

**PHA 5127**  
**Answers Homework 2**  
**Fall 2000**  
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Given information: 100 mg dose (IV bolus)  
1 compartment body model  
 $f_u = 0.50$ ,  $Q_H = 90$  L/hr

<u>Patient</u>	<u>Cp(0)</u>	<u>Cp(2 hrs)</u>
A	1.25 mg/L	0.89 mg/L
B	2.5 mg/L	1.27 mg/L

1. Why is the initial plasma concentration different for these two patients? Provide a **quantitative** explanation (consider distribution and binding properties) for this difference.

For a dose administered IV bolus,

$$Cp(0) = \frac{D}{V_d}$$

Since both patients received the same dose and achieved different initial concentrations,  $V_d$  must be different for these two patients.  $V_d$  may be calculated by rearranging the equation above to give

$$V_d = \frac{D}{Cp(0)}$$

For patient A,

$$V_d = \frac{100mg}{1.25mg / L} = 80L$$

For patient B,

$$V_d = \frac{100mg}{2.5mg / L} = 40L$$

While these calculations provide the  $V_d$  's for the two patients, they do not explain why the values are different.

Recall: For a drug that distributes well into all tissues and crosses membranes easily, the tissue volume into which a drug may distribute is 38 L (total tissue water). Plasma volume is 3 L. The volume of distribution may be related to these plasma and tissue volumes by

$$V_d = V_p + V_T \cdot \frac{fu}{fu_T}$$

$fu$  is given as 0.5. If we assume a tissue water volume of 38L for both patients,  $fu_T$  must be different in these patients. The expression above may be rearranged to give.

$$fu_T = \frac{V_T \cdot fu}{(V_d - V_p)}$$

For patient A,

$$fu_T = \frac{(38L)(0.5)}{(80L - 3L)} = 0.25$$

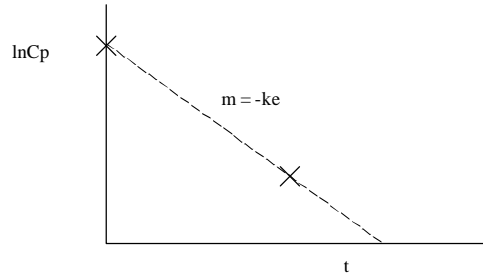
For patient B,

$$fu_T = \frac{(38L)(0.5)}{(40L - 3L)} = 0.51$$

Thus, the difference in  $V_d$  's may be explained by the 2-fold difference in tissue binding of the drug. (An alternative hypothesis is that patient A has more fat tissue leading to more binding of the drug. If more drug is bound, the free fraction decreases.)

2. Determine the half-life of the drug in each patient. At what time post-injection (if any) will the plasma concentrations be equal in both patients?

To find  $t_{1/2}$ ,  $k_e$  must be calculated from the data points given.



The slope (and, thus,  $k_e$ ) may be determined by a simple calculation or by plotting  $\ln C_p$  vs time on graph paper.

For patient A,

$$\begin{aligned}k_e &= -m \\ &= \frac{\ln(1.25) - \ln(0.89)}{(0 - 2)} \\ &= 0.17 \text{ hr}^{-1}\end{aligned}$$

The half-life ( $t_{1/2}$ ) is then,

$$\begin{aligned}t_{1/2} &= \frac{\ln 2}{k_e} \\ &= \frac{0.693}{0.17 \text{ hr}^{-1}} = \underline{4.1 \text{ hr}}\end{aligned}$$

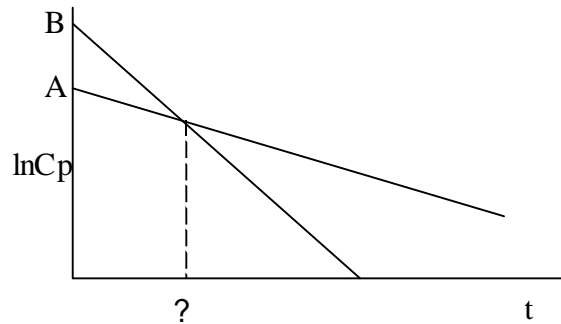
For patient B,

$$k_e = \frac{\ln(2.5) - \ln(1.27)}{(0 - 2)} = 0.34 \text{hr}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.34 \text{hr}^{-1}} = \underline{2.0 \text{hr}^{-1}}$$

Will the two patients ever have the same plasma concentration at any given time?

Patient B has a higher initial concentration but a larger elimination rate constant (i.e. steeper slope).



So, at some time  $t$ , concentration will be equal for both patients.

To find this time, set the concentration expressions equal to one another and solve for time  $t$ . (This is similar to the derivation of  $t_{1/2}$  performed in class.)

The plasma concentration at any time  $t$  is given by

$$C_p(t) = C_p(0) \cdot e^{-k_e t}$$

At some time " $t$ " after injection, the plasma concentrations for patients A and B will be equal.

Thus,

$$Cp_A(t) = Cp_B(t)$$

(Again, the time "t" may be found by calculation or by plotting the concentrations (semilog) for both patients.)

Inserting the Cp(t) expressions for both patients gives

$$Cp_A(0) \cdot e^{-k_e(A)t} = Cp_B(0) \cdot e^{-k_e(B)t}$$

This equality must be solved for t,

$$\begin{aligned} \frac{Cp_A(0)}{Cp_B(0)} &= \frac{e^{-k_e(B)t}}{e^{-k_e(A)t}} \\ &= e^{-k_e(B)t + k_e(A)t} \\ &= e^{[k_e(A) - k_e(B)]t} \end{aligned}$$

Taking the natural log of both sides give,

$$\ln \left[ \frac{Cp_A(0)}{Cp_B(0)} \right] = [k_e(A) - k_e(B)] \cdot t$$

and thus,

$$t = \frac{\ln \left[ \frac{Cp_A(0)}{Cp_B(0)} \right]}{[k_e(A) - k_e(B)]}$$

$$= \frac{\ln\left(\frac{1.25}{2.5}\right)}{(0.17 - 0.34)hr^{-1}} = \underline{4.1 \text{ hr}}$$

The plasma concentrations for both patients will be equal, roughly four hours after the IV bolus injection.

3. Calculate clearance and intrinsic clearance of this drug for each patient. Is this a high or low extraction drug? What is the extraction ratio?

Since hepatic metabolism is the only process of drug elimination, total clearance ( $CL_{TOT}$ ) is equal to the hepatic clearance ( $CL_{hep}$ ). Clearance may be calculated using

$$CL = k_e \cdot V_d$$

Intrinsic clearance ( $CL_{int}$ ) is contained in the "well-stirred" model for hepatic clearance,

$$CL_{hep} = \frac{Q_H \cdot CL_{int} \cdot fu}{Q_H + CL_{int} \cdot fu}$$

This may be solved for  $CL_{int}$ .

$$CL_{hep}(Q_H + CL_{int} \cdot fu) = Q_H \cdot CL_{int} \cdot fu$$

$$CL_{hep} \cdot Q_H + CL_{hep} \cdot CL_{int} \cdot fu = Q_H \cdot CL_{int} \cdot fu$$

$$\begin{aligned} CL_{hep} \cdot Q_H &= Q_H \cdot CL_{int} \cdot fu - CL_{hep} \cdot CL_{int} \cdot fu \\ &= CL_{int}(Q_H \cdot fu - CL_{hep} \cdot fu) \end{aligned}$$

$$CL_{int} = \frac{CL_{hep} \cdot Q_H}{(Q_H - CL_{hep}) \cdot fu}$$

For patient A,

$$\begin{aligned}
 CL &= k_e \cdot V_d \\
 &= (0.17 \text{ hr}^{-1})(80\text{L}) = \underline{13.6 \text{ L/hr}}
 \end{aligned}$$

Thus,  $CL_{\text{hep}} = 13.6 \text{ L/hr}$  as well. Since  $CL_{\text{hep}}$  is known,  $CL_{\text{int}}$  may be calculated:

$$\begin{aligned}
 CL_{\text{int}} &= \frac{CL_{\text{hep}} \cdot Q_H}{(Q_H - CL_{\text{hep}}) \cdot f_u} \\
 &= \frac{(13.6 \text{ L/hr})(90 \text{ L/hr})}{(90 \text{ L/hr} - 13.6 \text{ L/hr})(0.5)} = \underline{32.0 \text{ L/hr}}
 \end{aligned}$$

For patient B,

$$CL = (0.34 \text{ hr}^{-1})(40\text{L}) = \underline{13.6 \text{ L/hr}}$$

Since both patients have the same  $CL$ ,  $CL_{\text{int}}$  will also be the same ( $Q_H$  and  $f_u$  are unchanged).

$$CL_{\text{int}} = \underline{32.0 \text{ L/hr}}$$

For hepatic clearance,

$$CL_{\text{hep}} = E \cdot Q_H$$

Where  $E$  is the extraction ratio. Solving for  $E$  gives

$$\begin{aligned}
 E &= \frac{CL_{\text{hep}}}{Q_H} \\
 &= \frac{13.6 \text{ L/hr}}{90 \text{ L/hr}} = \underline{0.15}
 \end{aligned}$$

This is a low extraction drug ( $E \leq 0.2$ ).

- If this drug has an extraction ratio of 1, what would the half-life be for each patient? Will the half-life change if  $f_u$  increases? Why or why not?

If  $E = 1$ ,

$$CL_{TOT} = CL_H = E_H \cdot Q_H = 90L$$

$t_{1/2}$  depends on both  $CL$  and  $V_d$  since

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

and

$$CL = k_e \cdot V_d \rightarrow k_e = \frac{CL}{V_d}$$

Thus,

$$t_{1/2} = \frac{V_d \cdot \ln 2}{CL}$$

For patient A, the new  $t_{1/2}$  would be

$$t_{1/2} = \frac{(80L)(0.693)}{(90L/hr)} = \underline{0.62hr}$$

and for patient B,

$$t_{1/2} = \frac{(40L)(0.693)}{(90L/hr)} = \underline{0.31hr}$$

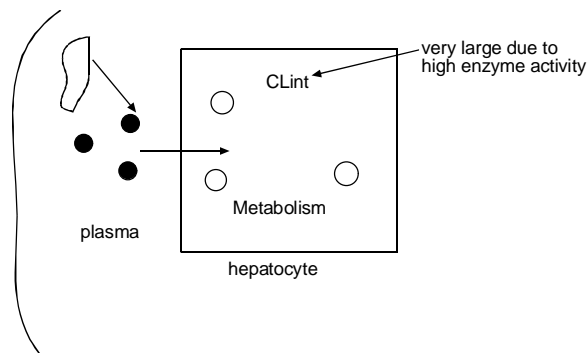
If  $f_u$  increases,  $t_{1/2}$  will change due to a change in  $V_d$  (for high extraction drugs,  $CL$  is independent of  $f_u$ ): If  $f_u$  increases (i.e. less binding in the plasma and more free drug available to distribute into the tissues),  $V_d$  also increases.

$$\uparrow V_d = V_p + V_T \cdot \frac{fu \uparrow}{fu_T}$$

From the  $t_{1/2}$  expression above,  $t_{1/2}$  would increase as well.

5. Explain (on a molecular level) how hepatic clearance is affected by the degree of plasma protein binding of high **and** low extraction drugs. Your response must include a description of the dynamic equilibria involved and relative enzyme activity.

For a high extraction drug,  $CL_H$  is not dependent on plasma protein binding. The enzyme activity ( $CL_{int}$ ) is so large that a significant concentration gradient exists between the plasma and the intracellular fluid of the hepatocyte. As free drug diffuses into the hepatocyte down the concentration gradient, more drug dissociates from the plasma proteins.  $CL_H$  approaches liver blood flow,  $CL_H \approx Q_H$ .



For low extraction drugs  $CL_{int}$  is not as large. No concentration gradient exists due to the slow enzyme activity (free drug is not being metabolized and there is no shift in the equilibria as shown above). Free concentrations are roughly equal in the plasma and the hepatocyte. The amount of free drug entering the hepatocyte is dependent on the degree of protein binding in the plasma. Thus,  $CL_H$  is dependent on protein binding and  $CL_H \approx fu \cdot CL_{int}$