Comparison of the Inhibitory Effects of Famotidine and Cimetidine on Hepatic Oxidative Metabolism of Cortisol in Humans

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The inhibitory effect of famotidine, a new H_2 -receptor antagonist, on hepatic oxidative metabolism of cortisol in six healthy volunteers was compared with that of cimetidine by monitoring the change in urinary 6β -hydroxycortisol (6β -OHF), an oxidative metabolite of cortisol. The ratio of 6β -OHF to 17-hydroxycorticosteroids (17-OHCS) in urine was measured before, during, and after treatment with famotidine and cimetidine for 3 days in a cross-over study. The ratio was decreased by 25%-35% of the original level after 1-3 days of oral treatment with cimetidine (800 mg, b. i. d.). The reduction vanished within 2 days after the last dose of cimetidine. The ratio was not significantly changed during oral treatment with famotidine (40 mg, b. i. d.). These findings indicate that famotidine, in contrast to cimetidine, does not affect the hepatic oxidative metabolism of cortisol in man, and it is suggested that famotidine does not affect the hepatic drug-metabolizing capacity in humans.

Key words : famotidine, cimetidine, H_2 -receptor antagonist, 6β -hydroxycortisol, enzyme inhibition

Introduction

Cimetidine, a histamine H_2 -receptor antagonist widely used for the treatment of peptic ulcer, has

been shown to inhibit the hepatic elimination of a number of drugs coadministered.¹⁻⁴⁾ A number of studies have demonstrated that this inhibitory action of cimetidine is based on its high affinity for cytochrome P-450 in hepatic microsomes arising from imidazole and cyano groups.⁵⁻⁷⁾ Ranitidine, an H_2 -receptor antagonist developed

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Fig. 1 Chemical structures of H_2 -receptor antagonists tested.

subsequently, has a furan ring structure and does not affect on oxidative drug-metabolizing enzyme activity in hepatic microsomes *in vitro* or *in vivo*.⁵⁻⁹⁾

Famotidine, a new H_2 -receptor antagonist containing thiazole ring structure (Fig. 1), has been reported to be clinically useful, since it exhibits inhibitory action of stimulated gastric acid secretion at least 20 times more potent than that of cimetidine.¹⁰⁾

On the other hand, it is well known that cytochrome P-450 in the hepatic microsomes mediates oxidation of various steroid hormones such as testosterone and cortisol. Previously, we reported that cimetidine, but not ranitidine and famotidine, inhibits testosterone hydroxylase activities in mouse hepatic microsomes *in vitro*.⁷⁾ These findings suggest that cimetidine, in contrast to ranitidine and famotidine, inhibits the oxidative metabolism of endogenous steroid such as testosterone as well as xenobiotics.

In this study, we compared the effect of famotidine on the oxidative metabolism of cortisol in man with that of cimetidine, and assessed the inhibitory potency of famotidine on hepatic drug-metabolizing capacity in man.

Subjects and Methods

Six normal volunteers, 1 female and 5 male

hospital pharmacists, aged 24 to 35 years old (mean 28), participated in the study. All subjects had normal hepatic and renal function. They were taking no medications.

All subjects received, on separate occasions, the oral dose of both famotidine (Gaster[®], 40 mg b. i. d.) and cimetidine (Tagamet[®], 800 mg b. i. d.) for 3 days. Successive treatment was given two weeks after the previous drug treatment. On Day 0 (just before treatment) and Day 1, 2, 3, 4, 5 and 7, random urine samples were taken for the evaluation of the oxidative metabolism of cortisol. Urine samples were stored frozen at -20°C until assay.

Oxidative metabolism of cortisol in the subjects was evaluated by the ratio of 6β -hydroxycortisol (6β -OHF) to 17-hydroxycorticosteroids (17-OHCS) in urine. Urinary 6β -OHF was determined by the method described in detail previously¹¹⁾ and urinary 17-OHCS was determined by the method of Nishikaze et al.¹²⁾ which is a modification of the procedure of Silber and Porter.¹³⁾

The ratio of 6β -OHF to 17-OHCS in urine on Day 0 in each subject were corrected as the 100% and statistical significance was evaluated using a paired t-test.

Results

Figure 2 shows the change in the ratio of 6β -OHF to 17-OHCS in urine obtained from the six subjects, before, during and after treatment with famotidine (40 mg, b.i.d.) or cimetidine (800 mg, b. i. d.) for 3 days. As regards cimetidine, the ratio began to decrease on Day 1 and to reach about 65% of the original level on Day 3. After the discontinuation of the treatment with cimetidine, the ratio rapidly returned to its original level within 2 days after the last dose of cimetidine. On the other hand, famotidine had no significant

Fig. 2 Changes in the ratio of 6β-OHF to 17-OHCS in urine obtained from 6 healthy volunteers before, during, and after 3 days of famotidine (40 mg, b.i.d.) (A) and cimetidine (800 mg, b.i.d.) (B) treatment. The amounts of 6β-OHF and 17-OHCS in random urine obtained from the subjects on Day 0 (mean ± S.D.) were 0.397 ± 0.217 μg/ml and 9.86 ± 3.38 μg/ml, respectively. In individuals, the initial ratio ranged from 0.029 to 0.049. The ordinate shows the percentage to the ratio on Day 0 in each subject. Each column represents the mean ± S.D. Shaded areas indicate the periods during administration. * Significantly different from Day 0 (P < 0.05). ** Significantly different from Day 0 (P < 0.01).

effect on the ratio.

Discussion

The results indicate that famotidine, in contrast to cimetidine, does not affect the oxidative metabolism of cortisol in man. The ratio of 6β-OHF to 17-OHCS in urine was decreased by 25, 30 and 35% of the original level after 1, 2 and 3 days of the treatment with cimetidine 800 mg/day, respectively. The rate of reduction (25-35%) was in accord with the data obtained by Feely et al.¹⁴⁾ using 300 mg/day cimetidine for 7 days and by Goto et al.¹⁵⁾ using 400-800 mg/day cimetidine for 1-14 days. Although the inhibitory mechanism

of cimetidine on the activity of the enzyme responsible for the formation of 6β-OHF from cortisol in human liver is not clear, the mode of the inhibition might have been of competitive type, since cimetidine inhibits the hepatic elimination of a number of drugs by competitive binding to cytochrome P-450.^{16,17)} Our findings suggest that cimetidine, but not famotidine, inhibits the hepatic oxidative metabolism of endogenous steroids in man as well as that of testosterone in mouse hepatic microsomes.⁷⁾ In this study, the therapeutic doses of famotidine (40 mg/day) and cimetidine (800 mg/day) used in the treatment of gastro-intestinal ulcer disease were selected. The concentrations of famotidine and cimetidine in the systemic circulation typically reach peak values in the 0.3-0.6 μM¹⁸⁾ and the 4-8.4 μM^{19,20)} range, respectively, some 2 hr after each oral therapeutic dose. Needless to say, the concentrations of both drugs in hepatic endoplasmic reticulum might differ. Considering that the values of inhibition constants of famotidine on testosterone 6β-, 7α- and 16α-hydroxylase activities in mouse hepatic microsomes were 2.3-10-fold larger than that of cimetidine⁷⁾ and the results obtained here, it is unlikely that famotidine inhibits the oxidative metabolism of endogenous steroids in man at the therapeutic dosage.

On the other hand, measurement of the ratio of 6β-OHF to 17-OHCS in urine is useful as a noninvasive method for evaluating the change in human hepatic oxidative drug-metabolizing capacity such as enzyme induction²¹⁻²⁴⁾ and inhibition,^{14,15)} because 6β-OHF is a polar metabolite formed by the oxidative metabolism of cortisol by hepatic microsomes. A significant correlation has been found between the urinary excretion of 6β-OHF and total body clearance of antipyrine, which is useful as an in vivo param-

eter of hepatic drug metabolism.²³⁾ Actually, the inhibitory effect of cimetidine documented in the present study confirmed the findings in a study of antipyrine steady state kinetics in man by Teunissen et al.²⁵⁾; that is, antipyrine metabolism was reduced by about 30% during treatment with 400 mg of cimetidine and the inhibition disappeared within 48 hr after cessation of treatment. Consequently, the present result is suggested that famotidine, in contrast to cimetidine, has no effect on the oxidative metabolism of xenobiotics in man. Recently, famotidine was found not to impair the clearance of diazepam and procainamide in man.²⁶⁾

In conclusion, it is suggested that famotidine should contribute to safer drug treatment than cimetidine, since it does not affect the oxidative metabolism of endogenous steroid and xenobiotics.

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