Protein Binding Displacement Interactions and their Clinical Importance

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Summary

The binding of drugs to proteins is an important pharmacokinetic parameter. Many methods are available for the study of drug protein binding phenomena and there are also many ways to interpret the binding data. Although much emphasis has been placed on the binding of drugs in the plasma, binding also takes place in the tissues. Displacement interactions involving plasma or tissue binding sites have been implicated as the causative mechanisms in many drug interactions. However, the importance of plasma binding displacement as a mechanism of drug interaction has been overestimated and overstated, being based largely on in vitro data. Because displaced drug can normally distribute out of the plasma compartment, increases of free drug concentrations are usually transient and therefore will not give rise to changed pharmacological effects in the patient. Those clinically important drug interactions formerly considered to be caused via displacement from plasma binding sites usually have another interaction mechanism involved; commonly decreased metabolism or renal elimination also takes place.

Plasma binding displacement interactions, however, do become important clinically in certain specific situations, namely, when the displacing drug is administered quickly to the patient by the intravenous route, during therapeutic drug monitoring, and in certain drug disposition studies which involve the use of a heparin lock for blood sampling.

Tissue binding displacement interactions have a greater potential to cause adverse effects in the patient as in this case drug will be forced from extravascular sites back into the plasma. The resulting increased drug plasma levels will lead to enhanced pharmacological effects and, possibly, frank toxicity. Displacement of drugs from binding sites simultaneously in both the plasma and in the tissues will combine the effects seen after displacement from the separate areas. Due to decreased binding in both areas, the free drug concentration in the plasma will increase leading to overactivity of the displaced drug.

Combinations of drugs are often necessary in the treatment of diseased patients; for example, a patient may suffer from more than 1 disease or perhaps have different symptoms of a single disease which may require separate and different treatment(s). Over the past decade there has been increasing concern about drug interactions because of the incidence of multidrug therapy. Drug interactions can take place at many different sites in the body – notably in the gastrointestinal tract, at plasma protein and tissue binding sites, in the liver, and in the kidney. A drug may also interact with the constituents within its formulation. Collectively, interactions at all the sites mentioned thus far will give rise to changed drug kinetics. Pharmacodynamic drug interactions can also take place when 2 drugs interact to give summation, potentiation or antagonism of therapeutic effect. A final
miscellaneous category encompasses those interactions which do not fall naturally into the previous 2 classifications, and includes interactions due to, for example, a drug giving rise to interference in the assay of a second drug or giving a changed outcome of a biochemical test.

The interaction mechanism considered in this article is that involving displacement of drugs from protein binding sites. Although much emphasis is put on the plasma protein binding of drugs, protein binding takes place in the tissues as well. In the tissues, drugs can be bound by various proteins including receptor proteins, storage proteins or enzymes (Tillement et al., 1980). Before discussing the clinical significance of protein binding displacement interactions, it would appear prudent to discuss briefly the proteins involved in drug binding, the methods used in the study of binding phenomena, interpretation of binding data and their application to the clinical situation. This will give the reader background information which will facilitate the interpretation and assessment of protein binding research data already published or which will become available in the future.

1. Proteins Involved in Drug Binding

1.1 Plasma

The major protein involved in the binding of drugs in plasma is albumin. Despite its large molecular weight, albumin is not exclusively retained in the plasma compartment but is also distributed extravascularly. Most of the albumin that moves out of the vascular system is returned to the plasma via the lymphatic circulation (Rothschild et al., 1973). The amount of albumin in interstitial fluid, for example, is comparable to that in plasma (Jusko and Gretch, 1976) but their respective volumes are 3 and 10L. For acidic drugs, binding can be decreased by a reduction in serum albumin concentration (Lunde et al., 1970). Hypoalbuminaemia can be due to many precipitating factors, e.g. burns, neoplastic disease and gastrointestinal tract diseases. Binding is also often reduced in cases of renal and hepatic failure (Hooper et al., 1974; Reidenberg et al., 1971).

For basic drugs, the glycoprotein α₁-acid glycoprotein is a major plasma binding protein. This glycoprotein has been shown to be important in the plasma binding of antidepressant drugs and β-blockers. Diseases which can elevate α₁-acid glycoprotein, e.g. Crohn’s disease, can therefore give rise to increased plasma binding of certain basic drugs (Piafsky et al., 1978).

1.2 Tissues

Albumin is also the chief drug binding protein in tissues (Jusko and Gretch, 1976); however, a number of other binding materials have been identified which account for the uptake of drugs and endogenous substances by various tissues, e.g. uptake of bilirubin by ligandin (Davis and Yeary, 1975) and uptake of certain cytotoxic agents by DNA (Allen and Creaven, 1974). Digoxin is found only in low concentration in plasma but binds strongly in the myocardium, with tissue : serum ratios reaching 60 or higher (Doherty et al., 1967).

2. Methods of Study of Protein Binding Phenomena

The measurement of protein binding in humans is largely restricted to studies involving either serum or plasma. Binding can also be quantified using buffered solutions of human serum albumin (bovine serum albumin has also been used). The materials required for these binding studies are easily accessible and the methodologies used (see below) are reasonably straightforward. The study of tissue binding in humans has obvious problems as far as the availability of binding material is concerned. Binding studies are therefore often limited to biopsy material or to postmortem tissue samples.

Usually the protein bound drug amount cannot be measured directly but is calculated by finding the difference between the unbound and total amount of drug in a sample after the physical sep-