PHAR 7632 Chapter 18

Distribution

Student Objectives for this Chapter

- To understand and describe the processes by which drugs are distributed throughout the body
- To understand the effect of protein binding on drug distribution and methods by which protein binding is measured

Drug distribution means the reversible transfer of drug from one location to another within the body. Once a drug has entered the vascular system it becomes distributed throughout the various tissues and body fluids in a pattern that reflects the physiochemical nature of the drug and the ease with which it penetrates different membranes. The ONE COMPARTMENT model assumes rapid distribution but it does not preclude extensive distribution into various tissues.

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PHAR 7632 Chapter 18

Distribution

Drug Distribution Patterns

Distribution can be thought of as following one of four types of patterns.

1) The drug may remain largely within the vascular system. Plasma substitutes such as dextran are an example of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.

2) Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.

3) A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action. Iodine is concentrated by the thyroid gland. The antimalarial drug chloroquine may be present in the liver at concentrations 1000 times those present in plasma. Tetracycline is almost irreversibly bound to bone and developing teeth. Consequently tetracyclines should only be given to young children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth. Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue. Another example is the distribution of a bone scan agent, ^{99m}Tc-MDP. A normal scan shows accumulation in bone, at the injection site and 'maybe' in organs of elimination (Saha, 1984). Polychlorinated biphenyls, PCB, are highly lipid soluble and extensively distributed into fat tissue, maybe, with very little leaving these tissues. DDT, dicophane, which is also very lipid soluble has very restricted use. Remember *Silent Spring* by Rachel Carson, 1962.

4) Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility. The highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.

Pattern 4 is the most common being a combination of patterns 1, 2 and 3.
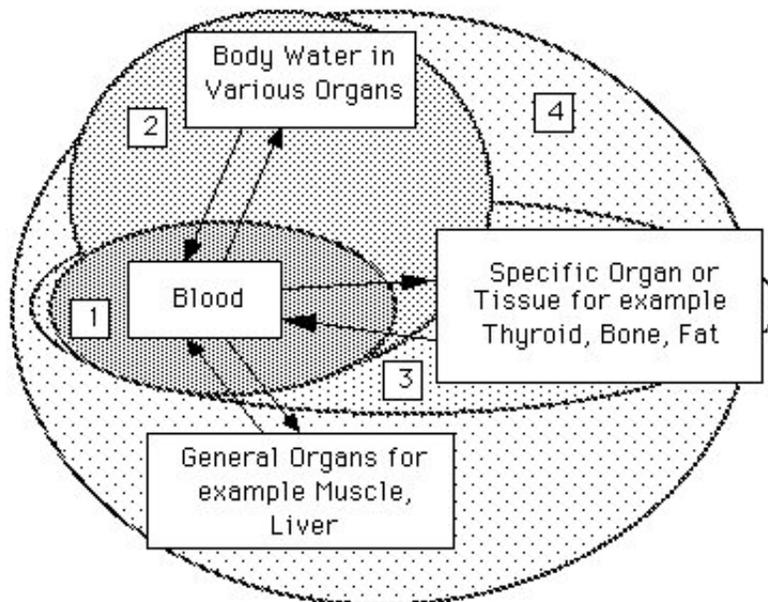
Diagram 18.2.1 Representing Various Volumes Distribution Patterns

Table 18.2.1 Apparent Volumes of Distribution (Rowland and Tozer, 1980)

Drug	Liters/Kg	Liter/70 Kg
Chloroquine	94 - 250	6600 - 17500
Nortriptyline	21	1500
Digoxin	7	500
Lidocaine	1.7	120
Theophylline	0.5	35
Tolbutamide	0.11	8

A useful indicator of the type of pattern that characterizes a particular drug is the apparent volume of distribution.

A value of V in the region of 3-5 liter (in an adult) would be compatible with pattern 1. This is approximately the volume of plasma. Pattern two would be expected to produce a V value of 30 to 50 liter, corresponding to total body water. Agents or drugs exhibiting pattern 3 would exhibit very large values of V if the drug concentration effect was acting on most of the dose. Chloroquine has a V value of approximately 17,000 liter. Drugs following pattern 4 may have a V value within a wide range of values. These patterns of variation have been used to determine body fluid volumes.

Table 18.2.2 Volumes Measured by Various Test Materials

Fluid substances	Volume (liter)	Test
Extracellular Fluid	13-16	Inulin, Na^{23}, Br^-, I^-
Plasma	3-4	Evans blue, I^{131} albumin, dextrans
Interstitial fluids	10-13	
Intracellular fluids	25-28	
Total body water	40-46	Antipyrine, D_2O, ethanol

References

- Rowland, M. and Tozer, T.N. 1980 **Clinical Pharmacokinetics: Concepts and Applications**, Lea & Febiger, Philadelphia, PA, p 44
- Saha, G.B. 1984 Fundamentals of Nuclear Pharmacy, 2nd ed. P239 Fig 12-26

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PHAR 7632 Chapter 18

Distribution

Factors Affecting Drug Distribution

Table 18.3.1 Factors Affecting Distribution

Rate of distribution -	Membrane permeability
	Blood perfusion
Extent of Distribution -	Lipid Solubility
	pH - pKa
	Plasma protein binding
	Intracellular binding

Rate of distribution

Membrane permeability

We have already covered some material about membrane permeability. The capillaries are typically lined with endothelium whose cells overlap, though to a lesser degree than epithelial cells. Also, the junctions between cells are discontinuous. Capillary walls are quite permeable. Lipid soluble drugs pass through very rapidly. Water soluble compounds penetrate more slowly at a rate more dependent on their size. Low molecular weight drugs pass through by simple diffusion. For compounds with molecular diameter above 100 Å transfer is slow.

For drugs which can be ionized the drug's pKa and the pH of the blood will have a large effect on the transfer rate across the capillary membrane.

There are two deviations to the typical capillary structure which result in variation from normal drug tissue permeability.

i) Permeability is greatly increased in the renal capillaries by pores in the membrane of the endothelial cells, and in specialized hepatic capillaries, known as sinusoids which may lack a complete lining. This results in more extension distribution of many drugs out of the capillary bed.

ii) On the other hand brain capillaries seem to have impermeable walls restricting the transfer of molecules from blood to brain tissue. Lipid soluble compounds can be readily transferred but the transfer of polar substances is severely restricted. This is the basis of the "blood-brain" barrier.

Membrane permeability tends to restrict the transfer and distribution of drugs once they are delivered to the tissue. The other major factor which determines the rate of drug distribution is blood perfusion.

Blood perfusion rate

The rate at which blood perfuses to different organs varies widely.

Table 18.3.2 Blood Perfusion Rate (Shargel and Yu, 1985)

Organ	Perfusion Rate (ml/min/ml of tissue)	% of cardiac output
Bone	0.02	5
Brain	**0.5**	**14**
Fat	0.03	4
Heart	**0.6**	4
Kidneys	**4.0**	**22**
Liver	**0.8**	**27**
Muscle	0.025	**15**
Skin	0.024	6

Total blood flow is greatest to brain, kidneys, liver, and muscle with highest perfusion rates to brain, kidney, liver, and heart. It would be expected that total drug concentration would rise most rapidly in these organs. Certain organs such as the adrenals (1.2/0.2%) and thyroid (2.4/1%) also have large perfusion rates.
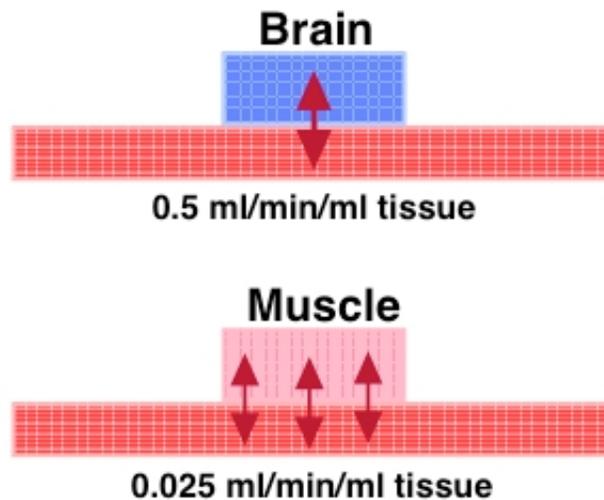
Diagram 18.3.1 Comparison between Drug transfer to Brain and Muscle

As an example; thiopental gets into the brain faster than muscle, whereas, penicillin gets into muscle more quickly than it gets into brain.

i) Thiopental is only partly ionized and passes into the brain or muscle easily. Perfusion limits the transport. Since brain has a higher perfusion rate the thiopental can transfer in and out more quickly.

ii) Penicillin is quite polar and is thus slowly permeable. Permeability limited transfer is faster in muscle as muscle capillaries are less restrictive. Thus transfer of penicillin is faster in muscle than brain.

In brain, perfusion or membrane permeability limits drug transport or distribution. Thiopental diffuses readily, thus perfusion limits its distribution. Since perfusion is higher to the brain than to muscle, transport to the brain is faster. Penicillin less readily diffuses thus it is diffusion which limits penicillin distribution. Muscle diffusion is easier thus distribution into muscle is faster for penicillin than distribution into brain.

References

- Shargel, L. and Yu, A.B.C. 1985 **Applied Biopharmaceutics and Pharmacokinetics**, 2nd ed., Appleton-Century-Croft, Norwalk, CT, Table 5-1, p 52

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PHAR 7632 Chapter 18

Distribution

Extent of Distribution

We can now consider factors which alter the extent of drug distribution

Plasma protein binding

Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution.

Proteins involved

Although drugs are bound to many macromolecules, binding to plasma protein is the most common. Of these plasma proteins, albumin, which comprises 50 % of the total proteins binds the widest range of drugs. Acidic drugs commonly bind to albumin, while basic drugs often bind to $alpha_1$-acid glycoproteins and lipoproteins. Many endogenous substances, steroids, vitamins, and metal ions are bound to globulins.

Table 18.4.1 Proteins with Potential Binding Sites for Various Drugs (Niazi, 1979 p103)

Drugs	Binding Sites for Acidic Agents
Bilirubin, Bile acids, Fatty Acids,Vitamin C, Salicylates, Sulfonamides,Barbiturates, Phenylbutazone,Penicillins, Tetracyclines, Probenecid	Albumins
	Binding Sites for Basic Agents
Adenisine, Quinacrine, Quinine,Streptomycin, Chloramphenicol,Digitoxin, Ouabain, Coumarin	Globulins, $alpha_1$, $alpha_2$, $beta_1$, $beta_2$, gamma

Forces involved

Groups on the protein molecules that are responsible for **electrostatic interactions** with drugs include:

the $-NH_3^+$ of lysine and N⁻ terminal amino acids,

the $-NH_2^+-$ of histidine, the - S⁻ of cysteine, and

the - COO⁻ of aspartic and glutamic acid residues.

In order to achieve reasonably stable complexes, however, it is likely that in most cases the initial electrostatic attraction is reinforced at close range by **van der Waal's forces** (dipole-dipole; dipole-induced dipole; induced dipole-induced dipole) and **hydrogen bonding**.

This is suggested by the frequently crucial role of protein configuration in the binding phenomenon. Agents which denature protein may cause the release of bound drug.

Often there may be competition between drugs, in which agents that are bound very tightly, such as coumarin anticoagulants, are able to displace less tightly bound compounds from their binding sites.

Table 18.4.2 Percent Unbound for Selected Drugs (Rowland and Tozer, 1989; Niazi, 1979 p101)

Drug	Percent Unbound (100 * fu)
Caffeine	90
Digoxin	77
Gentamicin	50
Theophylline	85
Phenytoin	13
Diazepam	4
Warfarin	0.8
Phenylbutazone	5
Dicumarol	3

Slight changes in the binding of highly bound drugs can result in significant changes in clinical response or cause a toxic response. Since it is the free drug in plasma which equilibrates with the site of pharmacological or toxic response, a slight change in the extent of binding, such as 99 to 98 % bound, which can result in an almost 100 % change in free concentration, can cause very significant alteration in response. For a large number of drugs, including warfarin and phenytoin, drug response will be dependent on free drug concentration. Alteration of free concentration by drug interaction or disease state can alter the intensity of action of these drugs. Examples include phenylbutazone and salicylates displacing tolbutamide to give an increased effect, hypoglycemia.

As you can see from Table 18.4.2, the extent of protein binding can vary considerably from one drug to another.

Protein binding determination

Spectral changes

Most drugs have distinct UV spectra because of the conjugated chromophores in the molecule. When a drug interacts with a protein the UV or visible spectrum may be changed because of alterations in the electronic configuration. These alterations can be quantitated and used to determine the extent of binding. Changes in fluorescence spectra can be used in the same way. Spectra for warfarin (Chignell 1973).

Gel filtration

This involves the use of porous gels that are molecular sieves. They separate components on the basis of size. Low molecular weight drugs are held on the gel whereas bound drug and protein are washed through.

Equilibrium dialysis
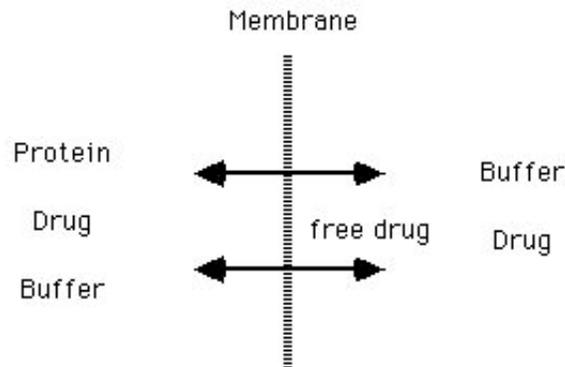
Diagram 18.4.1 Equilibrium Across a Semi-permeable Membrane

The protein solution (e.g. plasma) containing drug and a buffer solution are placed on opposite sides of a dialysis membrane.

After a sufficient time (maybe 12- 24 hours), free drug concentration will be the same on either side of the membrane. Protein binding can be determined by measuring the concentration of drug on either side of the membrane. On left the concentration will involve free and bound drug, whereas on the right there is no binding and the concentration will equal to the free drug concentration.

Ultrafiltration
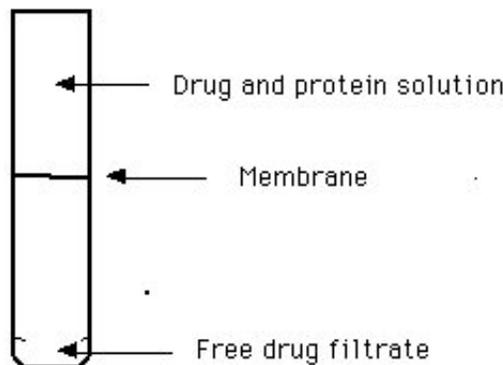
**Diagram 18.4.2 Ultrafiltration as a Method of Measuring Protein Binding**

A quicker method of separating free and bound drug is the ultrafiltration method. Drug and protein solution are placed in a filter membrane and liquid containing free drug is forced through the membrane by centrifugation.

Protein binding equilibria

With one type of binding site, protein binding can be described mathematically by the equation:
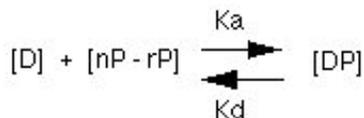
With [D] free drug concentration, [P] total protein concentration with 'n' binding sites per molecule, thus [nP] is the total concentration of protein binding sites and [rP] = [DP] is the concentration of bound drug or bound protein with r drug molecules bound per protein molecule. Typically there may be 1 - 4 binding sites per protein molecule.
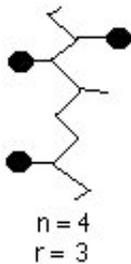
$$Ka = \text{association constant} = \frac{[\text{Concentration Bound}]}{[D] \bullet [\text{Protein Free}]} = \frac{[rP]}{[D] \bullet [nP - rP]}$$

$$\text{where } r = \frac{[DP]}{[P]_{total}} = \frac{[\text{Drug Bound}]}{[\text{Total Protein}]}$$

Plots

This can be rearranged to give

$$\frac{r}{[D]} = n \bullet Ka - r \bullet Ka$$

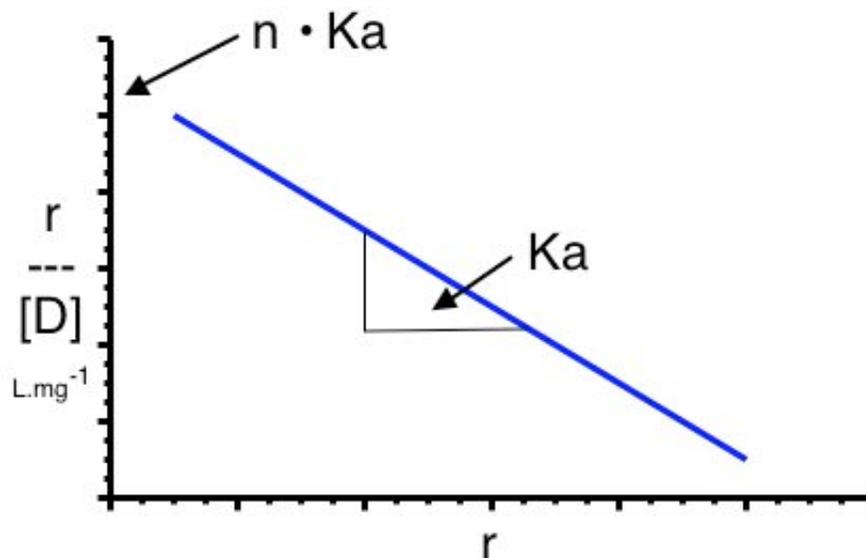thus plotting r/[D] versus r should give a straight line. This is called a **Scatchard** plot.

Figure 18.4.3 Scatchard plot of r/[D] versus r

Alternate rearrangement gives $\dfrac{1}{r} = \dfrac{1}{(n \bullet Ka \bullet [D])} + \dfrac{1}{n}$ Thus a plot of 1/r versus 1/[D] should also give a straight line. This is the double reciprocal plot.
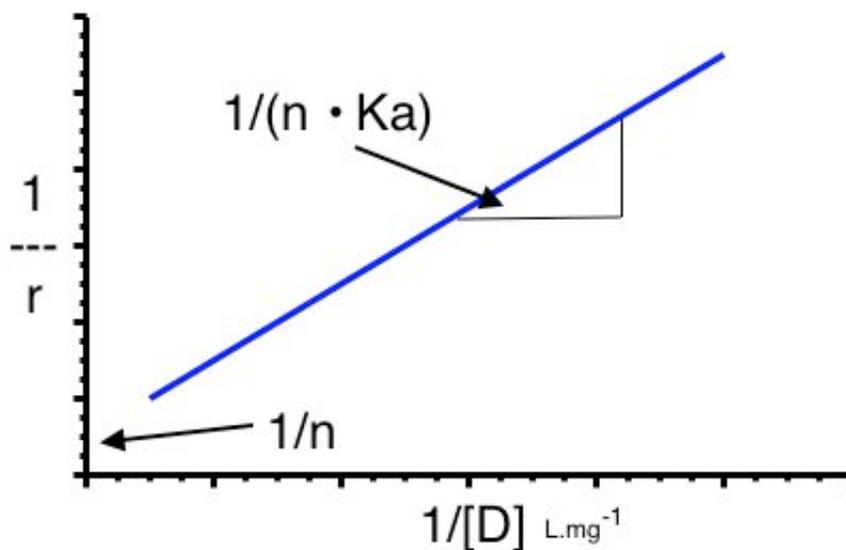

Figure 18.4.4 Double reciprocal plot of 1/r versus 1/[D]

With **one type of binding site** these plots produce straight lines which can be used to determine Ka and n values. With more than one

type of binding site, these plots are curved (Chignell, 1973)).

Tissue localization of drugs

In addition to plasma protein binding, drugs may bind to intracellular molecules. Certain of these may be actual drug receptors, and the interaction that occurs may represent the molecular basis of the pharmacological action.

The affinity of a tissue for a drug may be for any of several reasons, including binding to tissue proteins (such as albumin) or to nucleic acids, or in the case of adipose tissue, dissolution in the lipid material.

The concentration of chloroquine in the liver is due to the binding of the drug to DNA. Barbiturates distribute extensively into adipose tissue, primarily because of their high lipid solubility. Tetracyclines bind to bone thus should be avoided in young children or discoloration of permanent teeth may occur.

Unlike plasma binding, tissue binding of a drug cannot be measured directly as handling of the tissue results in disruption of the binding. This doesn't mean that tissue binding and changes in tissue binding are not important.

References

- Niazi, S. 1979 **Textbook of Biopharmaceutics and Clinical Pharmacokinetics**, Appleton-Century-Crofts, New York, NY ISBN 0-8385-8868-9
- Rowland, M. and Tozer, T.N. 1989 **Clinical Pharmacokinetics: Concepts and Applications**, 2nd ed., Lea & Febiger, Philadelphia, p 141
- Chignell, C.F. 1973 *Ann. New York Acad. Sci.*, **226**, p49, 53

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PHAR 7632 Chapter 18

Distribution

Other Distribution Considerations

Weight considerations

The apparent volume of distribution will often be proportional to the total body weight of a patient. In fact many V values found in the literature will be given as so many liter per kilogram total body weight. The assumption made is that the body composition is unchanged on a percentage basis, thus distribution will be identical no matter what the patient weighs. This works within some limits. For example body composition of the very young and the very old may be quite different from 'normal', that is the average subject in whom the parameter values may have been originally determined. The young and the old will be discussed in more detail later. Another group of patients in which body composition may be greatly altered from `normal' is the obese. These patients have a higher proportion of adipose tissue and lower percentage of water. Thus for drugs which are relatively polar, volume of distribution values may be somewhat lower than the total body weight may suggest. For example the apparent volume of distribution of antipyrine is 0.62 l/kg in normal weight subjects but 0.46 l/kg in obese patients (Abernethy et al., 1981). Other drugs such as digoxin and gentamicin are also quite polar and tend to distribute into water rather than adipose tissue.

Protein binding interactions

The role of protein binding in drug interactions can be quite involved (Rowland and Tozer, 1989). Although drugs may well displace each other from common binding sites, the clinical (and pharmacokinetic) importance of these interactions may require considerable investigation. For these effects to be important one drug must be extensively protein bound, while the displacer must have a high affinity for the same binding site. Therapeutically the major criteria is the free drug concentration. One result of a drug interaction is to tend to produce an increase in free drug concentration, however, that will cause an increase in elimination and thus an overall reduction in total drug concentration, potentially maintaining the free concentrations unchanged.

References

- Abernethy, D.R., Greenblatt, D.J, Divoll, M. et al. 1981 Alterations in drug distribution and clearance due to obesity, *J.P.E.T.*, **217**, p681-85
- Rowland, M and Tozer, T.N. 1989 **Clinical Pharmacokinetics**, Lea & Febiger, Philadelphia, pp 260-270

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