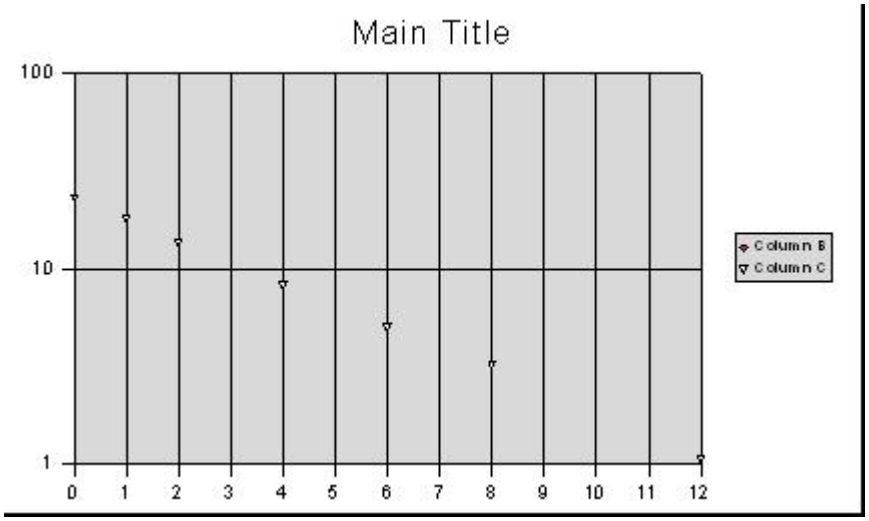
PHA 5127
Homework #2
Fall 2004

Question No. 1

A male patient, about 21 years old was admitted to the hospital due to acute intoxication. He was given a 400 mg i.v. bolus injection of a liver protecting drug XY. After therapeutic drug monitoring the plasma concentrations were reported as following (Note: The drug follows a one compartment body model, with first-order elimination)

Time (h)	***Conc. (mg/L)***
0	
1	18
2	13.5
4	8.2
6	5
8	3.2
12	1.05



1) Please calculate the AUC(0-12), AUC(0-∞), total CL, Volume of Distribution and half-life for the drug XY.

Ke=0.25 /h
$t_{1/2}$=ln2/ke=2.7h
Vd=Dose/C_0=400/23=17.39 L
CL=ke*Vd=0.25*17.39=4.35 L/h
AUC(0-12)=87.85
AUC(0-∞)=91.97

2) Suppose that the drug is only cleared hepatically and due to the liver damage by intoxication the hepatic clearance is decreased by 50%. Please calculate the new half-life of the drug.

CL/2=ke*Vd=> ke=CL/(2*Vd)=0.125
$t_{1/2}$=ln2/ke=> $t_{1/2}$=5.5h

3) Assume that XY is a high extraction. How would the following changes affect the hepatic clearance?

   a) decrease of Cl_{int} due to liver damage, ↔

   b) increase of the fraction unbound due to components of the intoxicating substance,↔

   c) decrease in liver blood flow ↓

4) Perform the same thoughts, assuming that XY was a low extraction drug. a)↓ b) ↑ c) ↔

Question 2:

Results of performed research suggest that drug metabolizing enzymes exhibit polymorphism. Therefore there are different part of the population that shows slow or fast metabolization of substrates of CYP2D6. Please calculate the hepatic clearance for a slow metabolizer (low extraction drug), assuming that for slow metabolizers the intrinsic clearance is decreased by 70%.
(Pharmacokinetic parameters for fast metabolizers: Cl_{hep}= 8.5 L/hr, fraction unbound:fu=0.4). Please calculate the new hepatic clearance, when the drug is metabolized by a slow metabolizer. (hepatic blood flow=90 L/hr)

fast metabolizer: Cl_{int}= Cl_{hep}/fu = 8.5L/h / 0.4 = 21.25 L/h
slow metabolizers: Cl_{hep}= Cl_{int}*0.3*0.4= 2.55 L/h

Question 3:

Please answer the following questions with true or false:

a) for high extraction drugs:

1) In case of a increasing fraction unbound, the extraction ratio of the drug stays the same,

   TRUE, only dependent on liver blood flow

2) In case of increased hepatic blood flow, the clearance stays the same

   FALSE : see above

b)for low extraction drugs:

1) In case of increasing fraction unbound, the extraction ratio of the drug stays the same,

   FALSE: $Cl_{hep} = Cl_{int} * fu$

2) In case increasing hepatic blood flow, the clearance of the drug stays the same.

   TRUE: independent of liver blood flow