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.

\[
\text{Blood flow} = 1500 \, \text{mL/min} \times 60 \, \text{min/h} \times \frac{1 \, \text{L}}{1000 \, \text{mL}} = 90 \, \text{L/h}
\]

\[
\text{CL}_\text{hep} = 90 \, \frac{\text{L}}{\text{h}} \times \frac{9.5 - 3.1 \, \text{ng/mL}}{9.5 \, \text{ng/mL}} = 61 \, \frac{\text{L}}{\text{h}}
\]
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

\[
CL_{hep} = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}} = \frac{70 \frac{L}{min} \cdot 0.25 \cdot 35000 \frac{L}{min}}{70 \frac{L}{min} + 0.25 \cdot 35000 \frac{L}{min}} = 69.4 \frac{L}{min} \approx Q_H
\]

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

\[
CL_{hep} = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}} = \frac{70 \frac{L}{min} \cdot 0.25 \cdot 0.35 \frac{L}{min}}{70 \frac{L}{min} + 0.25 \cdot 0.35 \frac{L}{min}} = 0.087 \frac{L}{min}
\]

\[
f_u \cdot CL_{int} = 0.25 \cdot 0.35 \frac{L}{min} = 0.0875 \frac{L}{min}
\]

\[
CL_{hep} \approx f_u \cdot CL_{int}
\]

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 \(CL_{hep} \approx f_u \cdot CL_{int}\) and intrinsic clearance is unchanged.

(ii) Change in blood flow has no effect on hepatic clearance of low extraction drugs.
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