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

\[ C_{p0} = \frac{D}{V_d} \]

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_{p0} )</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>500 L</td>
</tr>
</tbody>
</table>

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

\[ V_d = \frac{D}{C_{p0}} = \frac{500\text{mg}}{10\text{mg/L}} = 50L \]

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 \( f_{uT} \) = " " " " " " " " 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 conc by the total conc.

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 \( V_T \).

\[
V_{TW} = \text{total body water} - \text{plasma water} = 41L - 3L = 38L
\]

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.

(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.

(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?

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

(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?

(6) Changes in \( f_u \) are most important for highly bound drugs. How does an increase in \( f_u \) effect \( V_d \) and/or the resulting \( C_p \) when \( f_u \) is initially very small?