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Inhibition and Induction of Metronidazole and Antipyrine Metabolism

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Summary. The effect of cimetidine, antipyrine and phenobarbitone on the pharmacokinetics of intravenous metronidazole and oral antipyrine has been examined in 7 healthy volunteers. The administration of cimetidine for 24 h before and throughout the sampling period failed to alter the total clearance of metronidazole or the rate of formation of the hydroxy metabolite, whereas the total and partial clearances of antipyrine were decreased 0.74 and 0.6–0.7-fold, respectively, Seven days of phenobarbitone or antipyrine administration increased the total clearance of metronidazole 1.51- and 1.86-fold, respectively, and the total antipyrine clearance was 1.22 or 1.46-fold increased, respectively. The rate of metronidazole hydroxylation was significantly enhanced by both enzyme inducers. The partial clearance of antipyrine to the normetabolite was significantly increased by both inducers, wheras the rate of 4-hydroxylation was significantly increased only by prior antipyrine administration. The results indicate that the hydroxylation of metronidazole is not inhibited by cimetidine, but that it is inducible by phenobarbitone or antipyrine. It is suggested that metronidazole and antipyrine are metabolized by different enzymatic pathways.

Key words: metronidazole, antipyrine; cimetidine, phenobarbitone, drug interaction, drug metabolism, pharmacokinetics

Metronidazole ia a widely used antimicrobial, mainly eliminated by microsomal oxidation in the liver [1–3]. Interactions can be expected, therefore, between inducers and inhibitors of hepatic drug metabolism and metronidazole, possibly with therapeutic or toxicological implications. There are reports of therapeutic failure and/or a shortened half-life of metronidazole in patients treated with phenobarbitone [4–6]. After administration for 6 days of the mono-oxygenase inhibitor, cimetidine, a reduction in metronidazole clearance by about 30% has been reported [7].

The effect of enzyme induction on metronidazole metabolism has not so far been studied systematically, and the effect of cimetidine on the formation of metabolites of metronidazole is unknown. In addition, a comparison within individuals of the formation of metabolites from metronidazole and the well known probe drug for mono-oxygenase activity, antipyrine, might indicate whether the two drugs share metabolic pathways [8].

In the present study, the effects of the enzyme inhibitor, cimetidine, and the enzyme inducers, phenobarbitone and antipyrine, on the metabolism of metronidazole and antipyrine have been investigated.

Materials and Methods

Protocol

All the subjects studied were healthy volunteers, who participated after having given informed consent. The investigation protocol was approved by the Ethics Committee of Copenhagen County. 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.

Metronidazole Metabolism. Seven subjects (2 women and 5 men; age 24 to 37 years; weight 57 to 90 kg) were given metronidazole 500 mg (DAK) as an intravenous infusion over 20 min in a control experiment, and after each of the following pretreatments: cimet-

idine 1000 mg/day for 1 day continued throughout the sampling period (7 subjects), phenobarbitone 100 mg/day for 7 days (4 subjects), and antipyrine 1000 mg/day for 7 days (5 subjects). The metronidazole treatments were separated by at least 4 weeks and the order of the experiments was randomised. Only 2 subjects were given metronidazole after both the phenobarbitone and antipyrine pretreatments.

Blood was sampled in heparinized tubes before and 10, 20, 30, 40, 60 and 80 min and 2, 3, 5, 8, 12, 16, 24, 36 and 48 h, and urine was collected at intervals for 48 h after metronidazole administration. Plasma samples and aliquots of the urine samples were stored at −20 °C until analysed. Immediately following metronidazole administration after phenobarbitone pretreatment, one subject suffered neurotoxic symptoms with nystagmus for a few minutes, followed by a depressed level of consciousness and hypotension for about 1 h. After another hour he had recovered completely. Kinetic characteristics in him did not appear different from those in the other subjects.

Antipyrine Metabolism. After an overnight fast, antipyrine 1000 mg in aqueous solution was ingested, once on the day after each metronidazole infusion following a pretreatment, and once alone, 4 weeks before or after the metronidazole administration. About 24 h later a saliva sample was obtained and urine was collected for 48 h. Following the antipyrine pretreatment, saliva samples were collected before and 3, 6, 9, 12, 16 and 24 h after the antipyrine dose for measurement of its clearance. In one subject only antipyrine metabolism was studied after phenobarbitone pretreatment.

Antipyrine – Metronidazole Interaction. In random order and at intervals of at least one week, 10 subjects (5 women and 5 men; age 18 to 37 years; weight 54 to 85 kg) ingested metronidazole 500 mg (DAK) as tablets, or antipyrine 1000 mg in aqueous solution, or both drugs together. Plasma and urine were sampled at regular intervals for 48 h following metronidazole administration. About 24 h after antipyrine administration a saliva sample was collected.

Analytical Procedures

The plasma and urine concentrations of metronidazole and its major metabolites, hydroxymetronidazole (HM) and metronidazole acetic acid (MAA), were determined by HPLC, as previously described [3]. In the chromatograms of urine an unknown peak suggestive of 1-(2-hydroxyethyl)-5-nitroimidazole-2-carboxylic acid, a further oxidation product of HM, elutes before the MAA peak [3, 9]. A reference compound is not available to confirm its identity. The urinary content of glucuronide conjugates was estimated as the difference between determinations with and without prior enzymatic hydrolysis.

For the assay of saliva and urine for antipyrine and its metabolites the HPLC system was fitted with a Waters Novapak column and the effluent monitored at 244 nm. Saliva 200 µl was mixed with an equal amount of acetonitrile containing phenacetin as internal standard. After centrifugation, 5 µl of the supernatant was injected. The urine samples were assayed after hydrolysis with glucuronidase/aryl sulphatase (Boehringer) at 37 °C for 3 h. After addition of phenacetin as internal standard and saturation with NaCl the sample was extracted with chloroform/ethanol (9/1 v/v), as described by Teunissen et al. [10]. The organic phase was evaporated to dryness under reduced pressure at room temperature. The residue was dissolved in 100 µl methanol, diluted with 250 µl mobile phase and 5 µl was injected. The mobile phase was delivered at 0.5 ml/min and for the assay of saliva and urine, respectively, consisted of water/methanol (55/45 v/v) and phosphate buffer 0.01 M pH 6.8/methanol (60/40 v/v) containing sodium pyrosulphite. Reference metabolites used for the standard curves were norantipyrine and 4-hydroxyantipyrine (EGA-Chemie) and 3-hydroxymethylantipyrine (kindly donated by Drs. Danhof, Eichelbaum and Yoshimura).

Pharmacokinetic Calculations

When appropriate, the ESTRIP computer program [11] was used for the pharmacokinetic calculations. The area under the plasma concentration versus time curve of metronidazole or its metabolite (AUC) was calculated according to the trapezoidal rule with extrapolation to infinity. The total clearance of metronidazole was calculated as the ratio between the dose and the AUC. The other kinetic characteristics were calculated according to an open two-compartment model for intravenous administration [12]. The absorption of orally administered metronidazole was assumed to be complete [2, 3] and the half-life and apparent volume of distribution were calculated from the slope of the terminal log concentration versus time curve and the AUC. The partial clearances of metronidazole or its hydroxy metabolite were calculated as the amount excreted divided by the $AUC_{(0-48)}$ during urine collection.

The clearance of antipyrine was calculated from the concentration in the single saliva sample and an assumed volume of distribution estimated from body weight, height and age, as previously described [13].

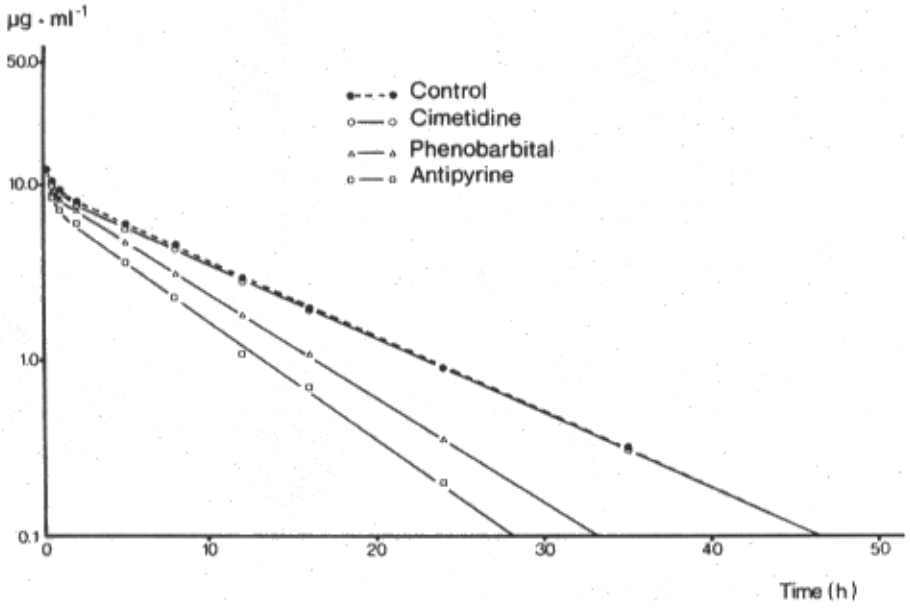

Fig. 1. Mean plasma concentration-time profiles of metronidazole after administration of 500 mg i.v. in a control experiment ($n = 7$) and after pretreatment with cimetidine ($n = 7$), phenobarbitone ($n = 4$) or antipyrine ($n = 5$)

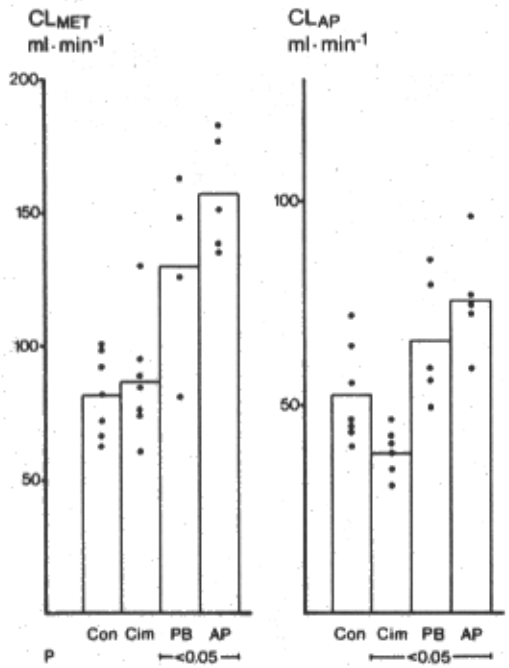

Fig. 2. Total clearance of metronidazole (CL_{MET}) and antipyrine (CL_{AP}) in a control experiment (Con) and after pretreatment with cimetidine (Cim), phenobarbitone (PB) or antipyrine (AP). The *bars* represent mean values

This method for the determination of antipyrine clearance is highly reproducible and is little influenced by biased estimation of the volume of distribution [14, 15]. After the antipyrine pretreatment, identical clearance estimates were obtained by using the one-sample method, adding the residual antipyrine from the preceding administration (salivary concentration times the estimated volume of distribution) to the dose, or by multiplying the disposition rate constant (slope of the log concentration-time curve) by the apparent volume of distribution (dose divided by time zero intercept minus predose concentration). A partial clearance was estimated for each of the major elimination pathways of antipyrine as the fraction of the dose excreted as the particular metabolite multiplied by the total clearance.

Statistical Analysis

The data from the intravenous metronidazole treatments were analysed by two-way analysis of variance with substitution of missing values [16]. Duncan's multiple range test was used for the post hoc comparison of means. The data from the two oral treatments were compard by a paired Student's *t*-test. A stepwise backward regression analysis was done by the method of least squares. *P*-values less than 0.05 were considered statistically significant.

Results

The administration of cimetidine for 24 h before and throughout the sampling period did not significantly alter the plasma kinetics of metronidazole (Figs. 1 and 2, Table 1). During cimetidine treatment the mean metronidazole clearance was 1.04 - times (0.90 to 1.18; 95% confidence limits) the control value, wheras the total saliva clearance of antipyrine was 0.74 - fold (0.58 to 0.90) reduced (Fig. 2).

After the administration of phenobarbitone or antipyrine for 1 week, the plasma concentrations of

metronidazole were decreased throughout the post-infusion period as compared to the control measurements (Fig. 1). The total clearance of metronidazole on average was 1.51 - (1.37 to 1.65) and 1.86 - (1.75 to 2.03) fold increased and the elimination half-life was 0.67 - (0.52 to 0.82) and 0.60 - (0.45 to 0.75) fold decreased by the phenobarbitone and antipyrine pretreatments, respectively (Table 1, Fig. 2). The apparent volume of distribution at steady state was not significantly altered by the enzyme inducers. The mean phenobarbitone and antipyrine - mediated enhancement of the total antipyrine clearance was to 1.22 - (1.06 to 1.38) and 1.46 - (1.30 to 1.62) times the control value, respectively (Fig. 2).

Table 1. Kinetics (mean ± SD) of metronidazole in a control experiment (Con) and after pretreatment with cimetidine (Cim), phenobarbitone (PB) or antipyrine (AP).

Pretreatment	$t_{½\beta}$ (h)	V_{ss} (l)	CL (ml/min)
Con ($n=7$)	7.3 ± 1.0	50.0 ± 7.3	83 ± 15
Cim ($n=7$)	7.4 ± 1.7	49.2 ± 6.3	87 ± 22
PB ($n=4$)	4.9 ± 1.3[a]	50.3 ± 4.1	130 ± 25[a]
AP ($n=5$)	4.4 ± 0.4[a]	55.1 ± 7.6	157 ± 21[a]

$t_{½\beta}$ is the elimination half-life, V_{ss} is the volume of distribution at steady state, and CL is the clearance. [a] denotes $p<0.05$ vs control

Table 2. Clearance (mean ± SD) of metronidazole by the 4 major elimination pathways, renal excretion (CL_R), glucuronidation (CL_{GL}), oxidation to the acetic acid metabolite (CL_{MAA}) and hydroxylation (CL_{HM}) in a control experiment (Con) and after pretreatment with cimetidine (Cim), phenobarbitone (PB) or antipyrine (AP). Values are in ml/min.

Pretreatment	CL_R	CL_{GL}	CL_{MAA}	CL_{HM}
Con ($n=7$)	12.0 ± 2.1	5.2 ± 2.3	13.1 ± 3.8	33.0 ± 8.9
Cim ($n=7$)	7.8 ± 1.7[a]	3.6 ± 0.8	11.3 ± 4.0	29.8 ± 11.7
PB ($n=4$)	9.4 ± 2.0	4.1 ± 0.8	14.7 ± 3.2	53.2 ± 12.3[a]
AP ($n=5$)	10.7 ± 1.9	4.2 ± 0.6	15.3 ± 4.2	57.0 ± 10.8[a]

[a] denotes $p<0.05$ vs control

Fig. 2. The clearance of metronidazole by hydroxylation (CL_{HM}) and the partial clearances of antipyrine to the nor- (CL_{NORAP}), 4-hydroxy ($CL_{4\text{-}OHAP}$) and 3-hydroxymethyl ($CL_{3\text{-}OHAP}$) metabolites of in a control experiment (Con) and after pretreatment with cimetidine (Cim), phenobarbitone (PB) or antipyrine (AP). The *bars* represent mean values

The clearance of metronidazole by hydroxylation (CL_{HM}) was not significantly altered, i.e. 0.90 - (0.70 to 1.10) times the control value, during cimetidine coadministration, but it was increased on average 1.49 - (1.29 to 1.69) and 1.73 - (1.5 to 1.93) fold after pretreatment with phenobarbitone and antipyrine, respectively (Table 2, Fig. 3). Coadministration of cimetidine decreased the partial clearance of antipyrine to the normetabolite 0.59 - (0.30 to 0.88) fold, wheras enzyme induction with phenobarbitone and antipyrine increased it to 1.32 - (1.03 to 1.61) and 1.76 - (1.47 to 2.05) times the control value, respectively (Fig. 3). On average the partial clearance of antipyrine by 4-hydroxylation was 0.68 - (0.38 to 0.98) fold decreased and 1.51 - (1.21 to 1.81) fold increased during cimetidine and after antipyrine administration, respectively, but it was not significantly affected by pretreatment with phenobarbitone, i.e. it was 1.22 - (0.92 to 1.52) times the control value (Fig. 3). The partial clearance of antipyrine to 3-hy-

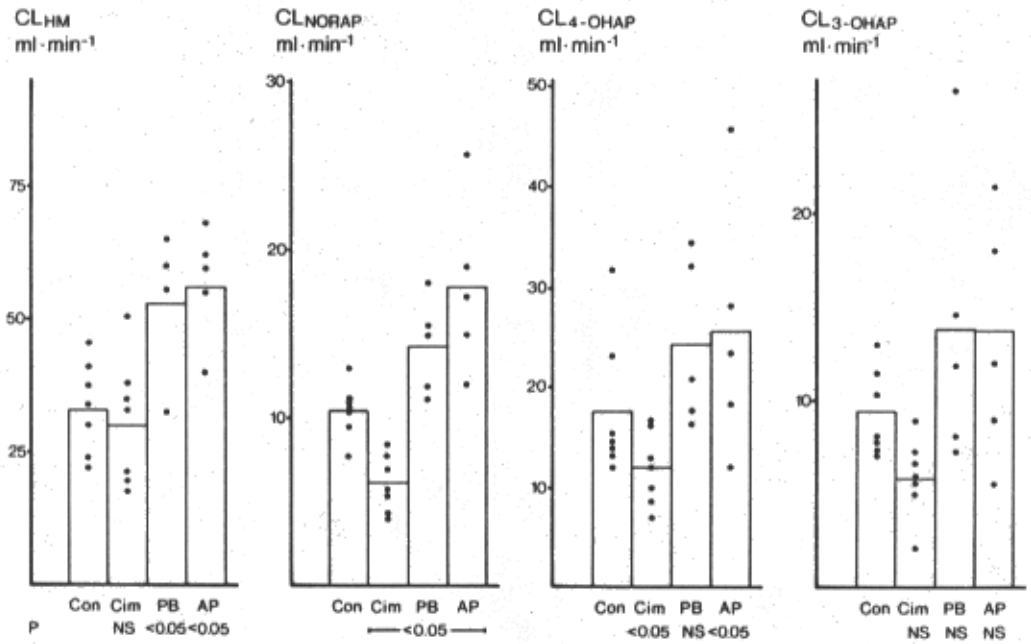

Fig. 3. The clearance of metronidazole by hydroxylation (CL_{HM}) and the partial clearances of antipyrine to the nor- (CL_{NORAP}), 4-hydroxy ($CL_{4\text{-}OHAP}$) and 3-hydroxymethyl ($CL_{3\text{-}OHAP}$) metabolites of in a control experiment (Con) and after pretreatment with cimetidine (Cim), phenobarbitone (PB) or antipyrine (AP). The *bars* represent mean values

droxymethylantipyrine was not significantly altered by any of the pretreatments, i.e. it was 0.63 - (0.07 to 1.19), 1.35 - (0.79 to 1.91), and 1.38 - (0.82 to 1.94) times the control value with cimetidine, phenobarbitone, and antipyrine respectively (Fig. 3). A backward stepwise multiple regression analysis excluded each of the partial clearances of antipyrine to the three main metabolites as a significant predictor of CL_{HM}, and left the total antipyrine clearance as an important predictor ($r = 0.84$, $p < 0.001$). The linear slope of the regression of CL_{HM} on the total antipyrine clearance was 0.73 – (0.52 to 0.94) and the intercept –0.21 (–12.9 to 12.5).

During cimetidine coadministration, the renal clearance of metronidazole was significantly decreased, wheras the rate of metronidazole elimination by oxidation to the acetic metabolite and glucuronidation was unchanged (Table 2). Pretreatment with phenobarbitone and antipyrine had no significant effect on the renal clearance of metronidazole, on its clearance by oxidation to the acetic acid metabolite or on glucuronidation (Table 2). The area under the plasma concentration versus time curve, the renal clearance and the fraction excreted as glucuronide conjugates of the hydroxy-metabolite of metronidazole were not significantly changed by any of the pretreatments (Table 3).

The coadministration of a single dose of antipyrine without pretreatment did not in any way alter the metabolism of orally administered metronidazole (Table 4).

Table 3. Kinetics (mean ± SD) of the hydroxy metabolite of metronidazole in a control experiment (Con) and after pretreatment with cimetidine (Cim), phenobarbitone (PB) and antipyrine (AP)

Pretreatment	AUC (μg h/ml)	CL_R (ml/min)	HM-gluc (%)
Con ($n = 7$)	70 ± 10	50 ± 9	13 ± 4
Cim ($n = 7$)	65 ± 14	45 ± 10	13 ± 4
PB ($n = 4$)	67 ± 9	50 ± 6	10 ± 5
AP ($n = 5$)	58 ± 7	55 ± 11	15 ± 4

AUC is the area under the plasma concentration time curve, CL is the clearance and HM-gluc is the fraction excreted as glucuronide conjugates

Discussion

In the present study, the administration of cimetidine for 24 h and throughout the postinfusion period failed to alter the total or the relative metabolic clearances of metronidazole, whereas the renal clearance was significantly decreased. It has recently been suggested that cimetidine in general inhibits the renal excretion of drugs which form cations, such as metronidazole [17]. In our subjects, the renal excretion of unchanged metronidazole accounted for less than 15% of the total clearance. The total clearance of metronidazole was reported to be decreased by 30% in 6 subjects after cimetidine treatment for 6 days [7]. The apparent discrepancy between that and the present result could be explained if the inhibition of metronidazole elimination required administration of cimetidine for several days, comparable to the delayed inhibiting effect of disulfiram on antipyrine elimination [18]. Cimetidine, however, exerts its full inhibiting effect on antipyrine metabolism within 24 h after the start of treatment [14]. During cimetidine coadministration the total and the relative clearances of antipyrine were decreased to the expected extent, i.e. the total clearance was reduced 0.74 - fold on average [14]. Thus, the activity of particular microsomal isozymes must have been inhibited in the present subjects. In several studies cimetidine has failed to inhibit the hydroxylation of other drugs, e.g tolbutamide and nortriptyline [19, 20]. A time course study would be required to demonstrate a delayed inhibitory effect of cimetidine on the elimination of metronidazole, but was considered beyond the scope of the present investigation.

After administration for 1 week of one of the enzyme inducers, phenobarbitone and antipyrine, the mean total clearance of metronidazole was increased 1.6 - and 1.9 - times, respectively. The volume of distribution was not significantly altered and the elimination half-life was decreased by about as much as the clearance had increased. The clearance of metronidazole by hydroxylation was increased to about the same relative extent as the total clearance, and was the only elimination pathway affected by the inducers. Reports of therapeutic failure and/or a

Table 4. Characteristic of the metabolism of metronidazole 500 mg orally and the clearance of antipyrine 1000 mg (CL_{AP}), each administered alone (control) and concomitantly (MET + AP). Mean ± SD for 10 subjects

	$t_{½}$ (h)	V (l)	CL (ml/min)	CL_R (ml/min)	CL_{GL} (ml/min)	CL_{MAA} (ml/min)	CL_{HM} (ml/min)	CL_{AP} (ml/min)
Control	6.7 ± 0.6	51 ± 4	89 ± 13	8.8 ± 1.3	4.3 ± 1.3	13.6 ± 3.1	31.5 ± 8.7	58 ± 12
MET + AP	7.0 ± 0.6	54 ± 6	90 ± 15	8.3 ± 1.0	3.8 ± 1.2	12.9 ± 3.3	30.4 ± 8.4	58 ± 18

$t_{½}$ is the half-life, V the volume of distribution and CL is the total clearance and by renal excretion, glucuronidation (CL), oxidation to the acetic acid metabolite (MAA) and hydroxylation (HM)

shortened half-life of metronidazole in patients treated with phenobarbitone are readily explained by the induction of metronidazole hydroxylation [4–6].

The increase in antipyrine clearance to 1.2-times its control value by phenobarbitone pretreatment was somewhat less than the 1.5-fold or greater increase reported by others [14, 21, 22]. However, in most of those studies the pretreatment was given for more than 7 days, and since phenobarbitone has a long half-life, its steady-state level and therefore maximal induction might not have been reached here. In contrast, the autoinduction of antipyrine metabolism after 7 days of administration was of the expected magnitude [21]. Accordingly, the recorded 60% increase in metronidazole clearance after phenobarbitone treatment for 7 days might have been even greater if the exposure period had been longer. The failure of the changes in the clearance of antipyrine to the 3-hydroxymethylmetabolite and in the effect of phenobarbitone on 4-hydroxylation to reach statistical significance may very well have been due to the small number of subjects and considerable interindividual variation. In agreement with the results it has previously been reported that N-demethylation followed by 4-hydroxylation of antipyrine are most sensitive to enzyme induction by phenobarbitone and antipyrine [22], whereas cimetidine has been shown also to inhibit 3-methylhydroxylation [14, 23].

Coadministration of a single dose of antipyrine did not affect metronidazole metabolism, and other investigators have shown that a single dose of metronidazole does not alter the microsomal oxidation of antipyrine [23].

The results indicate that the cytochrome P-450 isozyme(s) responsible for the hydroxylation of metronidazole, like those responsible for N-demethylating and hydroxylating antipyrine, is/are inducible by phenobarbitone and antipyrine. However, unlike those responsible for the oxidation of antipyrine, the isozyme(s) hydroxylating metronidazole do(es) not seem to be inhibited by cimetidine. Unlike antipyrine, metronidazole does not induce the metabolism of itself or other microsomally oxidized drugs [2, 24]. In addition, multiple regression analysis of the data excluded the partial clearances of antipyrine to all three major metabolites as significant predictors of the rate of metronidazole hydroxylation. If metronidazole and antipyrine shared a metabolic pathway, a strong correlation between the formation rates of the metabolites involved would have been expected [8]. Accordingly, it seems that metronidazole and antipyrine are metabolized by different cytochrome P-450 isozymes. The significant correlation between the total clearances of metronidazole and antipyrine does not necessarily suggest more than a similar regulatory mechanism.

It was previoulsy suggested that a compound eluting in the chromatograms of urine was a further oxidation product of hydroxymetronidazole [3, 11]. Unfortunately, a reference compound is not available for its identification and quantification. However, judged from the chromatograms the amount of the unidentified compound excreted did not change much during the present study. In agreement with this, the kinetic characteristics of hydroxymetronidazole, i.e. the area under the plasma concentration versus time curve, the renal clearance, and the fraction excreted as glucuronide conjugates, were not significantly altered by the pretreatments.

In conclusion, the results indicate that the microsomal enzyme(s) responsible for hydroxylation of metronidazole is(are) distinct from those responsible for the oxidation of antipyrine. They are not, at least immediately, inhibited by cimetidine, but nevertheless are highly inducible by phenobarbitone and antipyrine. The clinical implication of the study is that an increased therapeutic dosage of metronidazole should be considered if there is concomitant administration of an enzyme inducer.

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