PHA 5127 Dose Optimization I

Homework I (10 points)

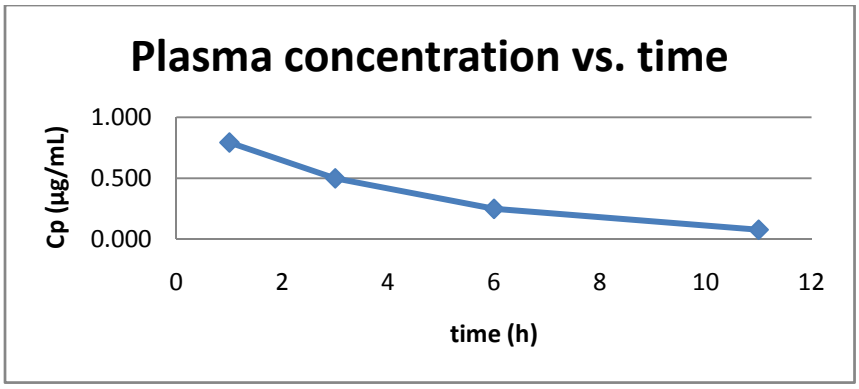
Due on Friday, 09/11/2009

Do not forget the units of the results. 0.1 points will be deducted for each time an answer is provided without the appropriate unit.

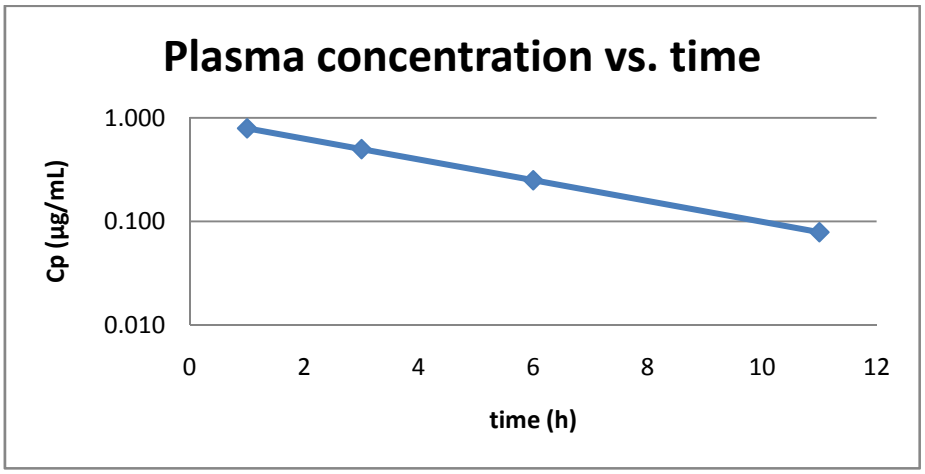
1. **500 mg Drug A was administered to a male patient (80 kg, 35 years old) through IV bolus injection. The following plasma concentrations (Cp) were observed.**

time (h)	Cp (µg/mL)
1	0.794
3	0.500
6	0.250
11	0.079

a) Plot Cp vs. time and determine the order of the elimination process **(0.75 points, 0.25 for each plot, and 0.25 for the conclusion that is first-order elimination)**



Semilogarithmic transformation of the y-axis



Plasma concentration vs. time profile is a straight line after semilogarithmic transformation. Thus, the elimination process is a first-order process.

b) Determine k_e and $t_{1/2}$ (half life) **(1 point, 0.5 for each correct answer)**

time (h)	Cp (µg/mL)	ln Cp (µg/mL)
0	1.000	0.0000
1	0.794	-0.2310
3	0.500	-0.6931
6	0.250	-1.3863
11	0.079	-2.5415

$$Slope = \frac{-0.6931 - (-0.2310)}{3 - 1\ h} = -0.231\ \frac{1}{h}$$

$$k_e = 0.231\ \frac{1}{h}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} = 3.0\ h$$

c) Estimate the initial concentration C_0 and the volume of distribution (Vd) **(1 point, 0.5 for each correct answer)**

$$C(t) = C_O * e^{-k_e * t}$$

$$\ln C(t) = ln\ C_O - k_e * t$$

$$ln\ C_O = \ln C(t) + k_e * t$$

$$ln\ C_O = \ln C(1) + k_e * 1$$

$$ln\ C_O = -0.2310 + 0.231 * 1 = 0$$

$$C_O = e^0 = 1\ \frac{\mu g}{mL}$$

$$C_O = \frac{Dose}{Vd}$$

$$Vd = \frac{500\ mg}{1.00\ \mu g/mL} = 500\ L$$

d) Calculate $AUC_{0\text{-}t(last)}$ and $AUC_{0\text{-}\infty}$ (Use trapezoidal rule) **(1 point, 0.5 for each correct answer)**

time (h)	Cp (µg/mL)	AUC (µg*h/mL)
0	1.000	0.90

1	0.794	1.29
3	0.500	1.13
6	0.250	0.82
11	0.079	

$$AUC_{0\text{-}t(last)} = (0.9+1.29+1.13+0.82)\ \mu g*h/mL = 4.14\ \mu g*h/mL$$

$$AUC_{t(last)-\infty} = \frac{C_{t(last)}}{k_e} = \frac{0.079\ \mu g/mL}{0.231\ 1/h} = 0.342\ \mu g*h/mL$$

$$AUC_{0-\infty} = (4.14 + 0.342)\ \mu g * h/mL = 4.482\ \mu g*h/mL$$

e) Calculate $\frac{AUC_{0-t(last)}}{AUC_{0-\infty}} * 100\%$ **(0.5 points)**

$$\frac{4.14\ \mu g * h/mL}{4.482\ \mu g * h/mL} * 100\% = 92.36\%$$

f) Predict the plasma concentration after 9 hours **(0.5 points)**

$$C(9) = 1.00\ \frac{\mu g}{mL} * e^{-0.2.31\ \frac{1}{h} * 9\ h} = 0.125\ \frac{\mu g}{mL}$$

2. For first-order elimination process, derive that the half-life ($t_{1/2}$) is independent of C_0 (1 point)

$$C(t) = C_O * e^{-k_e * t}$$

$$C(t_{1/2}) = C_O * e^{-k_e * t_{1/2}}$$

$$C(t_{1/2}) = \frac{1}{2} * C_O$$

$$\frac{1}{2} * C_O = C_O * e^{-k_e * t_{1/2}}$$

$$ln\left(\frac{1}{2} * C_O\right) = ln\ C_O - k_e * t_{1/2}$$

$$\ln(1) - \ln(2) + ln\ C_O = ln\ C_O - k_e * t_{1/2}$$

$$0 - \ln(2) = -k_e * t_{1/2}$$

$$t_{1/2} = \frac{\ln(2)}{k_e}$$

Equation for half-life does not contain C_0. Hence, it is independent of C_0.

3. Describe the fate of a drug after its administration (assume that a tablet has been administered orally). Hint: LADME (1.25 point)

- **Liberation: Disintegration of tablet (0.25 points)**
- **Absorption: Drug absorption into the systemic circulation (0.25 points)**
- **Distribution: Distribution of the drug throughout the body (0.25 points)**
- **Metabolism: Transformation of the parent drug into its metabolites (0.25 points)**
- **Elimination: Excretion of the drug from the body (0.25 points)**

4. **TRUE (T) or FALSE (F) (3 points, 0.5 points for each question)**

The plasma concentration time profile of a certain drug is not dependent on the dosage form

T **F**

For a zero-order elimination process the half-life is dependent on the plasma concentration at time point 0 (C_0)

T **F**

Therapeutic drug level monitoring (TDM) can be useful to optimize the dosage regimen for an individual patient

T **F**

Drugs with a low volume of distribution (Vd) have a narrow therapeutic window

T **F**

In the case of permeability limited distribution, the blood flow determines the rate of uptake

T **F**

In the case of perfusion limited distribution, the blood flow is not important for the rate of uptake

T **F**