

Pharmacokinetics made easy 2

VOLUME OF DISTRIBUTION

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Volume of distribution is one of the two major independent pharmacokinetic parameters. The other (clearance) was dealt with in the previous article (Aust Prescr 1988;11: 12-3).

What is volume of distribution (V_D)?

It is not a real 'volume'. It is the parameter relating the concentration of a drug in the blood to the total amount of the drug in the body. For example, if a drug has a blood concentration of 10 mg/L when there is 1000 mg of the drug in the body, the volume of distribution would be 100 L, i.e. dissolving 1000 mg in 100 L would give a concentration of 10 mg/L.

$$V_D = \frac{\text{total amount of drug in body}}{\text{blood or plasma concentration}} \quad \text{equation 1}$$

If volume of distribution is an 'imaginary' volume, what is it determined by? The major determinant is the relative avidity of the drug for tissue components as compared with blood. If a drug is very tightly bound by tissues and not by blood, most of the drug in the body will be held in the tissues and very little in the plasma, so that the drug will appear to be dissolved in a large volume and V_D will be large. Examples of drugs like this are the lipid soluble bases such as imipramine and chlorpromazine. Conversely, if the drug is tightly bound to plasma proteins and not to tissues, V_D can be very close to blood volume as is the case for warfarin.

Some examples of volumes of distribution are:

- warfarin 8 L,
- theophylline 30 L,
- quinidine 150 L,
- digoxin 420 L,
- imipramine 2100 L.

How is V_D measured?

The simplest method is illustrated in Fig. 1. A dose of 200 mg of a drug is given at time zero, blood samples collected and the drug concentrations measured. When the logarithm of drug concentration is plotted against time, a straight line results. If this is extrapolated back to time zero it gives the blood drug concentration before any drug is eliminated, i.e. when the whole dose (200 mg) is still in the body. In this case, the extrapolated concentration at time zero is 10 mg/L and the V_D is 20 L.

What is V_D used for?

In the previous article (Clearance. Aust Prescr 1988;11:12-3) we saw that clearance determines the drug concentration at steady state during continuous administration. If we just start with the maintenance dose, it takes some time to accumulate to steady state. To get close to steady state more quickly, a loading dose is often used and V_D is the determinant of the size of the loading dose. In the example given above, if we want to

get quickly to 10 mg/L we have to give enough drug to give a concentration of 10 mg/L when 'dissolved' in the 20 L volume of distribution — 200 mg in this example. The loading dose is given to 'fill up' the volume of distribution. Thus,

$$\text{Loading dose} = V_D \times \text{desired concentration} \quad \text{equation 2}$$

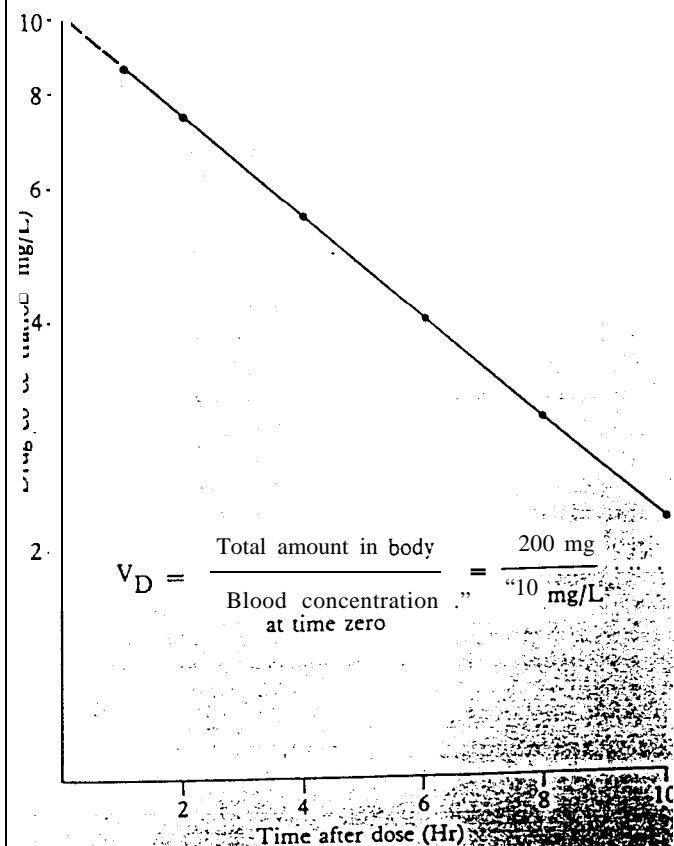
$$200 \text{ mg} = 20 \text{ L} \times 10 \text{ mg/L}$$

An example is calculating the loading dose of theophylline at the start of a theophylline infusion. The V_D of theophylline averages 0.5 L/kg (35 L in a 70 kg patient) so that the loading dose to achieve a plasma concentration of 10 mg/L (at the

Fig. 1.

Determination of 'D':

A dose of 200 mg was given and the first sample taken one hour later. Note that the drug concentration scale is logarithmic.



lower end of the therapeutic range) is $0.5 \text{ L/kg} \times 10 \text{ mg/L} = 5 \text{ mg/kg}$ or 350 mg in our patient. As the actual range of V_D in a number of patients is 0.3-0.7 L/kg, the actual concentration could be in the range 7-17 mg/L. The use of the loading dose is illustrated in Fig. 2.

diazepam concentrations and anticonvulsant effect follow blood diazepam concentrations. Concentrations and effect fall rapidly initially due to redistribution to other tissues and fitting can recur within 2-4 hours if more drug is not given, even though the elimination half-life is very long.

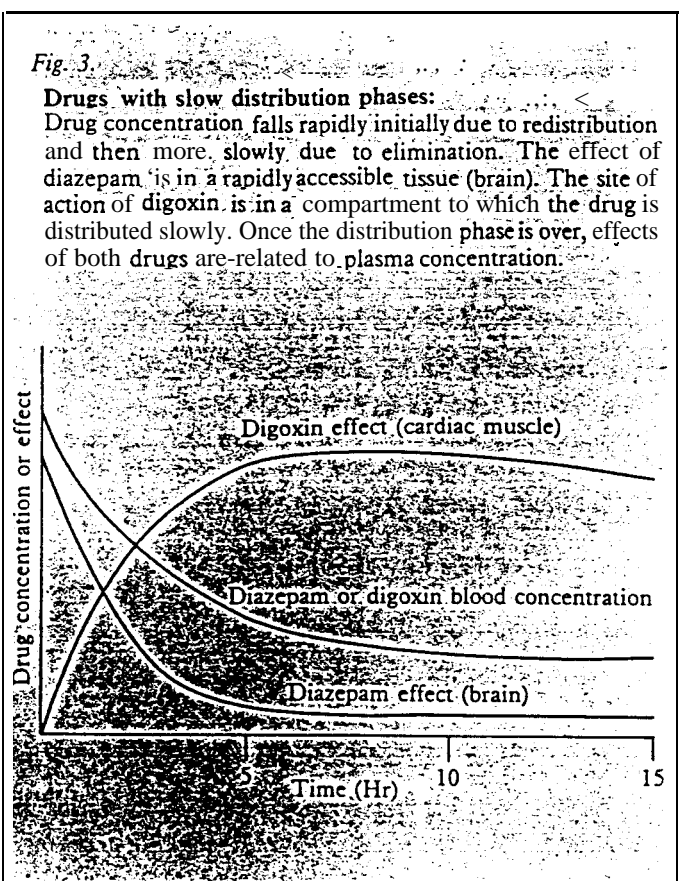
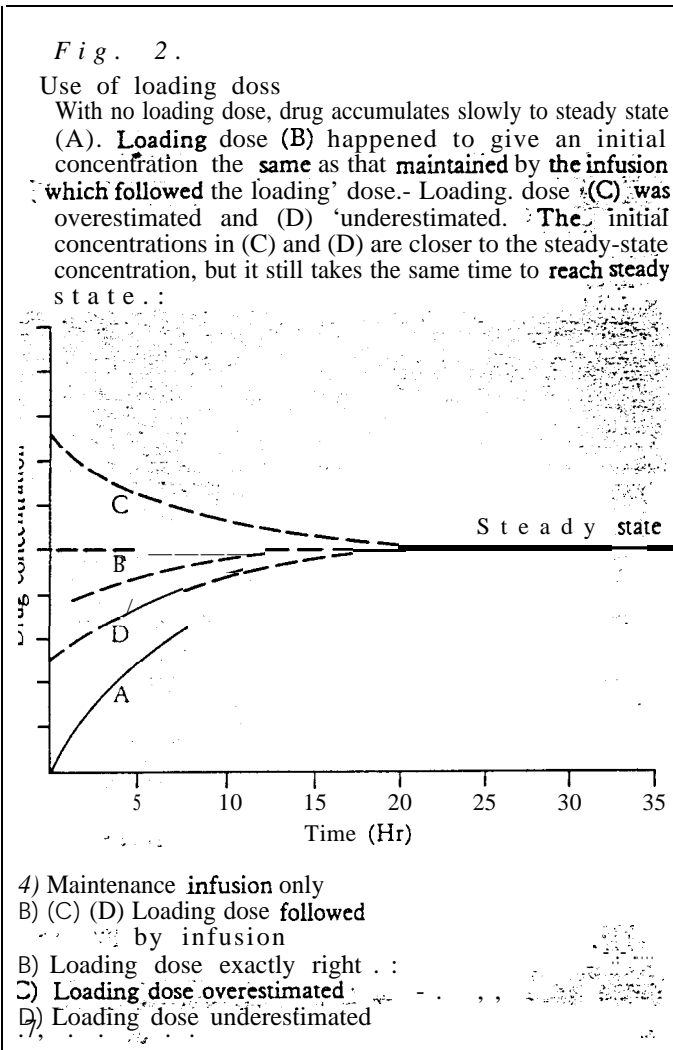
If the site of action for a toxic effect is in a rapidly accessible tissue compartment, the initial high concentrations after an intravenous bolus before redistribution occurs can cause serious toxic effects. In this case, the rate of intravenous injection must be slowed down to allow distribution to occur while the drug is being administered. Examples are the intravenous use of theophylline and lignocaine.

(b) Digoxin given intravenously. In this case digoxin distributes slowly to the site of action (inotropic effect) in the cardiac muscle. The effect increases as blood concentrations are decreasing due to redistribution of digoxin into less accessible tissues including the site of action in cardiac muscle. This has two consequences:

- (i) Even if digoxin is injected intravenously it will take about 6 hours to exert the full effect giving no advantage of intravenous over oral administration. Therefore, loading with digoxin is best carried out with divided oral doses at least 6 hours apart so that the full effect of each aliquot can be assessed before more is given.
- (ii) In the first 6-8 hours after administration, digoxin plasma concentrations bear no relationship to effect. Samples for plasma concentration monitoring must therefore always be taken at least 8 hours after a dose and preferably just before a dose.

In summary:

- (i) volume of distribution is the parameter used to calculate loading doses of drugs; and
- (ii) the rate of distribution from or to the site of action can be the major determinant of the duration or rate of onset respectively of drug effects.



Is the rate of distribution from blood to tissues important?

A drug is either injected directly into the blood or absorbed from the gut or injection site, etc. into the blood so that the immediate volume of distribution is blood volume and concentrations are initially high. The drug then distributes from blood into various tissues at a rate and to an extent which depends on the perfusion of the tissue and the avidity with which the components of the particular tissue bind the drug. Some tissues such as the brain are highly perfused and the drug distributes very rapidly from the blood into them. Distribution to less highly perfused and/or accessible tissues such as skeletal muscle and fat occurs more slowly. Fig. 3 illustrates how this can have opposite effects depending on whether the site of action of a drug is in a rapidly or slowly perfused tissue. Diazepam and digoxin have rather similar distribution characteristics, with blood concentrations falling relatively rapidly over 4-6 hours as the drug is redistributed from blood and readily accessible tissues into tissues such as muscle and fat. Both then have slow elimination phases with half-lives of 1-2 days.

Consider,

(a) Diazepam used intravenously in status epileptics. The site of action is in the brain which is highly perfused so that brain