Comparative effects of famotidine and cimetidine on 7-ethoxycoumarin *O*-deethylase activity in human livers

Cimetidine, one of the histamine H_2 -receptor antagonists, has been shown to bind to hepatic microsomal cytochrome P-450 and inhibit drug metabolism in humans and animals because of its imidazole ring and side chain structure (Serlin *et al.*, 1979; Henry *et al.*, 1982; Rendic *et al.*, 1983). Famotidine, a new potent histamine H_2 -receptor antagonist (Takagi *et al.*, 1982) has a thiazole ring with a side chain of amidine structure and has been reported to be free from inhibitory effect on antipyrine pharmacokinetics in healthy subjects (Staiger *et al.*, 1984).

We compared the effect of famotidine with that of cimetidine on hepatic microsomal drug metabolism in human liver biopsy specimens. Cytochrome P-450 linked drug metabolism was evaluated by 7-ethoxycoumarin *O*-deethylase activity according to the method of Greenlee *et al.* (1978). Liver biopsy specimens were obtained under laparoscopic control with a Vim-Silvermann needle for histological examinations and part of each specimen (25–50 mg wet weight) were used for the assay. Histology of the samples showed chronic persistent hepatitis or mild fatty infiltration. Each biopsy specimen was tested with a range of famotidine and cimetidine concentrations. The reaction mixture consisted of liver homogenate, 7-ethoxycoumarin (0.5 mM) and NADPH generating system (NADPH 1mM, glucose 6-phosphate dehydrogenase 1 unit and glucose 6-phosphate 2 mM) in a final volume of 50mM phosphate buffer pH 7.4. The incubation time was 15 min. Famotidine and cimetidine dissolved in dimethylsulphoxide were added in the reaction mixture and the same volume of the solvent was added in the control assay.

Our results (Table 1) on cimetidine were similar to those reported by Puurunen *et al.*

Table 1 Inhibition by famotidine and cimetidine of 7-ethoxycoumarin *O*-deethylase activity in human liver biopsy samples ($n = 6$)

Concentration (mM)	% of control activity	
	Famotidine	Cimetidine
0.05	102.2 $\pm$ 2.1	97.2 $\pm$ 2.5
0.2	97.7 $\pm$ 1.3	90.1 $\pm$ 3.4
1.0	95.3 $\pm$ 1.0	80.5 $\pm$ 4.0
2.0	91.6 $\pm$ 1.7	70.5 $\pm$ 4.7

Control activity was taken as 100%. Control activity of the enzyme was 0.14 $\pm$ 0.03 nmol min⁻¹ mg⁻¹ protein. Values are expressed as mean $\pm$ s.e. mean.

(1980). Famotidine also had an inhibitory effect on the activity but was less inhibitory than the same concentrations of cimetidine. A plasma concentration of famotidine at a therapeutic dose is about 0.2 μ M (Ryan, 1984), while that of cimetidine is about 10 μ M (Walkenstein *et al.*, 1978; Grahnen *et al.*, 1979). According to our results on 7-ethoxycoumarin *O*-deethylase it could be expected that famotidine has much less inhibitory effect on drug metabolism clinically than cimetidine.

Y. IMAI, M. INADA, S. TAMURA, S. KAWATA, Y. MINAMI & S. TARUI
The Second Department of Internal Medicine, Osaka University Medical School, Fukushima, Osaka, Japan 553

Received 17 March 1986,
accepted 16 June 1986

References

- Grahnen, A., Von Bahr, C., Lindström, B. & Rosen, A. (1979). Bioavailability and pharmacokinetics of cimetidine. *Eur. J. clin. Pharmac.*, **16**, 335–340.
- Greenlee, W. F. & Poland, A. (1978). An improved assay of 7-ethoxycoumarin *O*-deethylase activity: Induction of hepatic enzyme activity in C57BL/6J and DBA/2J mice by phenobarbital, 3 methylcholanthrene and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin. *J. Pharmac. exp. Ther.*, **25**, 596–605.
- Henry, D., Kitchingman, G. & Langman, M. (1982). H_2 -receptor antagonists: the problem of hepatic drug interaction. In *The clinical use of ranitidine*, eds Misiewicz, J. J. & Wormsley, K. G., pp. 83–88. Oxford: Medicine Publishing Foundation.
- Puurunen, J., Sotaniemi, E. & Pelkonen, O. (1980). Effect of cimetidine on microsomal drug metabolism in man. *Eur. J. clin. Pharmac.*, **18**, 185–187.
- Rendic, S., Kajfez, F. & Ruf, H. H. (1983). Characterization of cimetidine, ranitidine, and related structures' interaction with cytochrome P-450. *Drug Metab. Disp.*, **11**, 137–142.
- Ryan, R. R. (1984). Clinical pharmacology of famo-

- tidine: summary of data from the United States. *Ital. J. Gastroenterol.*, **16**, 171–174.
- Serlin, M. J., Sibeon, R. G., Mossman, S., Breckenridge, A. M., Williams, J. R. B., Atwood, J. L. & Willoughby, J. M. T. (1979). Cimetidine: interaction with oral anticoagulants in man. *Lancet*, **ii**, 317–319.
- Staiger, C. H., Korodnay, B., Devries, J. X., Weber, E., Muller, P., Simon, B. & Dammann, H. G. (1984). Comparative effects of famitidine and cimetidine on antipyrine kinetics in healthy volunteers. *Br. J. clin. Pharmac.*, **18**, 105–106.
- Takagi, T., Takeda, M. & Maeno, H. (1982). Effect of a new potent H₂-blocker (YM-11170) on gastric secretion induced by histamine and food in conscious dogs. *Arch. int. Pharmacodyn.*, **256**, 49–58.
- Walkenstein, S. S., Dubb, J. W., Randolph, W. C., Westlake, W. J., Stote, R. M. & Intoccia, A. P. (1978). Bioavailability of cimetidine in man. *Gastroenterology*, **74**, 360–365.

Lack of pharmacokinetic interaction between cholestyramine and acipimox, a new lipid lowering drug

Combined administration of cholestyramine, a major bile acid sequestering resin, together with absorbable hypolipidemic drug, is a common practice in the treatment of severe hyperlipoproteinemias (Illingworth *et al.*, 1981). However, cholestyramine interferes with the absorption of many acidic drugs but it may also affect basic or non charged drugs (Gallo *et al.*, 1965). Limited data are available on the kinetics of lipid lowering drugs when administered together with cholestyramine: clofibrate and fenofibrate would not be affected (De Sante *et al.*, 1979; Harvengt & Desager, 1980).

Acipimox (5-methylpyrazine carboxylic acid 4-oxide), an antilipolytic drug structurally related to nicotinic acid significantly reduces triglyceride and cholesterol levels in hyperlipemic patients (Sirtori *et al.*, 1981; Stirling *et al.*, 1985). Since the effect is more pronounced on triglycerides than on cholesterol levels, it would be reasonable to administer acipimox in combination with cholestyramine when required.

To evaluate a possible interference of cholestyramine with the absorption of acipimox, a randomized cross-over study was carried out by administering a standard dose of cholestyramine, together with a low dosage of acipimox, to seven healthy volunteers (age 27.6 ± 0.5 years, body weight 73.1 ± 2.1 kg; means $\pm$ s.e. mean).

With a 1 week interval between the two treatments, acipimox and acipimox + cholestyramine were administered at 09.00 h, after a 10 h fasting, as follows: 1 capsule of acipimox (150 mg) given with 200 ml orange juice or 1 capsule of acipimox + 200 ml orange juice containing 4 g of cholestyramine (Questran® Bristol), followed by two additional doses of the resin, 4 g each, given 8 and 16 h thereafter and preceded, on the previous day, by cholestyramine, 4 g three times daily. Blood samples, collected before and after drug administration (Figure 1), were transferred to

heparinized tubes and stored at -20° C. Also urines collected during the periods: 0–12, 12–24 and 24–32 h were stored at -20° C. Urinary and plasma levels of acipimox were determined by radioimmunoassay (Maggi *et al.*, 1984). The main pharmacokinetic parameters for unchanged acipimox were calculated.

Data were analyzed statistically by the paired Student's *t*-test.

Acipimox plasma levels are shown in Figure 1. When given alone, acipimox is rapidly absorbed, and the mean plasma levels decrease in a biphasic way with a rapid phase up to 10–12 h followed by a slower phase involving very low plasma levels thereafter. The administration of cholestyramine does not produce important variations of acipimox plasma levels, in fact only at 1 h, they are significantly reduced ($P < 0.05$).

Kinetic parameters are also shown in Figure 1. Cholestyramine does not produce any major modification in acipimox pharmacokinetics, the only difference being a small delay in the absorption of the drug, as indicated by a slight but significant ($P < 0.05$) increase in the $t_{\max}$ value.

Per cent urinary excretion of administered acipimox (calculated in all but one subject due to incomplete collection of urines) was $92.7 \pm 3.9\%$ and $1.7 \pm 0.2\%$ during 0–12 and 12–32 h, respectively; when cholestyramine was also administered, values were $79.7 \pm 11.2\%$ and $2.9 \pm 0.9\%$, respectively (NS). In both instances, the drug was rapidly excreted unchanged in the first 12 h, and a slower elimination phase ensues, so that a nearly complete disappearance occurred within 32 h. The pharmacokinetic parameters and the urinary excretion of acipimox described here are in close agreement with those already obtained by other authors (Musatti *et al.*, 1981).

In conclusion the kinetics of acipimox are not affected by cholestyramine, with the exception of a slight delay in the time required to reach