Case Study – 3
PHA 5127 – Fall 2006

1: Predict the changes in Cl_h given the following scenarios:

Parameter	Direction of change	effect on Cl_h for a low Extraction drug	effect on Cl_h for a high Extraction drug
fraction of unbound drug	Increases		
intrinsic clearance	Decreases		
hepatic blood flow	Increases		

2: True or False Questions

T F Total clearance is dependent on the half-life of the drug.

T F Volume of distribution and clearance are two major pharmacokinetic parameters, and they are dependent on each other based on equation: $CL = V_d \cdot k_e$

T F Clearance defines the amount of drug eliminated from body per unit time.

T F According to the equation: $AUC_\infty = \frac{Dose}{CL} = \frac{Dose}{V_d \cdot k_e}$, the change of volume of distribution does affect AUC_∞.

T F Intrinsic clearance is not dependent on blood flow, and it represents the activities of enzyme system when we talk about liver metabolism.

T F Liver blood flow affects high extraction drug much more than low extraction drug when drug major elimination pathway is hepatic elimination.

3: Gamma-hydroxybutyric Acid (GHB) is an abused drug and also an endogenous compound. Recently, a study in rats was carried out to understand pharmacokinetics of GHB. A couple of rats were given a dose at 100mg intravenously in this study. Blood samples were taken at several time points. A graduate student in this lab plotted concentration-time data. He found that drug concentration-time profile can be best described by a one-compartmental linear model. He also determined that total clearance is 150 mL/hr, and $t_{1/2}$ is 0.5 hr.

A: Calculate Volume of Distribution of GHB, GHB concentration at time zero, and AUC_{∞}.

B: If liver metabolism is the major elimination pathway for GHB in rat, blood flow rate in rat is 1.5 L/hr, what is the extraction ratio for GHB in liver?

C: According to the Question B, is GHB a high or low extraction drug? If the free fraction of GHB in plasma is 0.3, what is the intrinsic clearance?

D: If liver blood flow in rat reduces to 1.0 L/hr after 2 hrs due to an anesthesia procedure, what is the intrinsic clearance and total clearance (still based on information from question B and C)? Compared to the values before anesthesia, do they change or not? Why?