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Pharmacokinetics

Two Compartment Open Model

Solved Problems

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PROBLEM-9:
Following a 650 mg i.v. bolus dose of a drug to a 65 kg subject, the plasma drug concentration was found to decline biexponentially. The equation that best described the drug kinetics was:
$C = 67\ e^{-14t} + 33\ e^{-3t}$ where t is in hours and C is in µg/ml. Calculate the following:

SOLUTION-9:
Given data: $C = 67\ e^{-14t} + 33\ e^{-3t}$ which is biexponential and best fits for the two compartment kinetics model equation: $C = A\ e^{-\alpha t} + B\ e^{-\beta t}$
On comparison of two equations we have:
Hybrid constants: A = 67 and B = 33
Hybrid first order constant: for rapid distribution phase, $\alpha = 14$
Hybrid first order constant: for slow elimination phase, $\beta = 3$
Dose administered intravenously, $X_o = 650$ mg

a. Calculate the volume of the central compartment, V_c:
Formula, $V_c = X_o/C_o$
So, first calculate C_o and substitute the same in above equation
$C_o = A+B = 67 + 33 = 100$
$\therefore\ V_c = X_o/C_o = 650 / 100 = 6.5$ liters

b. Calculate the micro constants K_{12} and K_{21}
Remind the equations:

$$K_{12} = \frac{AB\ (\beta-\alpha)^2}{C_o\ (A\beta+B\alpha)} = \frac{(67\times33)\ (3-14)^2}{100\ (67\times3 + 33\times14)} = \frac{2,67,531}{66,300} = 4.04/\text{hr}$$

$$K_{21} = \frac{A\beta+B\alpha}{C_o} = \frac{(67\times3) + (33\times14)}{100} = \frac{663}{100} = 6.63/\text{hr}$$

c. Calculate the volume of peripheral compartment

$$\text{Formula, } V_p = \frac{V_c K_{12}}{K_{21}} = \frac{6.5 \times 4.04}{6.63} = 3.96 \text{ liters}$$

d. Calculate the apparent V_d at steady state

Formula, $V_{d,\,ss} = V_c + V_p = 6.5 + 3.96 = 10.46$ liters

e. Calculate volume of distribution by area, $V_{d,\,area}$

$$\therefore \text{Formula, } V_{d,\,area} = \frac{X_o}{\beta\,[AUC]}$$

So, first calculate AUC and substitute in above equation

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} = \frac{67}{14} + \frac{33}{3} = 15.8 \text{ liters}$$

$$\therefore V_{d,\,area} = \frac{X_o}{\beta\,[AUC]} = \frac{650}{3 \times 15.8} = 13.72 \text{ liters}$$

f. Calculate the elimination rate constant for the disposal of drug from the central compartment

$$\text{Formula, } K_E = \frac{\alpha\beta C_o}{A\beta + B\alpha} \text{ or } \frac{\alpha\beta}{K_{21}}$$

$$\therefore K_E = \frac{\alpha\beta}{K_{21}} = \frac{14 \times 3}{6.63} = 6.33/\text{hr}$$

g. Calculate the overall elimination half-life

$$\text{Formula, } t_{1/2} = \frac{0.693}{\beta}$$

Remember, in two compartment model, K_E represents elimination rate constant only from central compartment where β represents the overall elimination rate constant from the entire body.

$\therefore\ t_{1/2} = 0.693/\beta = 0.693/3 = 0.231$ hours

h. Calculate the total systemic clearance of the drug (use $V_{d,area}$ for calculation)

Formula, $Cl_T = \beta\, V_{d,\,area} = 3 \times 13.7 = 41.1$ liters/hour = 41,100 ml/ 60 min = 685 ml/min

i. Calculate the plasma level of the drug after 30 minutes of i.v. dose

$C = 67\, e^{-14t} + 33\, e^{-3t}$

Substitute, t = 0.5 hours in above equation, then

$C = 67\, e^{-14 \times 0.5} + 33\, e^{-3 \times 0.5} = 67\, e^{-7} + 33\, e^{-1.5} = (67 \times 0.000912) + (33 \times 0.22313) = 0.061104 + 7.363 =$ 7.42 μg/ml

j. Calculate the infusion rate if the drug is to be given as constant rate i.v. infusion (desired C_{ss} is 20 µg/ml)

Formula, $C_{ss} = \frac{R_o}{V_c\ K_E}$

$\therefore R_o = C_{ss} \times V_c\ K_E = 20 \times 6.5 \times 6.33 = 822.9$ mg/hr

k. Calculate the loading dose to attain the C_{ss} rapidly

Formula, $X_{o,L} = C_{ss}\ V_c = 20 \times 6.5 = 130$ mg.

GOOD LUCK

Reference: Bio-Pharmaceutics and Pharmacokinetics by: Brahmankar

Than'Q'