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Influence of Dose and Route of Administration on Disposition of Metronidazole and its Major Metabolites

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Summary. The influence of dose and route of administration on the kinetics of metronidazole and its major metabolites has been investigated in 8 healthy volunteers given 0.5 and 2.0 g i.v. and p.o. Metronidazole elimination kinetics from plasma could be described by an open two-compartment model. The systemic oral bioavailability of both doses was approximately 1. The total systemic clearance of the intravenous 2.0 g dose was 9% lower than that of the 0.5 g dose ($p < 0.05$). There were no significant dose-related differences in volume or rate of distribution. The elimination half-life was similar after the four treatments with metronidazole. The major elimination pathways, renal excretion and hepatic oxidation and glucuronidation, accounted for more than ⅔ of the total systemic clearance. Clearance both by hepatic oxidative metabolism and renal excretion was significantly lower after 2.0 than after 0.5 g i.v., whereas there was no significant difference after the oral doses. The results indicate that a high therapeutic dose of metronidazole may be eliminated at a reduced rate, but this is probably not of clinical importance. No single saturable elimination pathway was identified.

Key words: metronidazole; metabolism, pharmacokinetics, healthy volunteers

Metronidazole is an antimicrobial used in the treatment of a variety of disorders. It is administered in a wide range of doses from single administrations of 0.5 and 2.0 g used prophylactically for surgery and for trichomonas vaginitis, respectively, up to 10 g several times a week for radiosensitisation [1, 2].

Metronidazole kinetics has recently been the subject of a number of investigations. More than half of an 0.4 g dose is oxidatively metabolized by hepatic microsomal enzymes and about a fifth is excreted unchanged or after hepatic glucuronidation [3]. The plasma disappearance of metronidazole after oral and intravenous doses up to 2.0 g has been reported to be log-linear [4, 5, 6, 7]. However, 40% lower clearance of 1.0 and 2.0 g than of 250 mg doses has also been reported [8]. Knowledge of metabolite formation from doses above 0.4 g is incomplete and information on possible saturable elimination pathways is lacking.

In the present study the influence of dose and route of administration on the disposition of metronidazole and its major metabolites has been investigated.

Material and Methods

Protocol

Eight healthy volunteers, 2 females and 6 males, participated in the study after giving informed consent (age 30 ± 6 years; weight 68 ± 11 kg; mean ± SD). The investigation protocol was approved by the Ethics Committee of Copenhagen County. The subjects consumed alcohol socially, but none smoked or had received any drugs for at least two weeks before and throughout the study.

According to a cross-over design, the subjects received metronidazole 0.5 g and 2.0 g intravenously and orally. For intravenous administration a solution containing metronidazole 5 mg/ml (DAK) was infused over 20 min. Oral metronidazole was administered as 250 mg tablets (DAK) with 100 ml tap water, after an overnight fast which was continued for a further hour. The only side-effect encountered was slight abdominal discomfort after 2.0 g p.o. in 2 subjects.

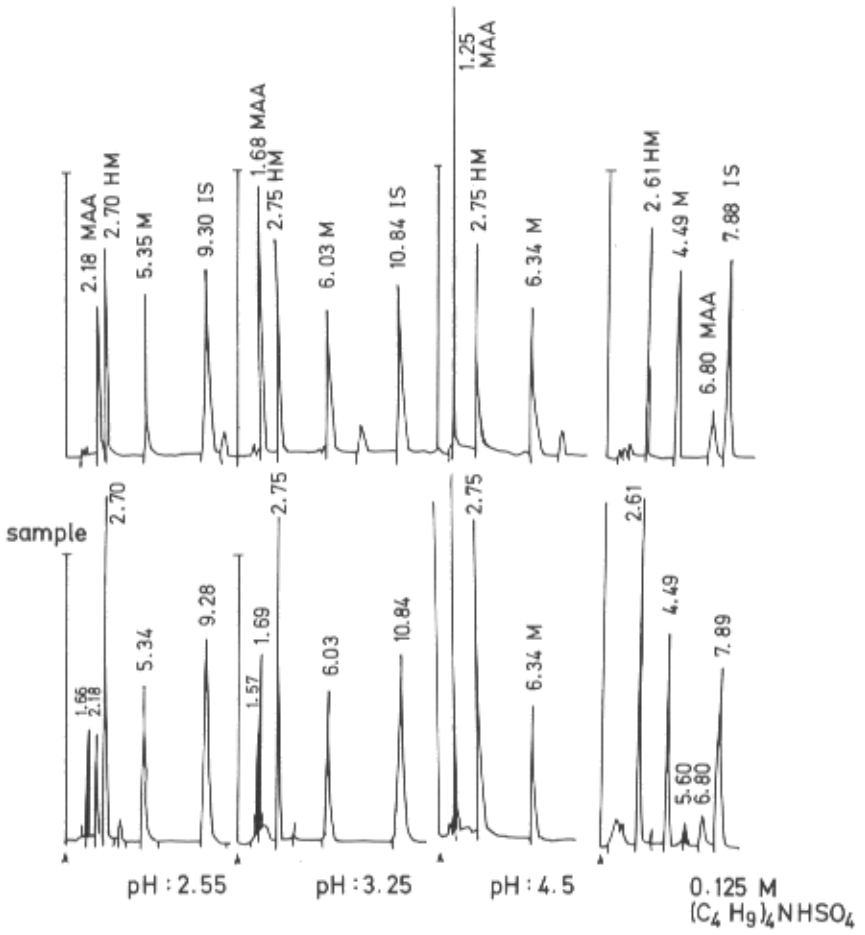

Fig. 1. Chromatograms of blank urine spiked with metronidazole (M) and its hydroxy (HM) and acetic acid (MAA) metabolites, 20 µg/ml, and the internal standard (IS) – upper panel, and a 1 in 5 diluted urine sample from a subject after metronidazole 2.0 g p.o. – lower panel, at increasing pH in the mobile phase or after addition of tetrabutylammonium hydrogen sulphate ($(C_4H_9)_4NHSO_4$). Arrows indicate injections. An unknown peak (filled peaks) eluted just before MAA, but fused with MAA at increasing pH, and was retained like MAA when quarternary ammonia was added to the eluent

Blood was sampled into heparinized tubes before and 10, 20, 30, 40, 60 and 80 min and 2, 3, 5, 8, 12, 16, 24, 36, 48 and 60 h after the i.v. dose and 15, 30, 60 and 80 min and 2, 3, 5, 8, 12, 16, 24, 36, 48 and 60 h after oral administration. Plasma was separated and stored at −20 °C. Urine was collected over the following time intervals: 0–5, 5–12, 12–24, 24–36, 36–48 and 48–60 h after each drug regimen. Aliquots of each sample were stored at −20 °C until analysed.

Analytical Procedures

Plasma was assayed for metronidazole and the two oxidative metabolites, 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (hydroxymetronidazole, HM) and 2-methyl-5-nitroimidazol-1-acetic acid (metronidazole acetic acid, MAA), by a modification of the HPLC method of Kay et al. [9]. Reference compounds were kindly supplied by Rhône-Poulenc Pharma Norden A/S.

Plasma 200 µl was mixed with 300 µl acetonitrile containing the internal standard, 1-(hydroxyethyl)-2-ethyl-nitroimidazole. After centrifugation, 150 µl supernatant was transferred to a microvial, which was left to evaporate until 40 µl remained. Twelve µl was injected into a HPLC system consisting of a Perkin-Elmer automatic injector ISS 100, series 10 isocratic pump, variable wavelength UV-detector LC-85 set at 320 nm and automatic integrator LCI 100, and a 12.5 cm column, i.d. 4.6 mm, packed with Spherisorb ODS 5 µ by a dilute slurry technique. The mobile phase was KH_2PO_4 0.01 M pH 3.0/acetonitrile/methanol (87.5/5/7.5; v/v/v) at a flow rate of 1.1 ml/min.

Urine samples were treated as described by Jensen and Gugler [10]. The chromatographic conditions were as above, except that the pH in the inorganic part of the mobile phase was adjusted to 2.55. If pH was increased to about 4, a peak that eluted before the MAA peak at low pH, fused with the MAA peak (Fig. 1). With tetrabutylammonium hydrogen sulphate added to the mobile phase, both the unknown and the MAA peaks eluted slowly and were well separated. The unknown peak varied in size with the known and if the molar UV absorption of the two materials was comparable, the amount of the unknown excreted in the urine would equal at least half the excreted amount of MAA.

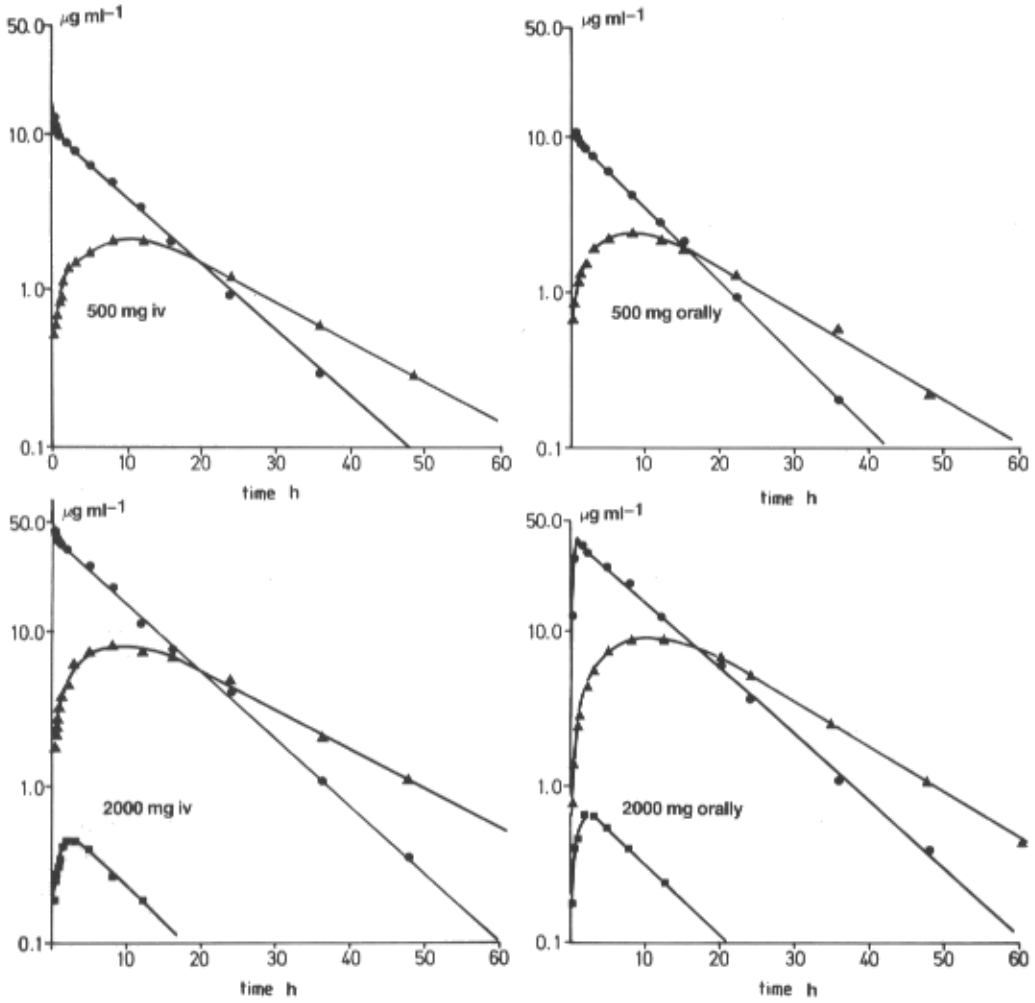

Fig. 2. Concentration of metronidazole, ●, hydroxymetronidazole, ▲, and metronidazole acetic acid, ■ (not detectable after 0.5 g doses) versus time after administration of metronidazole 0.5 and 2.0 g i.v. and p.o. to one subject

All urine samples were measured before and after glucuronide hydrolysis, the content of conjugates being estimated as the differences between these two assays. Hydrolysis was accomplished by incubating 0.5 ml urine with 2 ml sodium acetate 0.1 M pH 4.5 and 500 IU glucuronidase/arylsulphatase (100,000 IU/ml, Boehringer) for 16 h at 37 °C.

The day to day analytical coefficients of variation, estimated from a total of 400 duplicate samples, ranged from 3 to 8% in the concentration ranges encountered for all compounds.

Pharmacokinetic Calculations

Exponential fitting of the plasma concentration values of metronidazole versus time was done by a stripping procedure for kinetic studies, ESTRIP [11], adapted for a HP-85 microcomputer. The disappearance from plasma of metronidazole after intravenous administration of both doses could readily be described by the sum of two exponentials. Accordingly, an open two-compartment kinetic model with correction for distribution and elimination during infusion was employed [12].

The area under the plasma concentration versus time curve (AUC) was calculated according to the trapezoidal rule with extrapolation to infinity. Total systemic clearance of metronidazole was calculated as dose divided by AUC. The systemic bioavailability of metronidazole at each dose level was calculated as the ratio between the AUCs after oral and intravenous administration. For the oral administration, the lag time, absorption rate constant k_a and the elimination half-life $t_{½\beta}$ were estimated by the ESTRIP program. Clearance in each elimination pathway was estimated as the amount of parent compound or metabolite excreted in terms of metronidazole equivalents divided by the area under the plasma concen-

Table 1. Kinetics of the disappearance from plasma of metronidazole after intravenous administration of 0.5 and 2.0 g. Mean ± SD

Dose	k_{12} [h^{-1}]	k_{21} [h^{-1}]	k_{el} [h^{-1}]	$t_{½\alpha}$ [h]	$t_{½\beta}$ [h]	V_c [l]	V_{ss} [l]	CL [ml/min]	AUC [μg·h/ml]
500 mg	0.9 ± 0.7	2.1 ± 0.7	0.14 ± 0.02	0.4 ± 0.2	7.3 ± 0.9	36 ± 8	50 ± 7	83 ± 14	101 ± 17
t-test	NS	NS	NS	NS	NS	NS	NS	$p<0.05$	-
2000 mg	2.0 ± 2.3	2.9 ± 2.5	0.15 ± 0.10	1.0 ± 2.0	7.7 ± 1.7	38 ± 15	50 ± 8	74 ± 12	447 ± 67

k_{12} and k_{21} are the rate constants of distribution between the central and peripheral compartments, k_{el} is the elimination rate constant, $t_{½\alpha}$ and $t_{½\beta}$ are the half-lives of distribution and elimination, respectively, V_c and V_{ss} are the volumes of distribution of the central compartment and at steady state, CL ist the total body clearance and AUC is the area under the curve

Table 2. Kinetics after oral administration of 0.5 and 2.0 g metronidazole. Mean ± SD (or 95% confidence interval in brackets)

Dose	Lag time [min]	k_a [h^{-1}]	$t_{½\beta}$ [h]	Bioavailability	AUC [μg·h/ml]
0.5 g	4.6 ± 5.2	9.6 ± 9.0	8.0 ± 1.6	0.99 (0.94–1.04)	100 ± 16
t-test	NS	NS	NS	NS	-
2.0 g	3.0 ± 4.5	7.8 ± 4.7	7.6 ± 0.9	0.96 (0.92–1.00)	427 ± 53

k_a is the absorption rate constant, $t_{½\beta}$ the elimination half-life and AUC the area under the curve

tration of metronidazole versus time curve during urine collection. Residual hydroxymetronidazole present in the body at the end of the urine collection period (plasma concentration × volume of distribution at steady state, Vss, of metronidazole) was added to the amount excreted for estimation of clearance by hydroxylation.

Statistical Analysis

Kinetic characteristics estimated after only two doses were compared by Student's *t*-test for paired data. Parameters estimated after all 4 administrations were examined statistically by two-way analysis of variance and Duncan's multiple range test [13].

Results

The kinetics of metronidazole could readily be described by an open two-compartment model. The elimination parts of the log concentration versus time plots were linear after administration both of 0.5 and 2.0 g (Fig. 2). However, clearance of 2.0 g administered i.v. was 9% (4–14; 95% confidence interval) lower than that of the 0.5 g i.v. dose (Table 1). Assuming complete absorption there was a difference of 7% (5–9%) between the clearances of 2.0 and 0.5 g administered p.o. The residual standard deviation after two-way analysis of variance of metronidazole clearance after the 4 doses was 5% of the grand mean. On the other hand, there were no significant differences in the rate constants and volumes of distribution between the two intravenous administrations, or in elimination half-life, $t_{½\beta}$ between any of the 4 administrations (Tables 1 and 2). The absorption rate constant, k_a, was independent of the dose. The systemic bioavailability of both doses was approximately 1 (Table 2).

The hydroxy metabolite (HM) of metronidazole was found in plasma after all administrations, and its apparent half-life exceeded that of the parent compound (Fig. 2; Table 3). The AUC of HM was similar after oral and intravenous administration of corresponding doses, and the ratio between the AUCs of HM after the 0.5 and 2.0 g doses was not significantly different from 4 (Table 3). After administration of 0.5 g metronidazole, the acetic acid metabolite (MAA) was detected in plasma only in trace amounts. The small but measurable concentrations of MAA present in plasma after the 2.0 g doses did not allow estimation of kinetic details (Fig. 2; Table 3).

For each of the major elimination pathways for metronidazole a clearance is given in Table 4. Renal clearance and oxidative clearance, i.e. by oxidation to MAA and by hydroxylation to HM, were significantly smaller after i.v. administration of 2.0 g than after 0.5 g. There was no such significant difference after the oral doses. The estimated clearance by renal excretion and hydroxylation was higher after intravenous than after oral administration of 0.5 g, but no such difference was found between the two 2.0 g doses. Differences in clearance by glucuronidation did not attain statistical significance. Independent of the dose and route of administration, about 15% of hydroxymetronidazole was excreted as a glucuronide conjugate, whereas the acetic acid metabolite was not measurably conjugated.

The total recovery of dose found as parent compound and metabolites was significantly higher after i.v. administration of 0.5 g than after the other doses (Fig. 3). The ratios between the amounts recovered after oral and intravenous administration were 0.85 (0.72–0.92; $p<0.05$ vs 1.0) and 0.94 (0.83–1.05) for the 0.5 and 2.0 g doses, respectively.

Table 3. Plasma kinetics of the two oxidative products of metronidazole, the hydroxy (HM) and the acetic acid (MAA) metabolites. Mean ± SD

Dose	Hydroxy metronidazole				Metronidazole acetic acid	
	AUC [μg·h/ml]	$t_{½}$ [h]	C_{max} [μg/ml]	t_{max} [h]	C_{max} [μg/ml]	t_{max} [h]
0.5 g i.v.	65 ± 7	11.6 ± 1.6	2.4 ± 0.1	9.5 ± 2.0	-	-
t-test	NS	-	NS	-	-	-
0.5 g p.o.	62 ± 9	11.1 ± 1.8	2.2 ± 0.2	9.7 ± 2.7	-	-
2.0 g i.v.	239 ± 33	11.2 ± 3.0	8.3 ± 1.1	9.7 ± 2.7	0.69 ± 0.28	2.8 ± 1.2
t-test	NS	-	NS	-	NS	NS
2.0 g p.o.	227 34	11.8 3.3	7.6 1.1	9.5 2.0	0.72 0.25	3.3 2.0
s^2	-	3.2	-	2.5	-	-

AUC is the area under the curve, $t_{½}$ is the half-life and C_{max} is the peak concentration at time t_{max}. s^2 is the residual variance

Table 4. Clearance of metronidazole by the 4 major elimination pathways, renal excretion (CL_R), oxidation to the acetic acid metabolite (CL-MAA), hydroxylation (CL-HM) and glucuronidation (CL-gluc) and the % total systemic clearance (CL). The % of HM excreted as glucuronide conjugates is in brackets. Values are in ml/min or %, and are given as mean ± SD

Dose	CL_R	CL_{MAA}	CL_{HM}	CL_{gluc}	% of CL
0.5 g i.v.	12.0 ± 2.1[a, b]	13.3 ± 3.5[a]	32.6 ± 7.4[a, b] (14 ± 7)	5.1 ± 1.8	77 ± 6[a, b]
0.5 g p.o.	8.2 ± 1.8	12.6 ± 3.6	28.2 ± 8.0 (15 ± 6)	4.4 ± 1.2	66 ± 8
2.0 g i.v.	9.5 ± 1.6	10.6 ± 2.6	27.5 ± 5.2 (17 ± 5)	4.6 ± 0.8	71 ± 6
2.0 g p.o.	9.3 ± 2.2	11.3 ± 2.0	28.3 ± 5.7 (15 ± 7)	4.5 ± 1.2	66 ± 7
s^2	3.9	1.6	9.3 (15)	0.5	36

s^2 denotes the residual variance; [a] denotes $p < 0.05$ for 0.5 vs 2.0 g and [b] $p < 0.05$ for i.v. vs p.o. administration

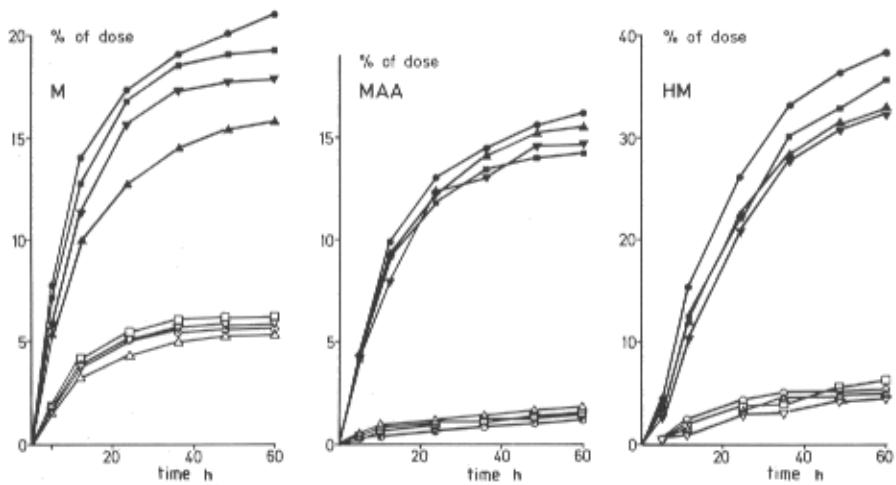

Fig. 3. Cumulative excretion of metronidazole, M, and its hydroxy (HM), and acetic acid (MAA) metabolites over 60 h after administration of metronidazole 0.5 g i.v., ●, 0.5 g p.o., ▲, 2.0 g i.v., ■, and 2.0 g p.o., ▼. Filled symbols represent total amount of compound and open symbols represent conjugates, expressed as % of dose. Values are mean of 8 subjects

Discussion

As reported by others, the pharmacokinetics of metronidazole could be described by an open two-compartment model after both 0.5 and 2.0 g doses [2, 5]. However, the clearance of the 2.0 g administered i.v. was significantly lower (9%) than that of the 0.5 g dose. Assuming complete absorption, a 7% difference in clearance was found between the oral 0.5 and 2.0 g doses. This indicates saturation of one or more of the elimination pathways. On the other hand, the difference was small and no systematic deviation of the elimination part of the log concentration versus time curves or lack of fit to the bi-exponential equations was apparent after the high doses. Moreover, there were no dose-related, significant differences in the rate constants and volumes of distribution after intravenous administration or in the elimination half-lives after oral or intravenous dosing. The major elimination pathways for metronidazole were investigated by studying the excretion of the parent compound and metabolites in urine collected for 60 h after administration, and, if detectable, their plasma concentration at the end of the collection. The fate of

71 and 77% of the i.v. doses of 2.0 and 0.5 g was accounted for, respectively. The estimated clearance of metronidazole by hepatic oxidative metabolism, i.e. by oxidation to the acetic acid metabolite (MAA) and by hydroxylation to HM, represented more than half of the total systemic clearance. Clearance by both oxidative pathways as well as by renal excretion was significantly lower after 2.0 g than after 0.5 g i.v. A similar dose-related difference in clearance by hepatic glucuronidation did not attain statistical significance. Accordingly, all the major pathways for metronidazole elimination appeared saturable to the same relatively small extent when 2.0 g was administered intravenously.

The rate constant of metronidazole absorption was independent of the dose and exceeded previously reported values [3, 14]. The systemic bioavailability of oral metronidazole in doses up to 0.8 g has been reported to be approximately 1 [3, 14–17]. According to the results here, oral doses of at least 2.0 g were almost completely absorped. In agreement, the ratio between total recovery of parent compound and metabolites after oral and intravenous administration of 2.0 g was approximately 1. However, the ratio of recovery after 0.5 g p.o. and i.v. was 0.85, in contrast to and significantly different from the estimated bioavailability. As a consequence, there was no dose-related difference in the estimated clearance through each elimination pathway after the oral treatments, whereas there were significant differences in clearance by hydroxylation and renal excretion between the two of 0.5 g administrations. The plasma AUC of hydroxymetronidazole was not significantly different after the oral and intravenous 0.5 g doses.

A possible explanation for the apparent discrepancy between the estimated bioavailability and the urinary recovery after the 0.5 g doses would be incomplete urine collection after the oral dose. However, the recovery ratio was below 1 in all 8 subjects; cf. the narrow 95% confidence interval. Others, too, have reported a similar urinary recovery ratio after oral and intravenous administration of 0.4 g [3]. Another possible mechanism for the apparent discrepancy would be greater extrarenal elimination of metronidazole and/or its metabolites, probably via faeces, after oral administration of the 0.4 to 0.5 g doses. Indeed, the ratio between urinary and faecal excretion of ^{14}C after intravenous administration of 0.46 g was 60/6 as compared to 77/14 after oral administration of 0.75 g radiolabelled metronidazole, albeit in two different studies (Oppermann J. et al. 1978, personal communication, 18).

Others have previously reported log-linear elimination kinetics of metronidazole in doses up to 2.0 g [2, 4–7]. The present data are consistent with this, if the results from the 2.0 g administrations only are considered. Moreover, after oral doses of 0.25, 0.5 and 1.0 g in 10 subjects, no significant difference in elimination half-life was found, whereas the ratio between the areas under the curve after 0.25 and 0.5 g and 0.25 and 1.0 g was slightly less than the anticipated 2 and 4, respectively [14]. In contrast, a reduction in the clearance of metronidazole of more than 40% has been reported after increasing intravenous doses from 0.25 g to 1.0 or 2.0 g [8]. Such a dramatic reduction in clearance should result in signs of zero-order elimination in the plasma disappearance curves after the high doses. However, details of that study, including information about metabolite formation, do not appear to have been published. Moreover, clearance of our 0.5 and 2.0 g doses was closer to that of the 0.25 g than of the 1.0 and 2.0 g doses of that study [8].

In agreement with previous studies the hydroxy metabolite of metronidazole was detected in plasma in considerable amounts, and its elimination half-life exceeded that of metronidazole [3, 5, 14–17]. The area under the plasma concentration versus time curve was independent of the route of administration, and the ratio between the areas after 0.5 and 2.0 g did not differ significantly from the expected 4. The acetic acid metabolite of metronidazole, MAA, was detected in plasma early and in very small amounts even though it accounted for more than 15% of the total systemic clearance. Thus, the kinetics of the hydroxy and acetic acid metabolite of metronidazole are classical examples of excretion and formation-limited drug metabolite kinetics, respectively [19].

In chromatograms of urine an unidentified peak was found that eluted before MAA at pHs below 4, and fused with MAA at a pH of about 4 (Fig. 1). Accordingly, the excretion of MAA may be overestimated if the pH is set too high in an HPLC system similar to that employed here. Paired-ion chromatography with quarternary ammonia caused the unknown and the MAA peaks to elute slowly and to be well separated, suggesting that the unknown peak, like MAA, is a carboxylic acid [20]. 1-(2-hydroxyethyl)-5-nitroimidazole-2-carboxylic acid, probably a further oxidation product of hydroxymetronidazole, has been identified as a metabolite of metronidazole by its chemical reactions and infrared spectra [21]. The quantity of this acid excreted amounted to half of that excreted as MAA [21], which is what would be expected here, if it was possible to quantitate the unidentified peak. Unfortunately, at present this metronidazole metabolite is not available for study.

In conclusion, the total systemic clearance of metronidazole was statistically significantly lower after 2.0 than after 0.5 g doses, indicating dose dependent kinetics. Absorption after oral administration was almost complete and independent of the dose. No single saturable elimination pathway could be identified with certainty. The dose-related differences in kinetics were small and are probably of no clinical significance.

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