

**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)

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

- 1) Please calculate the  $AUC(0-12)$ ,  $AUC(0-\infty)$ , total CL, Volume of Distribution and half-life for the drug XY.
- 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.
- 3) Assume that XY is a high extraction drug. How would the following changes affect the hepatic clearance?
  - a) decrease of  $Cl_{int}$  by 50% due to liver damage,
  - b) increase of the fraction unbound in plasma due lack of synthesis of albumin
  - c) decrease in liver blood flow
- 4) Perform the same thoughts, assuming that XY was a low extraction drug.

**Question 2:**

You know that drug metabolizing enzymes exhibit polymorphism. Therefore there are different part of the population that shows slower or faster metabolism. Some drugs are metabolized by CYP2D6. Please calculate the hepatic clearance for a fast and slow metabolizer, assuming that for slow metabolizers the intrinsic clearance is decreased by 70%.

(Pharmacokinetic parameters for the fast metabolizers:  $Cl_{hep} = 8.5$  L/hr, fraction unbound:  $f_u = 0.4$ ). Please calculate the new hepatic clearance, when the drug is metabolized by a slow metabolizer.  
(hepatic blood flow = 90 L/hr)

**Question 3:**

Please answer the following questions with true or false:

a) for high extraction drugs:

- 1) In case of an increasing fraction unbound in plasma, the extraction ratio of the drug stays the same,
- 2) In case of increased hepatic blood flow, the clearance stays the same

b)for low extraction drugs:

- 1) In case of increasing fraction unbound, the extraction ratio of the drug stays the same,
- 2) In case increasing hepatic blood flow, the clearance of the drug stays the same.