

Q1) Say true or false

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

T **F** For any drug, the AUC is affected by its dose and volume of distribution

T **F** As intrinsic clearance describes the liver's innate ability to clear unbound drug from intracellular water via metabolism or biliary excretion, the higher the liver blood flow, the higher will be a drug's clearance

T **F** For a high extraction drug that has predominant hepatic metabolism, the liver blood flow is a rate limiting step in its clearance

T **F** For a low extraction drug, the higher the protein binding the higher will be the clearance

Q2) Predict the changes in Hepatic Clearance (CL_H) for the following scenarios

Parameter	Change occurring	Effect on low extraction drug	Effect on High extraction drug
f_u	↓	↓	↔
CL_i	↑	↑	↔
Q_h	↑	↔	↑

For a low extraction drug :

$$CL_H = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}$$

$$CL_H = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H} = f_u \cdot CL_{int}$$

For a high extraction drug :

$$CL_H = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}$$

$$CL_H = Q_H$$

Q3) Predict changes in Oral bioavailability for the following scenarios

Parameter	Change occurring	Effect on low extraction drug	Effect on High extraction drug
f_u	↓	↔	↑
CL_i	↑	↔	↓
Q_h	↑	↔	↑

For a low extraction drug:

$$F = \frac{Q_H}{Q_H + f_u \cdot CL_{int}} \quad F = 1$$

For a high extraction drug:

$$F = \frac{Q_H}{Q_H + f_u \cdot CL_{int}} \quad F = \frac{Q_H}{f_u \cdot CL_{int}}$$

Q4) A patient is to be started on two medications (A and B) administered by IV bolus injections. Blood samples were taken at 1 and 4 hours following the first injections of drug A or B alone in order to determine whether concentrations were in an appropriate range for each drug. See table below for these levels and additional information.

Drug	Dose (mg)	Cp at 1h (mg/L)	Cp at 4h (mg/L)	E_H	f_u
A	400	1.22	0.76	0.1	0.3
B	1200	0.92	0.51	0.8	0.1

Assume liver blood flow of 90 L/h, where E_H is the extraction ratio and f_u is the fraction unbound. Renal elimination and hepatic metabolism are the only clearance pathways for both of these drugs.

- Calculate the CL (hepatic) for Drug B and CL (renal) for Drug B
- Also calculate the $AUC_{0-\infty}$ Drug B

$$k_e = \ln C_2 - \ln C_1 / (t_2 - t_1) = 0.20 \text{ /hr}$$

$$T_{1/2} = 0.693 / 0.2 = 3.45 \text{ hr}$$

$$C_0 = C_t / \exp(-k_e \cdot t)$$

$$C_0 = 1.13 \text{ mg/L}$$

$$V_d = \text{dose} / C_0$$

$$V_d = 1200 / 1.13 = 1062 \text{ L}$$

$$CL(\text{hepatic}) = Q_H * E_H = 90 * 0.8 = 72 \text{ L/hr}$$

$$Cl(\text{tot}) = V_d * Ke = 1062 * 0.20 = 212.4 \text{ L/hr}$$

$$CL(\text{renal}) = Cl(\text{total}) - Cl(\text{hepatic}) = 212.4 - 72 = 140.4 \text{ L/hr}$$

$$AUC_{0-\infty} = \text{dose} / Cl(\text{tot}) = 1200 / 212.4 = 5.65 \text{ mg}\cdot\text{hr/L}$$

We cannot use just the hepatic clearance to calculate the AUC, because the drug is cleared extra-hepatically as well