Volume of distribution and the effects of plasma protein and tissue binding

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

$$Cp_0 = \frac{D}{Vd}$$

where D is the dose and Vd is the volume of distribution. Vd relates the amount of drug in the body(D) to the plasma concentration(Cp). 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 Vd 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.

	Dose	Cp_0	Vd
Dug A	500 mg	10 mg/L	50 L
Drug B	500 mg	1 mg/L	500 L

Calculation of Vd: The expression above may be solved for Vd to give

$$Vd = \frac{D}{Cp_0} = \frac{500mg}{10mg/L} = 50L$$

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 Vd for these two drugs in the same patient?

-Cp 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 an the plasma and tissue volumes (V_P and V_T) and the degree of binding to plasma proteins and tissues:

$$Vd = V_P + V_T \cdot \frac{f_u}{f_{uT}} = V_P + V_T \cdot K_p$$

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

and (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}= total body water – plasma water

= 41L – 3L = 38L