PHA 5127 – Fall 2003

Case Study # 2 - Answers

1. a) 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	fu
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 fu is the fraction unbound. Both drugs are metabolized by CYP 3A4.

Calculate $t_{1/2}$, V_d, CL_{hep}, CL_{tot}, and F (bioavailability) for Drug A.

DRUG A:

$$k_e = \frac{\ln C_2 - \ln C_1}{(t_1 - t_2)} = \frac{\ln 0.76 - \ln 1.22}{(1-4)} = 0.16h^{-1} \qquad t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.16} = 4.33h$$

$$C_t = C_0 \cdot e^{-k_e \cdot t} \qquad \Rightarrow \qquad C_0 = \frac{C_t}{e^{-k_e \cdot t}} = \frac{1.22}{e^{-0.16 \cdot 1}} = 1.43mg/L$$

$$V_d = \frac{Dose}{C_0} = \frac{400}{1.43} = 280L$$

$$CL_{hep} = Q \cdot E_H = 90 \cdot 0.1 = 9L/h$$

$$CL_{tot} = Vd \cdot k_e = 280 \cdot 0.16 = 44.8L/h$$

$$F = 1 - E_H = 1 - 0.1 = 0.9$$

DRUG B:

For drug B the following results were obtained:

k_e (h^{-1})	0.2
$t_{1/2}$ (h)	3.47
C_0 (mg/L)	1.12
V_d (L)	1071
CL_{hep} (L/h)	72
CL_{tot} (L/h)	214
F	0.2

b) There is a drug-drug interaction between drug A and B wherein B displaces A from the binding sites on plasma proteins. If these two drugs are administered at the same time, fu for drug A will increase to 0.9. Also, drug B is a CYP3A4 inducer and the intrinsic hepatic clearance (CL_{int}) of drug A is increased by 30%.
Calculate the new CL_{hep} for drug A.

First, find original CL_{int}:

$$CL_{hep} = \frac{Q \cdot f_u \cdot CL_{\text{int}}}{Q + f_u \cdot CL_{\text{int}}}$$

$$9 = \frac{90 \cdot 0.3 \cdot CL_{\text{int}}}{90 + 0.3 \cdot CL_{\text{int}}}$$ re-arrange the equation to solve for CL_{int}

$$CL_{\text{int}} = 33.3 L/h$$

Second, find new CL_{hep}:

$$CL_{hep} = \frac{90 \cdot 0.9 \cdot 1.3 \cdot 33.3}{90 + 0.9 \cdot 1.3 \cdot 33.3} = 27.2 L/h$$

2. Important equations:

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

Well-stirred model: $E = \frac{f_u \cdot CL_{\text{int}}}{Q_H + f_u \cdot CL_{\text{int}}}$ Hepatic Clearance: $CL_H = \frac{Q_H \cdot f_u \cdot CL_{\text{int}}}{Q_H + f_u \cdot CL_{\text{int}}}$

Bioavailability: $F = 1 - E$

HED $\left(f_u \cdot CL_{\text{int}} >>> Q_H\right)$: $E \approx 1$ and $CL_H = Q_H$ and $F = \frac{Q_H}{f_u \cdot CL_{\text{int}}}$

LED $\left(f_u \cdot CL_{\text{int}} <<< Q_H\right)$: $E \approx \frac{f_u \cdot CL_{\text{int}}}{Q_H}$ and $CL_H \approx f_u \cdot CL_{\text{int}}$ and $F \approx 1$

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.

Drug	**Theophylline**			**Nicotine**		
Scenarios	**E**	**CL_H**	**F**	**E**	**CL_H**	**F**
Enzyme induction						
Increased plasma binding						
Higher hepatic blood flow						
Higher Vd						