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The plasma protein binding of metoclopramide in health and renal disease

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The plasma protein binding of metoclopramide was measured after addition of the drug (60 ng ml^{-1}) to plasma from 18 patients with renal disease and 18 age and sex matched healthy individuals. The mean free fraction in renal disease (0.59 range 0.41–0.71) was not significantly different from controls (mean 0.6 range 0.56–0.69). In both groups the binding ratio of metoclopramide was significantly related to plasma α_1-acid glycoprotein (AAG) concentration but not to albumin or plasma non-esterified fatty acids concentration. Metoclopramide bound to human serum albumin (HSA) to a limited extent and to human AAG to a greater extent indicating that AAG is the major binding protein for the drug in plasma.

Keywords metoclopramide plasma protein binding α_1-acid glycoprotein health renal disease

Introduction

Although albumin is the major drug-binding protein in plasma, some basic compounds bind to a variable extent to the acute phase protein, α_1-acid glycoprotein (AAG) (Piafsky, 1980). Since metoclopramide is a basic agent, we decided to examine the relationship between its plasma protein binding and the concentrations of AAG and albumin *in vitro*, in plasma from healthy individuals and in a group with known elevation of AAG (i.e. patients with chronic renal failure) (Piafsky, 1980).

Methods

Blood was withdrawn by direct venepuncture from 18 healthy drug-free volunteers and 18 consenting patients with chronic renal disease. Twelve of the patients had chronic renal failure with creatinine clearance below 10 ml min^{-1} in all cases. Six were on maintenance dialysis and six on chronic ambulatory peritoneal dialysis (CAPD) and were receiving a number of drugs including multivitamins, aluminium hydroxide and antihypertensives. The remaining six patients had the nephrotic syndrome without severe renal excretory impairment (creatinine clearance > 50 ml min^{-1}) and were receiving diuretics. Blood was collected in heparinised glass tubes (7.5 u heparin ml^{-1} added blood), stored on ice and centrifuged at 500 *g* within 30 min and the plasma stored at −20°C before being analysed (within 6 weeks). For each patient, a control volunteer who was sex- and age-matched (to within 4 years) was selected. Plasma protein binding was measured as described previously for theophylline (Buss *et al.*, 1983), except that [^{14}C]-metoclopramide (at a therapeutic concentration of 60 ng ml^{-1}) was added to the buffer after drying down under nitrogen. Purity of the radio-label was > 98% and recovery of radio-label from the dialysis

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cells was always > 95%. Equilibrium was attained in 2 h and the coefficient of variation of duplicate plasma samples was 4%.

Albumin and AAG were measured by laser nephelometry (Sternberg, 1977) and non-esterified fatty acids concentrations by the method of Duncombe (1964).

Results

Metoclopramide bound to albumin to a limited extent, changing little with increasing albumin concentration, so that at the albumin concentration seen in the healthy controls (50 g l^{-1}) the free fraction was approximately 0.86 (Figure 1). Addition of AAG (0.75 g l^{-1}) to HSA enhanced the plasma protein binding at all albumin concentrations so that the free fraction at 50 g l^{-1} albumin had fallen to approximately 0.64. Addition of AAG at a higher concentration (2.25 g l^{-1}) increased the binding further so that the free fraction of metoclopramide at 50 g l^{-1} albumin had fallen to 0.37.

In the plasma of healthy controls, the mean ± s.d. free fraction of metoclopramide was 0.60 ± 0.04 with very little intersubject variability (Figure 2). The mean plasma albumin in this group was 49.0 ± 4.20 g l^{-1} and there was no relationship between the degree of metoclopramide binding (expressed as the ratio of bound to free drug [B/F]) and the plasma albumin concentration (r = 0.302, n = 18, $P > 0.05$). The mean AAG concentration was 0.572 ± 0.110 g l^{-1} and there was a significant relationship between this variable and the binding ratio (B/F) of metoclopramide (r = 0.717, n = 18, $P < 0.001$). The mean NEFA concentration was 371.2 ± 101 μmol l^{-1} and its logarithm was not related to the binding ratio of metoclopramide (r = 0.455, $P > 0.05$).

In the patients with renal disease, the free fraction of metoclopramide in plasma was 0.59 (range 0.41–0.77) and not significantly different from age- and sex-matched control subjects (Figure 2). The renal disease group, however, had a significantly reduced albumin concentration (mean 33.3 g l^{-1} range 16–54, $P < 0.01$) and a significantly increased AAG concentration in plasma (mean 0.81 g l^{-1} range 0.31–1.48). NEFA concentration in plasma in renal disease (323 μmol l^{-1} range 161–569) was not significantly different from the control population. The binding ratio of metoclopramide was significantly related to plasma AAG concentration (r = 0.655, n = 18, $P < 0.05$) but not to albumin (r =

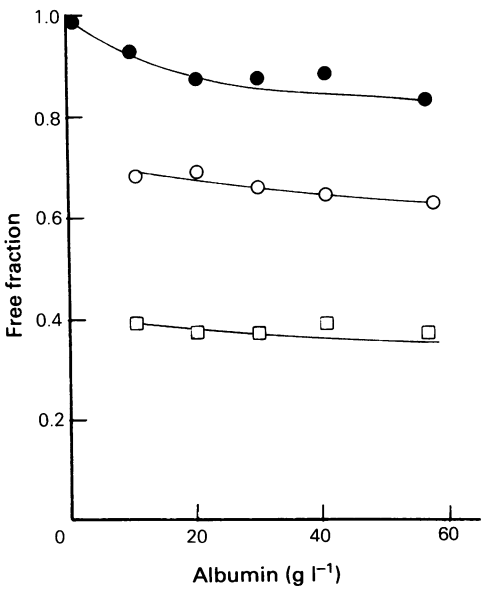

Figure 1 The free fraction of metoclopramide in solutions of human serum albumin (●) and HSA to which has been added α_1-acid glycoprotein (AAG) at concentrations of 0.75 g l^{-1} (○) and 2.25 g l^{-1} (□).

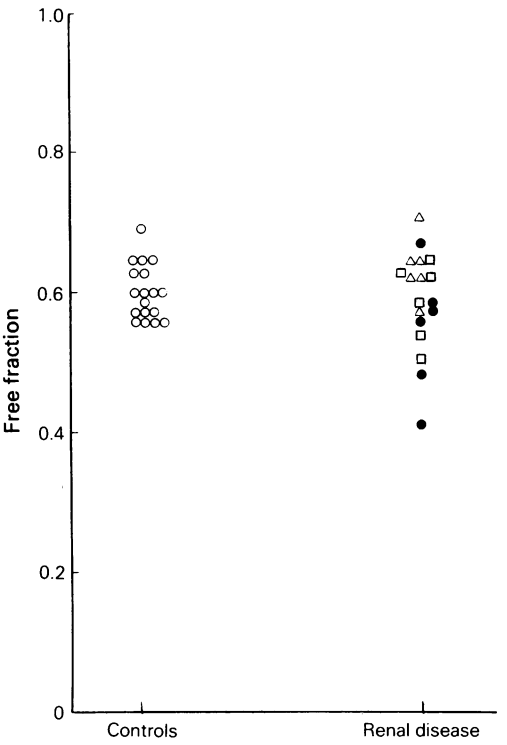

Figure 2 The free fraction of metoclopramide in normal individuals (○) and subjects with renal disease (△ = nephrotic syndrome, □ = CRF on CAPD, ● = CRF on haemodialysis).

-0.372, $P > 0.05$) or to log NEFA ($r = -0.105$, $P > 0.05$).

Discussion

Little is known of the plasma protein binding of metoclopramide in health or disease. The study indicates that metoclopramide plasma protein binding in plasma is relatively small in health (free fraction approximately 0.60) and varies little between individuals. The results of these experiments using protein solutions and in the plasma from normal subjects and patients with renal disease indicate that AAG is the major site for metoclopramide binding. Even over the range of AAG concentrations seen in health, the binding of metoclopramide is significantly related to AAG but not to albumin. At physiological concentrations of proteins, albumin appears to account for only 35% of the total binding at the plasma concentration of metoclopramide studied, a concentration present after the standard therapeutic dose of the drug (Bateman *et al.*, 1980), and AAG accounts for the remaining 65% of the total. The affinity of AAG for the drug is much less than that for another basic drug, lignocaine, even though AAG accounts for a similar proportion of the total binding (Routledge *et al.*, 1980). As with other drugs in which AAG is the major binding protein, NEFA does not appear to be a major determinant of the degree of protein binding.

Although the free fraction of metoclopramide was slightly lower in renal patients than in controls, the difference was not significant. This may have been partly because the AAG concentration was only 40% greater than in controls whereas larger percentage differences have been seen in other studies. Secondly the lower albumin concentration in the renal patients might have counteracted to a slight extent the effects of the raised AAG. Finally other unidentified factors such as endogenous inhibitors or structural changes in the proteins in renal disease might also have tended to reduce the extent of metoclopramide plasma protein binding.

Whatever the reasons, it certainly appears that metoclopramide should be added to the list of those drugs in which chronic renal dysfunction is not associated with reduced plasma protein binding (Reidenberg & Drayer, 1980). For some drugs (e.g. propranolol and lignocaine) plasma protein binding is actually greater in renal disease (Piafsky, 1980; Grossman *et al.*, 1982), although for metoclopramide any increase in binding is likely to be small.

Bateman *et al.* (1981) have observed a 50% reduction in total plasma metoclopramide clearance in chronic renal failure. The free (unbound) metoclopramide clearance was not measured but our results indicate that the change in free clearance was likely to be almost as great. Other factors therefore must be responsible for the change in total plasma clearance of the drug in renal disease. Similarly, it is unlikely that differences in metoclopramide plasma protein binding in health will be responsible for differences in drug response between subjects at any given total plasma metoclopramide concentration.

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