Br. J. clin. Pharmac. (1985), **19**, 823–825

The *ex vivo* plasma protein binding of theophylline in renal disease

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The plasma protein binding of theophylline was measured in 21 patients with renal disease and 21 healthy age and sex matched controls. The percentage of theophylline unbound to plasma was greater in patients with nephrotic sydrome and in chronic renal failure than in controls. In nephrotic syndrome the impairment of drug binding mirrored the marked degree of hypoalbuminaemia seen in this condition but in chronic renal failure the impairment of protein binding was greater than would be expected from the plasma albumin concentration changes. The percentage of theophylline free in plasma in renal disease may be increased (by as much as 50%). Such changes should be taken into account in interpreting the relationship between total plasma theophylline concentration and drug effect in renal disease.

Keywords theophylline renal disease protein binding

Introduction

We have observed that the plasma protein binding of theophylline in normal subjects (Buss *et al.*, 1983) and in patients with airways obstruction (Ebden *et al.*, 1984) shows remarkably little variability.

In view of the known influence of renal disease on the protein binding of drugs which bind to albumin, however (Gugler & Azarnoff, 1976), we have measured the protein binding of theophylline in plasma from such subjects.

Methods

Twenty-one patients with renal disease and 21 healthy controls matched for age (to within 3 years) and sex were studied. Fourteen patients had chronic renal failure with creatinine clearances below 10 ml/min of whom eight were on maintenance haemodialysis and the other seven chronic ambulatory peritoneal dialysis (CAPD). Five patients had the nephrotic syndrome without severe renal excretory impairment (creatinine clearance > 50 ml/min). The uraemic patients were receiving many drugs including multivitamins, aluminium hydroxide and antihypertensives and all the patients with nephrotic syndrome were receiving diuretics. After both patients and subjects gave informed consent (on an interdialysis day in the haemodialysis patients) plasma was obtained and theophylline plasma protein binding measured using the method of Buss *et al.* (1983).

Total non-esterified fatty acid concentrations were measured by a modification of the method of Duncombe (1964). Plasma albumin concentrations were estimated by immuno-nephelometry (Sternberg, 1977).

Results

Data are presented in Table 1. The percentage of unbound theophylline was increased in all

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three patient groups and plasma albumin concentration was reduced. The plasma non-esterified fatty acid concentrations were similar in all groups and not significantly different from control. When the binding ratio for all patients and controls was related to serum albumin concentration the relationship was significant ($r = 0.622$, $n = 42$, $P < 0.01$) with a slope similar to that obtained by plotting the corresponding values for human serum albumin solution. In the patients with renal excretory impairment, however, the binding was consistently lower than would be found in a similar concentration of human serum albumin (Figure 1 and Table 1).

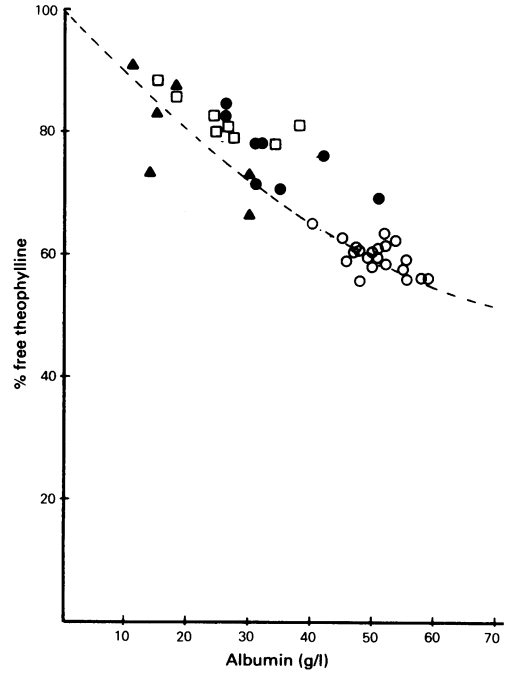

Figure 1 The relationship between the % of theophylline free in plasma and the plasma albumin concentration for patients (● chronic renal failure on haemodialysis, □ chronic renal failure on CAPD, ▲ nephrotic syndrome) and controls (○). The dotted line indicates this relationship in solutions of human serum albumin.

Discussion

To our knowledge, the plasma protein binding of theophylline in renal disease has not previously been reported. The fall in binding with low plasma albumin is expected since albumin is the major binding protein. Thus where albumin is being lost in the urine (nephrotic syndrome) the protein binding of theophylline was low.

The specific reason for the further depression of binding in those patients with renal excretory impairment has not been identified in this study but similar effects have been demonstrated on the binding of both several agents and we suspect that an endogenous inhibitor of binding and/or structural changes in albumin are responsible (Sjoholm *et al.*, 1976).

CAPD also appears to be associated with hypoalbuminaemia and in fact the plasma albumin and theophylline protein binding were lower in this group than in subjects with nephrotic syndrome, perhaps because marked hypoalbuminaemia was a more uniform finding in the CAPD group.

Although we have previously demonstrated that non-esterified fatty acids concentrations are

Table 1 Measured variables mean (range in parentheses) in patient groups and age- and sex-matched control subjects. The expected percentage free was calculated from human serum albumin solutions of equivalent concentration.

Parameters	*Haemodialysis patients mean* n = *8*	*Control mean (range)* n = *8*	*CAPD patients mean (range)* n = *7*	*Control mean (range)* n = *7*	*Nephrotic mean (range)* n = *6*	*Control mean (range)* n = *6*
Age (years)	42.8 (28–60)	44.4 (27–60)	42.8 (28–56)	44.8 (28–58)	29.6 (18–60)	31.0 (18–65)
Albumin (g/l)	36.0 (26–51)	48.7‡ (40–59)	26.3 (15–38)	50.6* (46–54)	19.6* (11–30)	53.7† (51–56)
NEFA (μmol/l)	377.2 (64–942)	415.6 (245–548)	359.6 (121–640)	494.1 (200–1157)	559.5 (74–1422)	468.5 (264–735)
Observed % free	76.4* (69.0–84.8)	61.1 (56.2–65.0)	82.2* (77.9–88.3)	58.9 (55.2–66.2)	78.8 (66.6–90.7)	58.8* (56.4–63.9)
Expected % free	68.1 (59.8–75.0)	60.9 (56.2–63.7)	74.7 (66.8–84.4)	60.0 (58.5–62.3)	80.2 (72.0–88.4)	58.5 (57.5–59.8)

*$P < 0.001$, † $P < 0.005$, ‡ $P < 0.05$ *vs* control group (Mann-Whitney U test)

related, albeit weakly, to theophylline protein binding (Buss *et al.*, 1983) no patient group had a significant elevation of this variable compared with its corresponding control group. This indicates that NEFA concentration is not a major determinant of plasma protein binding of the drug in renal disease. The normal levels in haemodialysis patients contrasts with the study of Grossman *et al.* (1982) who found an increase in this variable, although they, like us, found the NEFA concentrations to be normal in nephrotic syndrome. Other workers have found the plasma NEFA concentration to be normal in chronic, as distinct from acute renal failure, however, and our results are consistent with these findings (Losowsky & Kenwood, 1968).

There are two points of potential clinical significance in this finding. Firstly, it has been reported that theophylline clearance in renal disease is similar to that in normal controls (Krudjan *et al.*, 1982). This study measured total plasma theophylline clearance, however, so that if protein binding is reduced in renal disease, the plasma clearance of free (and presumably active drug) may be as much as a 50% lower than normal. Similarly the plasma theophylline concentration at any given total plasma drug concentration may be up to 50% greater in patients with renal disease than in controls. Since total plasma concentration is normally used to monitor therapy, such patients may show clinical toxicity at total plasma concentrations normally regarded as within the therapeutic range. Although in most patient with airways obstruction, total plasma drug concentration is a good guide to free theophylline concentration (Ebden *et al.*, 1983), measurement of free (rather than total) drug concentration may be more valuable in optimising dosage in patients with severe renal disease, should they require theophylline therapy.

We thank Dr G. A. Coles for allowing us to study patients under his care and Napp Laboratories for financial assistance. This work was originally published in abstract form (*Br. J. clin. Pharmac.* (1984), **17**, 229–230P).

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(*Received November 27, 1984, accepted January 24, 1985*)