

**PHA 5127 – Fall 2003**

**Case Study # 2**

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.

<b>Drug</b>	<b>Dose (mg)</b>	<b>Cp at 1h (mg/L)</b>	<b>Cp at 4h (mg/L)</b>	<b>E<sub>H</sub></b>	<b>fu</b>
<b>A</b>	400	1.22	0.76	0.1	0.3
<b>B</b>	1200	0.92	0.51	0.8	0.1

Assume liver blood flow of 90 L/h, where E<sub>H</sub> is the extraction ratio and fu is the fraction unbound. Both drugs are metabolized by CYP 3A4.

Calculate t<sub>1/2</sub>, V<sub>d</sub>, CL<sub>hep</sub>, CL<sub>tot</sub>, and F (bioavailability) for Drug A.

For drug B the following results were obtained:

<b>k<sub>e</sub> (h<sup>-1</sup>)</b>	0.2
<b>t<sub>1/2</sub> (h)</b>	3.47
<b>C<sub>0</sub> (mg/L)</b>	1.12
<b>V<sub>d</sub> (L)</b>	1071
<b>CL<sub>hep</sub> (L/h)</b>	72
<b>CL<sub>tot</sub> (L/h)</b>	214
<b>F</b>	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,  $f_u$  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.

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:  $E = \frac{f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}$       Hepatic Clearance:  $CL_H = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}$

Bioavailability:  $F = 1 - E$

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

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

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

<b>Drug</b>	<b>Theophylline</b>			<b>Nicotine</b>		
<b>Scenarios</b>	<b>E</b>	<b>CL<sub>H</sub></b>	<b>F</b>	<b>E</b>	<b>CL<sub>H</sub></b>	<b>F</b>
<b>Enzyme induction</b>						
<b>Increased plasma binding</b>						
<b>Higher hepatic blood flow</b>						
<b>Higher Vd</b>						