Pharmacokinetics

One Compartment Open Model

I.V. Bolus Administration

Solved Problems

by **G.S.N.K.Rao {Eswar}**

PROBLEM-1:

If the plasma concentration of viomycin after i.v. bolus administration was found to be 10.0 and 5.5 µg/ml at 2 and 4 hours respectively. Assuming one-compartment kinetics, calculate:

    a.   the half-life of the drug

    b.   the concentration of drug in plasma at zero time, C_o

    c.   the V_d, if dose administered was 300 mg

    d.   the total systemic clearance, Cl_T

    e.   the renal clearance, Cl_R if fraction excretion unchanged in urine is 0.8

SOLUTION-1:

a. Calculate the half-life of the drug?

Data given: $C_1 = 10.0$ µg/ml at $t_1 = 2$ hours

              $C_2 = 5.5$ µg/ml at $t_2 = 4$ hours

Formula to be used: $t_{1/2} = 0.693/K_E$ where, K_E = Elimination rate constant

So, to calculate $t_{1/2}$ we have to first determine K_E with the help of given data.

K_E can be determined from the slope of a line obtained by plotting *log concentration on y-axis vs time on x-axis*. (log C vs time is a plot for first order kinetics).

$K_E = -$ slope x 2.303

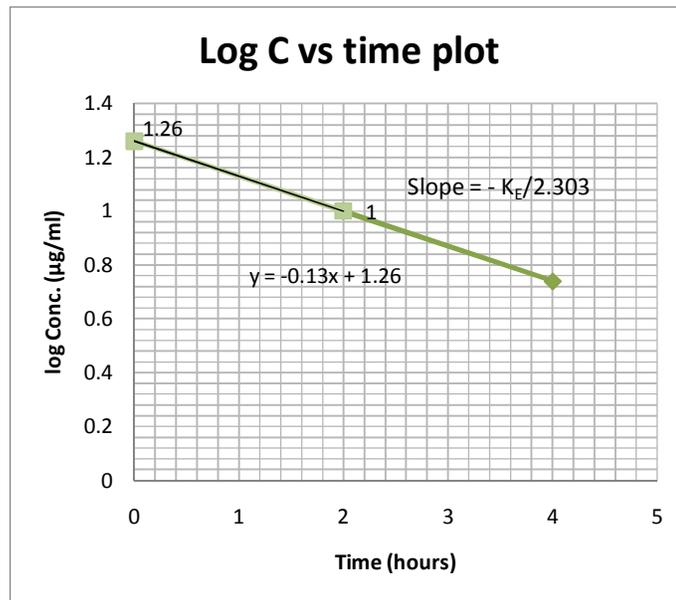 $\log C_1 = \log 10 = 1$

      $\log C_2 = \log 5.5 = 0.74$

Slope of the straight line of log C vs t is

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{1 - 0.74}{2 - 4} = \frac{-0.26}{2} = -0.13$$

$\therefore K_E = -$ slope x 2.303 $= -(-0.13)$ x 2.303 $= 0.299$ hr^{-1}

Then, $t_{1/2} = 0.693/K_E = 0.693/0.299$ hr^{-1} = 2.32 hours.

Half-life of the given drug, $t_{1/2}$ is 2.32 hours.

Log C vs time plot

b. Calculate the concentration of drug in plasma at zero time, C_o?

C_o is the plasma drug concentration at zero time after administration or initial plasma drug concentration. This can be obtained from the graph (log conc. vs time) by extrapolating the straight line and finding the Y-intercept which is equal to log C_o.

From graph, log C_o = 1.26

∴ C_o = Anti-log 1.26 = 18.2 µg/ml

c. Calculate the V_d, if dose administered was 300 mg

Volume of distribution, V_d of a drug when administered i.v. is given by, Formula: $V_d = X_o/C_o$

Where, X_o = Dose administered intra venously and

C_o = Plasma drug conc. at zero time after administration

$$\therefore V_d = \frac{X_o}{C_o} = \frac{300 \text{ mg}}{18.2 \text{ µg/ml}} = \frac{300 \times 1000 \text{ µg}}{18.2 \text{ µg/ml}} = \frac{300 \times 1000 \text{ ml}}{18.2} = \frac{300 \text{ lts}}{18.2} = 16.5 \text{ lts}$$

[NOTE: concentration units may be used either µg/ml or mg/liter; because 1 mg = 1000 µg and 1 liter = 1000 ml]

d. Calculate the total systemic clearance, Cl_T

Total Systemic Clearance, Cl_T is given by the formula, $Cl_T = K_E V_d$

∴ $Cl_T = K_E V_d$ = 0.299 hr^{-1} x 16.5 lts = 0.299/60 mins x 16.5 x 1000 ml

= (4933.5/60) ml/min = 82.23 ml/min

[NOTE: If K_E is not available then you can use 0.693/$t_{1/2}$ in place of K_E, based on half-life relation]

e. Calculate the renal clearance, Cl_R if fraction excretion unchanged in urine is 0.8

Renal Clearance, Cl_R can be given by the formulae:

Formula 1: $Cl_R = F \times Cl_T$; where F= Fraction excreted unchanged in urine   (or)

Formula 2: $Cl_R = K_e \times V_d$; where K_e = excretion rate constant   (or)

Formula 3: Cl_R = Rate of elimination by kidney / C

We can use either formula 1 or formula 2 to calculate Cl_R

Using formula 1: $Cl_R = F \times Cl_T = 0.8 \times 82.23$ ml/min = 65.78 ml/min.

Using formula 2: $Cl_R = K_e \times V_d$

First we have to calculate K_e and substitute that value in formula 2.

$K_e = F \times K_E = 0.8 \times 0.299$ hr^{-1} = 0.8×0.299 / 60 min = 0.003986 / min

$\therefore Cl_R = K_e \times V_d = 0.003986$ / min x 16.5 lts = $0.003986 \times 16,500$ ml/min = 65.78 ml/min

G.S.N. Koteswara Rao, M.Pharm., D.D.D., D.C.T., (Ph.D) (MBA)
Asst. Professor,
RAGHU College of Pharmacy,
Visakhapatnam.
www.raghupharmacy.com

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PROBLEM-2:

The equation that best fits the plasma level time curve of azlocillin after an i.v. bolus dose of 2000 mg (assuming one-compartment kinetics) is $C=143e^{-0.87t}$. Calculate:

a. apparent V_d

b. elimination $t_{1/2}$ of the drug

c. plasma drug concentration after 6 hours

d. the amount of drug that will be left in the body after 6 hours

e. when should the next dose be administrated if the drug becomes ineffective when the plasma level falls below 50 µg/ml?

f. the therapeutic index of the drug if the therapeutic range is 50 to 500 µg/ml

g. how much dose should be administrated to attain an instantaneous plasma concentration of 500 µg/ml

h. for how long will the plasma level lie in the therapeutic window if the above dose is given as i.v. bolus?

SOLUTION-2:

a. Calculate apparent V_d

Given data: i.v. bolus dose, $X_o = 2000$ mg.

$C=143e^{-0.87t}$ best fits for one-compartment kinetics first order equation $C = C_o e^{-K_E t}$

On comparison, $C_o = 143$ µg/ml and $K_E = 0.87$ hr^{-1}

Apparent Volume of distribution, V_d is given by the formula,

$$\therefore V_d = \frac{X_o}{C_o} = \frac{2000 \text{ mg}}{143 \text{ µg/ml}} = \frac{2000 \times 1000 \text{ µg}}{143 \text{ µg/ml}} = \frac{2000 \times 1000 \text{ ml}}{143} = \frac{2000 \text{ lts}}{143} = 14 \text{ lts}$$

[NOTE: Concentration units may be used either µg/ml or mg/liter; because 1 mg = 1000 µg and 1 lt = 1000 ml]

b. Calculate elimination $t_{1/2}$ of the drug

Formula: $t_{1/2} = 0.693/K_E$

Given, $K_E = 0.87$ hr^{-1};

$\therefore t_{1/2} = 0.693/K_E = 0.693/0.87hr^{-1} = 0.8$ hours.

c. Calculate plasma drug concentration after 6 hours

Substitute t=6 hours in given equation $C=143e^{-0.87t}$;

$C=143e^{-0.87 \times 6} = 143 \times 0.0054 = 0.77$ µg/ml.

d. Calculate the amount of drug that will be left in the body after 6 hours

The term 'C' represents plasma drug concentration whereas the term 'X' represents the drug content in the body. Hence the below two equations are similar:

$C = C_o e^{-KEt}$ and $X = X_o e^{-KEt}$

Where, X_o = amount of drug injected and X = amount of drug left in the body at time, t.

So, substitute t=6 in the above equation.

$X = X_o e^{-KEt} = 2000 \times e^{-0.87 \times 6} = 2000 \times 0.0054 = 10.8$ mg

So, after 6 hours of administration of drug, 10.8 mg will be left in the body

e. Calculate, when should the next dose be administrated if the drug becomes ineffective when the plasma level falls below 50 µg/ml?

Here, we have to calculate the time of next dose where C = 50 µg/ml

By applying log terms to the given equation $C = 143e^{-0.87t}$ we will get:

$\log C = \log 143 - 0.87t/2.303$ [similar to $\log C = \log C_o - kt/2.303$]

∴ Substitute C=50 in above equation;

$\log 50 = \log 143 - 0.87t/2.303$

$\Rightarrow 0.87t/2.303 = \log 143 - \log 50$

$\Rightarrow t = \dfrac{(\log 143 - \log 50) \times 2.303}{0.87} = \dfrac{(2.16 - 1.69) \times 2.303}{0.87} = 1.24$ hours

f. Calculate the therapeutic index of the drug if the therapeutic range is 50 to 500 µg/ml

$$\text{Therapeutic Index} = \frac{\text{Maximum Safe Conc. (MSC)}}{\text{Minimum Effective Conc. (MEC)}} = \frac{500}{50} = 10$$

The maximum the value of T.I., the greater is the safety with drug.

g. Calculate how much dose should be administrated to attain an instantaneous plasma concentration of 500 µg/ml

Formula: $X_o = C_o V_d = 500 \times 14 = 7000$ mg.

h. Calculate, for how long will the plasma level lie in the therapeutic window if the above dose is given as i.v. bolus?

Formula: $\log C = \log C_o - kt/2.303$

$\log 50 = \log 500 - 0.87 t/2.303$

$\Rightarrow t = \dfrac{(\log 500 - \log 50) \times 2.303}{0.87} = \dfrac{(\log 500/50) \times 2.303}{0.87} = \dfrac{\log 10 \times 2.303}{0.87} = 2.65$ hours

G.S.N. Koteswara Rao, M.Pharm., D.D.D., D.C.T., (Ph.D) (MBA)
Asst. Professor,
RAGHU College of Pharmacy,
Visakhapatnam.
www.raghupharmacy.com

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PROBLEM-3:

The half-life of propranolol in a 60 kg patient is 4 hours and V_d is 5.5 liter/kg. Determine:

a. The total systemic clearance of drug

b. What will be the renal clearance if fraction excreted unchanged in urine is 0.047?

c. If the drug is eliminated only by hepatic and renal routes, what will be the hepatic extraction ratio if blood flow to liver is 1.5 liter/min?

d. If the blood flow rate to the liver reduces to 0.8 lt/min in situations of CCF, what will be the new hepatic and total systemic clearance values?

e. What will be the % decrease in overall clearance of drug?

SOLUTION-3:

a. Determine the total systemic clearance of drug

Given, $t_{1/2}$ = 4 hours and V_d = 5.5 liters/kg

For 60 kg patient, V_d will be 60x 5.5 liters

Formula:

$$\therefore Cl_T = K_E\, V_d = \frac{0.693}{t_{1/2}} \times V_d = \frac{0.693}{4 \times 60\ min} \times 60 \times 5.5\ lt = 952.8\ ml/min$$

b. What will be the renal clearance if fraction excreted unchanged in urine is 0.047?

Renal Clearance, Cl_R can be given by the formulae:

Formula 1: $Cl_R = F \times Cl_T$; where F= Fraction excreted unchanged in urine   (or)

Formula 2: $Cl_R = K_e \times V_d$; where K_e = excretion rate constant   (or)

Formula 3: Cl_R = Rate of elimination by kidney / C

$$\therefore Cl_R = F \times Cl_T = 0.047 \times 952.8\ ml/min = 44.8\ ml/min$$

c. If the drug is eliminated only by hepatic and renal routes, what will be the hepatic extraction ratio if blood flow to liver is 1.5 liter/min?

Hepatic Extraction Ratio, ER_H is given by the

Formula: $ER_H = \dfrac{\text{Hepatic Clearance, } Cl_H}{\text{Blood flow, } Q_H}$ [Since, $Cl_H = Q_H \times ER_H$]

Blood flow to liver, Q_H is given as 1.5 liter/min

So, determine Cl_H and substitute its value in the formula to get ER_H

We know, $Cl_T = Cl_R + Cl_H$

$$\therefore Cl_H = Cl_T - Cl_R = (952.8 - 44.8)\ ml/min = 908\ ml/min$$

$$\therefore ER_H = \frac{\text{Hepatic Clearance, }Cl_H}{\text{Blood flow, }Q_H} = \frac{908 \text{ ml/min}}{1.5 \quad x \text{ 1000 ml/min}} = 0.6053$$

d. If the blood flow rate to the liver reduces to 0.8 lt/min in situations of CCF, what will be the new hepatic and total systemic clearance values?

$Cl_H = Q_H \times ER_H = 0.8 \text{ lt/min} \times 0.6053 = 8000 \text{ ml/min} \times 0.6053 = 484.24 \text{ ml/min}$

$Cl_T = Cl_R + Cl_H = (44.8 + 484.24) \text{ ml/min} = 529 \text{ ml/min}$

e. What will be the % decrease in overall clearance of drug?

$$\% \text{ decrease} = \frac{\text{Initial }Cl_T - \text{Final }Cl_T}{\text{Initial }Cl_T} \times 100 = \frac{952.8 - 44.8}{952.8} \times 100 = 44.47 \%$$

PROBLEM-4:

A dose of 325 mg of a new drug is injected intravenously to a healthy volunteer and the following blood data was obtained. Assume that the drug follows one compartment open model and calculate all possible pharmacokinetics parameters.

Time (hrs)	Plasma drug concentration, C (mg/lt)
2	18.3
4	10.1
6	5.8
8	3.3
10	1.8
12	1.0
16	0.31
20	0.21

SOLUTION-4:

Given data: pdc vs time profile and assumed to follow one-compartment open model and follows first order kinetics. Pharmacokinetic parameters that can be assessed for this profile are: K_E, $t_{1/2}$, C_0, V_d, Cl_T and AUC.

Elimination rate constant, K_E:

Hence a plot of log C vs time gives straight line whose slope is

$K_E = -$ slope x 2.303

$\log C_1 = \log 18.3 = 1.2625$

$\log C_3 = \log 5.8 = 0.7634$

Slope of the straight line of log C vs t is

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{\log 5.8 - \log 18.3}{6 - 2} = \frac{0.7634 - 1.2625}{4} = -0.125$$

$\therefore K_E = -$ slope x 2.303 $= -(-0.125)$ x 2.303 $= 0.288$ hr^{-1}

Biological half-life, $t_{1/2}$:

Then, $t_{1/2} = 0.693/K_E = 0.693/0.288$ hr^{-1} $= 2.41$ hours.

Half-life of the given drug, $t_{1/2}$ is 2.41 hours.

Initial Plasma drug concentration, C_0:

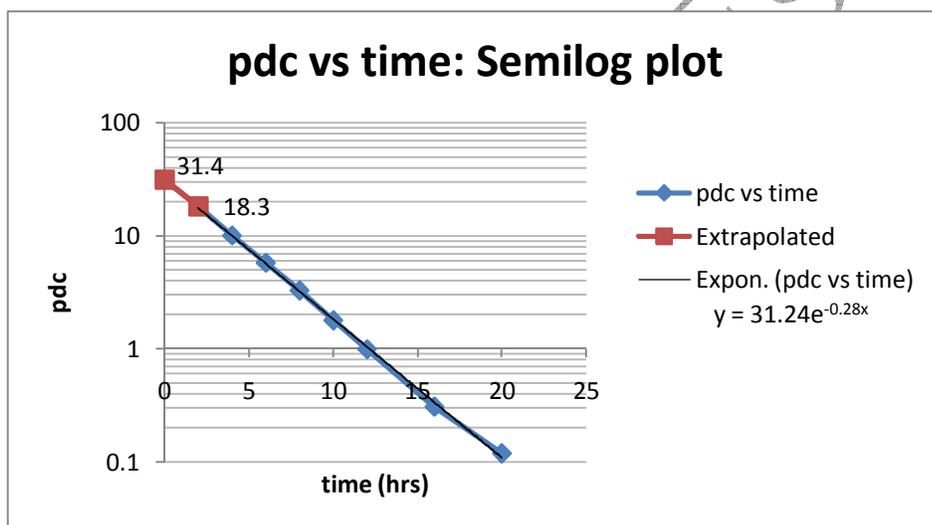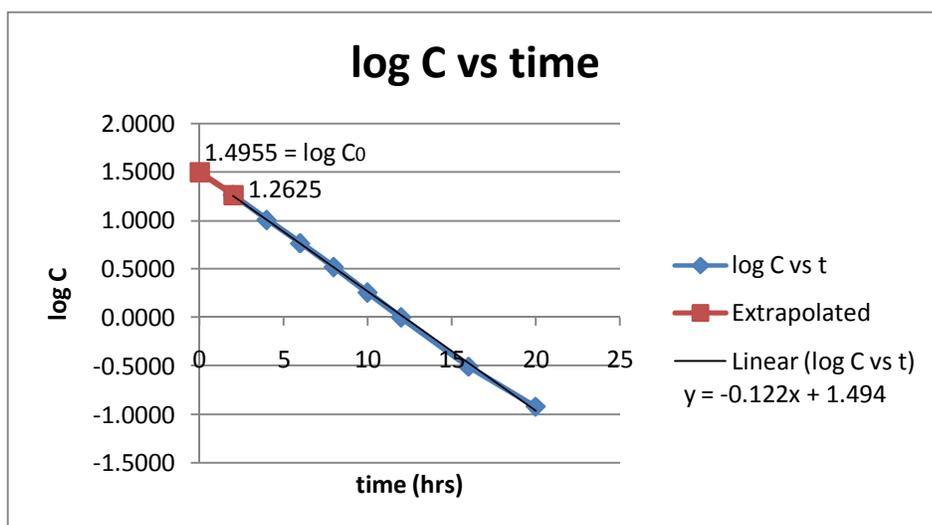From the plot of log C vs time, extrapolate the straight line towards y-axis.
The y-intercept is equal to log C_0
$\log C_0 = 1.4955$
$C_0 = $ Antilog $1.4955 = 31.3$ mg/lt or μg/ml

Volume of distribution, V_d:

$V_d = X_0/C_0 = 325$ mg/31.3 mg/lt $= 10.38$ lts

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log C vs time

pdc vs time: Semilog plot

Total Systemic Clearance, Cl_T:

$Cl_T = K_E \times V_d = 0.288 \, hr^{-1} \times 10.38 \, lts = 2.989 \, lts/hr$ or $16.48 \, ml/min$

Area Under the Curve, AUC:

Here, we have to remember that AUC for a plot obtained by values of a drug administered intravenously can be calculated by using the simple equation:

$$[AUC]_0^\infty = \frac{C_0}{K_E}$$

[NOTE: The AUC calculated from Trapezoidal rule will also give the same answer here for an intravenously administered drug kinetic profile]

$$\therefore [AUC]_0^\infty = \frac{C_0}{K_E} = \frac{31.3}{0.288} = 108.68 \text{ mg. hr/lt or } 108.68 \text{ µg. hr/ml}$$

GOOD LUCK

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