The effect of spironolactone on the liver microsomal enzyme system in patients

Spironolactone, an aldosterone antagonist, which is used as a diuretic agent was found to accelerate its own metabolism in animals due to an induction of the liver microsomal enzyme system (Feller & Gerald, 1971; Talcott & Stohs, 1972). However, the findings in man reported in the literature and based on studies in healthy young volunteers are somewhat confusing. Administering 100 mg spironolactone for 14 days to nine volunteers a decreased antipyrine half-life combined with an increased excretion of 4-hydroxy-antipyrine was observed, while 3-hydroxymethyl-antipyrine remained unchanged (Huffman *et al.*, 1973). On the other hand, there was no significant overall change in antipyrine clearance following the administration of 150 mg spironolactone daily for 7 days, but a reduction in antipyrine half-life was claimed in four of nine subjects (Taylor *et al.*, 1972).

As so far no data in patients were reported, we were interested in the present study whether changes in the hepatic microsomal enzyme system may occur in patients usually treated for a long term period because of cardiac failure or liver cirrhosis. These patients often get concomitantly many other drugs administered and therefore induction of the hepatic microsomal enzyme system would be of clinical importance.

The present study was performed in two different groups. In the first group eight patients (ages between 31 and 82 years, mean 64 years) with age related renal function and without proven liver disease and cardiac failure were investigated. Spironolactone in a dose of 150 mg spironolactone was given for 14 days. Before and after drug administration antipyrine elimination, γ -glutamyl-transpeptidase (γ -GT) in the plasma and D-glucaric acid and 6 β -hydroxycortisol urinary excretion were estimated as previously reported (Ohnhaus & Park, 1979).

In the second group six patients (ages between 44 and 75, mean 63 years) suffering from chronic cardiac failure were investigated being on treatment with spironolactone 100 to 150 mg/day at least for 2–3 months. As an additional treatment all patients received digoxin or digitoxin. In this group the same *in vivo* parameters of liver microsomal enzyme activity were measured as mentioned above. All patients were informed about the aims of the study and gave their written consent to it.

The *in vivo* parameters of liver microsomal enzyme induction measured before and after spironolactone administration in the first group are shown in Table 1. No significant difference in

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) of antipyrine, γ -GT plasma concentrations, D-glucaric acid and 6 β -hydroxy cortisol urinary excretion in patients before and after treatment with 150 mg spironolactone for 14 days.

	Before	After
Antipyrine elimination		
V_D (l)	31 $\pm$ 8.5	31 $\pm$ 7.5
$t_{1/2}$ (h)	13.6 $\pm$ 7.1	14.4 $\pm$ 7.5
CL (ml min)	30.5 $\pm$ 12.0	30.5 $\pm$ 14.7
D-glucaric acid		
(μ mol min ⁻¹ l ⁻¹)	39.4 $\pm$ 27.5	32.8 $\pm$ 24.2
γ -GT		
(μ mol min ⁻¹ l ⁻¹)	18.3 $\pm$ 13	29.8 $\pm$ 17
6 β -hydroxycortisol		
(μ g 24 h)	318 $\pm$ 209	437 $\pm$ 363

antipyrine elimination, γ -GT, D-glucaric acid and 6 β -hydroxycortisol was found in this group. The second group of patients treated by spironolactone for a long period of time showed comparable values of antipyrine clearance (29.8 $\pm$ 12.9 ml/min) and 6 β -hydroxycortisol urinary excretion (391 $\pm$ 205 μ g/24 h) despite an increased volume of distribution (57 $\pm$ 25 l) and a prolonged half-life of antipyrine (22.1 $\pm$ 12.9 h).

Based on previous studies spironolactone seemed to be a weak enzyme inducing agent in young healthy volunteers (Taylor *et al.*, 1972; Huffman *et al.*, 1973), whereby the increases in antipyrine clearance and 6 β -hydroxycortisol urinary excretion percentage-wise were similar to those found in healthy volunteers following the administration of antipyrine or phenobarbitone (Ohnhaus & Park, 1979). No such inducing effect on liver microsomal activity was seen in patients treated for 14 days or during a longer period of time by spironolactone. These differences in the enzyme inducing capability of spironolactone are probably based on the differences in the subjects investigated. In the present study diseased and mostly elderly patients were investigated, whereby in the second group all patients were suffering from cardiac failure. In this group a higher volume of distribution and a longer half-life of antipyrine was observed despite the antipyrine clearance being similar to the first group studied and comparable to the values reported in the healthy volunteers (Huffman *et al.*, 1973).

Therefore a pronounced enzyme inducing effect seems unlikely in patients treated with

spironolactone. As these patients receive concomitantly often many other drugs spironolactone seems an unlikely cause for an important drug interaction based on the induction of the liver microsomal enzyme system.

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Kinetic interactions of nadolol and propranolol with cimetidine

Cimetidine, an H₂-receptor antagonist, is used widely in the treatment of gastroduodenal ulcer disease. This agent appears to reduce liver blood flow in man (Feely *et al.*, 1981) and to inhibit oxidative drug-metabolizing enzymes (Pelkonen & Puurunen, 1980). The concurrent administration of cimetidine with propranolol or metoprolol impairs the clearance and increases the blood concentrations of these drugs (Feely *et al.*, 1981; Kirch *et al.*, 1982).

This study was designed to compare plasma concentrations of propranolol and nadolol, lipophilic and hydrophilic β -adrenoceptor blockers, respectively, following single doses of these drugs in the presence and absence of cimetidine.

Twelve healthy male volunteers aged 18–30 years, with normal renal and liver function, participated in this study. After an overnight fast, each subject, in a randomized, crossover fashion, received a single oral 80 mg dose of nadolol on each of two occasions and a single 80 mg dose of propranolol on each of two occasions. On two of the four occasions, each subject received cimetidine (300 mg, four times daily) for 2 days prior to and on the day that the β -adrenoceptor blocker was given. A 7 day wash-out period separated each of the four treatments.

Blood (plasma) samples were obtained with heparinized Vacutainers (lacking the plasticizer, TBEP, in the rubber stopper), at multiple times before and up to 48 h after nadolol ad-

ministration. Plasma samples were obtained at multiple times prior to and up to 24 h after ingestion of propranolol. Nadolol was assayed by gas-chromatography/mass spectrometry (Funke *et al.*, 1978) and propranolol concentrations were determined by a modified spectrofluorometric method reported by Shand *et al.* (1970).

Pharmacokinetic parameters were calculated using standard procedures (Gibaldi & Perrier, 1982). Data were analyzed using a two-way analysis of variance model and the means for each drug with and without cimetidine were compared using Duncan's Multiple Range Test.

As shown in Figure 1, cimetidine increased ($P < 0.01$) the 24 h area under the plasma concentration-time curve (531 vs 775 ng ml⁻¹ h) and peak plasma levels (82 vs 110 ng/ml) of propranolol. Nadolol kinetics were not altered significantly by cimetidine, except for a reduction (4.3 vs 3.3 h, $P < 0.05$) in time to reach peak concentrations. Cimetidine had no effect on elimination half-lives for either β -adrenoceptor blocker.

These results indicate the lack of significant kinetic interaction of cimetidine with nadolol and confirm the interactions of propranolol and this H₂-receptor antagonist (Feely *et al.*, 1981; Reimann *et al.*, 1981; Kirch *et al.*, 1982). Since cimetidine has been reported to depress liver blood flow (Feely *et al.*, 1981) and inhibit the drug-metabolizing enzymes (Pelkonen & Puurunen, 1980), it is not unexpected that drugs