PHA5127 – Dose Optimization I
Case Study 1
Fall 2013

Question 1

Drug A was administered to a patient as an IV bolus at a dose of 250 mg. The pharmacokinetic parameters of the drug were clearance (CL) at 5.7 L/h, volume of distribution of the central compartment (V_c), 25 L. Assuming that the drug follows a one compartment body model with first order elimination, compute the following parameters (make sure to provide unit for each parameter in your answer):

(1) Estimate the elimination rate constant (k_e) and the half-life using the relationship $k_e = \frac{CL}{V_c}$.

$$k_e = \frac{CL}{V_c} = \frac{5.7\ L/h}{25\ L} = 0.228\ h^{-1}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} = \frac{0.693}{0.228} = 3.04\ h$$

(2) Compute the initial plasma drug concentration C_0.

$$C(t) = \frac{Dose}{V_c}\exp(-k_e t) = \frac{250\ mg}{25\ L}\exp(-0.228 * 0) = 10\ mg/L$$

(3) Compute the area under the curve $AUC_{0-\infty} = \frac{Dose}{CL}$

$$AUC_{0-\infty} = \frac{Dose}{CL} = \frac{250\ mg}{5.7\ L/h} = 43.9\ mg.h/L$$

or

$$AUC_{0-\infty} = \int_0^\infty C_0 \exp(-k_e t)\, dt = \frac{C_0}{k_e} = \frac{10\ mg/L}{0.228\ h^{-1}} = 43.9\ mg.h/L$$

(4) Compute the concentration of the drug at 5 hour post dose if the doctor were to double the original dose.

$$C(5) = \frac{500\ mg}{25\ L}\exp(-0.228\ h^{-1} * 5\ h) = 6.5\ mg/L$$

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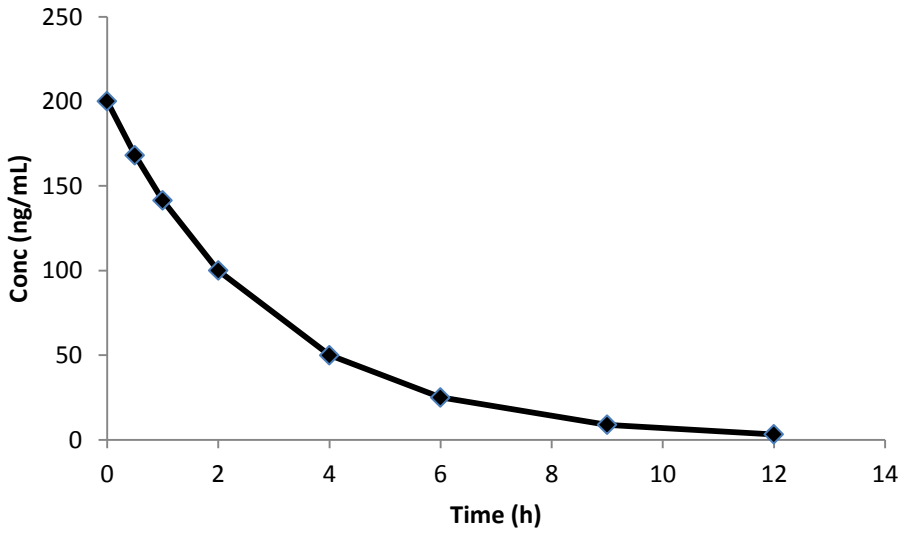
Question 2

For the drug concentration-time profile below, you are given the following information. The route of drug administration was via IV bolus and the dose given was 20 mg.

Time (h)	Conc (ng/mL)
0	200
0.5	168.18
1	141.42
2	100
4	50
6	25
9	8.84
12	3.13

(1) Plot the plasma concentration versus time in both linear and semi-log scale and determine the order of the elimination process.

The concentration-time profile is in linear scale.



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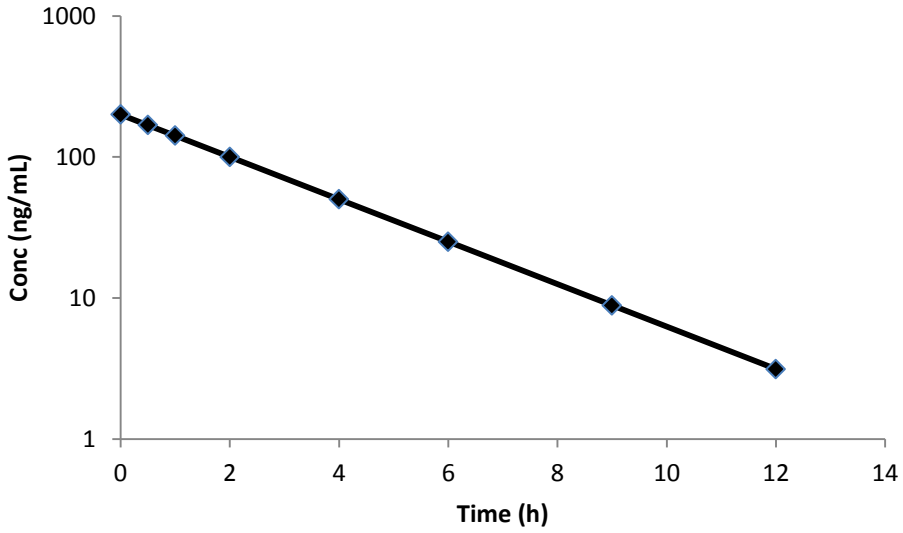
The log-concentration-time profile of the data



Since the log-concentration-time profile is a straight line, the drug kinetics follows a one-compartment with first-order elimination.

(2) Determine k_e and half-life of the drug.

To estimate k_e directly from the data, we take two points

$$k_e = \frac{\Delta logC}{\Delta t} = \frac{\ln(200) - \ln(100)}{2 - 0\ h} = 0.346\ h^{-1}$$

$$t_{1/2} = \frac{\ln(2)}{0.346\ h^{-1}} = 2\ h$$

(3) Compute the clearance (CL) and volume of distribution (V_d)

$$V_d = \frac{Dose}{C_0} = \frac{20\ mg}{200\ ng/mL} = \frac{20000\ \mu g}{200\ \mu g/L} = 100\ L$$

$$CL = V_d \times k_e = 100\ L \times 0.346\ h^{-1} = 34.6\ L/h$$

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(4) What are the expected concentrations of the drug at 14 h and 16 h?

Since the half-life of the drug is 2 h, the drug concentration is halved every 2 hours. So the expected concentrations at 14 h and 16 h are approximately 1.56 and 0.78 ng/mL, respectively.

(5) Use the trapezoidal rule to compute the $AUC_{0\text{-}12}$ of the profile above.

$$AUC_{0-12} = \frac{200 + 168}{2} \times 0.5 + \cdots + \frac{8.84 + 3.13}{2} \times (12 - 9)$$

Time (h)	Conc (ng/mL)	Partial AUC (ng.h/mL)
0	200	
0.5	168.18	92.045
1	141.42	77.4
2	100	120.71
4	50	150
6	25	75
9	8.84	50.76
12	3.13	17.955

The sum of the partial areas from 0 to 12 hours is $AUC_{0\text{-}12}$ = 583.87 ng.h/mL

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True or False

(1) The plasma concentration time profile of a drug is not dependent of the dosage form.

False

(2) For a zero-order elimination process, the change in drug concentration with time is not a constant.

False, $\frac{dC}{dt} = -k$ for a zero-order elimination process, therefore the change in drug concentration with time is, in fact, a constant.

(3) The concentration-time profile of a one-compartment body model with first-order elimination after an IV bolus administration is a straight line in the semi-log scale.

True