1. The drug ‘Snoozin’ is being evaluated as a new sleep aid. From the information provided in the graph below, what is its therapeutic index?

2. Cimetadine is a weak base with a pKa of 6.8. Assuming that all of a dose given po makes its way into the small intestine (pH=8) what percentage of it will be capable of diffusing into the neighboring blood vessels?

3. If a disease state caused the intestinal pH to decrease to pH=6, by how much would this affect drug diffusion compared to the above situation?

4. A patient visits her doctor with symptoms typical of a bladder infection. She is immediately prescribed a 400 mg dose of antibiotic ($t_{1/2} = 12$ h). The corresponding plasma concentration of drug is found to be 96 μg/ml. What is the volume of distribution of this drug?

5. What can you conclude about the distribution characteristics of the antibiotic above?

6. The slope of a natural log (ln) concentration vs time graph is calculated to be -0.06 min⁻¹. What is the half life of the drug?

7. The initial plasma concentration of a drug given iv at 9:00am is 250 mg/ml. If the half life of the drug is 6 hours, perform a calculation to predict the plasma concentration will be at 9:00pm that same day.

8. Can you think of another way to answer this question without doing a formal calculation? Use this method to double check your answer to question 7 (a great strategy to use on exams 😊).

9. A drug is most effective when plasma levels are at a concentration of 5 μg/ml. If the drug has a Vd of 20 L, what dose of drug would produce the most therapeutic effect?

10. A patient is diagnosed with pneumonia after presenting to his family doctor with a cough and shortness of breath. Given the severity of his symptoms it is felt that treatment with tobramycin should be initiated immediately, with the goal of reaching a therapeutic concentration of 4 mg/L as quickly as possible. Tobramycin distributes to extracellular fluid and has a half-life of 7.5 hours. Tablets are typically taken 3x per day. What loading and maintenance doses are required?
1. Therapeutic Index (TI) = TD$_{50}$/ED$_{50}$ = 250 mg/100 mg = 2.5

2. The dissociation equation for a weak base is: $B + H^+ \rightleftharpoons BH^+$  
   Only the unprotonated “B” form will diffuse  
   
   $\text{pH} = \text{p}K_a + \log \left( \frac{[B]}{[BH^+]} \right)$  
   $8 = 6.8 + \log \left( \frac{[B]}{[BH^+]} \right)$  
   $1.2 = \log \left( \frac{[B]}{[BH^+]} \right)$  
   $\frac{15.8}{1} = \frac{[B]}{[BH^+]}$  
   $\therefore BH^+ = 1 - B$  
   $\frac{15.8}{1} = \frac{[B]}{[1 - B]}$  
   substitute and cross multiply  
   $B = 15.8 - 15.8B$  
   $16.8B = 15.8$  
   $\% B = \frac{15.8}{16.8 \times 100} = 94\%$  

3. $\text{pH} = \text{p}K_a + \log \left( \frac{[B]}{[BH^+]} \right)$  
   $6 = 6.8 + \log \left( \frac{[B]}{[BH^+]} \right)$  
   $-0.8 = \log \left( \frac{[B]}{[BH^+]} \right)$  
   $\frac{0.158}{1} = \frac{[B]}{[BH^+]}$  
   $\therefore BH^+ = 1 - B$  
   $\frac{0.158}{1} = \frac{[B]}{[1 - B]}$  
   substitute and cross multiply  
   $B = 0.158 - 0.158B$  
   $\% B = \frac{0.158}{1.158 \times 100} = 13.6\%$  
   Therefore, drug diffusion will decrease by approximately 80% compared to the first scenario.

4. $V_d = \frac{\text{Dose}}{\text{Conc}} = \frac{400 \text{ mg}}{96 \text{ mg/L}} = 4.16 \text{ L}$
   *Make sure you convert to like units before performing the calculation so that you can cross them out. There are several ways to do this: 400mg = $4 \times 10^2 \mu g$ OR 96μg/ml = 0.096mg/ml = 96mg/L etc.

5. It distributes to the plasma compartment (refer back to lecture notes for volumes of known physiologic compartments)

6. $\text{slope} = -k \therefore k = -\text{slope} = -(0.06 \text{ min}^{-1}) = 0.06 \text{ min}^{-1}$  
   $t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.06 \text{ min}^{-1}} = 11.6 \text{ min}$
7. Relevant Equation \( \ln C_{12h} = \ln C_{0h} - kt \)

Known values: \( C_{0h} \), \( t \) and \( k \) (indirectly – get it from \( t_{1/2} \)); Unknown value: \( C_{12h} \)

\[
k = \frac{0.693}{t_{1/2}} = 0.693/6 \text{ hr} = 0.1155 \text{ hr}^{-1}
\]

\[
\ln C_{12h} = \ln(250 \text{ mg/ml}) - [(0.1155 \text{ hr}^{-1})(12 \text{ hr})] = 5.52 - 1.38 = 4.14
\]

\[
C_{12h} = \text{anti-ln}(4.14) = 63 \text{ mg/ml}
\]

8. You should also be able to solve this problem using only the definition of half life and some simple “mental math”...From 9:00am to 9:00pm is 12 hours or exactly 2 half lives. If the initial concentration at 9:00am is 250 mg/ml, then by 3:00pm (after one half life) it should be 125 mg/ml and by 9:00pm (after two half lives) it should be 62.5 mg/ml. Is this the answer that you got? I hope so!

\( \rightarrow \) Note that the slight difference in decimal points is due to rounding off. If you repeat Q9 and keep all your decimals you will also get 62.5 mg/ml.

9. Dose = Concentration \( \times \) Volume of Distribution = 5 mg/L \( \times \) 20L = 100 mg

Again, make sure you convert to like units first – see Q6

10. LD = Concentration at steady state \( \times \) Volume of Distribution = 4 mg/L \( \times \) 14 L = 56 mg

3x daily dosing is every 8 hours \( \therefore \) \( t = 8 \text{ hr} \)

\[
k = \frac{1}{t_{1/2}} = \frac{1}{7.5 \text{ hr}} = 0.13 \text{ hr}^{-1}
\]

\[
\text{MD} = (1-e^{-k(t)}) \times (LD) = (1-(2.718)^{-0.13(8)})(56 \text{ mg}) = 36.2 \text{ mg}
\]

Note: your answers may differ slightly from mine depending on the number of decimal places you use and how you round your numbers. If you’re very close that’s great – the answer will be obvious on a multiple choice exam. If you’re way off there’s likely a problem. Double check your formula, units etc. and give it another try. If you’re still stuck, check with a classmate or send me an email: jennifer.shabbits@ubc.ca
**PK Equation Sheet – you will be given this same information for exams**

\[
pH = pK_a + \log\left(\frac{\text{unprotonated}}{\text{protonated}}\right)
\]

\[
C = \frac{\text{dose}}{V_d}
\]

\[
t_{1/2} = \frac{0.693}{k}
\]

\[
C_t = C_0 e^{-kt}
\]

\[
\ln C_t = \ln C_0 - kt
\]

\[
LD = C_{ss} V_d
\]

\[
MD = (1-e^{-kt})(LD)
\]