20.201 '12 Pharmacokinetics Homework
11 October 2012

Please prepare your answers in electronic format and submit the answers before or on October 11. While this is not a graded problem set, \ RX Z LOO JHW credit for completing the problem set and submitting it. An answer key will be posted on the October 12, so no credit will be given for late submissions!

1) A drug was injected intravenously in 200 g rats at a dose of 185 mg/kg and blood samples were obtained at several times. The plasma concentrations are as follows:

Time (Hours)	Plasma Concentration (mg/ml)
0.2	4.2
0.4	3.83
1	2.9
2	1.83
4	0.726
6	0.288

a) What type of kinetics is observed? Zero order, first order, second order? Why?
b) Is there a plasma half-life for the drug? If so, what is it?
c) What is the rate constant for loss of the drug from plasma?
d) Calculate the volume of distribution of the drug.

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2) In addition to its role in phase II metabolism, glutathione provides one line of protection in the cell against electrophiles and oxidants. Answer the following questions:

a) Draw the structure of glutathione at pH 7.4. What is its net charge?
b) If the second order rate constant for the reaction of glutathione with cisplatin at 37 °C is 1 x 10^{-2} $M^{-1}s^{-1}$, what is the pseudo-first order rate constant of the reaction at 10 mM glutathione and what is the half-life of cisplatin under these conditions?

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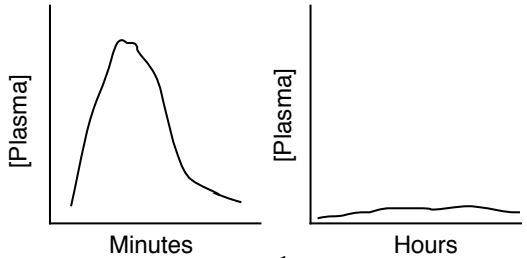
4) Glyceryl trinitrate, erroneously called nitroglycerin, is metabolized by reaction with glutathione-organic nitrate reductase, high levels of which are found in the liver.

a) Shown below are hypothetical profiles for the plasma pharmacokinetics of nitroglycerin following sublingual (under the tongue) and oral (swallowed) doses. Match each profile with the correct route of administration and rationalize your choices.
b) What is the relationship of the liver to the circulatory system that results in these pharmacokinetic profiles?



5) Two chemicals (A and B) behave identically in the body except that, while both chemicals are removed from the body by excretion in the urine, chemical B is also excreted in the bile and is subject to enterohepatic circulation.

a) Compare the pharmacokinetics of the two chemicals by sketching plots of the log(blood concentration) *versus* time for their clearance from blood. Explain the basis for the differences, if any. Assume i.v. injection with instantaneous distribution.
b) If the blood half-life of the chemical A is 10 hours, what is the first order rate constant for its clearance from the blood?
c) Sketch plots of log(blood concentration) *versus* time for chemical A if: (i) it is excreted in the urine; and (ii) it is excreted in both urine and bile.
d) Assume that chemical B is metabolized in the liver. Sketch plots of the log(blood concentration) *versus* time for chemical B in (i) presence and (ii) absence of liver failure.

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6) Kinetics of transport and metabolic processes.

a) Define the difference between zero-order and first-order pharmacokinetics using two examples: (1) the metabolism of a chemical; and (2) the transport of a chemical across a cell membrane
b) What is the predominant mechanism of transportation of foreign chemicals across cell membranes? What "order" is this process in terms of transport kinetics? Justify your answer.

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7) You are the Chief Pharmacokineticist at Acme Pharmaceuticals and you have begun pre- clinical testing of a new drug to treat excessive nose hair. The drug was injected rapidly into the tail vein of a rat and blood samples were withdrawn at various times. Answer the following questions about the pharmacokinetics of the new drug.

a) If the rate constant for elimination of the drug from blood is first order and has a value of 0.692 min^{-1}, what is the half-life of the drug (*i.e.*, $t_{1/2}$)? Either state the value of the half-life or write the equation used to calculate the half-life.
b) If the rate constant is zero-order with a value of 10 mg/min, how much of the drug has been eliminated after 1 min? How much of the drug is eliminated between the 5^{th} and 6^{th} minutes after injection? How much drug is eliminated after 10 min?
c) What factors might contribute to the elimination of the drug from the blood?

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8) The data shown below were obtained in pharmacokinetic studies of two different drugs given by rapid intravenous injection to Sprague-Dawley rats. Plasma samples were obtained at various times and the concentration of drug determined by HPLC.

a) What type of kinetics govern the plasma concentration of the drugs?
b) What is the plasma elimination rate constant and, if calculable, the half-life for each drug?
c) What is the volume of distribution of Drug A? (Assume a dose of 80 mg and that rats have the same water compartments as humans.) Explain the physiological significance of this volume.

Drug A

Time, hr	[A], mg/L
1	2
3	1.13
5	0.7
7	0.43
10	0.2
18	0.025

Drug B

Time, hr	[B], mg/L
1	2
3	1.75
5	1.55
7	1.35
10	1.23
18	0.95

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9) What is the definition of half-life ($t_{1/2}$)? Derive the equation for calculating $t_{1/2}$.

20.201 Mechanisms of Drug Actions

Fall 2013