For an iv bolus injection of a drug following a one-compartment body model, the initial concentration is

\[ C_{P_0} = \frac{D}{V_d} \]

where \( D \) is the dose and \( V_d \) is the volume of distribution. \( V_d \) relates the amount of drug in the body (\( D \)) to the plasma concentration (\( C_P \)). In other words, how large would your body have to be for a given amount of drug to yield a concentration equal to that seen in the plasma? Keep in mind, however, that \( V_d \) is not a true volume and the range is 7L (practical lower limit) to 40,000L.

Consider 500mg of two different drugs given to the same patient.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>( C_{P_0} )</th>
<th>( V_d )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>500 mg</td>
<td>10 mg/L</td>
<td>50 L</td>
</tr>
<tr>
<td>Drug B</td>
<td>500 mg</td>
<td>1 mg/L</td>
<td>500L</td>
</tr>
</tbody>
</table>

Calculation of \( V_d \): The expression above may be solved for \( V_d \) to give

\[ V_d = \frac{D}{C_{P_0}} = \frac{500mg}{10mg/L} = 50L \]

The 500 mg of Drug B appears to distribute into a larger volume, leaving less in the plasma. Thus, the plasma concentration is smaller. So, if the doses are the same, why is there a 10-fold difference in \( V_d \) for these two drugs in the same patient?

- \( C_P \) depends on dose and the extent of distribution. Drug distribution is a very complex process and depends on the perfusion of the tissues and various properties of the drug e.g. lipophilicity, ionization, binding, etc.

Many of the factors influencing drug distribution may be accounted for in a physiologic model which is based on the plasma and tissue volumes (\( V_P \) and \( V_T \)) and the degree of binding to plasma proteins and tissues:
\[
V_d = V_p + V_T \cdot \frac{f_u}{f_{uT}} = V_p + V_T \cdot K_p
\]

where \( f_u \) = unbound fraction of the drug in the plasma

and \( f_{uT} \) = unbound fraction of the drug in the tissue.

This rather simple expression may be used to illustrate the profound effect of plasma and tissue binding on the volume of distribution. When using this equation, remember two things:

1. no matter where you go, there you are
2. a small \( f_u \) or \( f_{uT} \) means that most of the drug is bound.

The fractions bound in the plasma and tissue are independent of each other (although net amounts are not) unless there are limited binding sites and saturation occurs. To calculate \( f_u \), simply divide the free cone by the total cone.

Note: \( V_T \) and \( f_{uT} \) can not be determined easily. For this discussion and any problem sets, assume that the tissue water volume (\( V_{TW} \)) is a sufficiently good approximation of \( V_T \).

\( V_{TW} = \text{total body water - plasma water} \)

\( = 41L - 3L = 38L \)

Sample problems.

1. Draw a simple diagram to illustrate the equilibrium between drug in the plasma and the tissue including both free and bound fractions.

Equilibrium between bound/unbound drug in plasma/tissue

\( fb \) is the fraction bound where

\[
fb = \frac{[\text{bound}]}{[\text{total}]} = 1 - f_u
\]
(2) For drug X, the volume of distribution is normally 35L and 80% of the drug is bound to plasma proteins. In patients with hypoalbuminemia, plasma protein binding is reduced to 60%. Calculate the expected volume of distribution.

For drug x, \( V_d = 35L \) and 80% plasma protein binding. What is \( V_d \) if binding is reduced to 60% in plasma? In order to calculate this, it must be assumed that no change occurs in the tissue binding. Recall the equation relating \( V_d \) to plasma/tissue binding:

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

In this problem \( fu \) changes from \( fu = 0.2 \) to \( fu = 0.4 \). However, before we can put this new value into the equation, we must find \( V_T/fu_T \) (or assume \( V_T = V_{TW} = 38L \) and solve for \( fu_T \)).

Solving for \( V_T/fu_T \):

\[
\frac{V_T}{fu_T} = \frac{V_d}{fu} - \frac{V_p}{fu} = \frac{1}{fu} (V_d - V_p) = \frac{1}{0.2} (35L - 3L) = 160L
\]

For \( V_T = V_{TW} = 38L \), \( fu_T \) is

\[
fu_T = \frac{V_T}{160L} = \frac{38L}{160L} = 0.24
\]

Now we can put in the new \( fu \) and determine the change in \( V_d \).

\[
V_d = V_p + V_T \cdot \frac{fu}{fu_T} = 3L + 38L \cdot \frac{0.4}{0.2}
\]

\[
= 3L + (160L)(0.4)
\]

\[
= 67L
\]

thus, \( V_d \) increased by almost a factor of 2.
(3) To obtain a plasma concentration of 10 mg/L for drug X in the question above, what dose would be required for the normal patient and the patient with lower plasma protein levels?

Want to achieve $C_{p0} = 10$ mg/L for each case in problem 2. Assume iv bolus.

Normal: $V_d = 35$

$$C_{p0} = \frac{D}{V_d}$$

or

$$D = C_{p0} \cdot V_d = (10 \text{mg} / \text{L})(35\text{L}) = 350\text{mg}$$

Hypoalbuminemia: $V_d = 67\text{L}$

$$D = C_{p0} \cdot V_d = (10 \text{mg} / \text{L})(67\text{L}) = 670\text{mg}$$

**Note:** This adjustment in dosage is for a single dose given to reach a target plasma concentration. Nothing should be stated or assumed (yet) about the dosage for continued drug therapy. Steady-state levels in multiple dosing depend on clearance NOT $V_d$.

(4) Determine the fraction of warfarin bound in tissue. $V_d$ is 10 L and the fraction unbound in plasma is 0.005.

The $V_d$ for warfarin is 10 L with the unbound fraction in plasma being 0.005. (Note: Handout stated “bound fraction”. Make this correction). Determine the bound fraction in tissue. Returning to the equation:

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

To determine the fraction bound, we must first find $fu_T$. In order to do this, we assume $V_T = V_{TW}$. Solving this equation for $fu_T$ gives

$$fu_T \cdot V_d = fu_T \cdot V_p + V_T \cdot fu$$

$$fu_T (V_d - V_p) = V_T \cdot fu$$

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

Putting in the values,
The fraction bound is then
\[ f_{bT} = 1 - f_{uT} = 1 - 0.027 = 0.973 \]

Thus, 97% of the warfarin in tissues is bound.

(5) Phenytoin and valproic acid have a high degree of plasma protein binding. When both drugs are given at the same time, valproic acid, which has a higher affinity for the binding site, displaces part of the bound phenytoin. What effect does this have on the volume of distribution of phenytoin?

Let \( x = \text{phenytoin}, \ O = \text{valproic acid} \)

(a)

(b)

If valproic acid displaces phenytoin at the binding sites on plasma proteins, \( f_u \) of phenytoin increases. Thus, \( V_d \) of phenytoin will also increase: \( (\leftrightarrow) = \text{no change} \)

\[
V_d (\uparrow) = V_p (\leftrightarrow) + V_r (\leftrightarrow) \times \frac{f_u(\uparrow)}{f_{uT}(\leftrightarrow)}
\]
(6) Changes in fu are most important for highly bound drugs. How does an increase in fu effect $V_d$ and/or the resulting $C_p$ when fu is initially very small?

Effects of a change in fu on $V_d$ and $C_p$ when drug is extensively bound to plasma proteins. The following diagram is from the book by Rowland and Tozer (p. 498)

![Diagram showing the relationship between fu and Vd, with curves for different fu values.]

So what is this diagram telling us?

- When there is a high degree of plasma protein binding, an increase in fu of 100 or 200% does not cause as much a change in $V_d$ as is seen when plasma protein binding is less extensive. If $V_d$ does not change dramatically, while there may be a slight decrease in overall concentration (recall: $\downarrow C_p = \frac{D}{V_d}$), there will be more free drug. Thus a change in fu from fu = 0.01 to fu = 0.2 (due to e.g. displacement by another drug having a higher affinity for the binding sites on plasma proteins) could be compared to a doubling of the dose. Again, $V_d$ is not the only consideration and the effects of binding will be addressed when we discuss clearance.

Let’s put some numbers in the $V_d$ expression to illustrate this. Consider a drug with high tissue binding, fuT = 0.1, and compare the $V_d$ values which result when fu in plasma is 0.5, 0.1, 0.01, and 0.005 and when each is increased by a factor of 2.

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

$$= 3L + 38L \cdot \frac{fu}{0.1}$$

<table>
<thead>
<tr>
<th>fu</th>
<th>Vd(L)</th>
<th>New fu</th>
<th>New Vd(L)</th>
<th>% increase in $V_d$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>193</td>
<td>1.0</td>
<td>383</td>
<td>98.45</td>
</tr>
<tr>
<td>0.1</td>
<td>41</td>
<td>0.2</td>
<td>79</td>
<td>92.68</td>
</tr>
<tr>
<td>0.01</td>
<td>6.8</td>
<td>0.02</td>
<td>10.6</td>
<td>55.88</td>
</tr>
<tr>
<td>0.005</td>
<td>4.9</td>
<td>0.01</td>
<td>6.8</td>
<td>38.78</td>
</tr>
</tbody>
</table>

* % increase = \[ \frac{\text{new } V_d - \text{old } V_d}{\text{old } V_d} \]

Thus, when fu is very small, fluctuation in fu has less effect on $V_d$ than when there is less initial binding to plasma proteins.