

PHA 5127
First Exam
Fall 1998
Answers by Jeff Stark

1. The volume of distribution of a lipophilic drug X is 1,000 L. Mark whether the following statements are True or False (5 pts)

T F plasma protein binding is more pronounced than tissue binding

T F the V_d indicates that this drug is highly metabolized in the tissue

T F the drug does not leave the plasma

T F not at all bound to tissue proteins

T F drug is able to cross membranes

2. Mark whether the following statements are True or False (5 points)

T F The hepatic clearance of a high extraction drug will increase if the hepatic blood flow is decreased.

T F The oral bioavailability of a low extraction drug is 70%-100%.

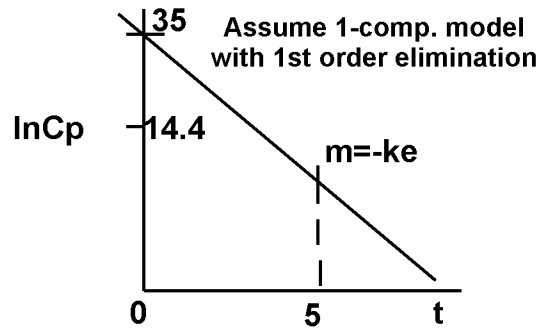
T F Drugs having a high extraction ratio undergo significant hepatic metabolism

T F F is the fraction of an oral dose that reaches the general (systemic) circulation.

T F The maximum volume of distribution possible for a drug which does not show tissue and plasma protein binding is that of the volume of the body.

3. A 10 year old 25 kg patient suffering from Status Asthmaticus was given an iv bolus of theophylline (400 mg). When the serum concentrations were measured at 0 and 5 hours after injection, drug levels were found to be 35 and 14.4 $\mu\text{g/ml}$, respectively. Assume a therapeutic range of 10-20 $\mu\text{g/ml}$ for theophylline.

Calculate the volume of distribution in this patient.



$$Cp_0 = \frac{D}{V_d}$$

which rearranges to:

$$V_d = \frac{D}{Cp_0} = \frac{400\text{mg}}{35\text{mg}} \cdot \frac{1000\text{mg}}{1\text{mg}} \cdot \frac{1\text{L}}{1000\text{ml}} = 11.4\text{L}$$

Calculate k_e and $t_{1/2}$ in this patient.

k_e is found from the slope:

$$k_e = -m = -\frac{\ln Cp_1 - \ln Cp_2}{t_1 - t_2}$$

$$= -\frac{\ln(35) - \ln(14.4)}{(0 - 5)\text{hr}} = 0.178\text{hr}^{-1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.178\text{hr}^{-1}} = 4\text{hr}$$

Calculate the clearance in this patient.

$$\begin{aligned} Cl &= k_e \cdot V_d \text{ (both were calculated above)} \\ &= (0.178 \text{ hr}^{-1})(11.4 \text{ L}) \\ &= 2.03 \text{ L/hr} \end{aligned}$$

4. The distribution of drugs A into the brain is driven by permeability limitations. The distribution of drug B into the brain is driven by perfusion limitations. Which of the two drugs will enter the brain faster (short explanation) (10 pts)

Drug A - permeability limited

Drug B - perfusion limited

Since the brain is a well perfused organ, Drug B will enter faster. With permeability limitations, Drug A will not enter the brain rapidly despite the high degree of perfusion.

5. Liposan is a highly lipophilic drug. It shows a very low extraction ratio. This drug has a very low extraction ratio and we would predict that the oral bioavailability would be relatively high since $F=1-E$. However, it has a low oral bioavailability. Discuss the potential reason. (10 pts)

Low extraction: $E \leq 0.3$ or 0.2

Would predict: $F = 1-E = 1-0.2 \approx 0.8$ (80-100%)

However, F is lower. Why?

Since considering only the extraction ratio does not explain the observed bioavailability, we must consider other factors. Possible reasons are:

- 1) poor dissolution from oral formulation
- 2) drug is so large that it does not cross membranes easily (possible but unlikely)
- 3) degradation in GI track prior to absorption (e.g. a pH-sensitive drug).

6. Explain in your own words what the volume of distribution describes. (no equations). (10 points)

V_d is hypothetical volume. It relates the plasma concentration to the amount of drug in the body. It is determined by the ability of the drug to distribute into tissues, and the degree of binding to plasma proteins and tissue components. It tells us where the drug is. The larger the V_d the more drug is outside of plasma.

7. Drugs that induce the hepatic P-450 system are likely to increase the plasma clearance of high extraction drug propranolol (a drug metabolized by these enzymes). Is this statement correct. Explain and provide your reasoning. (10 points)

For a high extraction drug,

$$Cl_H = Q_H \cdot E$$

$$= \frac{Q_H \cdot Cl_{int} \cdot fu}{Q_H + Cl_{int} \cdot fu} \text{ and } Cl_{int} \cdot fu \gg Q_H$$

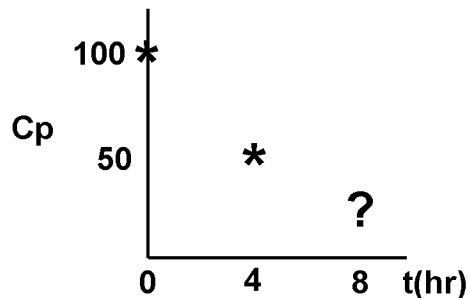
$$\approx \frac{Q_H \cdot Cl_{int} \cdot fu}{Cl_{int} \cdot fu} = Q_H$$

the statement above is **false**. For a high extraction drug, there is already sufficient metabolic activity to eliminate most (or all) of the drug presented. Thus, the hepatic clearance is dependent only on liver blood flow (Q_H).

Induction of the P-450 system will have no effect based on our understanding-definition of a high extraction drug.

8. A drug is given as an IV bolus injection. The initial plasma concentration (C_p) was 100 $\mu\text{g/ml}$. 4 hours later the plasma concentration was 50 $\mu\text{g/ml}$. What is the plasma concentration 8 hours after dosing if (10 pts)

a) the elimination is first order?



For 1st order, we know the half-life readily from the data given. In 4 hours, the concentration dropped to 1/2 the initial value. So, every 4 hrs, we expect the concentration to drop by one-half.

T(hr)	Cp(µg/ml)
0	100
4	50
8	25

b) the elimination is zero-order?

For zero order, the same amount is lost regardless of the initial value. During the first 4 hours, the concentration drops by 50 µg/ml. We would expect the same during the next 4 hour period.

T(hr)	Cp(µg/ml)
0	100
4	50
8	0

9. Discuss the advantages and disadvantages of pulmonary delivery. (10 pts)

Advantage	Disadvantage
Large surface area for absorption Systemic and local	If local delivery desired, only 10-20% enters lungs Expense

10.) Discuss why quite often tablets are taken with a full glass of water. (10pts)

The glass of water induces a faster gastric emptying. This will generally result in a faster absorption of the drug because of the larger surface area of the intestine.