PHA 5127 Dose Optimization I
Case Study 2 Answer Key

1. Drug A and drug B are both lipophilic drugs and of low molecular weight. The plasma protein binding for drug A is 95% and for drug B is 5%. Both drug A and drug B have a tissue binding 75%. The same doses (200mg) of the two drugs are given to a healthy volunteer through i.v bolus at two different times (2 weeks of wash out period in between), assume V_p =3L, V_T =38L for both drugs.

1.1 Calculate the volume of distribution and initial free drug concentration of drug A and drug B.

Since both drug A and drug B are lipophilic drugs, V_p=3L, V_T=38L

$f_u(A) = 1 - 0.95 = 0.05$ $\qquad$ $f_{u,T}(A) = f_{u,T}(B) = 1 - 0.75 = 0.25$

$f_u(B) = 1 - 0.05 = 0.95$

$$V_d(A) = V_P(A) + V_T(A) \cdot \frac{f_u(A)}{f_{u,T}(A)} = 3 + 38 \cdot \frac{0.05}{0.25} = 10.6L$$

$$C_0(A) = f_u(A) \cdot \frac{Dose}{V_d(A)} = 0.05 \cdot \frac{200}{10.6} = 0.94 mg/L$$

$$V_d(B) = V_p(B) + V_T(B) \cdot \frac{f_u(B)}{f_{u,T}(B)} = 3 + 38 \cdot \frac{0.95}{0.25} = 147.4L$$

$$C_0(B) = f_u(B) \cdot \frac{Dose}{V_d(B)} = 0.95 \cdot \frac{200}{147.4} = 1.29 mg/L$$

1.2 Suppose the healthy volunteer got liver disease, which results in a two-fold decrease of plasma protein binding for both drug A and drug B (assume tissue binding remains the same), recalculate the volume of distribution and initial free drug concentration of drug A and drug B. What conclusions could you make?

$$f_u'(A) = 1 - \frac{0.95}{2} = 0.525$$

$$f_u'(B) = 1 - \frac{0.05}{2} = 0.975$$

$$f_{u,T}(A) = f_{u,T}(B) = 0.25$$

$$V_d'(A) = V_p(A) + V_T(A) \cdot \frac{f_u'(A)}{f_{u,T}(A)} = 3 + 38 \cdot \frac{0.525}{0.25} = 82.8L$$

$$C_0'(A) = f_u'(A) \cdot \frac{Dose}{V_d'(A)} = 0.525 \cdot \frac{200}{82.8} = 1.27 mg/L$$

$$V_d'(B) = V_p(B) + V_T(B) \cdot \frac{f_u'(B)}{f_{u,T}(B)} = 3 + 38 \cdot \frac{0.975}{0.25} = 151.2L$$

$$C_0'(B) = f_u'(B) \cdot \frac{Dose}{V_d'(B)} = 0.975 \cdot \frac{200}{151.2} = 1.29 mg/L$$

By looking at the initial free drug concentration before and after disease, we could see that for drug with high plasma protein binding (drug A), the initial free drug concentration changed a lot (approximately 35%), but for drug with low plasma protein binding (drug B), the initial free drug concentration remains the same (1.29 mg/L), therefore we came to the conclusion that the free drug levels of drugs with high plasma protein binding are more prone to be affected by changes in plasma protein binding.

2. TRUE (T) or FALSE (F)

T F Volume of distribution decreases with time because there will be less and less drug remaining in the body.

T F Lipophilic drugs will be able to distribute throughout the body, so their volume of distribution cannot be smaller than total body water volume (41L).

T F A water-soluble drug will pass across muscle membranes faster than across brain membranes (assume permeability-rate limitations).

T F Low molecular weight, lipophilic drugs are generally taken up fast by highly perfused organs.

T F A weak acid, whose unionized form shows a high partition coefficient, is likely to cross most membrane barriers.

T F Assume a drug is substrate of a specific transport protein. Transporters only eliminate drugs from the body.

T F Assume a drug is substrate of a specific transport protein. Transporters do not use energy.

T F If two patients differ in the V_d (volume of distribution); the patient with the smaller V_d will show a higher starting concentration C_0 after i.v bolus injection (the same dose for both patients).

T F Consider a patient with myocardial infarction. The increase in plasma alpha-1- glycoprotein will result in movement of free drug to plasma and an increase in fu_T and a decrease in the fu in plasma.

T F Assuming that a protein drug does not bind to plasma and tissue component, the volume of distribution is likely to be 41 liters.