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Effect of Cimetidine on Microsomal Drug Metabolism in Man*

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Summary. The effect of cimetidine on human microsomal drug metabolism was studied. In five of six healthy volunteers therapeutic doses of cimetidine prolonged the half-life of antipyrine (range 12–37%; $p < 0.05$). Its clearance was decreased in five subjects (range 2–18%) and was increased in one subject (15%), the changes not being statistically significant. The volume of distribution increased on average by about 14% (range 9–19%; $p < 0.001$). Cimetidine in vitro inhibited the hydroxylation of benzo(a)pyrene and coumarin, as well as the O-deethylation of 7-ethoxycoumarin, by homogenised liver biopsies. The in vitro studies suggest that the effect of cimetidine on antipyrine elimination is due to inhibition of microsomal drug metabolism, which may prove an important drug interaction.

Key words: cimetidine, microsomal drug metabolism; man, interaction, liver microsomes, antipyrine kinetics

Cimetidine, a histamine H_2-receptor antagonist, is widely used in the treatment of peptic ulcer disease. We have previously found that cimetidine inhibits microsomal drug metabolism in the rat (Puurunen and Pelkonen 1979). It prolongs hexobarbital sleeping time and the plasma half-life of aminopyrine. Cimetidine in vitro inhibits aminopyrine N-demethylation and benzo(a)pyrene hydroxylation by rat liver microsomes, indicating that the in vivo effects mentioned above are due to inhibition of the microsomal cytochrome P-450-linked monooxygenase system. Since such an interaction might be clinically important, we have studied whether cimetidine also affects microsomal drug metabolism in man.

Materials and Methods

The effect of cimetidine on the kinetics of antipyrine was studied in six healthy volunteers (aged 25–41 years) with no history of liver disease. Antipyrine 20 mg/kg was given orally at 8 a. m. after an overnight fast, and blood samples were taken after 1, 3, 7 and 24 h. In four subjects (HS, JP, KN and OP) a further antipyrine test was done three days later, when they also took cimetidine 400 mg (Tagamet®, Smith Kline & French Laboratories, Philadelphia, Pennsylvania) perorally, 1, 6 and 12 h after antipyrine, the total dose being 1.2 g. In two subjects (ML and SR) the antipyrine test with cimetidine was done first and the control test without cimetidine followed one week later. Antipyrine in plasma was measured by gas chromatography (Prescott et al. 1973). The plasma elimination half-life was calculated from the linear portion of the log concentration-time curve. Plasma clearance was obtained by dividing the dose by the area under the plasma concentration-time curve calculated by the trapezoidal rule. Apparent volume of distribution was calculated by the relationship: aVd = plasma clearance/elimination rate constant.

The effect of cimetidine on in vitro drug metabolism was studied in liver biopsy samples from 11 patients. Benzo(a)pyrene hydroxylation (Nebert and Gelboin 1968), 7-ethoxycoumarin O-deethylation (Jacobson et al. 1974) and coumarin 7-hydroxylation (Jacobson et al. 1974) were determined in a total homogenate of liver biopsy material. Concentrations of substrates in incubation mixtures were 80 μM (benzo(a)pyrene) or 500 μM (7-ethoxycoumarin and coumarin). Incubation time was 15 min. Cimetidine

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Table 1. Effect of cimetidine on kinetics of antipyrine in six healthy volunteers

Subject	Half-life (h)			Clearance (ml/min)			Distribution volume (l/kg)		
	Without cimetidine	With cimetidine	Change (%)	Without cimetidine	With cimetidine	Change (%)	Without cimetidine	With cimetidine	Change (%)
ML	12.4	13.9	+12	33.9	33.3	− 2	0.46	0.50	+ 9
SR	5.1	6.3	+24	75.3	69.3	− 8	0.57	0.65	+14
HS	8.2	10.4	+27	41.9	37.3	−11	0.47	0.53	+13
JP	9.7	9.8	+ 1	47.8	55.1	+15	0.46	0.54	+17
KN	6.4	8.0	+25	63.4	60.4	− 5	0.64	0.76	+19
OP	11.3	15.5	+37	36.0	29.7	−18	0.53	0.59	+11
Significance	$p < 0.05$			Not significant			$p < 0.001$		

Table 2. Inhibition in vitro by cimetidine of drug-metabolizing enzymes in human liver biopsy samples

Cimetidine (mM)	Benzo(a)pyrene hydroxylase	7-ethoxycoumarin O-deethylase	Coumarin hydroxylase
	% of control activity		
0	100[a]	100[a]	100[a]
0.04	99 ± 8	101 ± 13	93
0.16	90 ± 13	96 ± 6	95
0.64	65 ± 11	84 ± 7	84
2.5	41 ± 5	73 ± 8	88
10	27 ± 1	50 ± 13	72

[a] Control activity taken as 100%. Control activities for the enzymes expressed as nmoles of metabolite formed/g liver wet weight/min were 2.7 ± 1.0 for benzo(a)pyrene hydroxylase (4 biopsies), 9.4 ± 4.4 for 7-ethoxycoumarin O-deethylase (5 biopsies) and 3.6 (3.0 and 4.2) for coumarin 7-hydroxylase (2 biopsies). Each set of cimetidine concentrations was tested on a homogenate from a single biopsy. Values are expressed as means ± SD

was added dissolved in dimethylsulphoxide. The biopsies were taken with a Thrucut needle for the histological confirmation of liver disease, and part of each specimen (10–20 mg wet weight) was used for assessment of drug metabolism. All biopsies exhibited moderate liver injury with inflammatory changes and/or fatty degeneration. Each complete set of cimetidine concentrations was always tested on a homogenate of a single liver biopsy. The number of biopsy samples used for the determination of cimetidine effect on enzymic reactions ranged from two (coumarin hydroxylase) to five (7-ethoxycoumarin O-deethylase). Statistical analysis was performed using Student's t-test for paired observations.

Results

The in vivo results are shown in Table 1. In five of the six subjects cimetidine prolonged the half-life of antipyrine (range 12–37%), and in one person it had no effect. The prolongation was statistically significant ($p < 0.05$). Antipyrine clearance decreased in five subjects (range 2–18%) and increased in one subject by about 15%; the change was not statistically significant. In all six subjects cimetidine increased the apparent volume of distribution (range 9–19%; $p < 0.001$).

Cimetidine in vitro inhibited the hydroxylation of benzo(a)pyrene and coumarin, and the O-deethylation of 7-ethoxycoumarin (Table 2). The inhibition was most marked with benzo(a)pyrene as a substrate, the IC_{50}-value being about 1 mM, whereas for 7-ethoxycoumarin O-deethylase it was about 10 mM and for coumarin hydroxylase it was even higher.

Discussion

The in vivo results indicate that cimetidine in therapeutic doses interacts with the kinetics of antipyrine. The half-life of antipyrine was prolonged by cimetidine, whereas the change in antipyrine clearance was less pronounced. The latter finding may perhaps be due to the increase in the apparent volume of distribution. How cimetidine increased the distribution volume of antipyrine is not clear from the present results. It was not due to incomplete absorption of antipyrine, since the latter was given one hour before the first dose of cimetidine. A similar increase in the distribution volume of antipyrine by cimetidine was recently found in three of six subjects by Serlin et al. (1979).

The in vitro studies in human liver biopsy homogenates strongly suggest that prolongation of the antipyrine half-life by cimetidine was due to inhibition of the cytochrome P-450-linked monooxygenase system in the liver. According to Burland et al. (1977) the blood concentration of cimetidine during treatment with 1.6 g/day is about 10 μM. In the present work the concentration of cimetidine required to inhibit the activity of liver enzymes was

higher. However, it has been reported that the concentration of cimetidine in bile is about 5-times higher than that in peripheral blood (Spence et al. 1977). Therefore, the concentration of cimetidine in the liver may exceed that in peripheral blood.

The activity of benzo(a)pyrene hydroxylase was inhibited by lower concentrations of cimetidine than those affecting 7-ethoxycoumarin O-deethylase and coumarin hydroxylase. In animal experiments it has been shown that both the control level and phenobarbital-inducible benzo(a)pyrene hydroxylase are strongly inhibited by SKF 525 A, aminopyrine and metyrapone, whereas the 3-methyl-cholanthrene-inducible benzo(a)pyrene hydroxylase is not inhibited by these compounds (Goujon et al. 1972). Similarly, we have found that cimetidine inhibits benzo(a)pyrene hydroxylase in control rat liver, but not the enzyme from 3-methylcholanthrene-pretreated rat liver (Pelkonen and Puurunen, unpublished). It seems plausible that differences in the inhibitory effect of cimetidine on human liver biopsy samples reflect the preferential interaction of cimetidine with certain form(s) of the cytochrome P-450. It may be that 7-ethoxycoumarin and coumarin are mainly metabolized in the human liver by the cytochrome(s) P-450 which is less effectively inhibited by cimetidine, whereas benzo(a)pyrene hydroxylation is preferentially effected by the cytochrome P-450 which is more effectively inhibited by cimetidine. The corollary is that cimetidine may inhibit the metabolism of some compounds but not that of others, depending on the specificity of the cytochrome P-450.

Many drugs and other exogenous compounds, as well as a number of endogenous compounds, such as steroid hormones, are metabolized by cytochrome P-450 (for review, see Testa and Jenner 1976). Therefore, through inhibition of their metabolism cimetidine may not only modify the effects of other drugs, but also change the balance of endogenous compounds in the body. It has been reported that cimetidine potentiates the hypoprothrombinaemic effect of warfarin (Flind 1978; Silver and Bell 1979). The present results suggest that this may be due, at least in part, to the inhibition of warfarin metabolism by cimetidine. After submission of the present paper several reports suggesting that cimetidine may interact with the microsomal metabolism of other drugs have been published (Serlin et al. 1979; Klotz et al. 1979; Hetzel et al. 1979). At least in patients receiving a drug which is metabolized by the cytochrome P-450 and has a low therapeutic ratio, there is a possibility of adverse reactions if cimetidine is given concomitantly.

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