

Lack of Effect of Cimetidine on the Pharmacokinetics and Metabolism of a Single Oral Dose of Metronidazole

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Summary. The time course of the effect of cimetidine on the pharmacokinetics of metronidazole was investigated in 6 healthy volunteers.

Cimetidine 1.0 g/day was administered for 9 days and metronidazole 500 mg was administered orally on the second and eighth days, and in a control experiment.

During cimetidine treatment the plasma kinetics of metronidazole and its partial clearance by renal excretion of the unchanged compound, glucuronidation, hydroxylation and oxidation to its acetic acid metabolite were not significantly different from the control values.

The results indicate that cimetidine does not influence the pharmacokinetics or metabolism of a single oral dose of metronidazole.

Key words: metronidazole, cimetidine; pharmacokinetics, drug interaction, drug metabolism, healthy volunteers

Cimetidine has been shown to be a potent inhibitor of the oxidative metabolism of many drugs [1]. Metronidazole is a widely used antimicrobial, mainly eliminated by microsomal oxidation in the liver [2-4]. It was recently reported that the plasma kinetics and partial metabolic clearances of metronidazole were not affected by treatment with cimetidine 1.0 g/day from 1 day prior to administration and throughout the elimination phase [5]. After administration of cimetidine for 6 days a reduction in total metronidazole clearance of about 30% has been reported by others [6]. The two

studies would be compatible if the inhibition of metronidazole elimination required administration of cimetidine for several days [5]. In order to pursue this hypothesis further and to reinvestigate the effect of cimetidine on the disposition of metronidazole, a time course study was performed.

Material and Methods

Six healthy volunteers (2 women and 4 men; aged 26 to 39 years; weight 47 to 90 kg) participated after giving their informed consent. The investigation protocol was approved by the local Ethics Committee. The subjects took alcohol socially, but none smoked or took any drugs except those under investigation for at least one month before and throughout the study. Dietary habits and physical activity were constant.

The subjects took cimetidine 200 mg t.d.s. and 400 mg at bedtime for 9 days. On Days 2 and 8 of cimetidine treatment each subject ingested metronidazole 500 mg as 2 × 250 mg tablets following an overnight fast, which was continued for another hour. Two weeks before or after cimetidine treatment the subjects took a further dose of metronidazole 500 mg.

Before and 2, 5, 8, 12, 16, 24, 36 and 48 h after metronidazole administration blood was collected in heparinized tubes. Urine was collected for 48 h. The plasma and urine concentrations of metronidazole and its glucuronide, hydroxy and acetic acid metabolites were determined by HPLC [4].

The pharmacokinetics of metronidazole was analysed according to a one-compartment model, assuming complete bioavailability and negligible

Table 1. Mean parameters of the metabolism of metronidazole 500 mg administered orally to 6 healthy volunteers in a control experiment (Control and after administration of cimetidine for 1 (Cim 1) and 7 days (Cim 7)

	$t_{1/2}$ (h)	V (l)	CL (ml/min)	CL _R (ml/min)	CL _{GL} (ml/min)	CL _{MAA} (ml/min)	CL _{HM} (ml/min)	Recovery (%)	AUC _{HM} ($\mu\text{M}\cdot\text{min}$)
Mean \pm SD									
Control	7.6 \pm 1.3	51 \pm 16	77 \pm 20	6.4 \pm 2.6	2.3 \pm 1.0	12.9 \pm 4.6	23.6 \pm 8.8	59 \pm 5	4.8 \pm 1.9
Cim 1	7.9 \pm 0.8	51 \pm 12	75 \pm 21	6.6 \pm 1.4	2.7 \pm 0.9	12.1 \pm 3.6	22.1 \pm 7.9	59 \pm 4	4.6 \pm 1.9
Cim 2	7.1 \pm 1.1	50 \pm 10	82 \pm 18	6.8 \pm 2.3	3.3 \pm 0.9	13.1 \pm 3.6	26.7 \pm 9.3	61 \pm 4	5.1 \pm 2.3

$t_{1/2}$ half-life, V volume of distribution, CL total clearance, CL_R renal clearance, CL_{GL} clearance by glucuronidation, CL_{MAA} clearance by oxidation to the acetic acid metabolite, CL_{HM} clearance by hydroxylation. Recovery: Urinary excretion of the mother compound and major metabolites in % of dose

duration of absorption and distribution [2-4]. The total clearance of metronidazole was determined as the product of the elimination rate constant and the apparent volume of distribution, estimated from the slope and zero time intercept of the log concentration-time curve, respectively. The partial clearances of metronidazole were determined as the product of the fraction of the dose excreted as the particular metabolite and the total clearance. The area under the plasma concentration-time curve of hydroxymetronidazole (AUC_{HM}) was determined by the trapezoidal rule.

The effect of time on the kinetic characteristics of metronidazole was analysed by two-way analysis of variance. P-values less than 0.05 were considered statistically significant. When appropriate, 95% confidence limits of the ratios between treatment and control values were calculated.

Results

The administration of cimetidine for 9 days did not significantly alter any of the kinetic characteristics of metronidazole (Table 1; Figs. 1, 2). After 1 and 7 days of cimetidine treatment the mean total clearance of metronidazole was 0.98-times (0.90 to 1.06, 95% confidence limits) and 1.08-times (0.95 to 1.21) the control value ($p > 0.05$), respectively, and the renal clearance was 1.11-times (0.80 to 1.41) and 1.15-times (0.73 to 1.57), the clearance by glucuronidation was 1.3-times (0.7 to 1.9) and 1.7-times (0.6 to 2.8), the clearance by hydroxylation 0.95-times (0.75 to 1.15) and 1.15-times (0.81 to 1.49), and the clearance by oxidation to the acetic acid metabolite was 0.96-times (0.88 to 1.02) and 1.04-times (0.92 to 1.16) the control values ($p > 0.05$).

Discussion

In the present study, treatment with cimetidine for 1 or 7 days before oral administration and throughout the sampling period did not alter the plasma kinet-

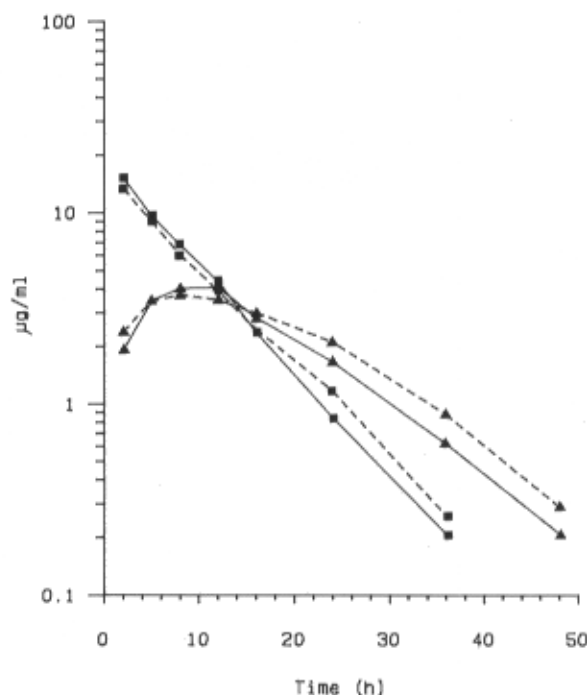


Fig. 1. Plasma concentration-time curves of metronidazole (■) and its hydroxymetabolite (▲) in Subject 4 after oral administration of metronidazole 500 mg in a control experiment (solid lines), and following administration of cimetidine 1 g/day for 7 days and throughout the sampling period (broken lines)

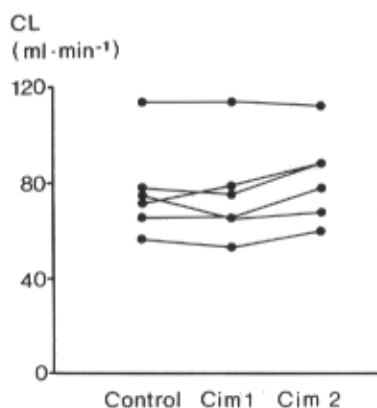


Fig. 2. Individual total metronidazole clearance values (CL) in 6 healthy volunteers in a control experiment and after administration of cimetidine for 1 day (Cim 1) and 7 days (Cim 7)

ics of metronidazole and its hydroxymetabolite or any of its partial clearances to a statistically or biologically significant extent. It is unlikely that cimetidine influenced the absorption or metronidazole, as the apparent volume of distribution and the fraction of the dose accounted for by urinary excretion of the mother compound and metabolites were unchanged.

It was recently reported that after administration of cimetidine for 24 h and throughout the sampling period, the mean total clearance of i.v. metronidazole was 1.04-times the control value (95% confidence limits 0.90 to 1.18-times the control value; [5]). After treatment with cimetidine for 7 days in the present study, the mean total metronidazole clearance was 1.08-times the control value (95% confidence limits 0.95 to 1.21-times the control value). Thus, the results of the two studies exclude a clinically important inhibiting effect of cimetidine on the elimination rate of 500 mg metronidazole. These data do not permit exclusion of interactions at higher dose levels.

As metronidazole is mainly eliminated by hepatic microsomal hydroxylation [2-4], a drug-drug interaction with cimetidine might have been expected [1]. In the present and the previous study, the rate of hydroxylation of metronidazole was not altered during cimetidine coadministration [5]. In other studies, cimetidine did not change the rate of hydroxylation of tolbutamide [8] and the plasma kinetics of oxidatively eliminated drugs, such as nortriptyline [9], the S-enantiomer of warfarin [10] and misonidazole [11]. The latter is a nitroimidazole like metronidazole, although mainly eliminated by N-demethylation. The cimetidine-mediated inhibition of the metabolism of the probe drug, antipyrine, shows large interindividual variation and it may be under genetic regulation [12, 13]. All these results suggest selectivity of the inhibitory effect of cimetidine on cytochrome P-450 isozymes.

Gugler and Jensen have reported a 30% decrease in the total clearance of metronidazole with an unchanged volume of distribution in 6 subjects after treatment with cimetidine 800 mg/day for 6 days [6]. Details of the effect on each elimination pathway were not reported [6]. The present results exclude one possible explanation of the apparent discrepancy between that study [6] and the previous results [5], namely that inhibition of metronidazole elimination required administration of cimetidine for several days, comparable to the delayed inhibitory effect of disulfiram on antipyrine elimination [7]. Moreover, cimetidine exerts its full inhibiting effect on the metabolism of other drugs, such as anti-

pyrine and theophylline, within 24 h of starting treatment [14, 15]. In the previous study, the ability of subjects to respond to cimetidine by inhibition of the activity of particular cytochrome P-450 isozymes was verified by the expected decrease in the total and partial antipyrine clearances measured on the day after metronidazole administration [5]. The apparent discrepancy between the present results and those of Gugler and Jensen [6] remains to be explained.

In the previous study [5], the renal clearance of metronidazole was reduced during cimetidine coadministration, in line with similar observations with other drugs which form cations [16]. The unaltered renal clearance of metronidazole in the present study could be explained if the inhibitory effect of cimetidine was only important at the high plasma concentration achieved during and immediately after the intravenous infusion used in the previous study [5], and not at the lower peak concentrations achieved after oral administration.

In conclusion, the coadministration of cimetidine did not significantly influence the pharmacokinetics and metabolism of single oral doses of metronidazole.

Acknowledgement. The HPLC equipment was kindly donated by the Lundbeck Foundation. We thank Ms. S. Hjerpsted for her expert technical assistance.

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Received: August 13, 1987

accepted in revised form: February 19, 1988

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