg/L)	Cp(late) (mg/L)	Residual [Col 3 - Col 2] (mg/L)
0.25	1.91	5.23	3.32
0.5	2.98	4.98	2.00
0.75	3.54	4.73	1.19
1.0	3.80	4.50	0.70
1.5	3.84	4.07	0.23
2	3.62	3.69	0.07
3	3.04		
4	2.49		
5.0	2.04		
6.0	1.67		
7.0	1.37		

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

$$Cp^{late} = 5.5 \times e^{-0.2 \times t}$$

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

*Wagner, J and Nelson, E. 1964 J. Pharm. Sci., **53**, 1392

Theory …

Working Equation

Amount Absorbed		Amount In Body		Amount Eliminated
A	=	**X**	+	**U**

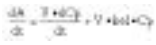
Differentiating each term gives

$$\frac{dA}{dt} = \frac{dX}{dt} + \frac{dU}{dt}$$

or

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

Theory … (contd)



$$dA = V \cdot dCp + kel \cdot V \cdot Cp \cdot dt$$

Integrating gives:

$$A = V \cdot Cp + kel \cdot V \cdot \int_0^t Cp \cdot dt$$

or

$$\frac{A}{V} = Cp + kel \cdot \int_0^t Cp \cdot dt$$

Theory … (contd)[2]

$$\frac{A}{V} = Cp + kel \cdot \int_0^t Cp \cdot dt$$

Amount absorbed Up to time t Divided by V

kel x AUC from t = 0 to t = t

At $t = \infty$; $Cp = 0$

$$\frac{A_{max}}{V} = kel \cdot \int_0^{\infty} Cp \cdot dt = kel \cdot AUC^{0-\infty}$$

If Absorption is First Order

- $(A_{max}-A)$ is the Amount Remaining to be Absorbed

$$\left(\frac{A_{max}}{V} - \frac{A}{V}\right) = \frac{Xg}{V} = \frac{Xg^0}{V} \cdot e^{-ka \cdot t} = \frac{F \cdot Dose}{V} \cdot e^{-ka \cdot t}$$

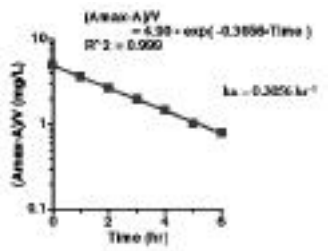
Plot ln(Amax-A)/V versus Time

kel = 0.2 hr^{-1} from IV data

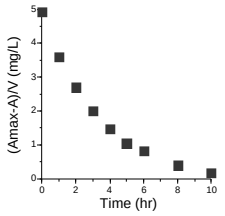
Example Data - W-N Method

Time (hr)	Concentration (mg/L)	Col 3 ΔAUC	Col 4 AUC	Col 5 kel• AUC	A/V [Col2+Col5]	(Amax-A)/V (mg/L)
0	0.0	0.0	0.0	0.0	0.0	4.9
1	1.2	0.6	0.6	0.12	1.32	3.58
2	1.8	1.5	2.1	0.42	2.22	2.68
3	2.1	1.95	4.05	0.81	2.91	1.99
4	2.2	2.15	6.2	1.24	3.44	1.46
5	2.2	2.2	8.4	1.68	3.88	1.02
6	2.0	2.1	10.5	2.1	4.1	0.8
8	1.7	3.7	14.2	2.84	4.54	0.36
10	1.3	3.0	17.2	3.44	4.74	0.16
12	1.0	2.3	19.5	3.9	4.9	-
∞	0.0	5.0	24.5	4.9	4.9	-

The Plot - Semi-log



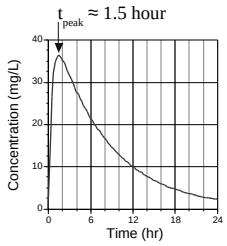
The Plot - Linear



By Inspection

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

Example



Example …

- t_{peak} ≈ 1.5 hour
- $t_{1/2\ (absorption)}$ ≈ 0.3 hour
- ka ≈ 2.3 hr^{-1}
- Actual value 2 hr^{-1}

Calculation of F

- F/V from only Oral Data
- Need to have Reference Data
  - Absolute Bioavailability
  - Relative Bioavailability
- Using Plasma Data
- Using Urine Data

F - Bioavailability, Fraction Absorbed

$$Cp = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[e^{-kel \cdot t} - e^{-ka \cdot t}\right]$$

- 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_{max} from Wagner-Nelson Derivation

$$A_{max} = F \cdot Dose = kel \cdot V \cdot AUC$$

therefore

$$F = \frac{kel \cdot V \cdot AUC}{Dose}$$

Comparing Two Dosage Forms

Since we don't know V unless we have prior information

$$\frac{F^A}{F^B} = \frac{kel^A \cdot V^A \cdot AUC^A}{Dose^A} \cdot \frac{Dose^B}{kel^B \cdot V^B \cdot AUC^B}$$

If $Dose^A = Dose^B$ and
we can assume that $kel^A = kel^B$ and $V^A = V^B$

$$F = \frac{F^A}{F^B} = \frac{AUC^A}{AUC^B}$$

Example Calculation

- Data: $AUC^A = 12.4$ mg.hr/L; $Dose^A = 250$ mg; $AUC^B = 14.1$ mg/L; and $Dose^B = 200$ mg
- Question: Calculate F
- Equation:
$$F = \frac{AUC^A}{Dose^A} \cdot \frac{Dose^B}{AUC^B}$$
- Result:
$$F = \frac{12.4}{250} x \frac{200}{14.1} = 0.70$$

Using Urine Data

- Starting with the equation for fe (last semester)

$$fe = \frac{U^\infty}{Xg^0} = \frac{U^\infty}{F \cdot Dose}$$

$$F = \frac{U^\infty}{fe \cdot Dose}$$

$$\frac{F^A}{F^B} = \frac{U^{\infty A}}{fe^A \cdot Dose^A} \cdot \frac{fe^B \cdot Dose^B}{U^{\infty B}}$$

Using Urine Data …

$$\frac{F^A}{F^B} = \frac{U^{\infty A}}{fe^A \cdot Dose^A} \cdot \frac{fe^B \cdot Dose^B}{U^{\infty B}}$$

- 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; $U^{\infty A}$ = 175 mg; $U^{\infty B}$ = 183 mg
- Question: What is F
- Equation:

$$F = \frac{U^{\infty A}}{U^{\infty B}}$$

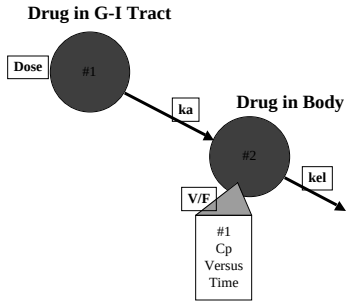
- Results:

$$F = \frac{175}{183} = 0.96$$

Data Analysis using Boomer

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

The Model



Parameter Values

- From Earlier - Method of Residuals
  - ka = 2.05 hr^{-1}
  - kel = 0.2 hr^{-1}
  - A = 5.5 mg/L = $\frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)}$

$$5.5 = \frac{F \cdot 250 \cdot 2.05}{V \cdot (2.05 - 0.2)}$$

$$\frac{V}{F} = \frac{250 \cdot 2.05}{5.5 \cdot 1.85} = 50.4 \text{ L}$$

Create the Parameter Table

Name	Type	Value	To	Name	From
Dose	1	250	1		
ka	2	2.05	2		1
kel	2	0.2	0		2
V/F	18	50.4	1	Cp	2

Fitting Oral Data Alone Using Boomer

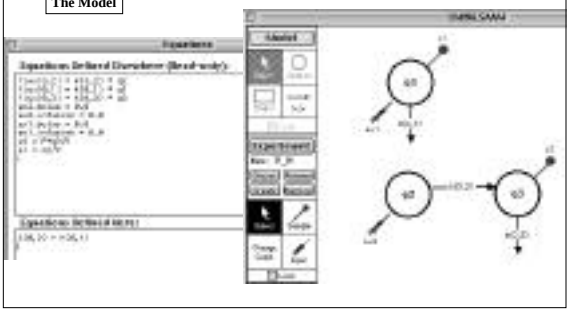
Open the .BAT file

Using the SAAM II

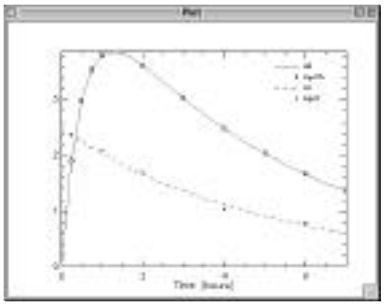
Start SAAM II
Load Program File

Fitting Oral and IV Data Together

The Model



Simultaneous Fit to IV and Oral data



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