compliance for antihypertensive medications: the usefulness of urine assays. *Clin. Ther. Res.*, **19**, 405–409.
SACKETT, D.L., HAYNES, R.B., GIBSON, E.S., HACKETT, B.C., TAYLOR, D.W., ROBERTS, R.S. & JOHNSON, A.L.

(1975). Randomised clinical trial strategies for improving medication compliance in primary hypertension. *Lancet*, **i**, 1205–1207.

DECREASED CLEARANCE OF DIFLUNISAL IN RENAL INSUFFICIENCY—AN ALTERNATIVE EXPLANATION

Verbeeck, Tjandramaga, Mullie, Verbesselt, Verberckmoes & de Schepper (1979) have shown that the total body clearance of the salicylic acid derivative diflunisal decreases with declining renal function. Diflunisal is eliminated by conversion to ester and ether glucuronides which are eliminated almost entirely in the urine (Tocco, Breault, Zacchei, Steelman & Perrier, 1975). Therefore the plasma half-life of diflunisal, but not of its metabolites, should be independent of renal function. Verbeeck *et al.* (1979) suggested that the rate of metabolism of diflunisal might be reduced in patients with renal failure, but they recognized that conjugation with glucuronic acid is not usually affected by a decline of renal function.

Levy (1979) has suggested that the diflunisal metabolites may be excreted entirely by the biliary route in patients with renal failure. An increase in the extent of enterohepatic recycling of diflunisal would result in a prolongation of the half-life of the drug.

Another explanation for the observations of Verbeeck *et al.* (1979) can be deduced from the properties of the metabolites of the drug. Ester glucuronides, but not ether glucuronides, are unstable under physiological conditions. For example, the ester glucuronide conjugates of clofibrac acid are hydrolysed in plasma at 37°C (Faed & McQueen, 1979a; Gugler, 1979). The plasma half-life of clofibrac acid is prolonged in patients with renal failure and is similar to the half-life of the conjugated drug, i.e. there is an equilibrium between the conjugated and unconjugated forms (Faed & McQueen, 1979b). Similarly, hydrolysis of the ester glucuronide conjugate of diflunisal *in vivo* would account for the reduction in the total body clearance of this drug in renal insufficiency. In contrast, the plasma clearance of lorazepam and of oxazepam is not affected by a reduction of renal function (Verbeeck, Tjandramaga, Verberckmoes & de Schepper, 1976; Odar-Cederlöf, Vessman, Alván & Sjöqvist, 1977), as these drugs are eliminated by metabolism to stable ether glucuronides. Although

the terminal half-life of oxazepam is prolonged by enterohepatic recycling in uraemic patients, the plasma levels of oxazepam are comparatively low during this terminal phase.

The clearance of drugs which are eliminated by biotransformation to stable metabolites is independent of renal function, and renal insufficiency should only affect the kinetics of drug metabolites and of drugs which are excreted unchanged (Kunin & Finland, 1959a, b). If a drug conjugate is unstable and its formation is reversible, the active drug will in fact be eliminated by excretion of the conjugate and not by the conjugation reaction *per se*. When renal excretion of an unstable drug conjugate such as an ester glucuronide is impaired, the half-life of the active drug will be prolonged. This is assumed to be the reason for the persistence of clofibrac acid in patients with renal failure (Faed & McQueen, 1979b), and it can provide a satisfactory explanation for the relationship between renal function and diflunisal clearance observed by Verbeeck and coworkers (1979). If this explanation is correct, there should be a gradual increase in the proportion of the conjugated diflunisal present as the stable ether glucuronide in the plasma in uraemic patients after the administration of single doses of the drug.

The lability of ester glucuronides *in vivo* may affect the kinetics of other acidic drugs in renal insufficiency. It should be noted, however, that ester glucuronides can undergo hydrolysis in plasma at room temperature (Faed & McQueen, 1979a), and the ester glucuronide concentration will be underestimated, and the drug level overestimated, unless care is taken to minimize such hydrolysis.

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References

- FAED, E.M. & McQUEEN, E.G. (1979a). Measurement of clofibric acid (CPIB) metabolites in plasma of patients on clofibrate therapy. *Clin. exp. Pharmac. Physiol.*, **6**, 267–273.
- FAED, E.M. & McQUEEN, E.G. (1979b). Plasma half-life of clofibric acid in renal failure. *Br. J. clin. Pharmac.*, **7**, 407–410.
- GUGLER, R. (1979). The effect of disease on the response to drugs. In *Clinical Pharmacology, Proc. 7th Int. Congr. Pharmac. Paris*, 1978, Vol. 6, ed. Duchêne-Marullaz, P. pp. 67–76. Oxford: Pergamon.
- KUNIN, C.M. & FINLAND, M. (1959a). Persistence of antibiotics in blood of patients with acute renal failure. III. Penicillin, streptomycin, erythromycin and kanamycin. *J. clin. Invest.*, **38**, 1509–1519.
- KUNIN, C.M. & FINLAND, M. (1959b). Restrictions imposed on antibiotic therapy by renal failure. *Arch. int. Med.* **104**, 1030–1050.
- LEVY, G. (1979). Decreased body clearance of diflunisal in renal insufficiency—an alternative explanation. *Br. J. clin. Pharmac.*, **8**, 601.
- ODAR-CEDERLÖF, I., VESSMAN, J., ALVÁN, G. & SJÖQVIST, F. (1977). Oxazepam disposition in uremic patients. *Acta Pharmac. Tox.*, **40**, Suppl. 1, 52–62.
- TOCCO, D.J., BREAUULT, G.O., ZACCHEI, A.G., STEELMAN, S.L. & PERRIER, C.V. (1975). Physiological disposition and metabolism of 5-(2',4'-difluorophenyl) salicylic acid, a new salicylate. *Drug Metab. Disp.*, **3**, 453–466.
- VERBEECK, R., TJANDRAMAGA, T.B., MULLIE, A., VERBESSELT, R., VERBERCKMOES, R. & DE SCHEPPER, P.J. (1979). Biotransformation of diflunisal and renal excretion of its glucuronides in renal insufficiency. *Br. J. clin. Pharmac.*, **7**, 273–282.
- VERBEECK, R., TJANDRAMAGA, T.B., VERBERCKMOES, R. & DE SCHEPPER, P.J. (1976). Biotransformation and excretion of lorazepam in patients with chronic renal failure. *Br. J. clin. Pharmac.*, **3**, 1033–1039.