PHA5127 – Dose Optmization I
Case Study 4
Fall 2013

Question 1

The drug concentration entering and leaving the liver were 9.5 and 3.1 ng/mL, respectively. Assume that the liver blood flow is 1500 mL/min. Estimate the hepatic clearance in unit of L/h.

First, we compute the liver blood flow in L/h.

$$Blood\ flow = 1500\ \frac{mL}{min} * 60\frac{min}{h} * \frac{1\ L}{1000\ mL} = 90\frac{L}{h}$$

$$CL_{hep} = 90\frac{L}{h} * \frac{9.5 - 3.1\frac{ng}{mL}}{9.5\frac{ng}{mL}} = 61\frac{L}{h}$$

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Question 2

In two scenarios, you have the intrinsic clearance of 35,000 L/min vs. 0.35 L/min. With a plasma protein binding of 75% and a liver blood flow 70 L/min, compute the following:

1. Hepatic clearance for (i) high extraction drug and (ii) low extraction drug

$$CL_{hep} = \frac{Q_H * f_u * CL_{int}}{Q_H + f_u * CL_{int}} = \frac{70\ \frac{L}{min} * 0.25 * 35000 \frac{L}{min}}{70\ \frac{L}{min} + 0.25 * 35000\ \frac{L}{min}} = 69.4\ \frac{L}{min} \approx Q_H$$

Thus for high extraction drug, the hepatic clearance approximates hepatic blood flow.

$$CL_{hep} = \frac{Q_H * f_u * CL_{int}}{Q_H + f_u * CL_{int}} = \frac{70\ \frac{L}{min} * 0.25 * 0.35 \frac{L}{min}}{70\ \frac{L}{min} + 0.25 * 0.35\ \frac{L}{min}} = 0.087\ \frac{L}{min}$$

$$f_U * CL_{int} = 0.25 * 0.35\ \frac{L}{min} = 0.0875 \frac{L}{min}$$

$$CL_{hep} \approx f_U * CL_{int}$$

Thus for low extraction drug, the hepatic clearance is approximately the unbound drug percentage multiplied by the intrinsic clearance.

2. Infer situations wherein (i) plasma protein binding increased by 2-fold and (ii) blood flow is decreased by 1.5-fold. Explain the effect of these two scenarios, assuming that intrinsic clearance is consistent.

For high extraction drug,

(i) Change in protein binding will not affect hepatic clearance since $CL_{hep} \approx Q_H$.
(ii) A 1.5-fold decrease in blood flow will also result in 1.5-fold decrease in hepatic clearance.

For low extraction drug,

(i) An increase in protein binding by 2-fold will result in an increase in hepatic clearance by approximately 2-fold, since $CL_{hep} \approx f_U * CL_{int}$ and intrinsic clearance is unchanged.
(ii) Change in blood flow has no effect on hepatic clearance of low extraction drugs.

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Question 3 TRUE or FALSE

1 For low extraction drugs that are 99% protein bound, a displacement by a competitor by 1% to 98% protein binding will result in a two-fold increase in the steady-state total drug concentration (total of bound plus free drug).

False

2 For high-extraction antibiotics that are 99.9% protein bound, displacement by a competitor by 0.1% to 99.8% protein bound will often result in an increase in their pharmacological effects.

True

3 Plasma protein binding is independent of liver blood flow

True

4 A change in the volume of distribution is often due to a change in systemic clearance

False

5 When hepatic biotransformation enzymes are induced, only high extraction drugs are affected.

False

6 Plasma protein binding is synonymous to tissue binding

False