they have fatal illnesses? In a study from a cancer ward less than one-third of patients suspecting themselves of having malignant disease wished to have it confirmed, and even fewer wanted information about their prognosis.[6] Nevertheless, in another group of patients who had cancer, and knew it, 81% thought that doctors should disclose the diagnosis.[5] In contrast doctors often seem reluctant to tell patients that they have cancer or are dying.[4 7]

In many ways problems of communication with patients with acute leukaemia are different. Though a rare disease, leukaemia is often publicised by books and the media, and its rapidly fatal course is well known. The combination of the terms "blood disease," "bone marrow examinations," and "treatment by injections" are quickly translated by most alert patients into a diagnosis of leukaemia. As a result it may not be necessary to make a decision whether to tell an adult patient; he will already know. Such was the pattern in several of our own patients with leukaemia. In those in whom the diagnosis has not suggested itself to the patient already the harrowing and prolonged nature of treatment makes disclosure of the diagnosis mandatory. Certainly few would agree to such measures unless they knew that their lives were at stake. There are, nevertheless, some patients with acute leukaemia who do not wish to have the diagnosis confirmed or who may be too ill throughout their illness to ask about it. Whether we should tell such patients just for the sake of being truthful is uncertain. Undoubtedly management is easier for doctors and nurses when the patient knows the diagnosis, but it is uncertain whether the patient is happier in knowing the diagnosis. "I don't want to go through all that wretched treatment again if I am likely to die a few months hence" said one patient who did, in fact, have a short but happy remission. Sometimes a knowledge of the diagnosis does bring peace of mind and acceptance, but if the diagnosis is disclosed prematurely, casually, or uncritically it may bring unnecessary grief for one who needs only comfort.

The results of our survey of our own patients have taught us that there can be no standard answer for the standard patient and relative with a standard disease. We believe that relatives must know the diagnosis and are obviously entitled to more hope than perhaps was given in the past. We have learnt that it is as important to listen to relatives as to talk to them. One relative, a general practitioner, was told by one of the doctors, "There's nothing to be said, is there?" Although she did not need information, she did need someone just to talk to. She felt deserted and left on her own to cope. The social chats that may seem trivial to us are comforting and reassuring to frightened and bewildered relatives.

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Today's Treatment

Clinical Pharmacology

Plasma protein binding of drugs

W E LINDUP, M C L'E ORME

Binding to plasma proteins is both a help and a hindrance to the distribution of drugs through the body. Transport in the bloodstream by binding to albumin helps the drugs to reach regions remote from the site of administration. Because bound drug cannot readily leave the capillaries, however, the rate of distribution of drug into the tissues will be controlled by the concentration gradient produced by the concentration of unbound unionised drug. Usually, it is the unbound drug concentration that is considered to be pharmacologically and toxicologically active. The fraction of unbound drug can also influence the rate of drug elimination. Binding does, therefore, affect both the duration and intensity of drug action.

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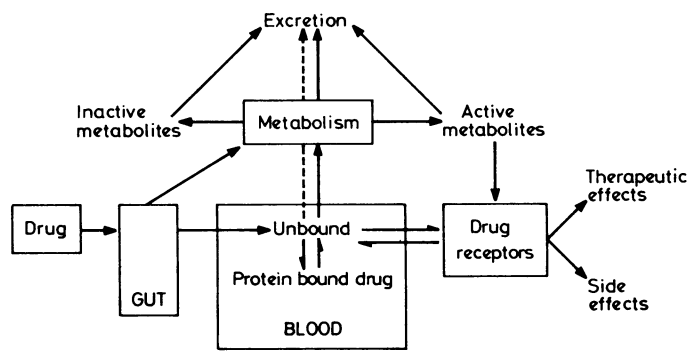
The binding and transport of endogenous and exogenous substances is one of several important functions of the plasma proteins (figure). The endogenous substances include bilirubin,



Protein binding and drug disposition.

fatty acids, L-tryptophan, vitamins, and many hormones. Most drugs also bind to one or other of the plasma proteins, at least to some extent. Albumin is quantitatively the major binding protein for acidic and neutral drugs. Bases are bound to a lesser extent by albumin, and there is growing evidence that globulins are the major binding proteins for basic drugs.

Albumin has high affinity binding sites, which are probably specific for bilirubin and the fatty acids, but the high affinity sites for various hormones are located among the globulins. The binding of bilirubin serves a protective function in the newborn, where it prevents kernicterus by reduction of the diffusion of undue amounts of bilirubin into the brain. In a similar way the rate of diffusion of highly bound drugs into various tissues can be restricted.

There is no precise definition of a "highly" bound drug, but only when the percentage of a drug bound exceeds about 70% is binding likely to exert much influence on the distribution and pharmacokinetics of a drug. In the case of highly bound drugs—for instance, warfarin, carbenoxolone, or phenylbutazone—the unbound fraction may be considerably less than 1% of the total plasma drug concentration. The interaction of most drugs with the plasma proteins is a dynamic, reversible process with dissociation of bound drug molecules from the drug-protein complex occurring very rapidly, probably within milliseconds or less. The rate of dissociation of drug molecules from plasma proteins is therefore not a limiting factor in the uptake of drug from the bloodstream by major organs, whose perfusion time may be several seconds or more.

Binding sites

The drugs which tend to have the highest affinity for albumin are organic anions—for instance, carbenoxolone, phenylbutazone, warfarin—and they are also usually fairly lipid soluble. Quantitatively, binding to plasma proteins may be described by the law of mass action and analysed in terms of the number of binding sites (n) and the apparent association constant (K), a measure of affinity. These two binding constants combine to regulate the fraction of unbound drug available.

Isolated fractions of albumin and certain other plasma proteins have been available for several decades, and these are used for in-vitro experiments to determine values for n and K. These values can often give a reasonable prediction of the likely extent of binding to plasma proteins in vivo. In the case of many drug-albumin interactions there appear to be one or two primary (high affinity) binding sites available, together with a larger but variable number of secondary (lower affinity) sites.

Now that the overall structure of albumin is becoming clearer efforts are being made to locate and classify the binding sites. In addition to the separate and specific binding sites for bilirubin and the fatty acids, it appears there are at least two further separate sites which bind drugs. One site has been found to bind the benzodiazepines, various aromatic carboxylic acids, and L-tryptophan. Another site binds various anionic drugs such as warfarin, phenylbutazone, several sulphonamides, and other drugs. This type of work should eventually make the prediction of drug-drug displacement interactions easier and show whether the binding of endogenous substances is affected.

Albumin has been the most extensively studied of the binding proteins, but recent work has shown that α_1-acid glycoprotein (orosomucoid) is an important binding protein for basic drugs (table).

Binding and drug disposition

DISTRIBUTION

When drug distribution is complete—that is, at "steady-state" or equilibrium—the drug concentration throughout extracellular water will equal the unbound concentration in plasma. Cerebrospinal fluid, which contains little albumin, often reflects the concentration of unbound drug in plasma. The apparent volume of distribution of a drug (V_d) gives an indication of the extent of binding and distribution of a drug. The V_d of a highly bound drug, calculated from the total plasma concentration, is relatively small and for phenylbutazone it is about 0·1 l/kg. Extensive tissue binding results in the large volumes of distribution seen for drugs such as digoxin (6 l/kg) and chlorpromazine (20 l/kg).

Drugs thought to interact with α_1-acid glycoprotein (orosomucoid)

Alprenolol	Imipramine
Chlorpromazine	Lidocaine
Dipyramidole	Propranolol
Disopyramide	Quinidine

RENAL EXCRETION

Protein-bound drug cannot undergo glomerular filtration and so only the unbound fraction can be filtered, which can prolong the half life of drugs that are neither actively secreted by the renal tubules nor rapidly metabolised. If an albumin-bound drug is subject to active renal excretion then binding is not usually a limiting factor. In fact, it tends to promote excretion by retaining drug in the bloodstream for delivery to the excretory system.

HEPATIC ELIMINATION

As the result of earlier work, largely with the long-acting sulphonamides, a misconception has arisen that the long half life of a highly bound drug is solely the result of binding. There are numerous examples, however, of highly bound drugs and dyes that are rapidly metabolised and excreted. Furthermore, the half life of a given drug may vary widely among different species. There is therefore good reason to believe that the efficiency of the processes of elimination in the liver and kidney is of prime importance and that binding is a secondary factor.

If the processes of elimination (uptake and metabolism) are efficient then binding to plasma proteins acts as a delivery system. The rate of metabolism of some highly bound drugs such as propranolol depends on the rate of delivery to the liver via the bloodstream; this is called flow-dependent hepatic elimination. At the other extreme there are drugs—for instance, warfarin—where only the unbound fraction is taken up by the liver and with this flow-independent type of elimination binding serves primarily as a storage depot. Other drugs have elimination characteristics intermediate between these two extremes. Plasma clearance values for drugs are usually calculated from total drug concentrations, and the interpretation of these results should take into account the fraction bound.

Factors affecting drug binding

The unbound fraction of drug present in plasma is dependent on the total concentrations of drug and albumin together with the values of n and K for the interaction. Any alteration in these binding constants, physiological or pathological in origin, will change the unbound fraction of drug.

Age is one physiological factor that may influence binding, and the unbound fraction appears to be higher in neonates and possibly in the elderly. There is, however, insufficient work on this topic to draw firm conclusions. Interindividual variations in the binding of basic drugs such as imipramine have been noted, and this may have a genetic basis. The presence of other drugs and the effects of disease are the two major factors that can affect binding.

DRUG DISPLACEMENT

The binding of one drug can be inhibited by the presence of a second drug, and the mechanism may be either competitive, when drugs bind to the same site, or non-competitive, with the inhibitory drug causing a conformational change in the albumin molecule that inhibits the binding of the first drug. The inhibition of binding is probably mutual in many cases but it is usually only an increase in unbound fraction of one of the drugs that is of interest. Drug-displacement interactions are complex phenomena, and comparison of the relative affinities of two drugs for albumin does not offer an easy way to predict displacement. The drug acting as a displacing agent usually has to be present in fairly high concentration, as well as have a high affinity for albumin, to cause appreciable inhibition of binding. The non-steroidal anti-inflammatory drugs are a typical group of displacing agents. Intravenous heparin inhibits binding indirectly by raising the plasma concentration of fatty acids, which are potent binding inhibitors.

An increase in unbound drug concentration results in redistribution of drug from the plasma to other parts of the body. The pharmacological effect is likely to be enhanced, and there will be increased elimination of drugs excreted by glomerular filtration. If the drug is removed by flow-dependent elimination processes in the liver and kidney, displacement may cause a short-lived increase in half-life because the displaced drug diffuses to more remote sites and less drug is transported to the sites of elimination. The clinical implications of displacement interactions for the fetus have not yet been explored, but studies in animals have shown that this type of interaction can appreciably increase the amount of drug reaching the fetus.

The pharmacokinetics of drug displacement interactions and their consequences are complicated and have still to be fully elucidated. Koch-Weser and Sellers[1] give a more detailed but non-mathematical discussion. In general, the extent of enhancement of pharmacological activity depends on several factors: the degree of displacement, the speed of the pharmacological response, and the effect of displacement on the rate of elimination of the drug. The potentiation of pharmacological activity is transient and fades as a new steady state is established during co-administration of the drugs. In clinical practice this potentiation may well be missed and may not present a serious hazard.

Experience has shown, however, that pairs of drugs which interact in relation to drug binding sites on plasma proteins also interact at sites of metabolism and excretion. Two examples of clinically important interactions affecting drug displacement concern warfarin and tolbutamide. Both are displaced by phenylbutazone and several other drugs, and in both cases inhibition of hepatic metabolism by the displacing drug is a major feature of the interaction. Drugs likely to be implicated in clinically important displacement interactions will be highly bound to albumin and have a small apparent volume of distribution and therapeutic index.

DISEASE

Several diseases affect drug binding, and the usual result is an increase in the unbound fraction. Disease may also affect metabolism and excretion, a situation similar to many displacement interactions. The effect of disease on albumin may be either quantitative or qualitative or both.

Hypoalbuminaemia, as a result of injury or disease, will increase the unbound fraction of drug. Adverse reactions to phenytoin and prednisone, for example, are more common in patients with hypoalbuminaemia. In patients with renal insufficiency the binding of acidic and neutral drugs to albumin is inhibited by accumulated endogenous metabolites and possibly also by the changes in the structure of albumin. The binding of a variety of drugs is also decreased by liver disease, mainly as a result of hypoalbuminaemia, but accumulated endogenous metabolites—for instance, bilirubin—may contribute.

In rheumatoid arthritis and other inflammatory conditions, when the albumin concentration is lowered, there will be a concomitant decrease in the binding of albumin-bound drugs. There is often, however, a considerable increase in the concentration of several globulins including α_1-acid glycoprotein (orosomucoid). Basic drugs such as propranolol are bound to this protein, and a considerable increase in the fraction of bound drug occurs in these circumstances.

Therapeutic drug monitoring

When the unbound fraction of drug is increased because of disease or other drugs the peak of unbound drug concentration during each dosage interval is higher than normal. The mean total drug concentration will be decreased so that the concentration of unbound drug will be within the usual range. Measurement of total drug concentration then would give the misleading idea that an increase in dosage was necessary to raise the total drug concentration into the therapeutic range. This would be potentially hazardous. In cases where inhibition of drug binding is suspected, measurement of the unbound drug concentration would be a better guide to treatment, but there are practical difficulties.

Methods for investigating drug binding to plasma proteins are too numerous to discuss here, but the most suitable in-vitro experimental methods are equilibrium dialysis, ultracentrifugation, and ultrafiltration. The concentration of drug in saliva or the erythrocyte/plasma drug concentration ratio may give a useful measure of in-vivo binding of selected drugs—for example, phenytoin. Unfortunately, none of these methods is suitable for large-scale routine use at present.

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A ward sister in a psychiatric hospital has developed chickenpox. Is it necessary to take any special precautions in her ward to prevent the infection spreading?

Patients with chickenpox appear to be infectious for a few hours before the onset of the rash and continue to shed virus until the skin lesions have crusted. If the sister worked in her ward during this period there is a risk of infection spreading to susceptible patients and staff. Most adults in Britain, however, are thought to be immune, and only an occasional patient in an adult psychiatric ward would be vulnerable. Firm epidemiological evidence is difficult to obtain, but in one small series presented by Evans and others about 90% of adults in England had antibody to chickenpox virus. No action would be required unless the susceptible contact had impaired immunity, in which case 1 g of antichickenpox immunoglobulin (zoster immune globulin, ZIG) should be given intramuscularly, preferably within 72 hours of exposure.[1 2]

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