

PHA 5127
Case Study II
Fall 2002

Review of important equations:

Extraction ratio: $E = \frac{C_{in} - C_{out}}{C_{in}}$ Clearance: $Cl = Q \cdot E$ and $Cl = k_e \cdot V_d = \frac{Dose}{AUC}$

Well-stirred model: $E = \frac{f_u \cdot Cl_{int}}{Q_H + f_u \cdot Cl_{int}}$ Hepatic clearance: $Cl_H = \frac{Q_H \cdot f_u \cdot Cl_{int}}{Q_H + f_u \cdot Cl_{int}}$

Bioavailability: $F = 1 - E$

High extraction ($f_u \cdot Cl_{int} \gg Q_H$): $E \approx 1$ and $Cl_H \approx Q_H$ and $F \approx \frac{Q_H}{f_u \cdot Cl_{int}}$

Low extraction ($f_u \cdot Cl_{int} \ll Q_H$): $E \approx \frac{f_u \cdot Cl_{int}}{Q_H}$ and $Cl_H \approx f_u \cdot Cl_{int}$ and $F \approx 1$

Question 1:

Theophylline is known to be a low hepatic extraction drug while nicotine is a high hepatic extraction drug. Predict the changes in E, Cl_H and F under different scenarios for these two drugs.

Scenarios	Theophylline			Nicotine		
	E	Cl_H	F	E	Cl_H	F
Enzyme induction	↑	↑	↔	↔	↔	↓
More binding	↓	↓	↔	↔	↔	↑
Higher hepatic blood flow	↓	↔	↔	↔	↑	↑
Higher V_d	↔	↔	↔	↔	↔	↔

Question 2:

A 75kg male patient was given a single i.v. dose of 30 mg cocaine which is known to have a half-life of 0.693 hr and a volume distribution of 2 L/kg.

(1) What is the clearance of cocaine? Is it solely metabolized by liver? Why?

(2) Predict $AUC_{0-\infty}$

Answers:

(1)

$$k_e = 0.693 / t_{1/2} = 1 \text{ hr}^{-1} \quad V_d = 2 * 75 = 150 \text{ L}$$

$$Cl = k_e \cdot V_d = 1 * 150 = 150 \text{ L/hr} > 90 \text{ L.hr}$$

There exists non-hepatic metabolism.

(2)

$$AUC_{0-\infty} = \frac{Dose}{Cl} = \frac{30}{150} = 0.2 \text{ mg} \cdot \text{hr} / \text{L}$$