PHA5127 – Fall 2006
Homework #5 Answers (10 points)

Please show all your calculations. Points will be deducted for answers with no or incorrect units!

1. Benjamin is given a single i.v. bolus injection of Drug A. Below is the information provided on the patient, the drug, and the therapy:

Patient Age (yrs)	45
Patient Height	5 feet 10 inches
Patient Weight (kg)	90
Patient Gender	Male
Dose (mg/kg)	10
Therapeutic range (μg/mL)	0.9 to 5.7

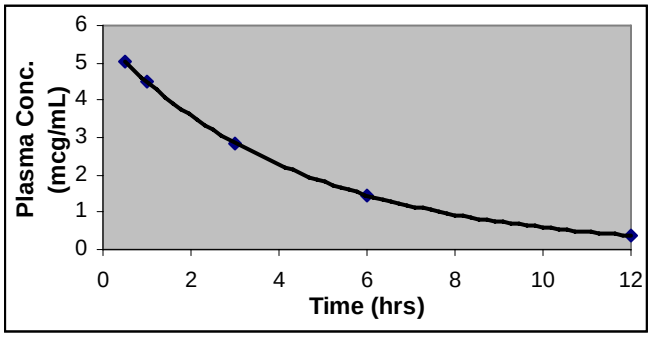
Time (hrs)	Plasma Concentration (μg/mL)
0.5	5.0
1	4.5
3	2.9
6	1.4
12	0.4

Assuming no loading dose is needed, devise a patient compliant dosing regimen for Benjamin for Drug A. (4 points)

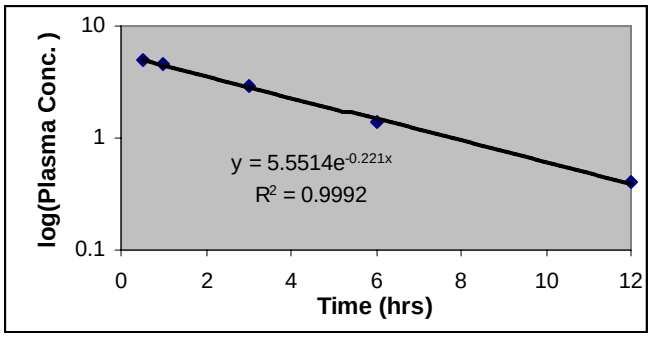
Answer:

Before we begin to determine the pharmacokinetic parameters, we need to know what elimination process the drug is following. If we plot the data points from the table above, we would get the following:

Notice, we do not get a straight curve, so we cannot assume that the drug is following a zero order elimination process.



Let's plot the data on a semi-log scale:



Notice we do get a fairly straight line, so we can assume that this drug follows a first-order elimination process.

In order to develop the dosing regime, we need to determine volume of distribution (V_d) and the elimination rate constant (k_e).

In order to determine V_d, we first need to determine the initial plasma concentration, C_o. There are several ways to determine C_o. The following just goes over two methods:

I. Using the semi-log plotted method, extend the straight line thru the y-axis and the concentration at the y-axis, when t = 0 hrs, is C_o which in this case is 5.6 μg/mL.

II. You can also use excel. Plot the time on the x-axis and the Plasma Conc. on the y-axis and put an exponential trendline thru the data points. When you select the trendline option, you should also be able to get the equation of the trendline. Using the trendline excel equation, you get C_o =5.6 μg/mL.

Once C_o is determine, V_d can be calculated as follows:

$$V_d = \frac{D}{C_o} = \frac{10\,{}^{mg}\!/\!_{kg} \times 90kg}{5.6\,{}^{\mu g}\!/\!_{mL} \times \left(\frac{1000mL}{1L}\right) \times \left(\frac{1mg}{1000\mu g}\right)} = 160L$$

(1 point.; deduct 0.25 for no/incorrect units)

There are several ways to get k_e. The following just goes over two methods:

I. Plot the above data points on a semi-log paper (with time on the x-axis and plasma conc. on the y-axis) and draw a straight line thru the data points. Select two data sets on the line and plug into equation as shown below. Say from the straight line, we get the concentration at 2 hrs which is 3.6 μg/mL and at 4 hrs which is 2.3 μg/mL.

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln\left(3.6\,{}^{\mu g}\!/\!_{mL}\right) - \ln\left(2.3\,{}^{\mu g}\!/\!_{mL}\right)}{4hr - 2hr} = 0.22hr^{-1}$$

(1 pt.; deduct 0.25 for no/incorrect units)

II. You can also use excel. From this exponential trendline equation, you get k_e = 0.22 hr^{-1}.

$$F = \frac{Cp_{ss,\max}}{Cp_{ss,\min}} = \frac{5.7\mu g/mL}{0.9\mu g/mL} = 6.3$$

$$\tau = \frac{\ln(F)}{k_e} = \frac{\ln(6.3)}{0.22hr^{-1}} = 8.4hrs \cong 8hrs$$

$$Cp_{ss.\max} = \frac{C_o}{\left(1-e^{-k_e\times\tau}\right)} = \frac{D/V_d}{\left(1-e^{-k_e\times\tau}\right)} = \frac{D}{V_d\times\left(1-e^{-k_e\times\tau}\right)}$$

$$D = Cp_{ss.\max}\times V_d\times\left(1-e^{-k_e\times\tau}\right) = \left(5.7\,\mu g/mL\right)\times 160L\times\left(1-e^{-0.22h^{-1}\times 8hrs}\right) = 755mg \cong 750mg$$

So, the most patient compliant dosing regimen for Benjamin of Drug A would be 750mg every 8hrs or 750mg 3 times a day. (1 pt. each; deduct 0.25 each for no/incorrect units; also deduct 0.25 each if not round up to feasible value)

You can double check your work by making sure $Cp_{ss,max}$ and $Cp_{ss,min}$ fall within the therapeutic range.

$$Cp_{ss,\max} = \frac{D}{V_d\times\left(1-e^{-k_e\times\tau}\right)} = \frac{750mg}{160L\times\left(1-e^{-0.22hr^{-1}\times 8hrs}\right)} = 5.7\,\mu g/mL$$

$$Cp_{ss,\min} = \frac{D\times e^{-k_e\times\tau}}{V_d\times\left(1-e^{-k_e\times\tau}\right)} = \frac{750mg\times e^{-0.22hr^{-1}\times 8hrs}}{160L\times\left(1-e^{-0.22hr^{-1}\times 8hrs}\right)} = 0.97\,\mu g/mL$$

2. For the following scenarios (in respect to question 1) for a multiple dose i.v. bolus therapy, determine what will happen (increase/decrease/stays the same) to the peak steady-state plasma concentration ($Cp_{max,ss}$) and the accumulation factor (r_{ss}) (0.5 points for each; 4 points total):

   a) The half-life ($t_{1/2}$) doubles but the total clearance (Cl) stays the same.

      If $t_{1/2}$ doubles, k_e is halved, hence V_d is doubled. So **$Cp_{max,ss}$ is decreased** and **r_{ss} is increased**.

   b) The initial plasma concentration (C_o) is halved but the volume of distribution (V_d) stays the same.

      If C_o is halved, then D is halved. So **$Cp_{max,ss}$ is halved/decreased** and **r_{ss} stays the same**.

   c) The number of doses/day is halved.

The number of doses/day is halved, τ is doubled. So **$Cp_{max,ss}$ is decreased** and **r_{ss} is decreased**.

d) A patient with liver failure taking a drug that is cleared 60% hepatically (as oppose to a normal patient).

Since the Cl_{Hep} is decreased, Cl is also decreased and hence k_e decreases. So **$Cp_{max,ss}$ is increased** and **r_{ss} is increased**.

Equations to consider:

$$Cp_{\max,ss} = \frac{D}{V_d \times \left(1 - e^{-k_e \cdot \tau}\right)}$$

$$r_{ss} = \frac{1}{1 - e^{-k_e \cdot \tau}}$$

$$t_{1/2} = \frac{\ln(2)}{k_e}, \quad k_e = \frac{Cl}{V_d}, \quad C_o = \frac{D}{V_d}, \quad Cl = xCl_{Hep} + yCl_y + zCl_z + ...$$

3. Fill in the blanks. Please select the best answer from the options given (0.5 points each; 2 points total):

a) Assuming that the dose and the half-life of Drug A and Drug B are the same, Drug A has twice the AUC than that of Drug B, so the initial plasma concentration for Drug A is __higher__ (higher/lower/the same as) that of Drug B.

$$AUC_\infty = \frac{D}{Cl} = \frac{C_0 \times V_d}{k_e \times V_d} = \frac{C_0}{k_e}$$

$$\uparrow AUC_\infty = \frac{\uparrow C_0}{k_e}$$

b) In looking at the clearance of a drug with a metabolite, if the elimination rate of a parent drug is much smaller than the elimination rate of a metabolite (i.e. $k_e << k_e^M$), then the half-life of the metabolite is _the same as_____ (larger/smaller/the same as) the half-life of the parent drug.
**See slides 224 and 225 and listen to the video for these slides.*

c) In a one compartment body model, the distribution of an i.v. bolus administered drug occurs _immediately_____ (over a period of time/immediately).
**See slide 199.*

d) For a drug that follows a first-order elimination, one compartment body model, saturation of enzymes or transporters __does not_____ (does/does not) occur.
**See slides 199 and 200.*