Lecture Notes on 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

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

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 (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 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.

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

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

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

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 V_d 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:

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

where fu = unbound fraction of the drug in the plasma

and fu_T = 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
and (2) a small fu or fu_T 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 fu, simply divide the free cone by the total cone.

Note: V_T and fu_T 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