

PHAR 7633 Chapter 9

Calculation of Bioavailability Parameters

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 Residuals including
 - drawing the C_p^{late} line
 - estimating the residual values
 - drawing the residual line (and possibly rescaling the time axis)
 - the method of Wagner and Nelson
 - the method of Inspectionand describe when each method may be most appropriate
- be able to calculate F using plasma (AUC) or urine (U^∞) 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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Calculation of Bioavailability Parameters

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

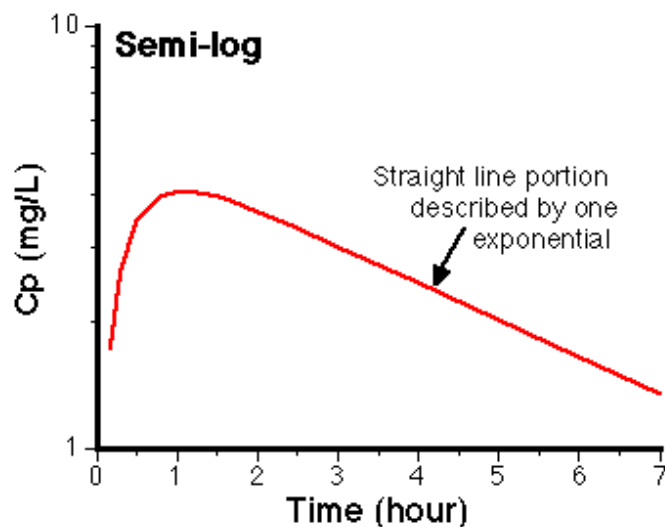


Figure 9.2.1 Semi-log plot of C_p versus Time after Oral Administration

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:

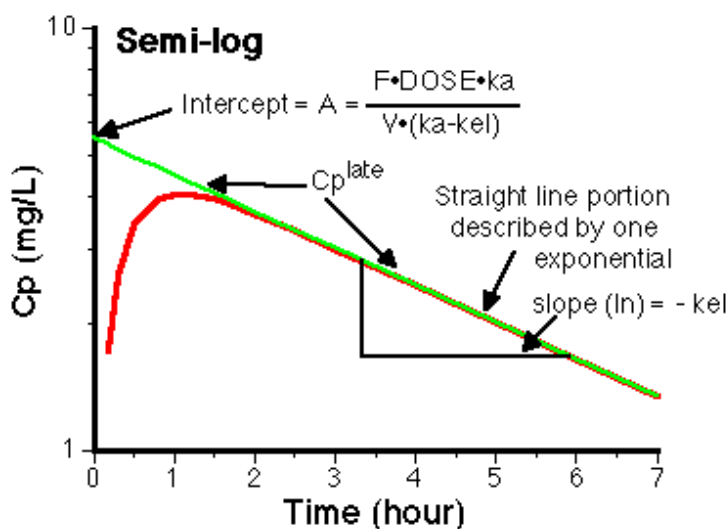


Figure 9.2.2 Semi-log Plot of C_p versus Time Showing C_p^{late} , Slope, and Intercept

then

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

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.

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

Equation 9.2.5 C_p versus Time including C_p^{late}

therefore

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

Equation 9.2.6 Difference or Residual versus Time

Plotting the $\ln(\text{Residual})$ 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

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

Equation 9.2.7 $\ln(\text{Residual})$ versus Time

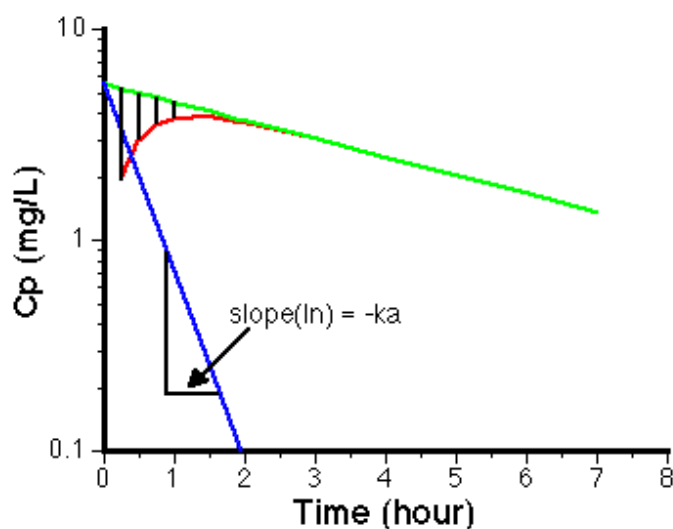


Figure 9.2.3 Semi-log of Plot of Residual versus Time

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)	$C_p(\text{late})$ (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		

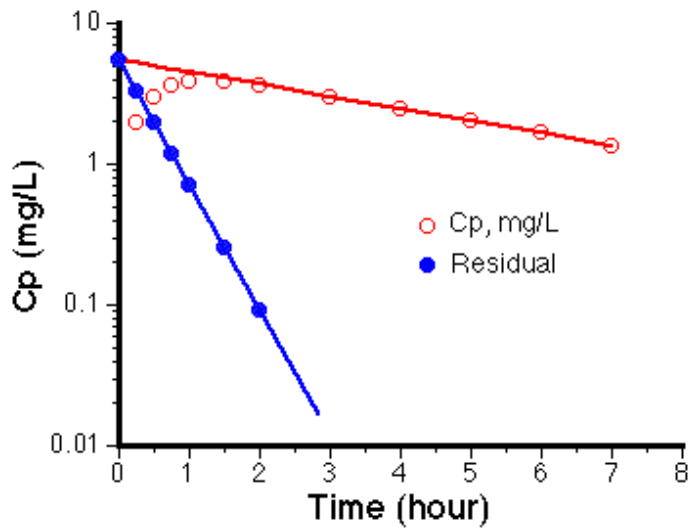
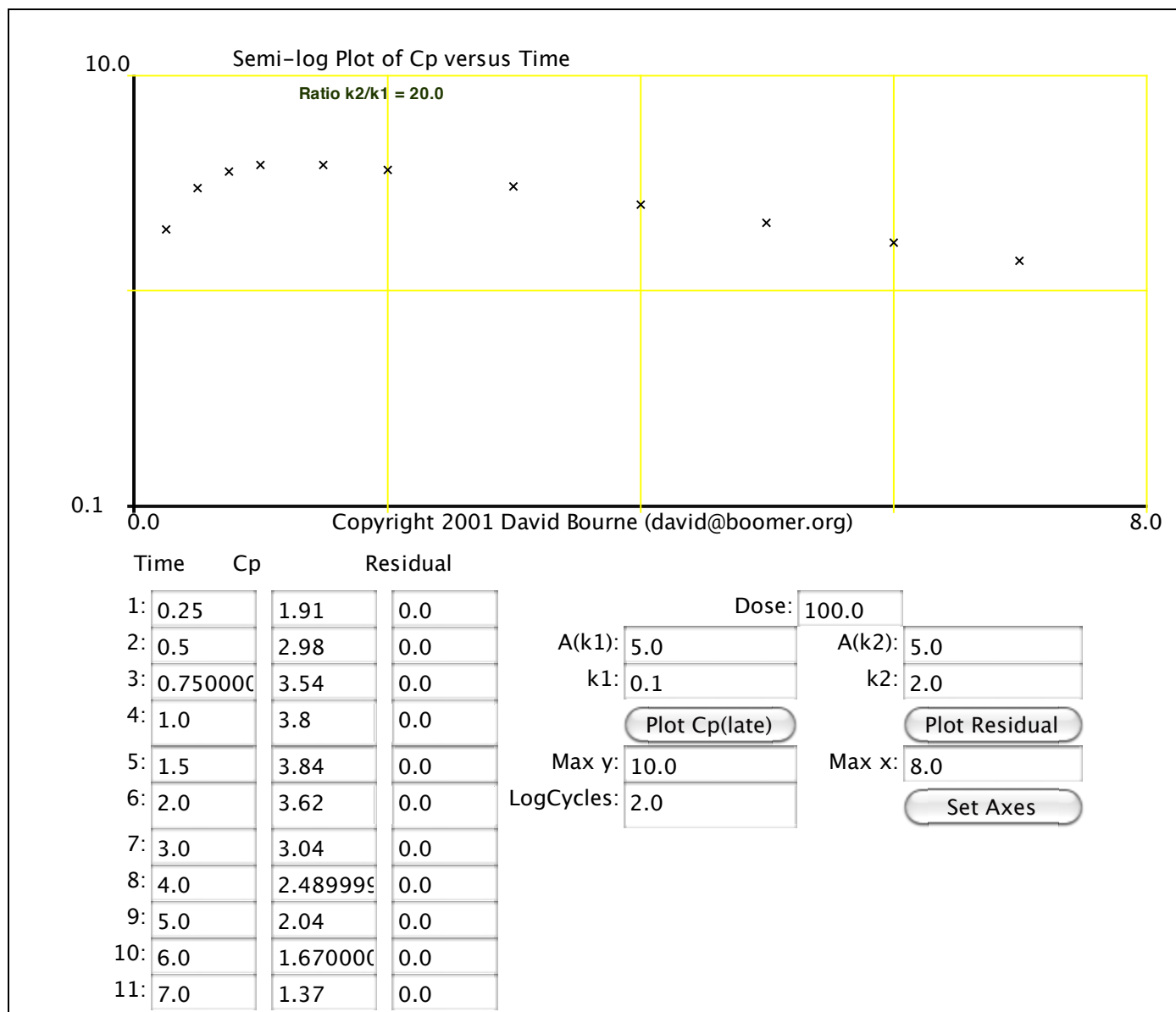


Figure 9.2.4 Figure Illustrating the Method of Residuals



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} .

Video/Audio Tutorial
PodCast Available

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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

$$\frac{dA}{dt} = \frac{V \bullet dC_p}{dt} + V \bullet k_{el} \bullet C_p$$

Equation 9.3.4 Rate of Change of Amount Absorbed

or

$$dA = V \bullet dC_p + V \bullet k_{el} \bullet C_p \bullet dt$$

Integrating gives:-

$$A = V \bullet C_p + V \bullet k_{el} \bullet \int_0^t C_p \bullet dt$$

Equation 9.3.5 Amount Absorbed versus Time

or

$$\frac{A}{V} = C_p + k_{el} \bullet \int_0^t C_p \bullet dt$$

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 TimeTaking this to infinity where C_p equals 0

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

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, X_g

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

Equation 9.3.8 Amount Remaining to be Absorbed

We can use this equation to look at the absorption process. If, and only if, absorption is a single first order process.

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

or

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

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 types of plots may reveal other absorption behavior. For example a straight line on linear graph paper might suggest that absorption follows zero order kinetics, such as with an infusion step or an attempted mimicking of zero order absorption with a patch or another slow release delivery device.

Table 9.3.1 Example Data for the Method of Wagner-Nelson

k_{el} (from IV data) = 0.2 hr^{-1}

Time (hr)	Plasma Concentration (mg/L)	Column 3 ΔAUC	Column 4 AUC	Column 5 $k_{el} * AUC$	A/V [Col2 + Col5]	$(A_{\max} - A)/V$
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 $(A_{\max} - A)/V$ versus time can be plotted on semi-log and linear graph paper.

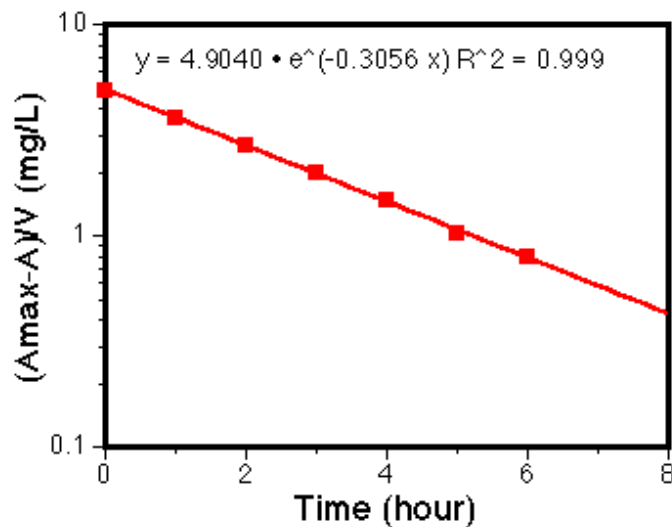


Figure 9.3.1 Semi-log plot of $(A_{\max} - A)/V$ versus Time

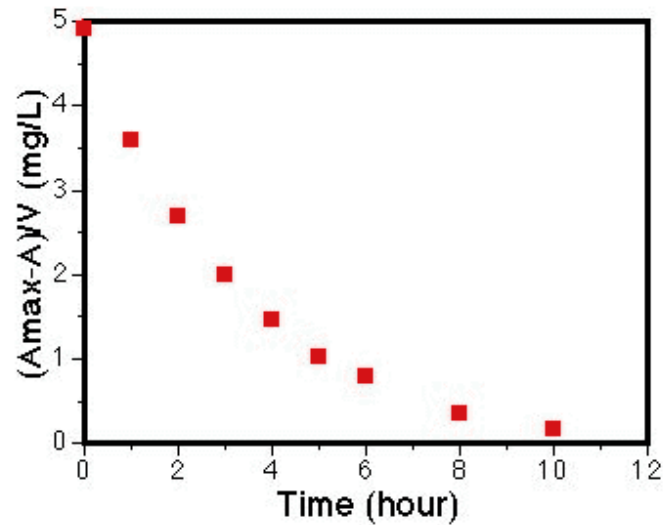


Figure 9.3.2 Linear plot of $(A_{\max}-A)/V$ versus Time

Plotting $(A_{\max}-A)/V$ versus time produces a straight line on semi-log graph paper and a curved line on linear graph paper. This would support the assumption that absorption can be described as a single first process. The first-order absorption rate constant, k_a , can be calculated to be 0.306 hr^{-1} from the slope of the line on the semi-log graph paper.

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 . A computer program providing non-linear regression analysis may be able to provide even more accurate estimates of k_a . Therefore, a quick, approximate method might be of interest. The method of inspection could be useful in this role. It is capable of providing a quick, approximate estimate of k_a for 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.

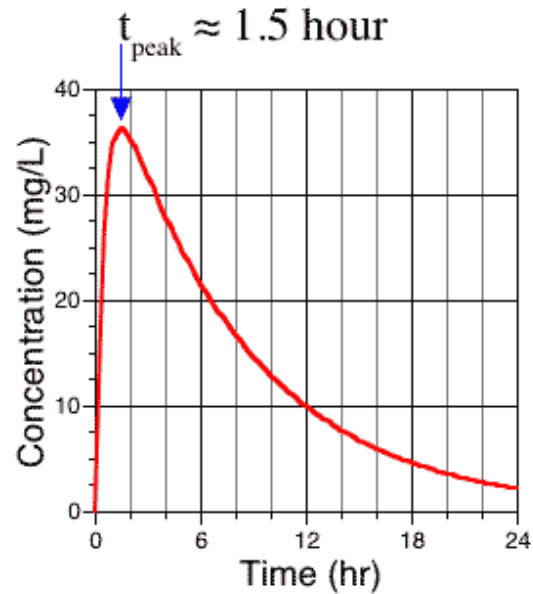


Figure 9.4.1 Linear Plot of Drug Concentration versus Time after Oral Administration Illustrating t_{peak}

With a t_{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 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 oral administration available that is 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 similar rates or use the estimate of the slowest rate to determine the wash-out period.

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

$$A_{max} = V \bullet k_{el} \bullet AUC$$

and since

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

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

Equation 9.5.3 Bioavailability or Fraction Absorbed

Now by giving two dosage forms A and B, and calculating AUC values for each we can calculate the relative bioavailability of dosage form A with respect to dosage form B, F_A/F_B .

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

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 represents 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

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

For practice try calculating the F from plasma or urine data. Compare your answers with the computer!

Student Objectives for this Chapter

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