The Absorption and Distribution of Drugs

THE ABSORPTION AND DISTRIBUTION OF DRUGS

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Preface

A knowledge of the absorption and the distribution of drugs is required for understanding their action, for designing new preparations, for improving drug safety and for minimizing undesirable side-effects. The object of this work is to provide an outline and perhaps some correlation of the extensive researches in this field which have been reported in the last few years. A completely comprehensive treatment would require several volumes and so a selection has had to be made and in general only established drugs have been included in the survey.

The book is aimed towards research workers, practitioners in medicine and pharmacy and others engaged in medical science and in the production of medicinal materials. It is hoped that it will also provide a basis for courses for senior undergraduate and postgraduate students in pharmacy and medicine and will present a key to the literature in this field to newcomers and provide a survey for those already familiar with the subject.

The material has been arranged according to a physicochemical rather than a therapeutic scheme. In this way it is hoped that the generalities of the effects of physical properties on absorption and distribution will be emphasized. The most important single property in this respect is the ionizing capacity of a drug; the chapters have therefore been grouped into sections on anionic, cationic and uncharged drugs at neutral pH. Within the charge groups, drugs have been further subdivided according to the ring systems in the molecules. From the sections on individual drugs it is then apparent that many anionic drugs are well absorbed from the stomach to give high plasma levels which may decline rapidly due to specific renal tubular secretion. Many cationic drugs are absorbed from the intestine but, owing to rapid absorption into the tissues, give only low plasma concentrations. Many uncharged drugs despite low water solubilities are readily absorbed by means of the gastric fluids to give high and stable plasma levels; renal tubular re-absorption of an uncharged drug may result in slow excretion which only occurs as the drug is metabolized to more polar derivatives. Polycyclic molecules are strongly bound to proteins and tissues, and in consequence cationic and uncharged polycyclic drugs may persist in the body over long periods.

Some treatment of the mathematical theories of drug absorption and disposition is given in Chapter 2, and appendices outline computer

methods for evaluating rate constants. The non-mathematical reader should not be deterred by these sections and may easily omit Chapter 2 at a first reading. I hope that if this is done, the rest of the book will show the value of the quantitative approach and so the reader will return to Chapter 2 to find out more about the mathematics involved. As in many other fields in medical science, the study of the absorption and the distribution of drugs is steadily becoming more quantitative, a trend which is likely to continue as automatic analytical equipment and digital computers are increasingly applied to experimental work in this field.

One problem is the differences which persist in the naming of some medicinal substances. In general the British official names for drugs have been used but where these differ appreciably the United States names have been given in parentheses at the first mention of the drug and have been included in the index.

This work, like many chemical reactions, required an active centre to initiate the chains of development and I wish to acknowledge that it was due to the initiative of Dr Frank Hartley, Dean of the School of Pharmacy, that the work was undertaken. I should also like to acknowledge with thanks the help of Mrs Magda Pasztor in obtaining copies of some of the journals cited.

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PART I

GENERAL CONSIDERATIONS

CHAPTER 1
Factors governing absorption and distribution

THE physical property of a drug molecule which is of cardinal importance in considering absorption and distribution is the solubility of the drug in body fluids. In assessing this property, it is necessary to consider not only the solubility in aqueous salt solutions at various pH values but also the solubilization of the drug by lipid and protein macromolecules present in most biological fluids.

The role of drug–macromolecule interactions is important in considering the biological availability of a drug; if the binding to macromolecules is too strong the availability of free diffusible drug may be too low to give the required biological response.

The object of any treatment of an individual with drugs is to produce a sufficient concentration of the material at the site of action to give an appropriate response. This process may require the drug to move from an aqueous environment through a lipid membrane and in most cases back to an aqueous environment. Compounds with solubilities in both water and lipid solvents are likely to be the most effective for this purpose, and organic weak electrolytes, in which category a large number of drug molecules are included, are particularly suitable, because their ionized forms are soluble in water but almost insoluble in lipid while the un-ionized forms have the converse solubilities. A small change in pH can cause a large change in the ratio of ionized to un-ionized molecules and so a large change in the lipid–water solubility ratio.

In addition to passive physical processes such as solution and diffusion activated transport processes across biological membranes must be considered. A drug of structure resembling that of a normal metabolite may be transported across a membrane by a specific active mechanism which requires energy; this type of transport is often stereospecific.

In general the main barriers to drug transport are lipid in nature, being the gastro-intestinal membranes, the capillary walls through which substances are moved from the blood into the various organs of the body and the cell membranes, which permit the contents of a cell to differ in composition from that of the cell environment.

Much research effort has been directed towards the elucidation of cell membrane structure. A realistic model of a common type of cell membrane would be a valuable tool in the design of drug molecules and

in formulating existing drugs so as to achieve an optimum effect. In the early 1960s there seemed every hope that this might be achieved. The electron microscope work of Robertson (1) indicated that there might in fact be a unit membrane common to a large variety of cells, and two approaches to the preparation of the basic film of this unit membrane appeared to offer promise of successful model building. However, subsequent work with both systems has failed to develop this promise and the whole concept of the unit membrane has been challenged by further electron microscope work and by the theories developed by Green (2) as a result of his studies of the intracellular membranes of mitochondria. These membranes contain elaborate sets of enzymes and it is difficult to envisage them arising from a standard unit structure. In Green's theory the membrane is formed by assembling subunits of lipoproteins, in which the lipid and protein parts are firmly bound by non-polar (hydrophobic) bonds, with the polar ends of both lipid and protein pointing outwards. In this type of structure the membrane is more likely to break into subunits than into separate lipid and protein films. This theory gives a better conception of variable membrane permeability to salts than the continuous lipid film theory.

The complexity of the subunit type of membrane structure is such that the possibility of developing a realistic model structure from comparatively simple components seems to be remote. Some success has however been claimed in re-assembling subunits obtained from the breakdown of cell membranes (3).

Some of the gross properties of lipid membrane barriers can be reproduced by a system in which a layer of organic liquid separates two aqueous solutions. In this system a weak electrolyte will diffuse spontaneously through the lipid layer from an aqueous solution buffered at one pH to one at a different pH so that at equilibrium there are differing concentrations of weak electrolyte in the two aqueous solutions. Systems of this type have been developed and studied by Doluisio and Swintosky (4) and by Perrin (5). This effect of differing concentrations at equilibrium is qualitatively explicable in simple theoretical terms.

The species which is equilibrated between the two aqueous solutions is the un-ionized molecule; for example, with a weak acid $HA = H^+ + A^-$, the concentration of HA is the same in the two aqueous solutions but since their pH values differ there is more A^- in the solution of higher pH than in the other. Consequently the total concentration $HA + A^-$ is also greater in this solution.

This effect is one of the important non-specific mechanisms for the biological transport of drugs and it is particularly apparent in orally

administered drugs. The pH of the stomach contents is normally much lower than that of other biological fluids, promoting spontaneous transport of anionic drugs into the blood stream. Cationic drugs are not absorbed to any extent until the stomach contents pass into the intestine where the pH is higher and the degree of ionization is reduced. Absorption of cationic drugs in the stomach and intestine may be increased by making their contents alkaline.

Other membrane barriers in the body show similar overall behaviour to the gastro-intestinal–blood barrier. Absorption of small lipid-soluble molecules is rapid, absorption of ionized species is relatively slow. The blood–brain barrier was at one time thought to have exceptional properties, but the work of Brodie and his associates on the transport of weak electrolytes across this barrier shows that it is in fact an ordinary lipid barrier of low permeability (6).

A considerable proportion of the effective drugs are weak electrolytes the lipid–water solubility properties of which can readily be varied, by change of pH, from a lipid–soluble un-ionized form to a water-soluble ionized form. There are of course many un-ionized drugs, but in general these are lipid-soluble, though their water solubility may be very low, and their effects are due to their solubilization in the body lipids. Two large classes of such compounds are the general anaesthetics and the steroids, both of which tend to become distributed throughout the accessible lipids of the body.

A key feature of many drugs which act on the neuromuscular system is the effect which they have on the permeability of lipid membranes to inorganic salts. The differing electrolyte compositions on the two sides of a cell membrane mean that there is an electrical potential difference across the barrier. This potential difference may be measured by means of micro-electrodes, one of which is inserted through the cell wall. In nerve and muscle cells, there is usually a higher concentration of potassium ions and a lower concentration of sodium ions in the intracellular fluid than in the surrounding fluid. If the permeability to sodium ions is increased the membrane potential drops and the membrane is said to be depolarized. Chemical transmitter substances such as acetylcholine are thought to trigger action currents by rapid changes of membrane potential. Anaesthetics and paralysing drugs act by changing the membrane potential over a period, so preventing the transmission of messages. Analgesics may act by producing a slow leakage at the nerve membranes so that only blurred impulses can be transmitted.

ROUTES OF ADMINISTRATION OF DRUGS

The effectiveness of a drug may be enhanced by choosing a particular route of administration. Where a rapid response is required direct intravenous injection is used to avoid delays due to transport across the gastro-intestinal–blood barrier. For drugs which are required to act rapidly on the central nervous system direct spinal injection into the cerebrospinal fluid is used. Where a prolonged action is required, as in some hormone treatments, a solid implant may be made from which slow absorption occurs over a very long period.

However, the oral route of administration is so simple, and painless that it is used wherever possible, particularly when repeated dosage over a long period is required. Usually absorption occurs in the gastro-intestinal tract after swallowing the drug, however, in some cases the dose is retained in the mouth and absorption occurs through the buccal membranes. The rectal route has similar advantages for long term treatment.

With gases and volatile liquids, administration through the lungs is a standard method; it has been extended to other substances by the use of aerosols.

Intramuscular injection is used for some treatments particularly for drugs which have a low solubility in water and for depot therapy where prolonged absorption from a suspension or solution in an oily vehicle is required. Procaine penicillin injected in this way as a microcrystalline suspension gives a slow solution into the blood stream over a period of several days.

Subcutaneous injection is used in a similar way. Absorption is generally slower than from muscle and complications due to necrosis and abscesses are likely to occur with some drugs. The rate of absorption from a subcutaneous injection can be reduced by including adrenaline (epinephrine) in the injection so as to constrict the local blood vessels and so reduce absorption into the blood. Subcutaneous pellets of solid material are also used for depot therapy. Cylindrical pellets of testosterone implanted in human subjects lose about 1% of their weight per day for about 60 days; the rate of loss then falls and absorption is apparently complete after about 200 days.

Intraperitoneal injection is another method used in some cases.

Application of drugs to the skin is used particularly for the treatment of skin disorders. This route has also been examined as a general method for the application of drugs. Absorption through the skin tends to be slow, but it is speeded by the use of organic solvents.

Dimethylsulphoxide has been proposed for this purpose, however it appears to have undesirable side-effects.

An electrophoretic effect has also been used to drive drugs through the skin; electrodes are applied so that the ionized drug is pushed through the epidermis by a potential gradient.

The modification of preparations of active substances so as to give optimum effectiveness by a particular route of administration is a major objective of pharmaceutical research. This optimization, in addition to leading to the most economical use of drugs, also reduces to a minimum the amount of medicinal material put into the body to achieve a required effect and in this way minimizes undesirable side-effects of the drug, a particularly important consideration when prolonged dosage is necessary.

SOLUBILITY

The solubility of a drug in water may give only a poor estimate of its solubility in vivo owing to the presence of macromolecular solubilizing agents such as proteins and lipids in biological fluids.

Solubility complications arose in sulphonamide therapy owing to the metabolic conversion of some of these compounds to very insoluble derivatives. For example, sulphathiazole is acetylated in vivo to give a compound the solubility of which is less than one-tenth that of the parent compound. This effect caused precipitation in the kidney as a consequence of which the use of this sulphonamide as an internal medicament, was abandoned.

The solubility of anaesthetic gases in the blood is an important factor governing their action. If the gas has a low solubility in blood, for example, cyclopropane, nitrous oxide and propylene have 0·5, 0·5 and 0·2 equilibrium blood–air concentration ratios respectively, then the concentration of anaesthetic in the alveolar air remains almost constant, the amount taken up by the blood being small. Consequently, the blood level of anaesthetic which governs its efficacy is mainly controlled by the rate of circulation of the blood, and is not greatly dependent on the rate of respiration. Conversely if the anaesthetic is highly soluble in blood, the alveolar air is almost completely depleted of anaesthetic at the end of each respiration, and the blood level is governed by the rate of respiration. A steady state between inspired air and blood concentration can be accelerated by the use of carbon dioxide to increase the respiration rate. Some high solubility anaesthetics are ether, chloroform

and halothane; these have blood–air concentration ratios of 15, 7 and 2 respectively at 38°C. These gases are used to give complete anaesthesia.

Solubility ratios, oil–water partition coefficients

Many attempts have been made to correlate the biological activities of series of related compounds with their physical properties. Mayer (7) achieved some success in relating the efficacy of anaesthetics to their oil–water partition coefficients. The best correlations arise in series of compounds where the biological activity is a non-specific toxicity.

Leo et al. (8) reviewed a number of parameters which have been used in the study of structure–activity relationships. They used the logarithm of the partition coefficient of drug between octanol and water as an index of relative oil–water solubility. A correlation for frog muscle narcosis taken from the measurements of Agin et al. (9) is shown in Fig. 1. P is the octanol–water partition coefficient and C is the minimum concentration for narcosis.

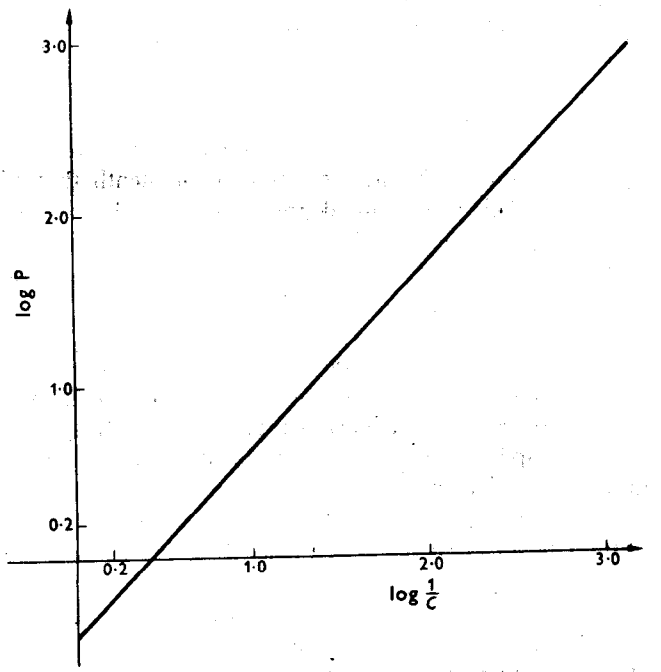


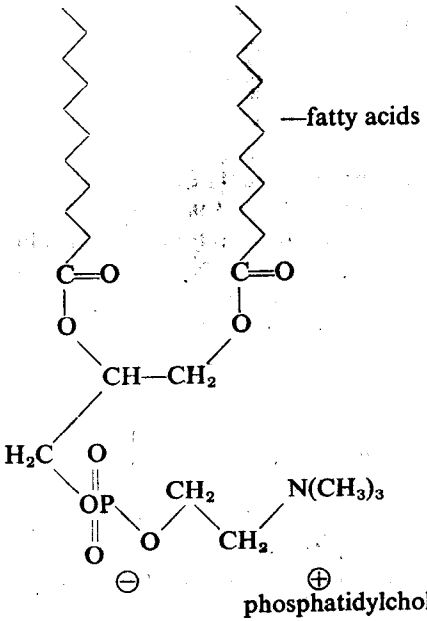
Fig. 1. Log partition coefficient plotted against log reciprocal of minimum narcosis concentration.

With weak electrolyte drugs the oil–water partition coefficient is very much a function of the pH of the aqueous phase. With cationic drugs, low pH gives almost complete ionization with a low oil–water coefficient whereas high pH suppresses the ionization and gives a high oil–water solubility ratio. With anionic drugs the converse is true.

Substitution of oxygen in a drug molecule by sulphur usually increases the oil–water ratio and may give a more rapid rate of absorption of the drug. For example, replacement of one of the oxygen atoms of pentobarbital by sulphur gives thiopental whose heptane–water partition coefficient is sixty times that of the parent compound. When injected intravenously, thiopental gives a very rapid rate of anaesthesia which lasts only briefly; pentobarbital acts more slowly and the effects last longer.

Solubilization

Solubilizing agents are used to enhance the biological activities of sparingly soluble substances in a number of contexts. One familiar



phosphatidylcholine

example is in the preparation of antiseptics, where the solubility of bactericidal substances such as cresol, chloroxylenol, hexachlorophane and iodine in water is increased by formulating them together with a surface active substance. Other groups of compounds which are often formulated with surfactants are steroids, antibiotics (particularly griseofulvin), sulphonamides, barbitones and the water-insoluble vitamins.

In these preparations the role of the surfactant is mainly to provide a reservoir of drug in the aqueous fluid, so that the concentration of non-solubilized material in equilibrium with that dissolved in the surfactant micelles remains constant while absorption proceeds. In some cases the surfactant may itself promote the rate of absorption.

The use of surfactants in pharmaceutical formulation has been reviewed (10). The original surfactants were alkali metal salts of fatty acids; however, cationic soaps such as cetyltrimethylammonium bromide (CTAB) and non-hydrolyzing anionic soaps such as sodium dodecyl sulphate (NaDS) are more generally used. For many pharmaceutical purposes the neutral non-ionic soaps such as cetomacrogol in which the polar end of the surfactant molecule consists of a long ethylene oxide polymer chain, are more suitable. The mildest surfactants from the biological point of view are the natural zwitterionic compounds such as the phosphatidylcholines.

DRUG–MACROMOLECULE INTERACTIONS

The total blood concentration is not necessarily the best measure of the biological availability of a drug. Most drugs interact to some extent with serum macromolecules. If the interaction is readily reversible, this effect may promote absorption by facilitating transfer to the site of action, however, if the drug is firmly bound to macromolecules there is likely to be a loss of efficacy. Drug–macromolecule interaction may play an important part in the consideration of absorption and distribution of the drug.

The basic experimental method used in studying drug binding by macromolecules is equilibrium dialysis. The macromolecule sol is contained in a dialysis sac which is immersed in an aqueous solution. The drug is included either in the sol or in the outer solution or in both. Diffusion of small molecules through the walls of the sac proceeds until equilibrium is reached. Both solutions are analysed at regular intervals for the drug.

From the results, calculation is made of the number of moles of drug bound by the total amount of protein in the sol. The simple mass action equation is then applied to the equilibrium

$$\text{drug} + \text{protein} = \text{complex}$$

If R moles of drug are bound to the protein contained in unit volume and N is the number of moles of binding site on the protein, then the concentration of complex at equilibrium is R and the concentration of unused sites is $(N - R)$. Let DF be the concentration of free drug, then K the equilibrium constant is given by

$$\mathrm{K} = \frac{[\text{complex}]}{[\text{free sites}]\,[\text{free drug}]}$$

$$\mathrm{K} = \frac{R}{(N - R).DF}$$

rearranging, $R = N.\mathrm{K}.DF/(1 + \mathrm{K}.DF)$

or, $$1/R = 1/N + 1/(N.\mathrm{K}.DF)$$

The last equation is the basis of the reciprocal plot method for interpreting experimental measurements of R and DF at a series of different total drug concentrations. A plot is made of $1/R$ against $1/DF$. If the theory is correct the plot should be a straight line of slope $1/(N\mathrm{K})$ and intercept $1/N$. From the value of N and the concentration of the sol, the number of binding sites per molecule of protein can be calculated.

An alternative procedure was used by Scatchard who rearranged the equation for R as

$$R/DF = N\mathrm{K} - R\mathrm{K}$$

and plotted R/DF against R. This plot should be a straight line of slope $-K$ and intercept $N\mathrm{K}$. Curvature of the plot is taken to indicate that more than one type of binding site is present on the protein.

Many experiments on protein binding have been made with macromolecules which are not well defined, as in biological fluids. The fraction of the small molecule which is bound is then determined, but it should be noted that this quantity will vary both with macromolecule and drug concentrations and it does not have much meaning unless these quantities are specified.

The binding of drugs to macromolecules in vivo should be taken into account in considering the distribution of a drug in the body. A model for drug distribution which is often used and which is considered in