cannot possibly be otherwise explained, it seems that this *in vitro* interaction is of clinical importance. In fact, even though it is known that cardiac failure can hinder theophylline clearance (Benowitz & Meister, 1983), our patient was in failure since she was admitted to intensive care. Neither is it possible to understand why serum concentrations dropped once the initial administration method was resumed. Finally, the increase of serum levels after administration into separate veins represents proof of the occurrence of a similar interaction. After having reached and maintained adequate concentrations, the patient improved clinically and was extubated and discharged from the intensive care unit in 4 days. However according to our observation, it is not possible to clearly explain if pH variation is due only to

vitamin C or dextrose solution too. Furthermore, T tube examination did not show any precipitate. However, it is known that interactions can occur even without obvious modifications of solution properties (Laurence, 1980).

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Protein binding of theophylline

The report of Gundert-Remy & Hildebrandt (1983) provides interesting and valuable information concerning the plasma protein binding of theophylline and its metabolites. Their finding of concentration-dependent protein binding of theophylline between 5–20 mg/l is, however, at variance with our observations (Buss *et al.*, 1983). Other authors have also suggested that theophylline protein binding could fall with increasing drug concentration. Fleetham *et al.* (1981) claimed to show concentration dependent binding between 1.5 and 45 mg/l. Shaw *et al.* (1982) indicated a reduction in binding over the range 5–30 mg/l. In contrast the data of Knott *et al.* (1984) appear to show no evidence of concentration-dependent binding, since salivary and total

plasma drug concentration were closely linearly related up to 26 mg/l. We therefore decided to re-examine this problem in two separate ways.

Firstly, the relationship between the free fraction of theophylline and drug concentration was examined in the data from two separate studies involving patients receiving the drug for chronic airways obstruction (Ebdon *et al.*, 1984a, b) in neither case was there a significant relationship between free fraction of theophylline and total plasma theophylline concentration up to 20 mg/l ($r = -0.23$, $n = 39$, $P > 0.05$ and $r = -0.30$, $n = 32$, $P > 0.05$ respectively). Both of these studies used equilibrium dialysis to measure free fraction of theophylline under conditions of controlled temperature (37°C) and pH (7.4) which was not

the case with some of the original studies of theophylline plasma protein binding (Buss *et al.*, 1983).

Secondly, we recently had the opportunity to measure total and free drug concentrations in the plasma of a 75 year old female admitted to the intensive care unit after an overdose of theophylline. Over the total plasma concentration range of 1 to 53 mg/l, there was no relationship between the total concentration and the free fraction of theophylline ($r = 0.244$, $n = 19$, $P > 0.05$) so that the free and total plasma concentrations correlated closely ($r = 0.999$, $n = 19$, $P < 0.001$) (Figure 1). This was despite the fact that the patient was hypoalbuminaemic (mean albumin $26 \text{ g/l} \pm \text{s.d.}$, $n = 19$) so that her free fraction of theophylline ($0.81 \pm 0.02 \text{ s.d.}$) was 30% greater than normally seen in patients (Ebden *et al.*, 1984a). Thus despite high drug concentration and low binding protein concen-

tration, no evidence of concentration dependent protein binding was seen.

All of the other quoted studies involve *in vitro* addition of drug to the plasma. Only Gundert Remy & Hildebrandt (1983) specify the vehicle used (aqueous solution) and it is possible that in the other studies, the addition of organic solvent containing theophylline caused denaturation of albumin in a volume-dependent rather than drug-concentration-dependent manner.

In our studies, trace doses of radiolabelled theophylline were evaporated to dryness and then added to buffer solution to avoid potential protein denaturation. This was then dialysed against patients' plasma which already contained theophylline.

Although the reason for the differing results is unclear, we believe that concentration-dependent binding of theophylline is unlikely to occur at therapeutic plasma concentrations of the drug, and is therefore unlikely to be a significant determinant of the response to a given total plasma theophylline concentration.

Figure 1 Relationship between free and total plasma theophylline concentrations in a 75 year old female patient after overdose (●). The hatched line indicates the same relationship for the data of Ebden *et al.* (1984a) in 39 patients aged between 18–80 years with chronic airflow obstruction.

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