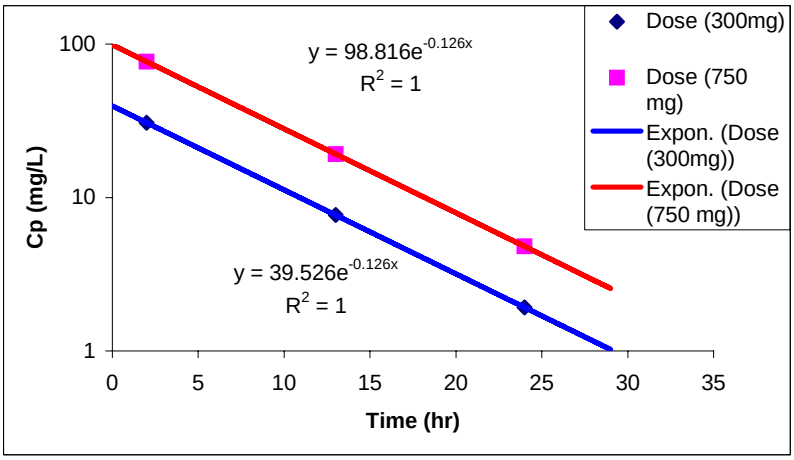
PHA 5127
Answers Case Study 5
Fall 2006

1. Given the following data collected after 300 mg dose and 750mg dose i.v. bolus (Table 1) with their corresponding semi-log plots and concentration vs. time equations (figure 1):

Time (hr)	Dose (300mg) **Concentration (mg/L)**	Dose (750mg) **Concentration (mg/L)**
2	30.72	76.8
13	7.68	19.2
24	1.92	4.8



a) figure out the Ke, Vd, CL and AUC_∞ for each dose with appropriate units;

$Given: Ke = 0.126\ \text{hr}^{-1} \quad C_{0\_300} = 39.53 mg/L \quad C_{0\_750} = 98.82 mg/L$

$\therefore\ Vd = 300/39.53 = 750/98.82 = 7.59\ \text{L} \qquad CL = Ke \bullet Vd = 0.96\ \text{L/hr}$

$$AUC_{\infty\_300} = 70.25+211.2+52.8+\frac{C_{24}}{Ke} = 70.25+211.2+52.8+15.23 = 349.48\ \text{mg/L} \bullet \text{h}$$

$$AUC_{\infty\_750} = 175.62+528+132+38.09 = 873.71\ \text{mg/L} \bullet \text{h}$$

$$or \quad AUC_{\infty\_300} = \frac{D}{CL} = \frac{300}{0.96} = 312.5\ \text{mg/L} \bullet \text{h} \quad AUC_{\infty\_750} = \frac{750}{0.96} = 781.25\ \text{mg/L} \bullet \text{h}$$

b) state why you can say this drug follows linear one compartment pharmacokinetics in the given dose range by using each of the above 4 parameters.

because Ke, $T_{1/2}$, CL, Vd are constants and independent of doses and concentration.

$$and \quad \frac{AUC_{\infty\_750}}{AUC_{\infty\_300}} = \frac{873.71\ \text{mg/L} \bullet \text{h}}{349.48\ \text{mg/L} \bullet \text{h}} = 2.5 = \frac{750\ \text{mg}}{300\ \text{mg}} = \frac{D_{750}}{D_{300}}$$

$\therefore$ *linear and one – compartment*

2. State if the following are True or False (0.5 points each)

T F a. "Linear pharmacokinetics" means that the plasma drug concentration versus time plots will result in a straight line. (F)

T F b. For a linear model the rate of elimination is proportional to the amount of drug remaining to be eliminated (T)

T F c. A one compartment model means that drug in the blood is in rapid equilibration with drug in extravascular tissues (T)

T F d. For a linear model the rate constant for elimination is proportional to the amount of drug remaining to be eliminated (F)

T F e. Since $CL = K_e \bullet Vd$, so if the volume of distribution increases the clearance must increase. (F)

T F f. At steady state (equal dose, equal interval multiple IV) accumulation stops because the amount of drug eliminated during the dosing interval is the same as the dose given at each dose time. (T)

T F g. If a drug is given as the same IV bolus dose every elimination half-life you would expect the C_{max_ss} to be twice the Cp(0) (first dose) value. (T)

T F h. The time it takes for plasma concentrations to reach steady state after repeated IV doses is dependent on the dosing interval and not on any characteristic of the drug such as volume of distribution or elimination rate constant. (F)

3. For the following scenarios for a multiple dose i.v. bolus therapy, determine what will happen to the average steady-state concentration, the peak concentration, and the fluctuation.

a) The clearance is increased.
b) The volume of distribution is decreased.
c) The dose is doubled.
d) The number of doses given per a day is doubled.

$$\overline{C_{ss}} = \frac{D}{Cl \bullet \tau} \qquad C_{\max\_n} = \frac{D}{V_d} \bullet \frac{1 - e^{n\square - k_e \square \tau}}{1 - e^{-k_e \square \tau}} \qquad C_{\max\_ss} = \frac{D}{V_d} \bullet \frac{1}{1 - e^{-k_e \square \tau}} \qquad F = \frac{C_{\max}}{C_{\min}} = e^{K_e \bullet \tau}$$

scenarios	$C_{avg,ss}$	C_{max_ss}	F
a) CL ↑	↓	↓	↑
b) V_d ↓	↔	↑	↑
c) D doubled ↑	↑	↑	↔
d) # of D doubled $\left(\tau \textit{ halved } \downarrow\right)$	↑	↑	↓