**Case Study 2**

**PHA 5127**

**Answer Provided by Jeffrey Stark, Graduate Student**

**Warm Up Questions:**

1. True. Actually, the total volume of body water as we discussed last time:

$$V_d = V_p + V_T \cdot \frac{fu}{fu_T}$$

If there is no binding, fu = $fu_T$ = 1. Thus,

$$V_d = V_p + V_T \cdot 1 = 3L + 38L = 41L$$

2. This question is dangerous. Think before you answer. Remember that fu and $fu_T$ are independent of one another. According to the equation, above, all we can say is that fu is equal to $fu_T$. However, we know nothing of the magnitude of either unbound fraction. Therefore, the statement is false.

***<u>Case Study Questions</u>***

Digoxin/Quinidine

1.The clues are present in the background information.

Note that digoxin is said to be highly bound to tissue (especially cardiac muscle) and that quinidine has a higher affinity for tissue binding sites than digoxin. If both drugs are given at the same time, we would expect quinidine and digoxin to compete for the same binding sites. Due to its higher affinity, quinidine wins and this means more free digoxin in the tissues.

→ What happens to the $V_d$ of digoxin?

Displacing digoxin causes an increase in $fu_T$. So,

$$V_d = V_p + V_T \cdot \frac{fu(\leftrightarrow)}{fu_T(\uparrow)}$$

If no change takes place in fu, the ration of $\frac{fu}{fu_T}$ decreases and $V_d$ is smaller.

→ What happens if quinidine therapy is discontinued?

The tissue binding of digoxin increases to its normal range, $fu_T$ goes down, and $V_d$ increases.

2. If absorption is rapid, we can use an iv bolus equation. However, since all of the drug is not entering systemic circulation (F=0.68), we must include a bioavailability term in our calculation. Note: don't be confused by all of the "f's" used. Unfortunately, we use "f" for fraction unbound/bound and for bioavailability. We will add another "f" to our repertoire when we come to multiple dosing!

Iv bolus: $Cp_0 = \frac{D}{V_d}$

↓

oral dose: $Cp_0 = \frac{f \cdot D}{V_d}$

(fast absorption)

We can solve this for the dose D and plug in the values provided.

$$D = \frac{Cp_0 \cdot V_d}{f}$$

$$= \frac{(1.5ng/ml)\cdot(400L)}{(0.68)} \cdot \frac{1000mL}{1L} \cdot \frac{1mg}{10^{-6}ng}$$

= 0.8823 mg = 882.3 μg

So, approx. 900μg

3. Recall:

$$Cp(t) = Cp_0 \cdot e^{-k_e t} = \frac{D}{V_d \cdot e^{-k_e t}}$$

Again, we assumed rapid absorption and that the iv bolus equation is a good approximation. To use this equation, we must find $k_e$.

$$k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{36hr} = 0.01925hr^{-1}$$

Now that we have $k_e$, we must solve the Cp(t) expression for t. Since we are concerned about the lower extreme of the therapeutic range, Cp(t) = 0.5 ng/ml.

$$Cp(t) = Cp_0 \cdot e^{-k_a t}$$

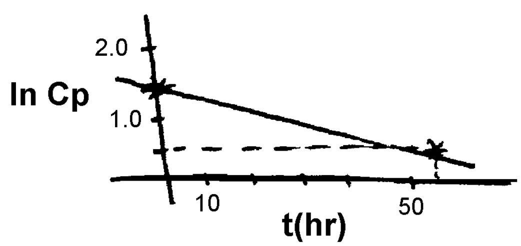
$$\frac{Cp(t)}{Cp_0} = e^{-k_e t}$$

$$\ln\left[\frac{Cp(t)}{Cp_0}\right] = -k_e t$$

$$t = -\frac{1}{k_e}\cdot\ln\left[\frac{Cp(t)}{Cp_0}\right]$$

$$= -\frac{1}{(0.01925hr^{-1})}\cdot\ln\left[\frac{0.5ng/ml}{1.5ng/ml}\right]$$

=5 7 hours




4. The first situation was sketched in the previous question. Now, let's consider the effects of quinidine co-therapy. As we concluded in question (1), when quinidine is given along with digoxin, we expect a smaller volume of distribution for digoxin due to less tissue binding. If the same dose of digoxin is given, how will this effect the initial concentration in the plasma.

Recall:

$$(\uparrow)Cp_0 \approx \frac{D(\leftrightarrow)}{V_d(\downarrow)}$$

Dividing by a smaller $V_d$ means a higher $Cp_0$.

The phrase "assume same Cl" was included for a reason. Although Cl and $V_d$ are independent kinetic parameters, we have the expression

$$Cl = k_e \cdot V_d$$

If only one of these (Cl or $V_d$) changes, there must also be a change in $k_e$. This will affect the slope of our graph. So, how does $k_e$ change when $V_d$ is smaller?

$$Cl = k_e \cdot V_d$$

$$(\leftrightarrow)\ (\uparrow)\ (\downarrow)$$

In order for Cl to remain constant, there must be a proportional increase in $k_e$. An increase in $k_e$ mans a faster rate of elimination → shorter $t_{1/2}$ → steeper slope in the graph.

5. To obtain the overall tissue binding, we start with the equation for $V_d$,

$$V_d = V_P + V_T \cdot \frac{fu}{fu_T}$$

Solving for $fu_T$ gives

$$fu_T = \frac{V_T \cdot fu}{(V_d - V_P)}$$

For this patient, $V_d$ = 400 and fu = 0.75.

So,

$$fu_T = \frac{(38L)(0.75)}{(400L - 3L)} = 0.0718$$

To find the fraction bound in tissue,

$$fb_T = 1 - fu_T$$

$$= 1\text{-}0.0718 = 0.928$$

Thus, 92.8% of the drug in the tissues is bound with only ~7% free.

Finding a similar expression for cardiac muscle is somewhat more complicated. To start, consider the fact that the total concentration of drug in the tissue (here, cardiac muscle) is the sum of the free and bound concentrations,

$$C_{card,tot} = C_{card,free} + C_{card,bound}$$

$$= C_{card,free} + fb_{card} \cdot C_{card,tot}$$

Solving for this $fb_{card}$ gives

$$fb_{card} = \frac{C_{card,tot} - C_{card,free}}{C_{card,tot}}$$

Recall that $C_{card,tot} = 70 \cdot Cp_{tot}$ (i.e. concentration in cardiac muscle is seventy times greater than that in plasma). Since we have more information on Cp (e.g. fu, fb, etc.), it will be easier to solve this problem using Cp. Now,

$$fb_{card} = \frac{70Cp_{tot} - C_{card,free}}{70 \cdot Cp_{tot}}$$

Since $Cp_{tot} = Cp_{free} + Cp_{bound}$,

$$fb_{card} = \frac{70 \cdot (Cp_{free} + Cp_{bound}) - C_{card,free}}{70 \cdot Cp_{tot}}$$

$$= \frac{70 \cdot Cp_{free} + 70 \cdot Cp_{bound} - C_{card,free}}{70 \cdot Cp_{tot}}$$

At equilibrium, $Cp_{free} = C_{card,free}$ (i.e. free concentrations are equal throughout the body). So,

$$fb_{card} = \frac{70 \cdot Cp_{free} + 70 \cdot Cp_{bound} - Cp_{free}}{70 \cdot Cp_{tot}}$$

$$= \frac{69 \cdot Cp_{free} + 70 \cdot Cp_{bound}}{70}$$

$$Cp_{free} = fu \cdot Cp_{TOT}$$

$$Cp_{bound} = fb \cdot Cp_{TOT} = (1 - fu) \cdot Cp_{TOT}$$

Inserting these relationships into the expression for $fb_{card}$ gives

$$fb_{card} = \frac{69 \cdot fuCp_{TOT} + 70 \cdot (1 - fu) \cdot Cp_{TOT}}{70 \cdot Cp_{TOT}}$$

$$= \frac{69 \cdot fu + 70(1 - fu)}{70}; \; fu = 0.75$$

$$=0.989$$

Thus, 98.9% of drug in cardiac muscle is bound.