PHA5127 – Dose Optmization I
Homework 4
Fall 2013

Question 1

Indicate what changes are expected in the following scenarios for low and high extraction drugs. List the effect on the following pharmacokinetic parameters: hepatic clearance (CL_{hep}), bioavailability (F), half-life ($t_{½}$), free steady-state drug concentration ($fC_{p,ss}$), and total steady-state drug concentration ($C_{p,ss}$). Use the following symbols ↑, ↓, ↔ to indicate increase, decrease and no changes, respectively. (5 points)

Scenarios	High Extraction Drug				
	CL_{hep}	F	$t_{½}$	$fC_{p,ss}$	$C_{p,ss}$
Drug is 99% protein bound. A displacement by a competitor by 1% resulted in 98% protein binding.	↔	↓	↑	↑	↔
An increase in liver blood flow	↑	↑	↓	NA	NA
Tissue binding decreased	↔	↔	↓	NA	NA
Induction of hepatic enzymes responsible for the drug metabolism	↔	↓	↔	NA	NA
Inhibition of hepatic enzyme responsible for the drug metabolism	↔	↑	↔	NA	NA

Scenarios	Low Extraction Drug				
	CL_{hep}	F	$t_{½}$	$fC_{p,ss}$	$C_{p,ss}$
Drug is 99% protein bound. A displacement by a competitor by 1% resulted in 98% protein binding.	↑	↔	↑	↔	↓
An increase in liver blood flow	↔	↔	↔	NA	NA
Tissue binding decreased	↔	↔	↓	NA	NA
Induction of hepatic enzymes responsible for the drug metabolism	↑	↔	↓	NA	NA
Inhibition of hepatic enzyme responsible for the drug metabolism	↓	↔	↑	NA	NA

Note: The effect of displacement of protein binding on $fC_{p,ss}$ and $C_{p,ss}$ was discussed during the case study 4. As the effects of the other scenarios on these two components were not discussed in the lectures so far, students are not required to answer them in the homework.

PHA5127 – Dose Optmization I
Homework 4
Fall 2013

Question 2

If a patient was administered 400 mg of a high extraction drug through IV bolus injection. The peak plasma concentration was 0.8 mg/L and the half-life of the drug was 7 hours. (5 points)

(1) Assuming that the renal clearance of the drug in this patient was 5 L/h and that the drug is eliminated renally and hepatically (no other clearance pathway is involved), compute the hepatic clearance and $AUC_{0\text{-infinity}}$.

$$V_d = \frac{Dose}{C_0} = \frac{400\ mg}{0.8\ mg/L} = 500\ L$$

$$t_{1/2} = \frac{\ln(2)}{7\ h} = \frac{0.693}{7\ h} \cong 0.1\ h^{-1}$$

$$CL = V_d \cdot k_e = 500\ L * 0.1\ h^{-1} = 50\ L/h$$

$$CL_{hep} = CL - CL_{renal} = 50 - 5 = 45\ L/h$$

$$AUC_\infty = \frac{Dose}{CL} = \frac{400\ mg}{45\ L/h} = 8.9\ mg.h/L$$

(2) This drug is 99.9% protein bound. A displacement by a competitor by 0.2% resulted in 99.7% protein binding. Compute the oral bioavailability, assuming that the liver blood flow is 70 L/h and that no other physiological changes were involved).

In this case, the fraction unbound increases by 3-fold from 0.1% to 0.3%.

$$CL_{hep} = Q_H \cdot E$$
$$E = \frac{CL_{hep}}{Q_H} = \frac{45\ L/h}{70\ L/h} = 0.64$$
$$F = 1 - E = 1 - 0.64 = 0.36$$

For high extraction drug, $F \approx \frac{Q_H}{f_u \cdot CL_{int}}$, if $f'_u = 3 * f_u$, $F' = \frac{F}{3} = 0.33F = 0.33 * 0.36 = 0.12$. Oral bioavailability is 12%.