*International Journal of Pharmaceutics*, 54 (1989) 1–13
Elsevier



IJP 01855

**Invited Review**

# The influence of disease on plasma protein binding of drugs

T.-J. Grainger-Rousseau *, J.C. McElnay [1] and P.S. Collier

*Pharmacy Practice Research Group, School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, Belfast (Northern Ireland)*

(Accepted 24 April 1989)

*Key words*: Plasma protein binding; Disease state; Albumin; $\alpha_1$-Acid glycoprotein

## Introduction

In our paper in 1978 (Harron et al., 1978) we described an in vitro system for the correlation of drug/protein binding with variable plasma protein profiles. Since plasma protein binding is an important determinant in drug pharmacokinetics, especially for those drugs which are highly bound, factors which influence plasma proteins quantitatively (i.e. change the plasma protein profile) will influence various pharmacokinetic parameters, notably the apparent volume of distribution and clearance. Probably the two most important patient factors which can influence plasma protein profiles are age and disease. In elderly patients, in general, there is a reduction in plasma albumin concentration and an increase in globulin concentrations; total plasma protein concentration declines in the elderly. In the present short review, however, we have concentrated on the influence of disease on the plasma protein binding of drugs and in particular the contributions to knowledge on this subject over the past 10 years i.e. since the publication of our paper in 1978. While considering the influence of disease on plasma protein binding one must bear in mind that albumin is the main binding protein in the plasma. It can bind both acidic and basic drugs, two drug binding sites having been identified (sites I and II; Tillement et al., 1984; Birkett and Wanwimolruk, 1986; Wanwimolruk and Birkett, 1986). The other major drug binding protein in the plasma is $\alpha_1$-acid glycoprotein (AGP). This binds basic drugs (Piafsky, 1980; Kremer et al., 1988).

The influence of disease on the protein binding of drugs is far reaching and complex. The unpredictable nature of protein binding due to inter- or intra-individual variation, and variation within disease states, complicates the matter. The complex nature of this subject has been reviewed by Tillement et al. (1978), Piafsky (1980) and Holtzman (1984). Piafsky's review addressed the subject specifically with regard to basic drugs. A section of the proceedings of a recent symposium on Drug Protein Binding and Transport was devoted to the influence of disease on plasma protein binding (Tillement and Lindenlaub, 1986). Although there is no clear-cut way to predict clinically significant consequences of protein binding alterations in disease states, common factors which may be responsible for the changes observed in pathological conditions have been elucidated. These include, alteration in the albumin concentration (as in renal or hepatic disease), alteration in albumin distribution due to an increased unidirectional

* John Wakeford Scholar, Bulawayo, Zimbabwe.
*Correspondence:* J.C. McElnay, Pharmacy Practice Research Group, School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland.

TABLE 1

*The influence of diseases on drug plasma protein binding*

| Drug | Disease | % Free or free fraction (control vs patient) | Sig. diff. | Clinical sig./ comment | References |
|---|---|---|---|---|---|
| Carbamazepine | Alc. liver disease, renal failure rheumatoid arthritis, ulcerative colitis | 22.7% vs 19.5% | Y | Not clinically sig. Caution in interpreting total drug concentrations. Correlation with AGP shown. | Barruzi et al., 1986. |
| Diazepam | Early pregnancy<br>Mid pregnancy<br>Late pregnancy | 1.8% vs 1.9%<br>1.8% vs 2.1%<br>1.8% vs 2.6% | N<br>Y<br>Y | Large $V_d$ and therapeutic index means change is not clinically important in chronic use. If used in status epilepticus may have potentiated action in late pregnancy due to increased free fraction. | Perucca et al., 1981 |
| | Uraemia | 2.9% vs. 4.5% | – | Not indicated. Site II not affected by carbamylation. Endogenous binding inhibitors implicated. | Calvo et al., 1982. |
| | Uraemia<br>Kidney transpl.<br>Nephrotic syndr. | 1.64% vs. 3.23%<br>1.50% vs. 2.11%<br>1.60% vs 3.55% | Y<br>Y<br>Y | Not indicated, but an important difference implicated when interpreting kinetic data with regard to type of renal disease and the protein involved in binding. | Grossman et al. 1982. |
| | Chronic cardiac failure | ≈ 1% vs 1.5% | N | Does not alter diazepam binding site affinity. | Fitchl et al., 1983. |
| | Acute uraemia<br>Chronic uraemia | 2% vs 6%<br>2% vs 4% | Y<br>Y | Large therapeutic index means that drug effect can be monitored clinically as clinical end point can be determined safely | Tiula and Neuvonen, 1986. |
| | Age-related decrease in renal function | 1.8% vs 3.0% | Y | Pharmacokinetic changes but no clinical implication | Tiula and Elfving, 1987 |
| Digitoxin | Chronic cardiac failure | 6% vs 5.9% | N | Not significant | Fitchl et al., 1983. |

TABLE 1 (continued)

| Drug | Disease | % Free or free fraction (control vs patient) | Sig. diff. | Clinical sig./ comment | References |
|---|---|---|---|---|---|
| Digitoxin | End-stage renal disease (haemodialysis) | 2.0% vs 2.5% | N | Difference too small to have any therapeutic consequence | Lohman and Merkus, 1987. |
| Disopyramide | MI | 0.25 vs 0.15 (at 2 mg/l) 0.53 vs 0.32 (at 5 mg/l) | Y | Binding varies with drug and protein conc. May be clinically significant as AGP conc. decreases post MI. | David et al., 1983. |
| | MI | 0.2 vs 0.13 | Y | Not indicated. Pharmacokinetic change suggested. Interpretation of total drug levels caution. | Caplin et al., 1985 |
| Flecainide | MI | 39% vs 47% | Y | Not indicated. Endogenous compounds may lead to displacement and decreased binding. | Caplin et al., 1985. |
| Imipramine | Chronic cardiac failure | 19% vs 18% | N | Drug binding not affected | Fitchl et al., 1983 |
| Lignocaine | Uraemia | 30.7% vs 20.8% | Y | Interpreting kinetic data with regard to the type of renal disease and the protein involved in binding may be important. | Grossman et al., 1982. |
| | Kidney transpl. | 33.7% vs 24.6% | Y | | |
| | Nephrotic syndr. | 30.4% vs 34.2% | N | | |
| | NIDDM | 32% vs 30% | N | Not indicated (but no change expected). | O'Byrne et al., 1988. |
| Lorcainide | Cardiac arrhythmia | 26.03% vs 24.70% | N | Not significant | Somani et al., 1984. |
| | Renal disease | 26.03% vs. 29.04 | N | Not significant. | |
| Metoclopramide | Renal disease | 0.6 vs 0.59 | N | Not significant | Webb et al., 1986. |
| Phenylbutazone | Alc. hepatitis | 6% vs 13% | Y | Not known. Bilirubin and hypoalbuminaemia implicated in binding defect. | Brodie and Boobis, 1978. |
| | Alc. cirrhosis | 6% vs 19% | Y | | |
| Phenytoin | Early pregnancy * | 9.7% vs 10.6% | Y | Important in drug monitoring | Perucca et al., 1981. |
| | Mid pregnancy | 9.7% vs 10.9% | Y | | |

TABLE 1 (continued)

| Drug | Disease | % Free or free fraction (control vs patient) | Sig. diff. | Clinical sig./ comment | References |
|---|---|---|---|---|---|
| Phenytoin | Late pregnancy | 9.7% vs 12.6% | Y | interpretation. Decreased albumin concentration in pregnancy implicated. | |
| | Chronic cardiac failure | ≈ 15% vs 15% | N | Not significant. | Fitchl et al. 1983. |
| | Acute uraemia<br>Chronic uraemia | 10% vs 25%<br>10% vs 24% | Y<br>Y | Important clinically in drug monitoring, although free conc. remains the same due to pharmacokinetic compensation. | Tiula and Neuvonen, 1986. |
| | Age-related decrease in renal function | 10% vs 13.5% | Y | Important in drug monitoring. | Tiula and Elfving, 1987 |
| Prednisolone | Porto-systemic shunt | 17.7% vs 28.6% | Y | Not significant as elimination and $V_d$ altered, therefore, normalising free conc. | Bergrem et al., 1983. |
| | Nephrotic syndr. | $2.26 \times 10^3$ vs $4.20 \times 10^3$ $M^{-1}$ (albumin $K_a$)<br>$2.12 \times 10^7$ vs $3.44 \times 10^7$ $M^{-1}$ (transcortin $K_a$) | Y<br>N | Not known. Altered pharmacokinetic disposition, due to change in binding. | Frey and Frey, 1984. |
| Propranolol | Chronic cardiac failure | 14% vs 14% | N | AGP binding not affected. | Fitchl et al. 1983. |
| | Cancer, MI and IHD, infection, heart failure, COPD, CVA, miscell. | 10.8% vs 5.5% | Y | Not clinically significant but may be important when interpreting drug levels. | Paxton and Briant, 1984. |
| | Acute uraemia<br>Chronic ureaemia | 10% vs 9%<br>10% vs 8.9 | N<br>N | Not significant.<br>Not indicated. | Tiula and Neuvonen, 1986 |
| Salicylate | Acl. hepatitis<br>Alc. cirrhosis | 27% vs 34%<br>27% vs 41% | N<br>Y | Not known. Bilirubin and hypoalbuminaemia implicated in binding defect. | Brodie and Boobis, 1978. |
| Sulphadiazine | Alc. hepatitis<br>Alc. cirrhosis | 46% vs 58%<br>46% vs 51% | Y<br>N | Not known. Bilirubin and hypoalbuminaemia implicated in binding defect. | Brodie and Boobis, 1978. |

TABLE 1 (continued)

| Drug | Disease | % Free or free fraction (control vs patient) | Sig. diff. | Clinical sig./ comment | References |
|---|---|---|---|---|---|
| Sulphisoxazole | Uraemia | 5.2% vs 21.8% | | Not indicated. Carbamylation of drug binding site I implicating in defect; site II not affected. | Calvo et al., 1982. |
| Theophylline | Acute illness<br>in COPD | 54.6% vs 69.7%<br>7.4 vs 8.1 ($\mu$g/ml) | Y<br>N | Not significant as free concentration is not changed significantly. | Zarowitz et al. 1985. |
| Tolfenamic acid | Renal disease<br>Liver disease | 0.08% vs 0.17%<br>0.08% vs 0.29% | Y<br>Y | Not clear. High affinity for red blood cells means that these may act as reserve binding sites when free fraction increases. | Laznicek and Senius, 1986 |
| Valproic acid | Renal disease | 8.4% vs 20.3% | Y | Not clear. May lead to increased incidence of toxicity. Important in drug monitoring interpretation. | Gugler and Mueller, 1978. |
| | Early pregnancy *<br>Mid pregnancy<br>Late pregnancy | 9.4% vs 11.5%<br>9.4% vs 12.1%<br>9.4% vs 14.6% | Y<br>Y<br>Y | Important in drug monitoring. Decreased albumin serum concentration implicated in binding defect. | Perucca et al., 1981. |
| | IDDM | 6.2% vs 7.6% | Y | Not significant if diabetes is well controlled. If poorly controlled increased free conc. may be greater. | Gatti et al., 1987. |
| Verapamil | Arrhythmia | – | – | Not indicated. Pharmacokinetic change may be implicated. | McGowan et al., 1982. |
| | Liver disease | 0.099 vs 0.16 | Y | Clinical end point effective to titrate dose so change not significant in therapy. Change may be relevant when interpreting kinetic data and total drug concentrations. | Giacomini et al., 1984. |
| Warfarin | Chronic cardiac failure | 1% vs 1% | N | No change expected. | Fitchl et al., 1983. |

TABLE 1 (continued)

| Drug | Disease | % Free or free fraction (control vs patient) | Sig. diff. | Clinical sig./ comment | References |
|---|---|---|---|---|---|
| Warfarin | NIDDM | 1.1% vs 1% | N | Not indicated (but no change expected) | O'Byrne et al., 1988. |
| Zomepirac | Uraemia | 1.4% vs 4% | Y | Decrease due to endogenous inhibitors Not clinically sig. | Pritchard et al., 1983. |

Y, yes; N, no; MI, myocardial infarction; Transpl, transplant; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; CVA, cerebro-vascular accident; AGP, $\alpha_1$-acid glycoprotein; $K_a$, drug–protein association constant; miscel, miscellaneous; $V_d$, apparent volume of distribution; Alc, alcoholic, NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

* Although pregnancy is not a disease, it can give rise to changed binding; therefore it has been included in this table.

permeability of capillaries, impaired return of albumin to the plasma compartment, due to impaired drainage of the lymph vessels (Barre et al., 1983), conformational changes of the protein molecule resulting in changes in drug binding affinity e.g. glycosylation of albumin (Shaklai et al., 1984) and an increase in the concentration of endogenous compounds which may compete with drugs for binding sites. Examples of this latter effect, which can cause an alteration in the affinity of the binding protein for a particular drug, include binding competition by free fatty acids in stress or hyperlipidaemia, bilirubin in jaundice (Barre et al., 1983) and 2-hydroxybenzoylglycine in uraemia (Fiset et al., 1986). An increase in AGP concentration in the plasma in various disease states causing stress or inflammation (Piafsky et al., 1978; Piafsky, 1980) can increase the plasma binding of basic drugs. AGP may be variable in concentration (0.38–1.05 g/l) in physiological conditions such as pregnancy (Krauer, 1984; Dwyer, 1988); however, the clinical implications of this are controversial. Most commonly a decrease in total body albumin is seen in a range of debilitating disease states including burns, cancer, cardiac failure, cystic fibrosis, renal failure, nutritional deficiency, liver diseases, and after surgery (Tillement et al., 1978; Øie, 1986). Examples of alterations in protein binding in specific disease states are shown in Table 1. The more important disease states involved are discussed below.

## Common disease states which lead to altered plasma protein binding

*Cardiac disease*

Cardiac diseases are life-threatening and, therefore, drug therapy plays an important role in the medical management of these conditions, particularly during acute phases. Increased concentrations of AGP have been shown to occur after myocardial infarction (MI). Many antiarrhythmic drugs are basic in nature and therefore bind to AGP. A reduction in their free serum concentration, due to increased binding, would theoretically reduce the therapeutic effects achieved from a particular total (free + bound) serum concentration. David et al. (1983) have published a study on disopyramide plasma protein binding after MI, with a follow-up for an average of 75 days post MI. Their data indicated that the AGP concentration increased from days 1–5 and then gradually decreased to the pre-infarct levels several months later (73.5 ± 7.8 days). A negative correlation of disopyramide free fraction (free concentration/ total concentration) and plasma AGP concentration was demonstrated: however, large inter- and intra-patient variations in protein concentration

and drug free fractions existed. A concentration dependent binding pattern over the therapeutic range of disopyramide (2–5 mg/l) was also shown. Caplin et al. (1985) have studied the change in serum protein binding of the antiarrhythmic drugs flecainide and disopyramide post MI. These drugs are both bound to AGP, the latter more strongly bound than the former. In their study the AGP levels increased from 1.04 g/l to 1.80 g/l (normal range 0.55–1.40 g/l; Schmid, 1975) in the first 5 days post MI. The serum binding of disopyramide increased from 80% to 87% over the same period, while for flecainide the serum binding decreased from 61% to 53%. The authors concluded that for weakly bound drugs such as flecainide the binding may be inhibited by endogenous compounds competing for binding sites; however, strongly bound compounds e.g. disopyramide were not displaced and exhibited increased binding. Krauss et al. (1986) showed that lignocaine has a concentration-dependent binding mainly to AGP, although serum albumin also plays a role. Again increased AGP concentrations post MI will influence this drug's pharmacokinetics. Shand (1984) had previously reviewed the implications of an increased AGP concentration with respect to lignocaine plasma binding. He concluded that, while there was evidence of accumulation of lignocaine in MI patients, there remained doubt whether the free drug plasma concentrations of lignocaine needed to be measured since the effectiveness of lignocaine can readily be determined clinically.

Fitchl et al. (1983) studied the serum protein binding of diazepam, digitoxin, warfarin and phenytoin (as marker drugs bound to serum albumin) and propranolol and imipramine (as markers bound to AGP) in severe chronic cardiac failure. They concluded that binding of all the marker drugs was not altered significantly. The importance of plasma protein binding on the pharmacodynamics of drugs active on the myocardium has been well illustrated, however, by Gillis and Kates (1986). In their study, the myocardial uptake of the antiarrhythmic drug propafenone and its effect (QRS widening) were considered using the perfused rabbit heart. A positive correlation was shown between the steady state free fraction of propafenone in the perfusing solution and the maximal effect over a range of binding values (0–92%). Variable binding was achieved by altering the AGP concentration in the perfusing solution. The variability of AGP in MI in man may, therefore, have an effect on the pharmacodynamics of propafenone which is 98% bound in human serum.

*Renal disease*

The kidneys are major organs of elimination and detoxification. Poor kidney function may, therefore, alter the protein binding of drugs in plasma by virtue of accumulation of drug metabolites and endogenous waste compounds which may compete with or alter the affinity of binding proteins for drugs.

Pritchard et al. (1983) have investigated the plasma binding of the non-narcotic analgesic, zomepirac in renal patients. This drug, which is highly bound to plasma proteins (98%), exhibited decreased plasma protein binding in uraemia (% free 4% vs 1.4%). They showed that zomepirac binding was unaffected by its metabolites or free fatty acids, and thus concluded that the decrease in binding was due to a decreased affinity of the albumin, possibly due to the presence of other endogenous inhibitors. The clinical implication of the 3-fold increase in free fraction was not indicated, and may not be significant.

Frey and Frey (1984) reported altered plasma protein binding of prednisolone in patients with the nephrotic syndrome. They found that nephrotic patients had a higher prednisolone association constant ($K_a$) for albumin compared to controls ($4.20 \times 10^3\ M^{-1}$ vs. $2.26 \times 10^3\ M^{-1}$) and tended also to have higher association constants for transcortin, the specific binding protein for prednisolone. This latter difference was, however, not significant. The concentration of prednisolone bound to transcortin and albumin was, however, lower in nephrotic patients than in control subjects (unbound prednisolone was not significantly different). Consequently, the total prednisolone concentration in plasma was lower in nephrotic patients. The decreased binding was due to lower transcortin and albumin concentrations in nephrotic patients which decreased the binding capacity for both proteins. Although these alterations in

protein binding in part explain the altered disposition of prednisolone in the nephrotic syndrome, the clinical implication of the changed binding is not known.

Tiula and Neuvonen (1986) reported that uraemia increased the free fraction of diazepam and phenytoin, but not propranolol (which is bound to AGP), within their respective therapeutic ranges. Further studies by Tiula and Elfving (1987) showed altered protein binding of phenytoin, diazepam and propanolol in age-related decreased renal function. The free fraction of phenytoin and diazepam was increased due to an age related decrease in renal function concurrent with a degree of hypoalbuminaemia in elderly patients. The change in propranolol free fraction was shown to be significantly correlated to the AGP levels. Although this study did not show whether significant clinical effects occur due to these changes in protein binding, the changes in free fraction may explain the changed pharmacokinetic profiles noted for these drugs in elderly patients. Previous work on phenytoin suggested that although there was an increased free fraction of phenytoin (due to the increased serum urea and associated with decreased renal function) the hepatic clearance increased in proportion and thus at steady-state a lower total (free + bound), but unchanged therapeutic free, phenytoin concentration was present (Rowland, 1984).

Calvo et al. (1982) studied the effect of carbamylation (the addition of urea to the amino acid residues of proteins) of plasma proteins and uraemia on drug binding using the model drugs suphisoxazole (a drug bound to site I on the albumin molecule) and diazepam (bound to site II). They showed that carbamylation decreased the site I binding of suphisoxazole but had no effect on the site II binding of diazepam. They also showed, however, that other displacers (endogenous) in uraemia did cause displacement of diazepam from site II. The clinical significance of this changed binding was not discussed in their report. Grossman et al. (1982) found the binding of diazepam to be decreased in 3 renal conditions, namely nephrotic syndrome, uraemia and after kidney transplant. The binding ratio (bound concentration : free concentration) was shown to be correlated to serum albumin concentrations. With lignocaine, which is bound primarily to AGP, the free fraction was reduced in uraemia and in renal transplant recipients. This increased binding correlated with the increased AGP concentrations in these conditions. This latter study, therefore, highlighted the fact that the type of protein involved in binding and the type of renal disease involved is of importance in determining the alteration of binding of a particular drug.

Although there are alterations in the binding of digitoxin (a neutral drug) in uraemic patients during haemodialysis, and between haemodialysis, this change is small and hence unlikely to be of any therapeutic significance (Lohman and Merkus, 1987). These latter authors pointed out that previous reports of decreased digitoxin binding during haemodialysis was an in vitro artefact, due to heparin-induced lipolysis (releasing free fatty acids) occurring after the collection of blood samples for binding determinations. The free fatty acids compete with digitoxin for albumin binding sites. The use of a lipase inhibitor in the collection tubes prevents the lipolysis and therefore the displacement of digitoxin. Their work further corroborates this conclusion, in that saliva levels of digitoxin in patients undergoing haemodialysis and treated either with or without heparin were similar (0.41 ng/ml).

In an earlier study Jacobi et al. (1983) examined the plasma protein binding of lignocaine in two patients with end stage renal disease. They reported that although the patients had elevated AGP concentrations, unbound fractions of the drug were high (0.55 and 0.68). The clearance of total and unbound lignocaine in haemodialysis was negligible and no dosage adjustment was necessary.

The percentage protein binding of the antiarrhymic drug lorcainide has been shown not to differ significantly between patients with end stage renal disease, cardiac patients and normal volunteers (70.96, 75.30 and 73.97, respectively). This kinetic study also showed no significant differences in the drug half-lives in the 3 conditions so dosage adjustment was not indicated (Somani et al., 1984).

The non-steroidal anti-inflammatory drug,

tolfenamic acid, is 99.9% bound to plasma proteins in normal plasma i.e. percentage free is 0.1%. Laznicek and Senius (1986) reported that the percentage free increased to 0.17% ($P < 0.001$) in renal disease. These authors indicated, however, that tolfenamic acid shows a lipophilic affinity for red blood cells which may act as reserve binding sites, so that in conditions where increases in free fraction occur, these reserve sites may be available to bind excess free drug, thus maintaining a relatively constant active free drug concentration in vivo. Metoclopramide free fraction does not change in renal disease compared to healthy volunteers (0.59 vs 0.60). This drug has been shown to bind mainly to AGP and to a limited extent to albumin (Webb et al., 1986).

Fiset et al. (1986) published work on the protein binding of the cephalosporin ceftriaxone and the inhibiting effect of 2-hydroxybenzoylglycine, a specific binding inhibitor present in uraemia. Ceftriaxone showed concentration-dependent binding over the therapeutic range and also showed an increase in free fraction in the presence of 2-hydroxybenzoylglycine. The therapeutic consequence of this binding inhibition is, however, unclear as the increase in free fraction in renal disease may be compensated for by non-renal handling of the drug.

A useful summary has been presented by Reidenberg and Drayer (1984), in their review of drug protein binding in renal diseases. They pointed out that renal disease mainly affects the protein binding of acidic drugs. The main effect is a decrease in the protein binding caused either by a decrease in the concentration of albumin (due to loss from the body) or competitive inhibition of drug binding by endogenous inhibitors. These endogenous materials may also cause alteration in the albumin structure leading to altered binding of drugs.

*Hepatic diseases*

In hepatic diseases the compromised ability of the liver to manufacture albumin may result in hypoalbuminaemia (eg. Pacifici et al., 1986). There may also be an increase in endogenous compounds such as bilirubin, which can act as a binding inhibitor for some drugs. Brodie and Boobis (1978) reported that the binding of phenylbutazone, salicylate and sulphadiazine was decreased in patients with alcoholic liver disease (cirrhosis and hepatitis) when compared to controls.

A decreased binding of verapamil in patients with liver disease, with the free fraction increasing significantly from 0.099 to 0.16, has been reported (Giacomini et al., 1984). This change in the unbound fraction was shown to be correlated with lowered albumin and AGP concentrations. Verapamil is, however, highly extracted in the liver and, therefore, its clearance would be insensitive to changes in binding, meaning that steady-state total drug concentrations after oral dosing would not be expected to change. The free fraction is, however, expected to be $\approx 60\%$ higher in liver disease. The clinical end point for verapamil is clearly defined (prolongation of PR interval), thus titration of dosage in altered binding states can be carried out pharmacodynamically. Conflicting results on verapamil protein binding in liver disease are, however, apparent in the literature eg. Echizen and Eichelbaum (1986) cited data indicating that there was no change in the protein binding of verapamil in liver disease.

In an early review on the influence of liver disease on plasma protein binding Blaschke (1977) concluded that the clinical implications of protein binding changes in liver disease were unclear and unpredictable, due to the complex nature of liver function on drug disposition. There is a lack of data on the clinical implications of the changed binding. The situation has changed little over the years and indeed at a recent symposium Williams (1986) maintained that carefully designed experimental studies needed to be carried out to determine effective pharmacodynamic relationships between free drug concentrations and liver disease.

*Diabetes mellitus*

Patients with diabetes mellitus have high levels of circulating glucose in their blood which can lead to non-enzymatic glycosylation of several proteins including albumin. This glycosylation has been shown by Ruiz-Cabello and Erill (1984), and more recently by Kemp et al. (1987), to be im-

plicated in decreased binding of the acidic drugs suphamethoxazole and phenytoin, both of which bind to site I on the albumin molecule. Kearns et al. (1988) have shown that a significant correlation exists between phenytoin free fraction and the extent of glycosylation of albumin. In contrast Gatti et al. (1987), who studied the serum protein binding of phenytoin and valproic acid in sera from insulin-dependent diabetes mellitus (IDDM) patients and control subjects, reported no significant changes in the free fractions of phenytoin, but a significant increase in the free fraction of valproic acid in IDDM serum. The valproic acid free fraction was found to be correlated to the free fatty acid concentration in the IDDM serum rather than the serum albumin or glycosylated protein concentrations. This is not surprising since valproic acid is itself a fatty acid and is therefore involved in competition with endogenous fatty acids for albumin binding sites. Recent studies in these laboratories (Grainger-Rousseau, 1988) have also shown that the serum from IDDM patients has a decreased capacity for valproic acid binding (Fig. 1).

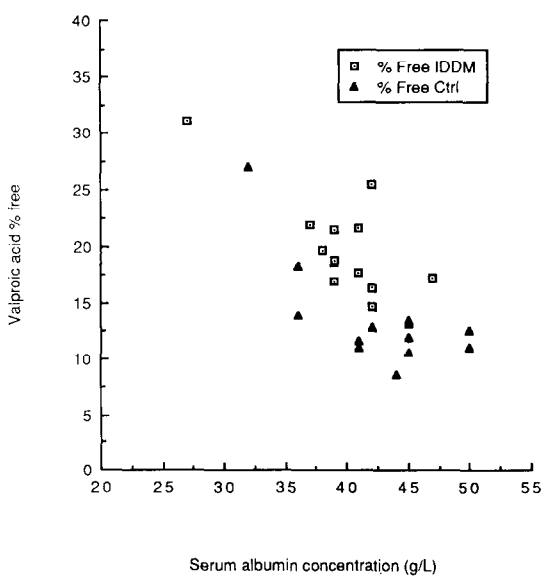


Fig. 1. Scattergram of valproic acid % free vs serum albumin concentration in serum from IDDM patients and age-matched controls. (Total serum concentration 90 μg/ml).

In non-insulin dependent diabetic patients O'Byrne et al. (1988) showed that the plasma protein binding of lignocaine and warfarin was unchanged when compared with control subjects. Earlier work by Miller et al. (1978), however, showed a 25% increase in the free fraction of tolbutamide (0.032 to 0.040) due to an age-related decrease in albumin concentration, and concluded that this may partially explain the higher incidence of hypoglycaemic reactions in elderly patients receiving tolbutamide therapy.

*Other diseases*

*Respiratory disorders.* Zarowitz et al. (1985), reported that theophylline protein binding was altered in acutely ill patients with chronic obstructive pulmonary disease (COPD) when compared to controls with uncomplicated COPD. The total theophylline concentration in acutely ill patients was 11.8 μg/ml vs 13.7 μg/ml in controls. Although a higher dose was administered to acutely ill patients, the free concentration was similar, 7.4 μg/ml vs 8.1 μg/ml. Theophylline is bound mainly to albumin which was found to be decreased in the serum of the acutely ill patients. The authors concluded that there may be a tendency towards theophylline toxicity in acutely ill asthmatics due to an increase in free theophylline plasma concentrations, although none was reported in the patients in their trial.

Pulmonary infections are a major factor in the morbidity and mortality of cystic fibrosis (CF). The pulmonary infection is often recurring and requires intermittent antibiotic treatment. Antibiotics used in the treatment of pulmonary infections in CF have been reported to exhibit altered pharmacokinetics (Kelly and Lovato, 1984). The pharmacokinetics of flucloxacillin, a highly serum protein-bound penicillin has, for example, been shown to be altered in CF patients when compared to controls (Collier et al., 1986). One factor that may contribute to this altered kinetic picture is altered serum protein binding. Recent work carried out in these laboratories (Grainger-Rousseau, 1988) showed that CF patients had a significantly greater percentage free flucloxacillin than age- and sex-matched controls over the concentration range 5–100 μg/ml (Fig. 2).

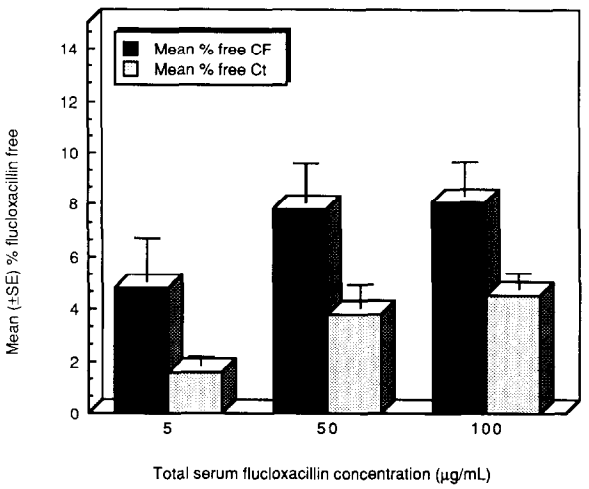


Fig. 2. Comparison of flucloxacillin serum protein binding (mean ± S.E.M.) in 6 cystic fibrosis patients and age- and sex-matched control subjects at 3 total serum flucloxacillin concentrations.

*Acute illness.* The binding of basic drugs to the acute phase reactant AGP has been well documented and several disease states have been associated with increases in AGP concentrations in plasma. These include cancer, MI, acute infection and inflammation. Paxton and Briant (1984) have found increased plasma binding of propranolol in elderly patients with various acute illnesses which resulted in elevated AGP levels. Baruzzi et al. (1986) also discussed the alteration in serum binding of the anticonvulsant carbamazepine in disease states associated with increased AGP levels. A caution in the interpretation of total serum concentrations of carbamazepine under such conditions is warranted, since this anticonvulsant has a narrow therapeutic range (4–12 µg/ml). An increased plasma protein binding of the basic drugs propranolol and chlorpromazine due to disease-induced elevations of AGP has also been reported by Piafsky et al. (1978).

## Conclusion

It is clear from this short review of published research that disease can have a major influence on the binding of drugs to plasma proteins, by a variety of mechanisms. It has, however not been made clear, in many of the published reports, what the clinical implications of this changed binding are.

From a pharmacokinetic point of view a decreased binding in plasma will facilitate drug distribution out of the plasma compartment and therefore increase the apparent volume of distribution of the drug concerned. Any increased free drug concentrations in the plasma will also lead to increased drug elimination by glomerular filtration and metabolism (assuming the drug does not have a high extraction ratio; Gibaldi and Koup, 1981; McElnay and D'Arcy, 1983). Together these effects will tend to maintain free drug concentrations in the plasma compartment at levels comparable to normal subjects and therefore maintain the pharmacodynamic effects within normal limits. Although the free drug concentration may remain normal, if decreased binding occurs the total drug concentration will decrease due to increased drug distribution and elimination. This phenomenon has obvious implications during therapeutic drug monitoring, since the therapeutic effect will be achieved from a lower total plasma drug concentration. In such a situation, to avoid possible toxicity, it is important that drug dosage is not increased, based on the low plasma total drug concentration. For a drug with a high extraction ratio, plasma binding displacement will lead to an increased apparent volume of distribution and an increased half-life, but clearance will remain unaffected. If given by multiple dosing i.v. the mean steady state total serum concentration will remain unchanged (with lesser fluctuations between peak and trough), but since the free fraction is increased due to displacement, the steady-state free concentration (and therefore therapeutic effect) will increase. This will also be the case for orally administered drugs with a high renal extraction ratio. However, if the displaced drug is given orally, and has a high hepatic extraction ratio, no change in therapeutic effect would be expected since the fraction escaping first pass metabolism (which is already low) will be decreased further. In this latter case, steady state total drug concentrations will decrease and steady state free drug concentrations will approximate to predisplacement levels.

Theoretically an increased plasma protein binding, eg. to AGP in disease states, will decrease the apparent volume of distribution and increase the steady state total plasma concentration of drugs with low extraction ratios. From a pharmacokinetic standpoint, however, the free (and pharmacologically active) drug concentration should remain at approximately normal levels. If the drug has a high extraction ratio essentially the opposite effects to those described above for high extraction drugs will take place.

The situation will also obviously change if drug elimination is inhibited by the disease eg. renal or liver failure. More detailed information on pharmacodynamics is required to help clarify the situation. Such data could be easily generated during routine therapeutic drug monitoring of patients with various diseases requiring treatment with drugs which are highly bound to plasma proteins.

## References


Barre, J., Houin, G., Brunner, R.F., Bree, F. and Tillement, J.-P., Disease induced modifications of drug pharmacokinetics. *Int. J. Clin. Pharmacol. Res.*, 3 (1983) 215–226.

Baruzzi, A., Contin, M., Perucca, E., Albani, F. and Riva, R., Altered serum protein binding of carbamazepine in disease states associated with an increased $\alpha_1$-acid glycoprotein concentration. *Eur. J. Clin. Pharmacol.*, 31 (1986) 85–89.

Bergrem, H., Ritland, S., Opendal, I. and Bergran, A., Prednisolone pharmacokinetics and protein binding in patients with portosystemic shunt. *Scand. J. Gastroenterol.*, 18 (1983) 273–276.

Birkett, D.J. and Wanwimolruk, S., Albumin as a specific binding protein for drugs and endogenous compounds. In: J.-P. Tillement and E. Lindenlaub (Eds.), *Protein Binding and Drug Transport. Symposia Medica Hoechst. Vol. 20* Schattauer, Stuttgart, New York, (1986) pp. 11–24.

Blaschke, T.F., Protein binding and kinetics of drugs in liver disease. *Clin Pharmacokinet.*, 2 (1977) 32–44.

Brodie, M.J. and Boobis, S., The effect of chronic alcoholic ingestion and alcoholic liver disease on binding of drugs to serum proteins, *Eur. J. Clin. Pharmacol.*, 13 (1978) 435–438.

Calvo, R., Carlos, R. and Erill, S., Effects of carbamylation of plasma proteins and competitive displacers on drug binding in uraemia. *Pharmacology*, 24 (1982) 248–252.

Caplin, J.L., Johnston, A., Hamer, J. and Camm, A.J., The acute changes in serum binding of disopyramide and flecainide after myocardial infarction. *Eur. J. Clin. Pharmacol.*, 28 (1985) 253–255.

Collier, P.S., Steen, H., Redmond, A. and Wallwin, J., Pharmacokinetics and bioavailability of flucloxacillin in cystic fibrosis. In *Proceedings of 5th Mediterranean Congress of Chemotherapy*, Cairo, Egypt, Abstract (1986) 0166.

David, B.M., Ilett, K.F., Whitford, E.G. and Stenhouse, N.S., Prolonged variability in plasma protein binding of disopyramide after acute myocardial infarction. *Br. J. Clin. Pharmacol.*, 15 (1983) 435–441.

Dwyer, R., Flynn, R.J., Duly, E. and Moore, J., The effect of labour and epidural analgesia on plasma concentrations of drug binding proteins. *Br. J. Clin. Pharmacol.*, 26 (1988) 635–636 P.

Echizen, H. and Eichelbaum, M., Clinical pharmacokinetics of verapamil, nifedipine and diltiazem. *Clin. Pharmacokinet.*, 11 (1986) 425–449.

Fiset, C., Valee, F., LeBel, M. and Bergeron, M.G. Protein binding of ceftriaxone: Comparison of three techniques of determination and the effect of 2-hydroxybenzoylglycine, a drug binding inhibitor in uraemia. *Ther. Drug Monit.*, 8 (1986) 483–489.

Fitchl, B., Meister, W. and Schmied, R., Serum protein binding of drugs is not altered in patients with severe chronic cardiac failure. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 21 (1983) 241–244.

Frey, F.J. and Frey, B.M., Altered plasma protein binding of prednisolone in patients with the nephrotic syndrome. *Am. J. Kid. Dis.*, 3 (1984) 339–348.

Gatti, G., Crema, F., Attardo-Parrinello, G., Frantino, P., Aguzzi, F. and Perucca, E., Serum protein binding of phenytoin and valproic acid in insulin-dependent diabetes mellitus. *Ther. Drug Monit.*, 9 (1987) 389–391.

Giacomini, K.M., Massoud, N., Wong, F.M. and Giacomini, J.C., Decreased binding of verapamil to plasma proteins in patients with liver disease. *J. Cardiovasc. Pharmacol.*, 6 (1984) 924–928.

Gibaldi, M. and Koup, J.R., Pharmacokinetic concepts. Drug binding, apparent volume of distribution and clearance. *Eur. J. Clin. Pharmacol.*, 20 (1981) 299–305.

Gillis, A.M. and Kates, R.E., Influence of protein binding on the myocardial uptake and pharmacodynamics of propafenone. *J. Cardiovasc. Pharmacol.*, 8 (1986) 1163–1167.

Grainger-Rousseau, T.-J., *Influence of disease on serum protein binding of drugs.* MSc Thesis, The Queen's University of Belfast, 1988.

Grossman, S.H., Davis, D., Kitchell, B.B., Shand, D.G. and Routledge, P.A., Diazepam and lidocaine plasma protein binding in renal disease. *Clin. Pharmacol. Ther.*, 31 (1982) 350–357.

Gugler, R. and Mueller, G., Plasma protein binding of valproic acid in healthy subjects and in patients with renal disease. *Br. J. Clin. Pharmacol.*, 5 (1978) 441–446.

Harron, D.W.G., McElnay, J.C., D'Arcy, P.F. and Collier, P.S., An in vitro system for the correlation of drug/protein binding with variable plasma protein profile. *Int. J. Pharm.*, 1 (1978) 61–64.

Holtzman, J.L., The role of protein binding in drug therapy. *Ration. Drug Ther.*, 18 (1984) 1–5.

Jacobi, J., McGory, R.W., McCoy, H. and Matzke, G.R., Hemodialysis clearance of total and unbound lidocaine. *Clin. Pharm.*, 2 (1983) 54–57.

Kearns, G.L., Kemp, S.F., Turley, C.P. and Nelson, D.L.,

Protein binding of phenytoin and lidocaine in pediatric patients with Type I diabetes mellitus. *Dev. Pharmacol. Ther.*, 11 (1988) 14–23.

Kelly, H.W. and Lovato, C., Antibiotic use in cystic fibrosis. *Drug Intell. Clin. Pharm.*, 18 (1984) 772–783.

Kemp, S.F., Kearns, G.L. and Turley, C.P., Alteration of phenytoin binding by glycosylation of albumin in IDDM, *Diabetes*, 36 (1987) 505–509.

Krauer, B., Dayer, P. and Anner, R., Changes in serum albumin and $\alpha_1$-acid glycoprotein concentration during pregnancy: an analysis of foetal-maternal pairs. *Br. J. Obstet. Gynaecol.*, 91 (1984) 875–881.

Krauss, E., Polnaszek, C.F., Scheeler, D.A., Halsall, H.B., Eckfelot, J.H. and Holtzman, J.L., Interaction between human serum albumin and $\alpha_1$- acid glycoprotein in the binding of lidocaine to purified protein fractions and sera. *J. Pharmacol. Exp. Ther.*, 239 (1986) 754–759.

Kremer, J.M.H., Wilting, J. and Janssen, H.M., Drug binding to human alpha-1-acid glycoprotein in health and disease. *Pharmacol. Rev.*, 40 (1988) 1–47.

Laznicek, M. and Senius, K.E.O., Protein binding of tolfenamic acid in the plasma from patients with renal and hepatic disease. *Eur. J. Clin. Pharmacol.*, 30 (1986) 591–596.

Lohman, J.J.H.M. and Merkus, F.W.H.M., Plasma protein binding of digitoxin and some other drugs in renal disease. *Pharm. Weekbl. (Sci Ed.)*, 9 (1987) 75–78.

McElnay, J.C. and D'Arcy, P.F., Protein binding displacement interactions and their clinical importance. *Drugs*, 25 (1983) 495–513.

McGowan, F.X., Reiter, M.J., Pritchett, E.L. and Shand, D.G., Verapamil plasma binding: Relationship to $\alpha_1$-acid glycoprotein and drug efficacy. *Clin. Pharmacol. Ther.*, 33 (1983) 485–490.

Miller, A.K., Adir, J. and Vestal, R.E., Tolbutamide binding to plasma proteins of young and old human subjects. *J. Pharm. Sci.*, 67 (1978) 1192–1193.

O'Byrne, P.O., O'Connor, P. and Feely, J., Plasma protein binding of lignocaine and warfarin in non-insulin dependent diabetes mellitus. *Br. J. Clin. Pharmacol.*, 26 (1988) 648 P.

Øie, S., Drug distribution and binding. *J. Clin. Pharmacol.*, 26 (1986) 583–586.

Pacifici, G.M., Viani, A., Taddeucci-Brunnelli, G., Rizzo, G., Carrai, M. and Schulz, H.-U., Effects of development, ageing and renal and hepatic insufficiency as well as hemodialysis on the plasma concentrations of albumin and $\alpha_1$-acid glycoprotein: implications for binding of drugs. *Ther. Drug Monit.*, 8 (1986) 256–265.

Paxton, J.W. and Briant, R.H., $\alpha_1$-acid glycoprotein concentrations and propranolol binding in elderly patients with acute illness. *Br. J. Clin. Pharmacol.*, 18 (1984) 806–810.

Perucca, E., Ruprah, M. and Richens, A., Altered drug binding to serum proteins in pregnant women: therapeutic relevance. *J. Roy. Soc. Med.*, 74 (1981) 422–426.

Piafsky, K.M., Disease induced changes in the plasma binding of basic drugs. *Clin. Pharmacokinet.*, 5 (1980) 246–262.

Piafsky, K.M., Borgå, O., Odar-Cederlof, I., Johansson, C. and Sjovqist, F., Increased plasma protein binding of propranolol and chlorpromazine mediated by disease induced elevations of plasma $\alpha_1$-acid glycoprotein. *N. Engl. J. Med.*, 299 (1978) 1435–1439.

Pritchard, J.F., O'Neill, P.J., Affrime, M.B. and Lowenthal, D.T., Influence of uraemia, haemodialysis and nonesterified fatty acids on zomepirac plasma protein binding. *Clin. Pharmacol. Ther.*, 34 (1983) 681–688.

Reidenberg, M.M. and Drayer, D.E., Alteration of drug protein binding in renal disease. *Clin. Pharmacokinet.*, 9 Suppl. 1 (1984) 18–26.

Rowland, M., Protein binding and drug clearance. *Clin. Pharmacokinet.*, 9, Suppl. 1 (1984) 10–17.

Ruiz-Cabello, F. and Erill, S., Abnormal serum protein binding of acidic drugs in diabetes mellitus. *Clin. Pharmacol. Ther.*, 36 (1984) 875–881.

Schmid, K., $\alpha_1$-acid glycoprotein. Chapter 4 In F.W. Putnam (Ed.), *The Plasma Proteins, Structure, Function and Genetic control, 1,* 2nd edn., Academic Press, 1975, pp. 184–222.

Shaklai, N., Garlick, R.L. and Bunn, H.F., Nonenzymatic glycosylation of human serum albumin alters its conformation and function. *J. Biol. Chem.*, 259 (1984) 3812–3817.

Shand, D.G., $\alpha_1$-acid glycoprotein and plasma lidocaine binding. *Clin. Pharmacokinet.*, 9, Suppl. 1 (1984) 27–31.

Somani, P., Simon, V., Gupta, R.K., King, P., Shapiro, R.S. and Stockard, H., Lorcainide kinetics and protein binding in patients with end-stage renal disease. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 223 (1984) 121–125.

Tillement, J.-P., Houin, G., Zini, R., Urien, S., Albengres, E., Barre, J., Lecomte, M. d'Athis, P. and Sebille, B., The binding of drugs to blood plasma macromolecules: recent advances and therapeutic significance, *Act. Drug Res.*, 13 (1984) 60–94.

Tillement, J.-P., Lhoste, F. and Giudicelli, J.F., Disease and drug protein binding, *Clin. Pharmacokinet.*, 3 (1978) 144–154.

Tillement, J.P. and Lindenlaub, E. (Eds.), *Protein Binding and Drug Transport, Symposia Medica Hoechst, Vol. 20,* Schattauer, Stuttgart, 1986.

Tiula, E. and Elfving, S., Serum protein binding of phenytoin, diazepam and propranolol in age-related decrease in renal function. *Annals Clin. Res.*, 19 (1987) 163–169.

Tiula, E. and Neuvonen, P.J., Effect of total drug concentration on the free fraction in uraemic sera. *Ther. Drug Monit.*, 8 (1986) 27–31.

Wanwimolruk, S. and Birkett, D.J., Structure binding relationships for sites I and II on albumin. In J.-P. Tillement and E. Lindenlaub (Eds.) *Protein Binding and Drug Transport. Symposia Medica Hoechst, Vol. 20* Schattauer, Stuggart-New York, 1986, pp. 134–154.

Webb, D., Buss, D.C., Fifield, R., Bateman, D.N. and Routledge, P.A. The plasma protein binding of metoclopramide in health and renal disease. *Br. J. Clin. Pharmacol.*, 21 (1986) 334–336.

Williams, R.L., Protein binding in hepatic disease: pharmacokinetic and clinical implications. In J.-P. Tillement and E. Lindenlaub (Eds.), *Protein Binding and Drug Transport. Symposia Medica Hoechst, 20,* Schattauer, Stuggart-New York, 1986, pp. 375–395.

Zarowitz, B., Shlom, J., Eichenhorn, M.S. and Popovich, J., Alternations in theophylline protein binding in acutely ill patients with COPD. *Chest*, 87 (1985) 766–769.