

# PHAR 7632 Chapter 9

## Calculation of Bioavailability Parameters

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### Bioavailability Calculations

#### Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to calculate  $k_a$  using
  - the method of Inspection
  - the method of Residuals including
    - drawing the  $C_p^{\text{late}}$  line
    - estimating the residual values
    - drawing the residual line (and possibly rescaling the time axis)
  - the method of Wagner and Nelsonand describe when each method may be most appropriate
- be able to calculate  $F$  using plasma (AUC) or urine ( $U^\infty$ ) data
- understand the difference between absolute and relative bioavailability and be able to convert between these values

On many occasions you will be able to get the parameter values from tables and references. However, you should also know how to get these values from the data. The two parameters we will concentrate on in this Chapter are  $k_a$  and  $F$ . These values can be used to compare dosage forms or brands. In Chapter 8 we saw the effect changing  $k_a$  or  $F$  has on the plasma concentration time curve. In this chapter we will calculate  $k_a$  and  $F$  from drug concentration *versus* time data.

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### Method of Residuals

Starting with the equation for  $C_p$  versus time

$$C_p = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet [e^{-kel \bullet t} - e^{-ka \bullet t}]$$

Equation 9.2.1  $C_p$  versus Time after Oral Administration

this can be written as

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

Equation 9.2.2 Simplified Equation for  $C_p$  versus Time

$$\text{where } A = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)}$$

Equation 9.2.3 The Intercept, A

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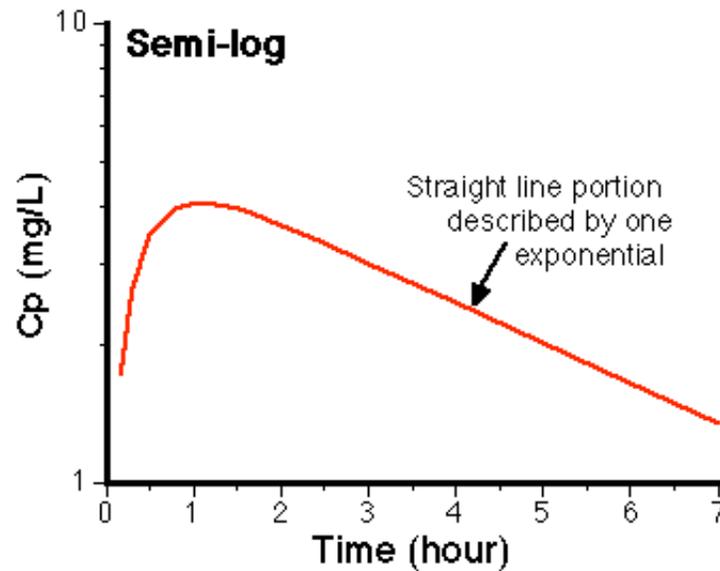


Figure 9.2.1 Semi-log plot of  $C_p$  versus Time after Oral Administration

Click on the figure to view the Java Applet window  
Java Applet as a [Linear Plot](#)

If one of the rate constants ( $k_a$  or  $k_{el}$ ) is much larger than the other, **the method works best if the difference is at least five times**, then the faster differential will approach zero more quickly, and at later times can be ignored. If we plot  $C_p$  versus time on semi-log graph paper we will see that the slope will approach a straight line.

The equation for this straight line portion can be obtained from the equation for  $C_p$  by setting the faster term (usually  $e^{-k_a \cdot t}$ ) to zero:

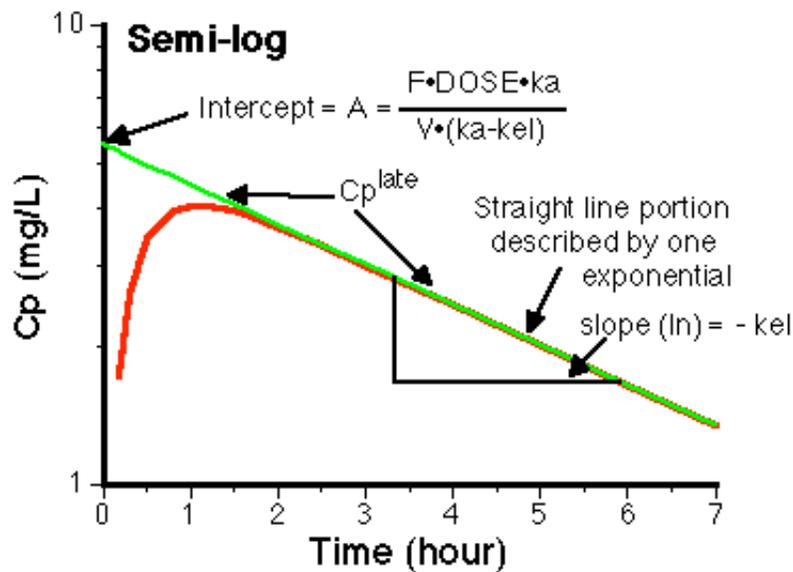


Figure 9.2.2 Semi-log Plot of  $C_p$  versus Time Showing  $C_p^{late}$ , Slope, and Intercept

then

$$C_p^{late} = A \cdot e^{-k_{el} \cdot t}$$

**Equation 9.2.4  $C_p^{late}$  versus Time**

and plotting  $C_p^{late}$  versus time gives a straight line on semi-log graph paper, with a slope (ln) =  $-k_{el}$  and intercept = A.

Now looking at the equation for  $C_p$  versus time again.

$$C_p = A \bullet e^{-k_{el} \bullet t} - A \bullet e^{-k_a \bullet t} = C_p^{late} - A \bullet e^{-k_a \bullet t}$$

**Equation 9.2.5  $C_p$  versus Time including  $C_p^{late}$** 

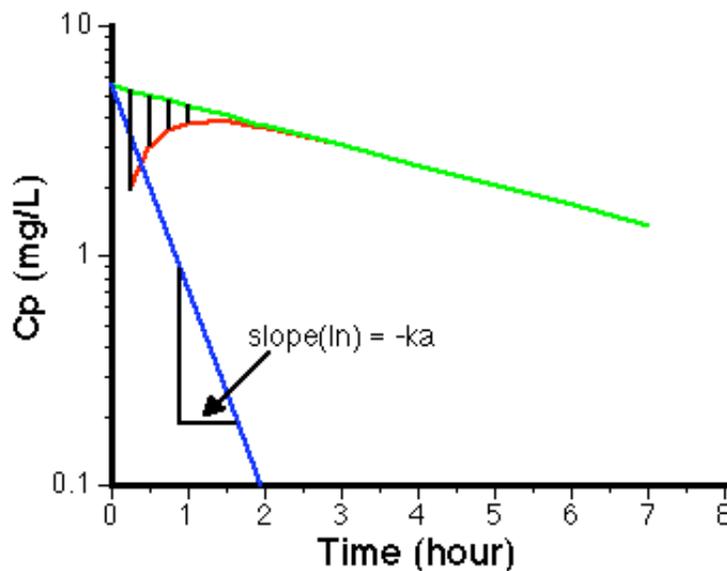
therefore

$$\text{Difference or Residual} = C_p^{late} - C_p = A \bullet e^{-k_a \bullet t}$$

**Equation 9.2.6 Difference or Residual versus Time**

Plotting the ln (Residual) versus time should give another straight line graph with a slope (ln) equal to  $-k_a$  and the same intercept as before, i.e. A

$$\ln(\text{Residual}) = \ln(A) - k_a \bullet t$$

**Equation 9.2.7 ln(Residual) versus Time**

**Figure 9.2.3 Semi-log of Plot of Residual versus Time**

This is the method of residuals or "feathering".

It can give quite accurate values of  $k_{el}$ ,  $k_a$ , and  $V/F$  if :

- i) one rate constant is at least five times larger than the other
- and
- ii) both absorption and elimination are first order processes.

## An Example Calculation Using the Method of Residuals

Table 9.2.1 Example Data for the Method of Residuals

Time (hr)	Plasma Concentration (mg/L)	Cp(late) (mg/L)	Residual [Col3 - Col2] (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
2.0	3.62	3.69	0.07
3.0	3.04		
4.0	2.49		
5.0	2.04		Residual = $5.5 * e^{-2.05 * t}$
6.0	1.67	$C_p^{late} = 5.5 * e^{-0.2 * t}$	
7.0	1.37		

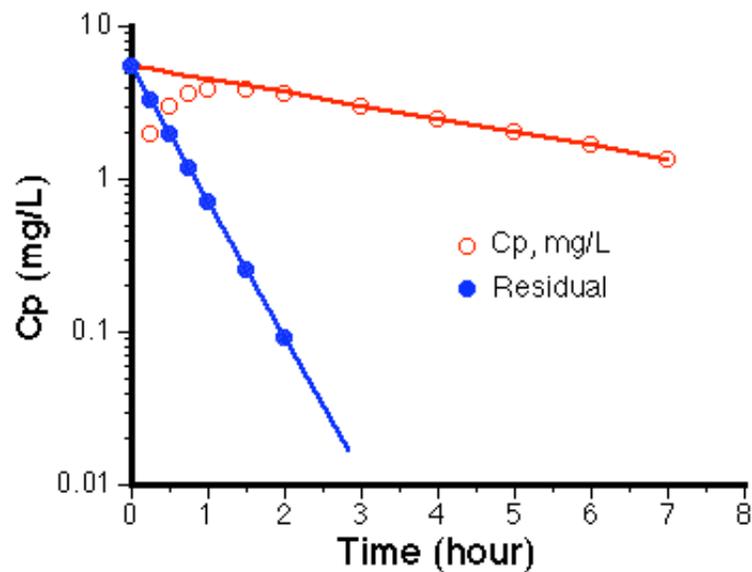
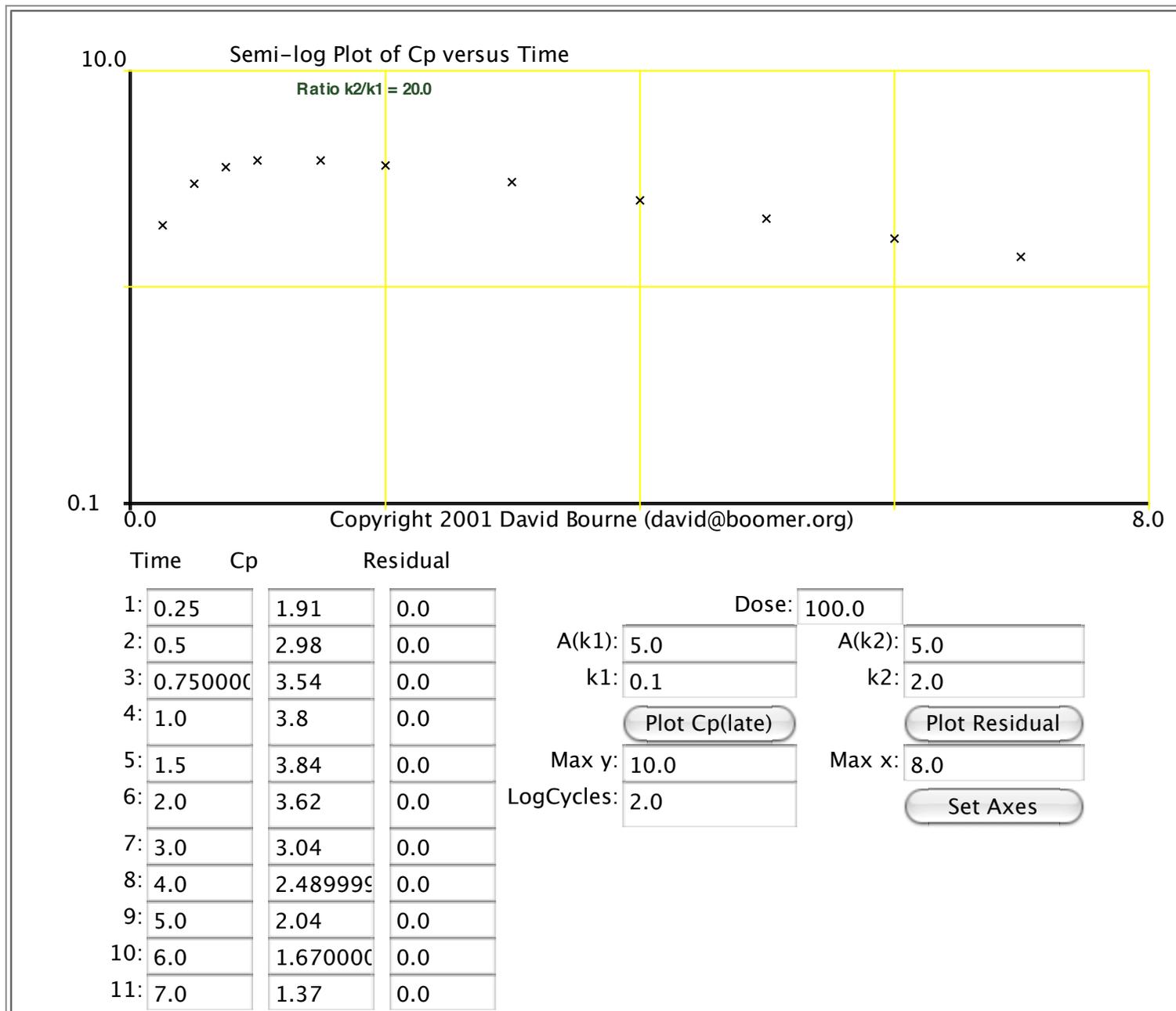


Figure 9.2.4 Figure Illustrating the Method of Residuals



The objective of this panel is to illustrate the **Method of Residuals** for determining information about the drug absorption process.

**First:** Draw the  $C_p^{late}$  line by changing the intercept ( $A(k_1)$ ) and slope ( $k_1$ ) values. Press the Cp(late) button to plot the line and calculate the residual values.

**Second:** Draw the Residual line by changing the intercept ( $A(k_2)$ ) and slope ( $k_2$ ) values. Press the Plot Residual button to plot the residual line.

By trial and error best fit lines can be drawn and the parameters determined.

Up to eleven (11) different data points can be entered instead of the example data provided. Leave fields empty if there are fewer than 11 data points in your data set.

**For practice** try calculating the absorption rate constant,  $k_a$ , using the method of residuals. Compare your answers with the computer! Note the value of the ratio  $k_a/k_{el}$ .

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### Wagner-Nelson Method

Another method of calculating  $k_a$  is the Wagner-Nelson method

#### Advantages:

- i) The absorption and elimination processes can be quite similar and accurate determinations of  $k_a$  can still be made.
- ii) The absorption process doesn't have to be first order. This method can be used to investigate the absorption process. I have used this type of method to investigate data obtained after IM administration and found that two absorption steps maybe appropriate. Possibly a fast step from drug in solution and a slower step from drug precipitated at the injection site. The method can provide very useful information about the absorption processes with different dosage forms.

#### Disadvantages:

- i) The major disadvantage of this method is that you need to know the elimination rate constant, from data collected following intravenous administration.
- ii) The required calculations are more complex.

### Theory

The working equations can be derived from the mass balance equation:

$$\begin{aligned} \text{Amount Absorbed (A)} \\ = \text{Amount in Body (X)} + \text{Amount Eliminated (U)} \end{aligned}$$

**Equation 9.3.1 Mass Balance Equation**

or

$$A = X + U$$

**Equation 9.3.2 Mass Balance Equation**

Differentiating each term with respect to time gives:-

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

**Equation 9.3.3 Differentiated Equation**

or

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

Equation 9.3.4 Rate of Change of Amount Absorbed

or

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

Integrating gives:-

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

Equation 9.3.5 Amount Absorbed *versus* Time

or

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

Amount absorbed up to time t divided by V
kel • AUC from t = 0 up to t = t

Equation 9.3.6 Amount Absorbed divided by Volume *versus* Time

Taking this to infinity where Cp equals 0

$$\frac{A_{max}}{V} = kel \bullet AUC_0^\infty$$

Equation 9.3.7 Maximum Amount Absorbed divided by Volume of Distribution

Finally ( $A_{max} - A$ ), the amount remaining to be absorbed can also be expressed as the amount remaining in the GI, Xg

$$\frac{Xg}{V} = \frac{A_{max}}{V} - \frac{A}{V}$$

Equation 9.3.8 Amount Remaining to be Absorbed

We can use this equation to look at the absorption process. If absorption is first order

$$\frac{Xg}{V} = \frac{Xg^0}{V} \bullet e^{-ka \bullet t}$$

or

$$\left[ \frac{A_{max}}{V} - \frac{A}{V} \right] = \frac{Xg^0}{V} \bullet e^{-ka \bullet t}$$

Thus a plot of  $\ln(A_{max} - A)$  versus time will give a straight line for first order absorption with a slope(ln) = -ka. Note that linear or other plots may reveal other absorption behavior.

**Table 9.3.1 Example Data for the Method of Wagner-Nelson**

kel (from IV data) = 0.2 hr<sup>-1</sup>

Time (hr)	Plasma Concentration (mg/L)	Column 3 ΔAUC	Column 4 AUC	Column 5 kel * AUC	A/V [Col2 + Col5]	(A <sub>max</sub> - A)/V
0.0	0.0	0.0	0.0	0.0	0.0	4.9
1.0	1.2	0.6	0.6	0.12	1.32	3.58
2.0	1.8	1.5	2.1	0.42	2.22	2.68
3.0	2.1	1.95	4.05	0.81	2.91	1.99
4.0	2.2	2.15	6.2	1.24	3.44	1.46
5.0	2.2	2.2	8.4	1.68	3.88	1.02
6.0	2.0	2.1	10.5	2.1	4.1	0.8
8.0	1.7	3.7	14.2	2.84	4.54	0.36
10.0	1.3	3.0	17.2	3.44	4.74	0.16
12.0	1.0	2.3	19.5	3.9	4.9	-
∞	0.0	5.0	24.5	4.9	4.9	-

The data (A<sub>max</sub>-A)/V versus time can be plotted on semi-log and linear graph paper.

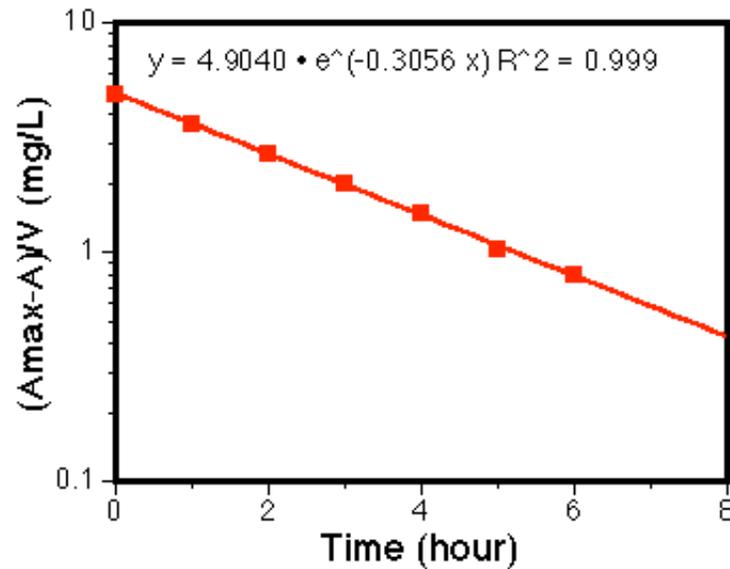


Figure 9.3.1 Semi-log plot of  $(A_{\max}-A)/V$  versus Time

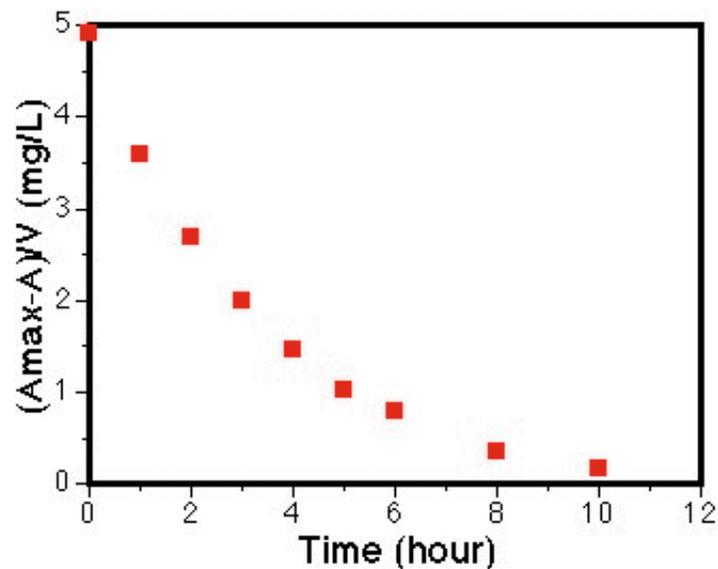


Figure 9.3.2 Linear plot of  $(A_{\max}-A)/V$  versus Time

Plotting  $(A_{\max}-A)/V$  versus time produces a straight line on semi-log graph paper and a curved line on linear graph paper. From the slope of the line on the semi-log graph paper  $k_a$  can be calculated to be  $0.306 \text{ hr}^{-1}$ .

**For practice** try calculating the absorption rate constant,  $k_a$ , [using the Wagner-Nelson Method](#). Compare your answers with the computer!

#### References

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

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### Method of Inspection

The method of Residuals and the Wagner-Nelson methods are useful technique for determining good estimates of  $k_a$ . Non-linear regression analysis may be able to provide even more accurate estimates of  $k_a$ . However, another more approximate method might be of interest. This is the method of inspection. It is capable of providing a 'ball-park' or approximate estimate of  $k_a$  for quick estimation, checking the results obtained from other methods or as an initial estimate for more detailed analysis.

### Requirements for the Method of Inspection

- We assume that  $k_a$  is much larger than  $k_{el}$ . That is, that  $k_a$  is at least five time greater than  $k_{el}$ . This is the same requirement as for the Method of Residuals when  $k_a$  is greater than  $k_{el}$ .
- Assume that absorption is complete (i.e. approximately 95 % complete) at the time of the peak concentration. This follows from the first assumption

### The Method

The first step is to estimate the time of the peak drug concentration **by inspection**. If we assume that the time of peak is approximately five time the absorption half-life:

$$t_{peak} = 5 \times t_{1/2(absorption)}$$

Equation 9.4.1 Time of Peak Concentration

or

$$t_{1/2(absorption)} = \frac{t_{peak}}{5}$$

Equation 9.4.2 Drug Absorption Half-Life,  $t_{1/2}$  (absorption)

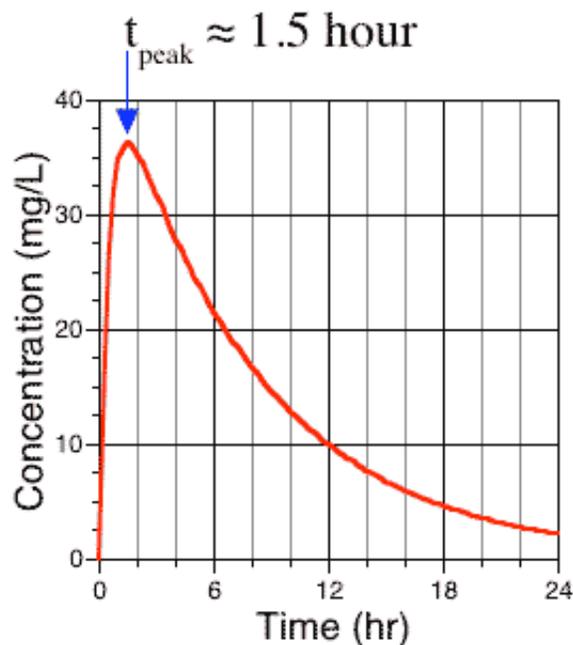
From this value for  $t_{1/2}$  (absorption) we can estimate the absorption rate constant.

$$k_a = \frac{\ln(2)}{t_{1/2(absorption)}} \text{ or } \frac{0.693}{t_{1/2(absorption)}}$$

Equation 9.4.3 Absorption rate constant

## An Example

Considering the results illustrated in Figure 9.4.1 the time of peak can be estimated to be approximately 1.5 hours.



**Figure 9.4.1 Linear Plot of Drug Concentration versus Time after Oral Administration Illustrating  $t_{\text{peak}}$**

With a  $t_{\text{peak}}$  of 1.5 hour the  $t_{1/2}$  (absorption) can be estimated as  $1.5/5 = 0.3$  hour. Finally  $k_a$  can be estimated as  $\ln(2)/0.3$  or  $0.693/0.3 = 2.3 \text{ hr}^{-1}$ . For comparison the  $k_a$  value used to calculate these data was  $2 \text{ hr}^{-1}$ .

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#### Calculation of F

So far we have looked at the equation for calculating  $C_p$  as a function of time, and then methods of determining  $k_a$  and  $k_{el}$ . That is the method of residuals, the Wagner-Nelson method and the method of inspection. Now to continue, we can look at methods of calculating F, the extent of absorption, i.e. the fraction of the dose which is absorbed.

Returning to the equation for  $C_p$  as a function of time

$$C_p = \frac{F \bullet Dose \bullet k_a}{V \bullet (k_a - k_{el})} \bullet [e^{-k_{el} \bullet t} - e^{-k_a \bullet t}]$$

Equation 9.5.1 Drug Concentration *versus* Time after Oral Administration

We can calculate  $k_a$  and  $k_{el}$  given  $C_p$  *versus* time data. From the method of residuals, the intercept can be determined as

$$Intercept = \frac{F \bullet Dose \bullet k_a}{V \bullet (k_a - k_{el})}$$

Since we know the dose and have calculated  $k_a$  and  $k_{el}$ , it is possible to calculate F/V. However, with only data from a single administration available that's all we can determine, we cannot separate V and F. Of course if we have IV data for  $k_{el}$  and V, we could use this to determine F.

Thus F must be determined by comparison with another dose administration. If the other dosage form is an intravenous dose then the F value is termed the **absolute** bioavailability. In the case where the reference dosage form is another oral or other non IV product, the value for F is termed the **relative** bioavailability.

#### Using plasma data

When a bioavailability study is conducted at least two dosage forms are administered to each subject. One dosage form is the product to be tested, while the other dosage form is a standard or reference dosage form. This may be an IV dose, oral solution or most commonly the original manufacturer's product. The doses are given with sufficient time between administrations for the drug to "washout" or be completely eliminated. We usually assume that each subject eliminates each dosage form at the same rate.

During the derivation of the Wagner-Nelson equations we calculated  $A_{max}$ , the maximum amount absorbed as:-

$$A_{max} = V \bullet k_{el} \bullet \int_0^{\infty} C_p \bullet dt$$

Equation 9.5.2  $A_{max}$ , Total Amount Absorbed

or

$$A_{max} = V \bullet kel \bullet AUC$$

and since

$$A_{max} = F \bullet Dose$$

therefore

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

**Equation 9.5.3 Bioavailability or Fraction Absorbed**

Now by giving two dosage forms A and B, and calculating AUC values for each.

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

**Equation 9.5.4 Bioavailability of Product A Relative to Product B**

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

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

**Equation 9.5.5 Bioavailability, F, from AUC Comparison**

Thus a relative bioavailability, F, can be calculated. If dosage form B is an IV administration then  $F^B = 1$  and  $F = F^A$  and thus  $F^A$  can be called the absolute bioavailability.

**Example**

$AUC^A = 12.4$  mg.hr/L [Dose = 250 mg] and  $AUC^B = 14.1$  mg.hr/L [Dose = 200 mg] then

$$F = \frac{12.4}{250} \times \frac{200}{14.1} = 0.70$$

**Using Urine Data**

We can do the same thing using urine data alone.

Since

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

**Equation 9.5.6 Fraction Excreted as Unchanged Drug, fe**

therefore

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

and for two dosage forms

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

as before if  $Dose^A = Dose^B$  and  $fe^A = fe^B$  then

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

### Example

250 mg dose;  $U^{\infty,A} = 175$  mg;  $U^{\infty,B} = 183$  mg

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

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**For practice** try [calculating the F](#) from plasma or urine data. Compare your answers with the computer!

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