Pharmacokinetics

One Compartment Oral Administration

Solved Problems

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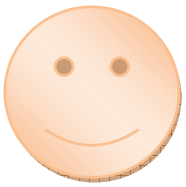


PROBLEM-5:

A 59 kg male received 2 mg/kg of an antibiotic orally. The following plasma concentration versus time data is obtained. Assume that the drug follows one compartment open model and is completely absorbed. Calculate the following:

a. Elimination rate constant (K_E) and Biological half-life ($t_{1/2}$)
b. Absorption rate constant (K_a) and Absorption half-life
c. Volume of distribution (V_d)
d. T_{max} and C_{max}
e. AUC

Time (hrs)	Plasma drug concentration, pdc (µg/ml)
0.25	2.2
0.5	3.8
0.75	5
1	5.8
1.5	6.8
2	7.1
2.5	7.1
3	6.9
4	6.2
6	4.8
8	3.5
12	1.9
18	0.8
24	0.3

SOLUTION-5:

Given data: pdc vs time data

Dose administered: 2 mg/kg for 59 kg = 59 x 2 mg = 118 mg

a. Calculate Elimination rate constant (K_E) and Biological half-life ($t_{1/2}$)

As per one-compartment open model, upon oral administration, elimination rate constant (K_E) can be obtained by drawing a plot of log C vs time (We have to assume the process is following first order kinetics, hence plot is drawn between log C vs time).

From that plot we can observe Absorption phase, Plateau phase and Elimination phase. Check the linear portion of the elimination phase (terminal portion) and find out the slope whose value is equal to $-K_E/2.303$.

Slope of elimination phase:

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{\log 1.9 - \log 3.5}{12 - 8} = \frac{0.27875 - 0.54407}{4} = \frac{-0.26532}{4} = -0.06633$$

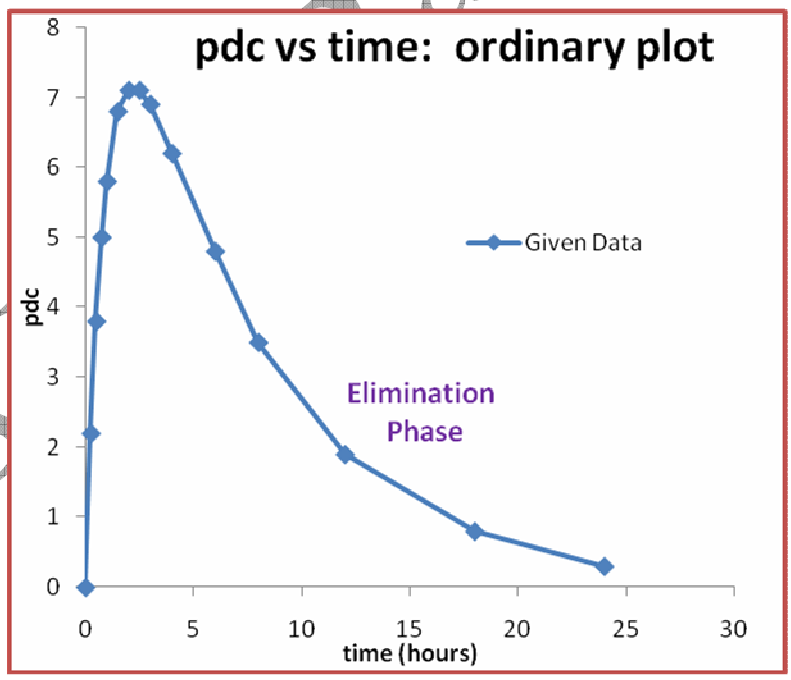
$\therefore K_E = -$ slope $\times 2.303 = -(-0.06633) \times 2.303 = 0.153$ hour^{-1}

Biological half-life, $t_{1/2} = 0.693/K_E = 0.693/0.153 = 4.5$ hours

b. Calculate Absorption rate constant (K_a) and Absorption half-life

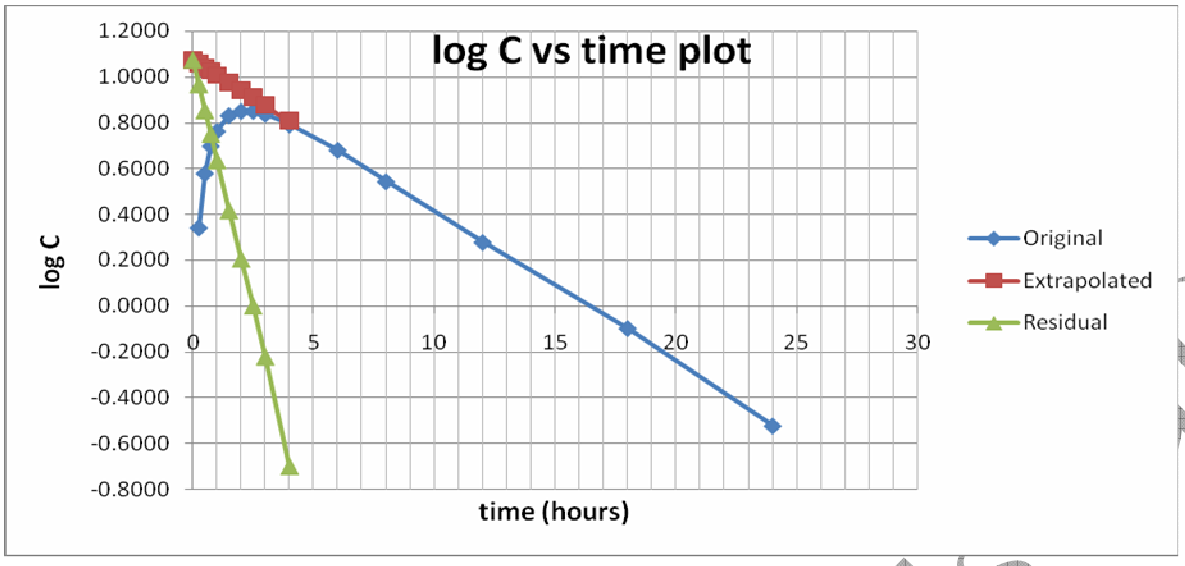
METHOD OF RESIDUALS:

From the graph, we got elimination rate constant by dealing with terminal portion or elimination phase of the plot. To get the absorption rate constant, first extrapolate the terminal portion towards y-axis and find out the log C values with respective time points. Then find out the difference between original log pdc and log extrapolated pdc values which are to be noted as log residual pdc values. Plot log residual pdc vs time line on the same graph sheet. Slope of this residual line is equal to $-K_a/2.303$.



Plot: Plasma drug conc. vs time (It gives curve rather than straight line)

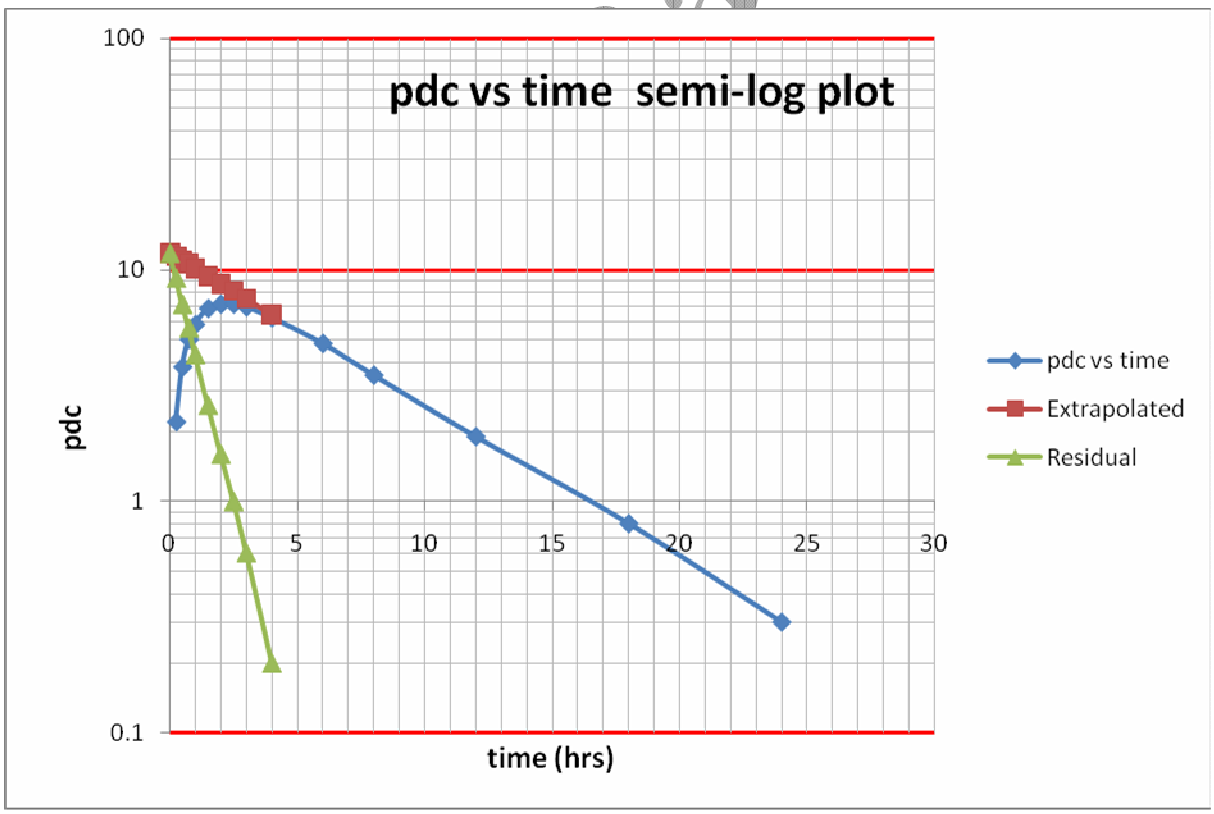
[**NOTE:** No need to draw this pdc vs time plot, just for your idea, it was given]



Plot: log C vs time (Actual view you will get on a graph sheet)

[**NOTE:** As we assumed drug is following first order kinetics, log C vs time plot is linear comparing to pdc vs time plot which represents zero order kinetics]

You can use semi-log graph sheet for this plot and graph will come like below: (Then no need to calculate the log values for all concentrations as you did for earlier plot of log C vs time on ordinary graph sheet.



Time (hrs)	Plasma drug concentration, pdc (µg/ml)	log C	Extrapolated pdc (µg/ml)	log extrapolated pdc	Residual pdc (µg/ml)	log residual pdc
0.25	2.2	0.3424	11.4	1.0569	9.2	0.9638
0.5	3.8	0.5798	10.9	1.0374	7.1	0.8513
0.75	5	0.6990	10.6	1.0253	5.6	0.7482
1	5.8	0.7634	10.1	1.0043	4.3	0.6335
1.5	6.8	0.8325	9.4	0.9731	2.6	0.4150
2	7.1	0.8513	8.7	0.9395	1.6	0.2041
2.5	7.1	0.8513	8.1	0.9085	1.0	0.0000
3	6.9	0.8388	7.5	0.8751	0.6	-0.2218
4	6.2	0.7924	6.4	0.8062	0.2	-0.6990
6	4.8	0.6812	4.8	-	-	-
8	3.5	0.5441	3.5	-	-	-
12	1.9	0.2788	1.9	-	-	-
18	0.8	-0.0969	0.8	-	-	-
24	0.3	-0.5229	0.3	-	-	-

Slope of residual line:

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{0.4150 - 0.6335}{1.5 - 1} = \frac{-0.2185}{0.5} = -0.437$$

$\therefore$ Absorption rate constant, K_a = – slope x 2.303 = – (–0.437) x 2.303 = 1.01 $hour^{-1}$

Absorption half-life, $t_{1/2} = 0.693/K_E = 0.693/1.01 = 0.69$ hours

c. Calculate Volume of distribution (V_d)

From one-compartment open model oral administration kinetics, the basic equation is:

$\log C = \log A - K_E t/2.303$ (Straight line equation of terminal phase)

where, $A = \frac{K_a F X_o}{V_d (K_a - K_E)}$

Where, F = Fraction of drug absorbed and X_o = Dose administered

The y-intercept of the terminal portion of the plot is equal to log A value which is equal to 1.072.

$\therefore$ A = anti-log 1.072 = 11.8

$$\frac{K_a F X_o}{V_d (K_a - K_E)} = 11.8$$

It is assumed that drug administered is absorbed completely, so F=1 and X_o is given as 2 mg/kg for 59 kg = 59 x 2 mg = 118 mg

$$V_d = \frac{K_a F X_o}{11.8 (K_a - K_E)} = \frac{1.01 \times 1 \times 118}{11.8 (1.01 - 0.153)} = \frac{119.18}{10.11} = 11.79 \text{ liters}$$

d. Calculate T_{max} and C_{max}

T_{max}: Time at which C_{max} is observed

$$\text{Formula, } T_{max} = \frac{2.303 \log K_a/K_E}{(K_a - K_E)} = \frac{2.303 \log 1.01/0.153}{1.01 - 0.153} = \frac{2.303 \times 0.8196}{0.857} = 2.202 \text{ hrs}$$

C_{max}: Maximum plasma drug concentration

$$\text{Formula, } C_{max} = \frac{FX_o}{V_d} \times e^{-K_E T_{max}}$$

$$= \frac{1 \times 118}{11.79} \times e^{-0.153 \times 2.202} = 10.01 \times e^{-0.3369} = 10.01 \times 1.4006 = 14.02 \text{ µg/ml}$$

e. Calculate AUC

AUC: Area Under the Curve

Trapezoidal Rule: The area under the plot can be divided into number of trapezoids as per the sampling times. Then area of each trapezoid is to be calculated by using its formula and finally all the areas added together to get the AUC. However for calculating the area of terminal zone, we have to use the formula: C^*/K_E.

$$AUC_0^{\infty} = AUC_0^t + AUC_t^{\infty}$$

$$AUC_0^t = \sum_{i=0}^{i=n} \frac{(C_{n-1} + C_n)}{2}(t_n - t_{n-1})$$

$AUC_t^{\infty} = \frac{C^*}{K_E}$ where, C^* = last plasma drug concentration noted

$$AUC_0^t = \frac{(C_1 + C_2)}{2}(t_2 - t_1) + \frac{(C_2 + C_3)}{2}(t_3 - t_2) + \frac{(C_3 + C_4)}{2}(t_4 - t_3) + \ldots\ldots$$

$$AUC_0^t = \frac{(0 + 2.2)}{2}(0.25 - 0) + \frac{(2.2 + 3.8)}{2}(0.5 - 0.25) + \frac{(3.8 + 5)}{2}(0.75 - 0.5) +$$

$$\frac{(5 + 5.8)}{2}(1 - 0.75) + \frac{(5.8 + 6.8)}{2}(1.5 - 1) + \frac{(6.8 + 7.1)}{2}(2.0 - 1.5) +$$

$$\frac{(7.1 + 7.1)}{2}(2.5 - 2) + \frac{(7.1 + 6.9)}{2}(3 - 2.5) + \frac{(6.9 + 6.2)}{2}(4 - 3) +$$

$$\frac{(6.2 + 4.8)}{2}(6 - 4) + \frac{(4.8 + 3.5)}{2}(8 - 6) + \frac{(3.5 + 1.9)}{2}(12 - 8) +$$

$$\frac{(1.9 + 0.8)}{2}(18 - 12) + \frac{(0.8 + 0.3)}{2}(24 - 18) = \textbf{65.2 µg. hr/ml}$$

$$AUC_t^{\infty} = \frac{C^*}{K_E} = \frac{0.3}{0.153} = 1.96\ \mu g.hr/ml$$

$$\therefore AUC_0^{\infty} = AUC_0^t + AUC_t^{\infty} = 65.2 + 1.96\ \mu g.hr/ml = 67.16 \mu g.hr/ml$$

WAGNER-NELSON METHOD:

The principle involved in Wagner Nelson method is: A plot has to be drawn between log % ARA vs time. Where, ARA = Amount Remained to be Absorbed or simply Unabsorbed amount.

Here no need to assume whether the kinetics is zero order or first order based on the plot we can determine which kinetics the process is going on.

If %ARA vs time gives straight line it means the drug follows zero order kinetics whereas if the plot of log %ARA vs time gives straight line it means the drug follows first order kinetics.

Then how we can find out the amount remained to be absorbed? Yes, we an find out that value by calculating the total amount of drug absorbed by infinite time and then subtracting the amount absorbed at particular time intervals to estimate the ARA at the respective time.

For e.g., if 100 mg of drug is absorbed by infinite time (assume absorbed at the rate of 10 mg per hour.) Then at 4th hour assume 40 mg was absorbed then ARA = 100 – 40 = 60 mg at 4th hour. Similarly at 7th hour; ARA = 100 – 70 = 30 mg.

Amount absorbed up to 't' time can be given by the equation, $\frac{X^t}{V_d}$ whereas amount absorbed by infinite time can be taken as $\frac{X^{\infty}}{V_d}$. So ARA at certain time 't' can be obtained by using the equation: $\frac{X^{\infty}}{V_d} - \frac{X^t}{V_d}$

Then, our next step is to know how to calculate the values for above two equations.

We have already studied that, $X^t = X_A + X_E = CV_d + K_E V_d [AUC]_0^t$

$$\therefore \frac{X^t}{V_d} = C + K_E [AUC]_0^t$$

Similarly, $X^{\infty} = C^{\infty} V_d + K_E V_d [AUC]_0^{\infty} = 0 + K_E V_d [AUC]_0^{\infty} = K_E V_d [AUC]_0^{\infty}$

[NOTE: At infinite time, there is no concentration of drug in plasma hence $C^{\infty} = 0$]

$$\therefore \frac{X^{\infty}}{V_d} = K_E [AUC]_0^{\infty}$$

Amount Remained to be Absorbed, ARA at certain time = $\frac{X^{\infty}}{V_d} - \frac{X^t}{V_d}$

[AUC] can be determined by Trapezoidal rule.

Time (hrs)	Plasma drug concentration, C (µg/ml)	$[AUC]_0^t$	$K_E[AUC]_0^t$	$\frac{X^t}{V_d} = C + K_E[AUC]_0^t$	$\frac{X^\infty}{V_d} - \frac{X^t}{V_d}$	log ARA
0.25	2.2	0.28	0.04	2.24	8.04	0.91
0.5	3.8	1.03	0.16	3.96	6.32	0.80
0.75	5	2.13	0.33	5.33	4.95	0.69
1	5.8	3.48	0.53	6.33	3.95	0.60
1.5	6.8	6.63	1.01	7.81	2.47	0.39
2	7.1	10.11	1.55	8.65	1.63	0.21
2.5	7.1	13.66	2.09	9.19	1.09	0.04
3	6.9	17.16	2.62	9.52	0.76	-0.12
4	6.2	23.71	3.63	9.83	0.45	-0.35
6	4.8	34.71	5.31	10.11	0.17	-0.77
8	3.5	43.01	6.58	10.08	0.2	-0.70
12	1.9	53.81	8.23	10.13	0.15	-0.82
18	0.8	61.91	9.47	10.27	0.01	-2.00
24	0.3	65.21	9.98	10.28	-	

$$\frac{X^\infty}{V_d} = K_E[AUC]_0^\infty = 0.153 \times 67.16 = 10.28$$

Plot of log ARA vs time gives straight line hence absorption process is said to be following first order kinetics.

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{0.39 - 0.60}{1.5 - 1} = \frac{-0.21}{0.5} = -0.42$$

$\therefore K_A = -$ slope x 2.303 = 0.42 x 2.303 = 0.97 hour^{-1}

PROBLEM-6:

A drug is administered orally or injected intramuscularly to a healthy volunteer and the following plasma concentration of the drug versus time data obtained. Calculate the absorption rate constant and state the order of the absorption process.

Time (hrs)	Plasma drug concentration, C (mg/ml)
0.25	0.6
0.5	1.2
0.75	1.8
1	2.3
1.5	3.4
2	4.3
3	6.0
6	5.6
12	2.3
18	0.9
24	0.4

SOLUTION-6

Wagner Nelson is used to calculate the absorption rate constant and also to determine the order of absorption process.

The principle involved in Wagner Nelson method is: A plot has to be drawn between log % ARA vs time. Where, ARA = Amount Remained to be Absorbed or simply Unabsorbed amount.

Here no need to assume whether the kinetics is zero order or first order based on the plot we can determine which kinetics the process is going on.

If %ARA vs time gives straight line it means the drug follows zero order kinetics whereas if the plot of log %ARA vs time gives straight line it means the drug follows first order kinetics.

Then how we can find out the amount remained to be absorbed? Yes, we an find out that value by calculating the total amount of drug absorbed by infinite time and then subtracting the amount absorbed at particular time intervals to estimate the ARA at the respective time.

For e.g., if 100 mg of drug is absorbed by infinite time (assume absorbed at the rate of 10 mg per hour.) Then at 4^{th} hour assume 40 mg was absorbed then ARA = 100 – 40 = 60 mg at 4^{th} hour. Similarly at 7^{th} hour; ARA = 100 – 70 = 30 mg.

Amount absorbed up to 't' time can be given by the equation, $\frac{X^t}{V_d}$ whereas amount absorbed by infinite time can be taken as $\frac{X^\infty}{V_d}$. So ARA at certain time 't' can be obtained by using the equation: $\frac{X^\infty}{V_d} - \frac{X^t}{V_d}$

Then, our next step is to know how to calculate the values for above two equations.

We have already studied that, $X^t = X_A + X_E = CV_d + K_E V_d [AUC]_0^t$

$$\therefore \frac{X^t}{V_d} = C + K_E [AUC]_0^t$$

Similarly, $X^\infty = C^\infty V_d + K_E V_d [AUC]_0^\infty = 0 + K_E V_d [AUC]_0^\infty = K_E V_d [AUC]_0^\infty$

[NOTE: At infinite time, there is no concentration of drug in plasma hence $C^\infty = 0$]

$$\therefore \frac{X^\infty}{V_d} = K_E [AUC]_0^\infty$$

Amount Remained to be Absorbed, ARA at certain time $= \frac{X^\infty}{V_d} - \frac{X^t}{V_d}$

[AUC] can be determined by Trapezoidal rule.

Time (hrs)	Plasma drug concentration, C (mg/ml)	$[AUC]_0^t$	$K_E [AUC]_0^t$	$\frac{X^t}{V_d} = C + K_E [AUC]_0^t$	$\frac{X^\infty}{V_d} - \frac{X^t}{V_d}$
0.25	0.6	0.1	0.02	0.62	9.38
0.5	1.2	0.3	0.05	1.25	8.75
0.75	1.8	0.7	0.11	1.91	8.09
1	2.3	1.2	0.18	2.48	7.52
1.5	3.4	2.6	0.39	3.79	6.21
2	4.3	4.5	0.68	4.98	5.02
3	6.0	9.7	1.46	7.46	2.54
6	5.6	27.1	4.07	9.67	0.33
12	2.3	50.8	7.62	9.92	0.08
18	0.9	60.4	9.06	9.96	0.04
24	0.4	64.3	9.65	10.0	

K_E can be obtained from plot of log C vs time assuming that elimination process follows first order kinetics.

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{\log 2.3 - \log 5.6}{12 - 6} = \frac{0.3617 - 0.7482}{6} = -0.064$$

Elimination rate constant, K_E = – slope x 2.303 = 0.064 x 2.303 = 0.15 hr^{-1}

$$[AUC]_0^\infty = [AUC]_0^t + \frac{C^*}{K_E} = 64.3 + \frac{0.4}{0.15} = 67 \text{ µg. hr/ml}$$

$$\frac{X^\infty}{V_d} = K_E [AUC]_0^\infty = 0.15 \times 67 = 10.05$$

Here, plot of ARA vs time gives straight line hence absorption process is said to be following **zero order** kinetics.

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{6.21 - 7.52}{1.5 - 1} = \frac{-1.31}{0.5} = -2.62$$

$\therefore$ Absorption rate constant, $K_A = -$ slope $= 2.62$ mg.ml^{-1}hr^{-1}

Reference: Bio-Pharmaceutics and Pharmacokinetics by: Brahmankar
: V. Venkateswarlu