SULPHAPHENAZOLE AND DRUG OXIDATION IN MAN

Sulphaphenazole is a potent inhibitor of tolbutamide metabolism in man (Christensen *et al.*, 1963; Schulz & Schmidt, 1970; Rowland & Matin, 1973; Pond *et al.*, 1977) and may increase the half life of the hypoglycaemic agent by up to eight-fold. Tolbutamide oxidation to hydroxytolbutamide is the rate limiting step for the *in vivo* elimination of the drug and hence sulphaphenazole inhibits the cytochrome P-450 enzyme responsible for this hydroxylation. To investigate the extent of sulphaphenazole inhibition of mixed function oxidases in man, we have studied the oxidation of antipyrine, sparteine and cortisol before and after sulphaphenazole administration in six healthy, non-smoking, male volunteers (aged 23–35 years; weight 64–86 kg) who were not taking any other drugs. The study was approved by the Mersey Regional Hospital Ethical Committee and the nature of the study explained to each volunteer.

The volunteers received antipyrine (600 mg orally; capsules prepared by the hospital pharmacy) on two occasions. One week after the first dose the subjects took sulphaphenazole (1 g twice daily) for 6 days and on the sixth day received antipyrine again. Saliva samples were taken immediately before and at 2, 4, 6, 9, 12 and 24 h after antipyrine. Urine was collected from 0–24 h into containers with sodium metabisulphite (about 1 mg ml⁻¹ final concentration) added to stabilise antipyrine metabolites. Saliva antipyrine and urinary antipyrine and metabolites were measured by high performance liquid chromatography (Danhof *et al.*, 1979). Urinary 6 β -hydroxycortisol was measured

by radioimmunoassay (Park, 1978). In a second study volunteers received sparteine sulphate (100 mg orally) on two occasions. For 5 days before and on the same day as the second dose, sulphaphenazole (1 g twice daily) was given. Urine was collected from 0–24 h following sparteine administration for the determination of sparteine and dehydrospartheine metabolites in urine (Eichelbaum *et al.*, 1982).

Sulphaphenazole had no effect on either saliva antipyrine pharmacokinetics or on the percentage excretion of antipyrine and its metabolites in urine (Table 1). Thus there is no change in the clearance of antipyrine to each of its three main oxidative metabolites, 3-hydroxymethylantipyrine (3-OHMeAP), 4-hydroxyantipyrine (4-OHAP) and norantipyrine (NorAP). There was no change in either the excretion of 6 β -hydroxycortisol, the major oxidative metabolite of cortisol (Park, 1978), or in the excretion of sparteine and its dehydrometabolites.

It has been established by several groups (Christensen *et al.*, 1963; Schulz & Schmidt, 1970; Rowland & Matin, 1973; Pond *et al.*, 1977) that sulphaphenazole, at the dose used in the present study, markedly inhibits the cytochrome P-450 enzyme responsible for tolbutamide hydroxylation. Therefore our data indicate sulphaphenazole to be a relatively selective mixed function oxidase inhibitor since it did not influence the oxidation of antipyrine to its three main oxidative metabolites, nor did it inhibit the oxidation of either sparteine or cortisol. These data also suggest that the cytochrome P-450 enzyme responsible for tolbutamide

Table 1 The effect of sulphaphenazole (1 g twice daily for 5 days) on the saliva pharmacokinetic parameters of antipyrine, the urinary excretion of antipyrine and its metabolites, 6 β -hydroxycortisol, sparteine and dehydrospartheine metabolites. Values are mean $\pm$ s.d.

	Control	Sulphaphenazole
<i>Antipyrine saliva pharmacokinetic parameters</i>		
Half-life (h)	11.80 $\pm$ 2.70	12.40 $\pm$ 1.80
Clearance (l h ⁻¹)	3.10 $\pm$ 0.54	3.10 $\pm$ 0.52
Volume of distribution (l kg ⁻¹)	0.72 $\pm$ 0.07	0.77 $\pm$ 0.07
<i>Excretion of antipyrine metabolites in urine (% of dose)</i>		
Antipyrine	2.3 $\pm$ 0.8	1.9 $\pm$ 0.7
3-OHMeAP	8.1 $\pm$ 2.5	7.9 $\pm$ 1.5
4-OHAP	30.9 $\pm$ 10.6	28.2 $\pm$ 5.8
NorAP	15.6 $\pm$ 7.4	16.5 $\pm$ 3.8
<i>Urinary 6β-hydroxycortisol</i>		
(μ g 24 h ⁻¹)	344 $\pm$ 74	322 $\pm$ 19
Urinary $\frac{\text{sparteine}}{\text{dehydrospartheine}}$	0.70 $\pm$ 0.51	0.42 $\pm$ 0.29
(ratio)		
Urinary recovery of sparteine and metabolites (%)	66.0 $\pm$ 18.3	73.8 $\pm$ 16.5

hydroxylation is distinct from those involved in the oxidation of antipyrine, sparteine and cortisol. In this context it is interesting to note that although tolbutamide has been shown to exhibit genetic polymorphism (Scott & Poffenberger, 1979) its metabolism is not associated with the better known polymorphism of debrisoquine 4-hydroxylation (Idle *et al.*, 1979).

We are grateful to Ciba-Geigy for supplying the

sulphaphenazole.

D.B. BACK, B.K. PARK, J.F. TJIA & S.N. NEWBY
*Department of Pharmacology and Therapeutics,
University of Liverpool, P.O. Box 147, Liverpool
L69 3BX*

Received April 18, 1983,
accepted June 6, 1983

References

- CHRISTENSEN, L.K., HANSEN, J.M. & KRISTENSEN, M. (1963). Sulphaphenazole induced hypoglycaemic attacks in tolbutamide treated diabetics. *Lancet*, **ii**, 1298–1301.
- DANHOF, M., DEGROOT-VAN DER VIS, E. & BREIMER, D.D. (1979). Assay of antipyrine and its primary metabolites in plasma, saliva and urine by HPLC and some preliminary results in man. *Pharmacology*, **18**, 210–223.
- EICHELBAUM, M., BERTILSSON, L., SAWE, J. & ZEKRON, C. (1982). Polymorphic oxidation of sparteine and debrisoquine: Related pharmacogenetic entities. *Clin. Pharmac. Ther.*, **31**, 184–186.
- IDLE, J.R., SLOAN, T.P., SMITH, R.L. & WAKILE, L.A. (1979). Application of the phenotyped panel approach to the detection of polymorphisms of drug oxidation in man. *Br. J. Pharmac.*, **66**, 430–431P.
- PARK, B.K. (1978). A direct radioimmunoassay for 6 β -hydroxycortisol in human urine. *J. steroid Biochem.*, **9**, 963–966.
- POND, S.M., BIRKETT, D.J. & WADE, D.N. (1977). Mechanisms of inhibition of tolbutamide metabolism: Phenylbutazone, oxyphenbutazone, sulphaphenazole. *Clin. Pharmac. Ther.*, **22**, 573–579.
- ROWLAND, M. & MATIN, S.B. (1973). Kinetics of drug-drug interactions. *J. Pharmacokin. Biopharm.*, **1**, 553–567.
- SCHULZ, E. & SCHMIDT, F.H. (1970). Abbauehemmung von Tolbutamid durch Sulfaphenazol beim Menschen. *Pharmac. Clin.*, **2**, 150–154.
- SCOTT, J. & POFFENBARGER, P.L. (1979). Pharmacogenetics of tolbutamide metabolism in humans. *Diabetes*, **28**, 41–51.

EFFECT OF RANITIDINE AND CIMETIDINE TWICE DAILY ON THE 24 H INTRAGASTRIC ACIDITY IN MAN

Ranitidine is a new specific histamine H₂-receptor antagonist. Its inhibitory action lasts up to 12 h, so that ranitidine can be prescribed twice daily.

Some workers report that cimetidine likewise can be used twice daily in the treatment of peptic ulcer disease (Eckardt, 1981; Kerr, 1981).

The aim of the present study was, therefore, to compare the effect of twice daily administration of ranitidine, cimetidine and placebo on the 24 h intragastric acidity in man.

Eight healthy subjects (five male, three female) with a mean age of 25 years participated in this study. Each subject underwent the test on three different occasions, receiving in a double-blind cross-over randomized fashion ranitidine (150 mg twice daily), cimetidine (400 mg twice daily) and placebo at 08.00 h and 20.00 h. A nasogastric tube was positioned 1 h before the beginning of the test. The menu (breakfast at 08.00 h, mid-morning drink at 10.30 h, lunch at 13.00 h, coffee-break at 15.30 h, dinner at 19.00 h and

night-cap at 22.30 h) was identical during the three studies.

Starting at 08.00 h in the morning, a 5–10 ml sample of gastric contents was aspirated at 1 hourly intervals using syringe suction according to Walt *et al.* (1981). Gastric juice was titrated with 0.1 N NaOH to pH 7.0. The results were expressed in terms of mean hourly H⁺-concentration (mmol/l). Statistical analysis was made using the Wilcoxon-test for paired samples.

The effects of the different regimens on 24 h gastric acidity are illustrated in Figure 1.

Compared with placebo, gastric H⁺-concentration between 08.00 h and 19.00 h was diminished by cimetidine from 17.15 $\pm$ 4.61 ($\pm$ s.e. mean) mmol/l to 10.43 $\pm$ 1.92 mmol/l (P < 0.01, 39%-inhibition) and by ranitidine to 4.79 $\pm$ 1.10 mmol/l (P < 0.01 vs placebo and cimetidine, 72% inhibition).

Nocturnal H⁺-activity (20.00 h to 07.00 h) was decreased by cimetidine 400 mg twice daily from 28.69 $\pm$ 6.44 mmol/l to 16.12 $\pm$ 2.73 mmol/l (P < 0.01, 44%