PHA5127 – Fall 2005
Homework #1 (10 pts max)

Please show your calculations and make sure your numerical answers have units!

1. 500 mg of drug A was administered to a patient as a single i.v. bolus dose. The following plasma concentrations were observed. (3 points max)

Time (hrs)	Conc. (mg/L)
0.5	3.2
1	3.0
5	2.2
10	1.6
15	1.0

Calculate the following parameters of the drug based on the above plasma concentrations:

a. Elimination rate constant (0.5 pts; -0.1pts for no units)
b. Half-life (0.5 pts; -0.1pts for no units)
c. Initial plasma concentration (0.5 pts; -0.1pts for no units)
d. Volume of distribution (0.5 pts; -0.1pts for no units)
e. Based on the volume of distribution. Is the drug being distributed exclusively to the extracellular fluid? Yes/No. Give a reason for your answer. (0.5 pts)
f. $AUC_{0 \text{ to infinity}}$ using trapezoidal rule (0.5 pts; -0.1pts for no units)

Answer:

a. $$k_e = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1} = -\frac{\ln\left(2.2\,mg/L\right) - \ln\left(3.0\,mg/L\right)}{5hr - 1hr} = 0.08hr^{-1}$$

b. $$t_{1/2} = \frac{\ln(2)}{k_e} = \frac{\ln(2)}{0.08hr^{-1}} = 8.7hr$$

c. $$C_o = C \times e^{k_e \cdot t} = 3.0\,mg/L \times e^{0.08hr^{-1} \cdot 1hr} = 3.25\,mg/L$$

d. $$V_d = \frac{D}{C_o} = \frac{500mg}{3.25mg/L} = 154L$$

e. No. The volume of distribution is much higher than 18L, which it would be if it were being exclusively distributed to the extracellular fluid, so the drug must be distributing to other parts of the body.

f. Calculate AUC using: $$AUC = AUC(0 - t_z) + \frac{C_{last}}{k_e}$$

$$AUC(0 - t_z) = 0.5 \times \sum\left((C_n + C_{n+1}) \times (t_{n+1} - t_n)\right)$$

Time, t_n	Plasma Conc. (mg/L), C_n	AUC(0-t) (mg*hr/L)

0	3.25	X
0.5	3.2	1.6
1	3	1.6
5	2.2	10.4
10	1.6	9.5
15	1	6.5

AUC(0-t)=29.6 mg*hr/L

$$\frac{C_z}{k_e} = \frac{1.0 mg/L}{0.08 hr^{-1}} = 12.5 \, mg \cdot hr / L$$

$$AUC = AUC(0 - t_z) + \frac{C_{last}}{k_e} = 29.6 \, mg \cdot hr / L + 12.5 \, mg \cdot hr / L = 42.1 \, mg \cdot hr / L$$

2. (2 pts max)
   a. Define perfusion limited distribution. (0.5 pts)
   b. What types of drugs will have this type of distribution into tissue? (0.5 pts)
   c. The distribution for perfusion-limited drugs depends on what? (0.5 pts)
   d. Which organ would a higher rate of uptake of perfusion-limited drugs: Liver or skin? Why? (0.5 pts)

Answer:

a. Perfusion limited distribution is a type of drug distribution into tissue that occurs for drugs and tissues with high permeability.
b. Drugs that have high lipophilicity and, in the case of ionizable drugs, are primarily in the non-ionic form.
c. Distribution to a specific tissue depends on how much and how quickly the blood gets to the specific tissue.
d. Liver due to its higher blood flow rate. (1350 mL/min for liver vs. 300 mL/min for skin).

3. 200 mg of drug B was administered and the following plasma concentrations were observed: (2.5 pts max)

Time (hrs)	Conc. (mg/L)
2	180
5	150
10	100

   a. Is this drug eliminated by first-order or zero-order process? Give a reason for your answer. (0.5 pts)

   Calculate the following parameters of the drug based on the above plasma concentrations:
   b. Initial plasma concentration (0.5 pts; -0.1pts for no units)

c. Plasma concentration at t = 20 hrs (0.5 pts; -0.1pts for no units)
d. Does the rate of decrease in plasma concentration of this drug depend on the concentration? Why? (1.0 pts)

Answers:

a. Zero-order process. The amount eliminated is constant (i.e. 10 mg/hr). However, the fraction of drug eliminated per an hour is not constant.
b. $C_0 = C + k_e \cdot t = 180\,{}^{mg}/_{L} + 10\,{}^{mg}/_{L \cdot h} \times 2hr = 200\,{}^{mg}/_{L}$
c. $C = C_0 - k_e \cdot t = 200\,{}^{mg}/_{L} - 10\,{}^{mg}/_{L \cdot h} \times 20hr = 0\,{}^{mg}/_{L}$
d. No. For a zero-order distribution process, the rate of decrease in concentration is independent of concentration and depends only on the rate constant k. This means that the same amount of drug will disappear in a given amount of time regardless of how much drug is present. First-order distribution processes are depended on plasma concentration.

4. Which of the following is true about the volume of distribution, V_d: (2.5 pts max)
   a. It indicates the extend of drug distribution into tissue. **TRUE** (0.5 pts)
   b. The larger the V_d, the lower the amount of drug found in the plasma. **TRUE** (0.5 pts)
   c. For a drug that can cross membranes easily, the plasma binding is stronger than the tissue binding for a particular drug. So the V_d for this drug is less than 41L. **TRUE** (0.5 pts)
   d. An increase in the plasma protein binding will result in a lower V_d. **TRUE** (0.5 pts)
   e. If the V_d of a small lipophilic drug is 18L, it can be assumed to distribute only to the extracellular fluid. **FALSE** (0.5 pts)