Experiment 1

Pharmacokinetics of ibuprofen as an example of the first-order kinetics in an open one-compartment body model. Simultaneous fitting of two data sets - blood and urine by means of TopFIT 2.0 software

Theoretical knowledge: One-compartment body model, drug concentration in blood and urine after single oral dose, calculation of pharmacokinetic parameters: K, k_a, V_d, Cl, AUC

400 mg of ibuprofen in a single oral dose has been administered to a patient. The concentrations of the drug in plasma and urine are shown in the table 1 and 2.

Table 1. The change of concentration of ibuprofen in plasma

Time [h]	Concentration [mg/L]
0.25	17.8
0.5	26.6
0.75	33.2
1	34.0
2	30.4
3	19.7
4	13. 5
6	6.5
9	2.2
12	0.6

Table 2. The change of concentration of ibuprofen in urine

Time [h]	Concentration [mg/L]	Urine volume [mL]
2	25.4	290
4	132.0	70
6	29.1	210
8	20.7	170
10	4.9	170
12	8.2	120
24	0.4	200

1. Plot the drug concentrations in plasma versus time on a graph paper
2. Calculate the absorption and elimination rate constants ($\boldsymbol{k_a}$ and $\boldsymbol{K}$) using the method of residuals

Methods of residuals

The method of residuals is used in pharmacokinetics for resolving a curve into its various exponential components. The terms feathering, peeling and stripping are also used to described this technique.

A drug administered orally is absorbed by apparent first-order kinetics and confers the characteristics of one-compartment model on the body. The following equation (Bateman) has been employed to describe the time course for such a drug in the body:

$$C = \frac{k_a \cdot F \cdot X_0}{V \cdot (k_a - K)} (e^{-K \cdot t} - e^{-k_a \cdot t}) \qquad (1)$$

where ***C*** is the plasma concentration of drug at any time ***t*** following the administration dose X_0, ***V*** is the apparent volume of distribution, ***F*** is the fraction of the orally administered dose which is absorbed, and k_a and ***K*** are the apparent first-order absorption and elimination rate constant, respectively. A plot of the logarithm of plasma drug concentration versus time following oral administration will be biexponential with a terminal linear phase having a slope of ***K***.

Above equation can be transformed into the following expression:

$$C = B \cdot e^{-K \cdot t} - A \cdot e^{-ka \cdot t} \qquad (2)$$

where ***A*** and ***B*** are intercepts on the y axis for each exponential segment of the curve.

Assuming $k_a >> K$ $(k_a/K \geq 3)$, the value for the second exponential will become insignificantly small with time (i.e., $e^{-ka \cdot t} \approx 0$) and can therefore be omitted.

When this is the case, drug absorption is virtually complete. Equation then reduces to:

$$C' = B \cdot e^{-K \cdot t} \qquad (3)$$

$$\ln C' = \ln B - K \cdot t \qquad (4)$$

This equation, which represents first order drug elimination, will yield a linear plot on semilog paper. The slope is equal to ***K,*** apparent first-order elimination rate constant.

The value for k_a can be obtained by using the method of residuals.

The Eq. 3 is substituted into the Eq. 2:

$$C = C' - A \cdot e^{-ka \cdot t}$$

$$C' - C = A \cdot e^{-ka \cdot t}$$

$$\ln(C' - C) = \ln A - k_a \cdot t \qquad (5)$$

The new line obtained by graphing the logarithm of residual plasma concentration against time represents the k_a phase. The slope is equal to k_a, apparent first-order absorption rate constant.

The values of ***K*** and k_a are obtained by the following procedure:

a) Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis.
b) Obtain the slope (a), the y-intercept (b) and regression coefficient of the terminal elimination phase by least square method. The slope is equal to ***–K***.
c) Calculate the extrapolated concentration values (C'_1, C'_2, C'_3 and C'_4) by substituting the time values t_1, t_2, t_3 and t_4 in the equation where the slope and the y-intercept were previously calculated.

d) Calculate the residual concentration values (C' – C) at the corresponding time points. A plot of the logarithm of the residual concentrations versus time will yield a straight line with a slope of $-k_a$ and a zero time intercept equal to lnA.

3. Calculate:

a) the half-life $t_{0.5} = \frac{0.693}{K}$

b) C_0 from the elimination curve

c) C_0 from the equation: $AUC = \frac{C_0}{K}$, if *AUC* = 134.8 mg·h/L (determined by the trapezoidal rule)

d) volume of distribution: $V_{area} = \frac{F \cdot dose}{K \cdot AUC} \quad where \quad F = 1$

e) clearance: $Cl = \frac{0.693 \cdot V}{t_{0.5}} = K \cdot V$

f) time (t_{max}) needed to reach the maximum concentration C_{max}:

$$t_{\max} = \frac{1}{k_a - K} \cdot \ln \frac{k_a}{K}$$

g) C_{max} from the Bateman equation, using t_{max} value

h) amounts of ibuprofen excreted in urine samples:

$$X_{u_i} = C_i \cdot V_i$$

i) cumulative amounts of ibuprofen in urine samples

4. TopFit

TopFit is a computer program for non-compartmental data analysis and linear and non-linear compartmental modeling with the option of simultaneous effect fitting. TopFit allows simultaneous analysis of several data sets. Also, simulations of plasma levels and effect kinetics can be performed.

Enter the plasma concentration and the cumulative amount of drug in urine into the TopFit by using the following procedure:

I. MAIN MENU
   i. Edit header (4) save (F1)
   ii. Edit data (5)
      1. FORMULATION DATA
         a. Type of input (Absorption/tablet)
         b. Name of formulation (ibuprofen in plasma)
         c. Edit dosing table (F7)
            i. Unit of time (h), unit of dosing (mg/individual), time = 0 h, Dose = 400 mg
            ii. Save (F1)
         d. Edit data sets (F8)
            i. Sample matrix (plasma), type of weighting function ($1/y^2$), unit of measurement (mg/L), unit of time (h)
            ii. Save (F1)
         e. Edit data sets (F8) table (F8)
            i. File the measurement table (time, concentration value)
            ii. Save (F1) × 2
      2. New (F6)
      3. Enter the cumulative amounts of ibuprofen in urine

a. Type of input
b. Name of formulation (ibuprofen in urine)
c. Edit dosing table (F7)
   i. Unit of time (h), unit of dosing (mg/individual), time = 0 h, Dose = 400 mg
   ii. Save (F1)
d. Edit data sets (F8)
   i. Sample matrix (urine), type of weighting function ($1/y^2$), unit of measurement (mg), unit of time (h)
   ii. Save (F1)
e. Edit data sets (F8) table (F8)
   i. File the measurement table (time, cumulative amounts)
   ii. Save (F1) $\times$ 3

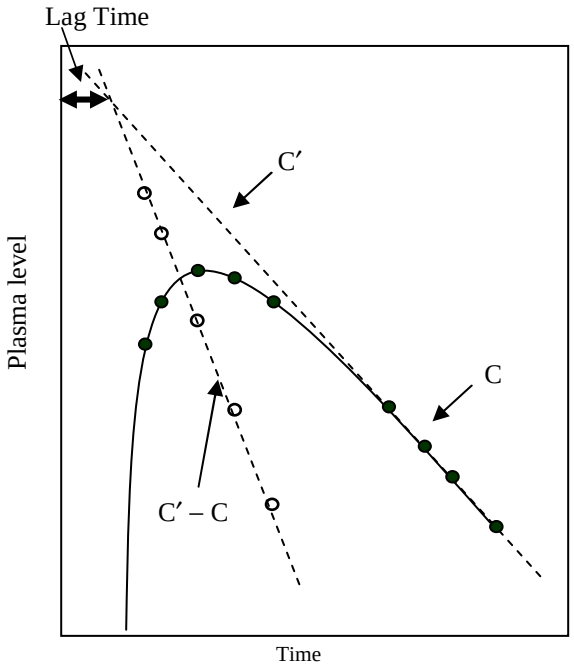
II. MAIN MENU
   i. Enter methods menu (8)
   ii. Standard compartment models (2)
   iii. One compartment (1)
   iv. Select data sets (1)
      1. Select both formulations
      2. Ready (F1)
   v. Start iteration (6)
   vi. Results Menu
      1. View graphics (2)
         a. Change Y-axis to logarithmic Edit (F3)
         b. Graph (F1)
         c. Exit (F10)
      2. View results (1)
         a. select as follows: Residuals; Parameters, eigenvalues and coefficients
         b. Save (F1)
   vii. Rewrite the values of pharmacokinetic parameters

Lag Time (t_{lag})

In some individuals, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility. The delay prior to the commencement of first-order drug absorption is know as *lag time*.

The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level-time curve intersect at a point greater than *t = 0* on the *x axis*. The time at the point of intersection on the x axis is the lag time.

The lag time, t_0 represents the beginning of drug absorption and should not be confused with pharmacologic term onset time, which represent latency, e.g., the time required for the drug to reach minimum effective concentration.



If we take under consideration the lag time the equation 1 becomes:

$$C = \frac{k_a F X_0}{V(k_a - K)}(e^{-K(t-t_{lag})} - e^{-k_a(t-t_{lag})}) \qquad (6)$$

5. Compare the values obtained using the method of residuals with those obtained by Topfit. Discuss the differences.

References:

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