Disposition of oral metronidazole in hepatic cirrhosis and in hepatosplenic schistosomiasis

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SUMMARY   The pharmacokinetics of metronidazole 500 mg orally were determined in patients with hepatosplenic schistosomiasis and normal controls in the Sudan, and in cirrhotics and normal controls in Bristol. Plasma metronidazole levels were above the minimum inhibitory concentration of most susceptible anaerobic bacteria for four to six hours post-dose in all groups. Liver disease did not markedly influence the disposition of single oral doses of metronidazole. Cirrhotics showed some prolongation of metronidazole half-life, and somewhat greater metronidaole concentrations 24 hours after the dose. Concentrations of the oxidative metabolite of metronidazole were lower in Sudanese patients and normal controls than in normal British subjects. In chronic liver disease adjustment of metronidazole dosage is probably not required provided renal function is unimpaired.

Metronidazole has been in clinical use for many years and has been effective in the treatment of infections as diverse as amoebiasis, giardiasis, trichomoniasis, and those caused by anaerobic bacteria.[1] Recently, it has been shown that metronidazole is as effective as neomycin in the management of encephalopathy in chronic liver disease.[2] Despite the increasing clinical indications for the use of metronidazole its disposition in various diseases in man has only recently been examined. Methodological differences in its measurement by bioassay have given varying results.[1] These differences may in part be due to the differing sensitivities of organisms used in bioassays to the metabolites of metronidazole. These problems have, however, been overcome by the development of a specific high pressure liquid chromatographic (HPLC) assay for metronidazole and its major metabolite.[3][4] This has led to a re-examination of metronidazole pharmacokinetics in normal subjects[5][6] and prompted us to examine the disposition of metronidazole in two clinically relevant liver disorders.

We have examined the pharmacokinetics of metronidazole after oral dosing in (1) hepatic cirrhosis, where metronidazole may be used to treat anaerobic infections and may be useful in hepatic encephalopathy, and (2) periportal hepatic fibrosis due to hepatosplenic schistosomiasis where metronidazole may be required for the treatment of concurrent amoebiasis, giardiasis, anaerobic infection, or hepatic encephalopathy.

Methods

PATIENTS

The study was conducted at the Bristol Royal Infirmary, England, and the Soba University Hospital, Khartoum, Sudan. Patients and controls gave informed consent to inclusion in the study, which was approved by the respective local ethical committees. Metronidazole pharmacokinetics were determined in six patients with histologically proven schistosomal periportal fibrosis, eight normal Sudanese control subjects, six patients with histologically confirmed cirrhosis, and five normal British control subjects. The British and Sudanese normal control subjects all had normal standard liver function tests and urea and electrolyte concentrations. They had no past history of liver disease or jaundice and physical examination was normal.

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None of the controls was on other medication, though some of the patients did continue with their regime of diuretics. Patients and controls had not received any antimicrobial agent for at least two weeks before the study day. In addition to clinical details, the urea and electrolyte concentrations, standard liver function tests, and full blood counts were measured in patients and normal subjects.

On the study day an intravenous cannula was inserted into a forearm vein and kept patent with a weak heparin solution (50 IU heparin/ml normal saline). After collection of a pre-dose sample, 500 mg metronidazole was ingested (as two-and-a-half tablets of Flagyl, which were from the same batch in all studies). In the schistosomiasis study metronidazole was taken after an overnight fast, while in the cirrhosis study metronidazole was ingested half an hour before breakfast. Blood samples were collected at 10, 20, 30, and 45 minutes and at one, two, three, four, six, 10, and 24 hours after the dose. Plasma was separated and immediately frozen, and samples from the Sudan were transported frozen. The plasma samples were analysed for metronidazole and its oxidative metabolite (1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole) by HPLC.[4]

Antipyrine clearance was determined in five cirrhotics and five normal British subjects at least one week before metronidazole dosing. After an overnight fast 1200 mg antipyrine was given orally and blood samples were collected at three, six, nine, 12, and 24 hours post-dose. Plasma was separated and frozen for later analysis. Antipyrine was assayed by a spectrophotometric method.[7]

CALCULATIONS

The plasma half life (T1/2) of metronidazole was calculated from least squares regression analysis of the terminal exponential plasma concentration-time

profile. The area under the plasma concentration-time profile (AUC) of metronidazole was calculated as follows: the area up to the end of sampling (X) was calculated using the trapezoidal rule; subsequent area extrapolated to infinity (Y) was calculated from regression analysis of the terminal log concentration-time slope. Total AUC of metronidazole was X plus Y.

Assuming complete absorption, negligible first-pass elimination, and a one-compartment model based on the data of Houghton and colleagues,[5] the apparent volume of distribution of metronidazole (Vd) was estimated as:

$$Vd = \frac{Dose}{Cpo}$$

where Cpo is the back extrapolated plasma concentration at time zero. Clearance (Cl) was calculated as:

$$Cl = \frac{Vd \times 0.693}{T1/2}$$

and expressed as ml/min/kg body weight. There were insufficient data to calculate the above parameter for the metabolite of metronidazole. Therefore the AUC of metabolite was calculated up to the end of sampling (24 hours) by using the trapezoidal rule.

The clearance of antipyrine was calculated in a similar manner to that of metronidazole as shown above.

Group values were compared using Student's *t* test for unpaired data. Significance was assumed at $p < 0.05$.

Results

The clinical and laboratory data from patients with schistosomiasis and cirrhosis are shown in Tables 1 and 2 respectively. All patients had normal urea and

Table 1 *Clinical details of patients with hepatosplenic schistosomiasis*

Subject no., liver histology	Age (yr), sex	Weight (kg)	Hepato-megaly*	Spleno-megaly*	Varices*	Ascites*	Serum albumin (g/l)	Serum globulin (g/l)	Alkaline phospha-tase (KA units)	Bilirubin (μmol/l)	AsAT‡ (IU/l)
1 Periportal fibrosis	28F	57	++	+	+	+	31	47	6	3	6
2 Periportal fibrosis	20F	58	++	++	−	+	34	33	5	4	5
3 Periportal fibrosis	28F	47	+++	+	+	+	33	45	30	7	30
4 Periportal fibrosis and ova	50M	63	+	++	++	++	17	50	17	13	17
5 Periportal fibrosis and ova	20M	68	+	++	+	++	22	48	4	3	4
6 Periportal fibrosis	27M	60	++	+	−	+	23	65	11	3	11

* − absent, + mild, ++ moderate, +++ gross.
‡ AsAT: aspartate aminotransferase.

Table 2   *Clinical details of patients with hepatic cirrhosis*

Subject no., liver histology	Age (yr), sex	Weight (kg)	Hepato- megaly*	Spleno- megaly*	Varices*	Ascites*	Serum albumin (g/l)	Serum globulin (g/l)	Alkaline phospha- tase (KA units)	Bilirubin (μmol/l)	AsAT‡ (IU/l)
1 Cryptogenic cirrhosis	64M	90	++	+	+	++	45	45	39	38	13
2 Alcoholic cirrhosis	67M	65	+	+	−	+	30	50	123	34	61
3 Alcoholic cirrhosis	52F	42	++	−	−	−	35	37	23	32	22
4 Cryptogenic cirrhosis	60F	40	++	+	+	++	29	26	6	17	36
5 Alcoholic cirrhosis	60M	80	+++	+	+	++	15	47	17	24	63
6 Primary biliary cirrhosis	49F	56	+	+	+	+	30	54	96	>200	61

* − absent, + mild, ++ moderate, +++ gross.
‡ AsAT: aspartate aminotransferase.

electrolyte concentrations. Both groups of patients had liver function tests consistent with decompensated liver disease. Sudanese and British control subjects had normal liver function tests and urea and electrolyte concentrations.

SCHISTOSOMIASIS STUDY
Concentration versus time plots for metronidazole and its metabolite in patients and normals are shown in Figs 1 and 2 respectively. Mean values for metronidazole pharmacokinetic measurements are shown in Table 3. There were no significant

differences in metronidazole mean AUC, mean plasma T1/2, and mean plasma clearance in the two groups. The mean AUC of the metabolite of metronidazole was 13% lower in patients than controls, but this difference was not significant (p= 0·5). Mean maximum metronidazole concentrations (C_{max}) were 11·9±1·2 μ/ml (mean ± SEM) and 12·2±1·5 in patients and controls respectively. Mean times to maximum concentration of metronid- azole (T_{max}) were 0·93±0·25 hours and 0·87±0·07 hours in patients and normal subjects respectively. These differences were not significant.
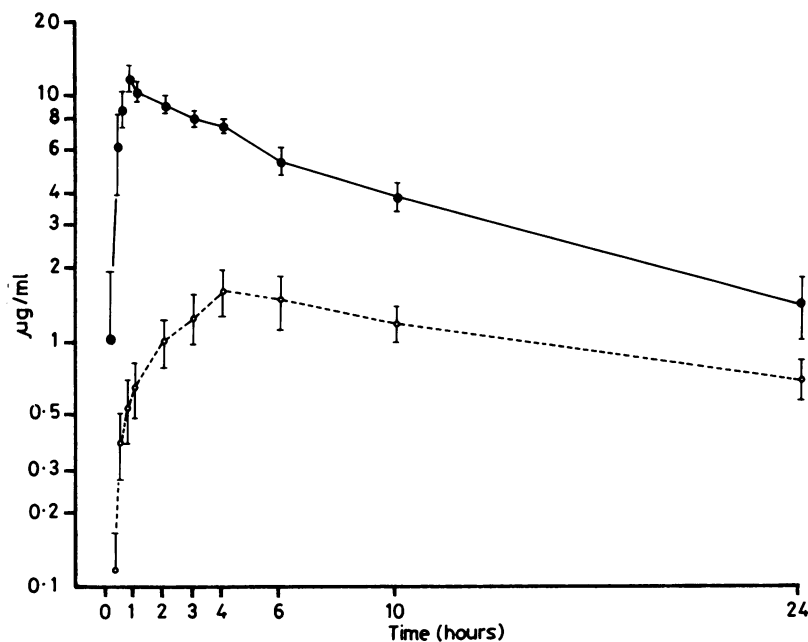

Fig. 1   *Mean ± SEM plasma concentrations of metronidazole and its oxidative metabolite in eight patients with hepatosplenic schistosomiasis following metronidazole 500 mg orally.* ● *Metronidazole.* ○ *Metabolite.*
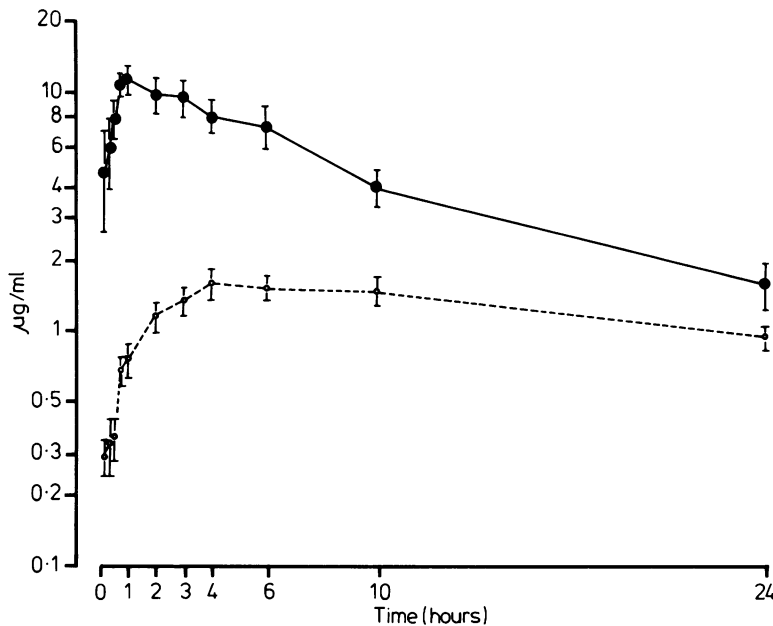
Fig. 2 *Mean ± SEM plasma concentrations of metronidazole and its oxidative metabolite in six normal Sudanese control subjects after metronidazole 500 mg orally.*

● *Metronidazole.* ○ *Metabolite.*

CIRRHOSIS STUDY
Concentrations versus time plots for metronidazole and its metabolite in cirrhotics and controls are shown in Figs 3 and 4 respectively. Mean values for pharmacokinetics measurements are shown in Table 4. Metronidazole AUC and plasma T1/2 were greater (p 0·15 and p 0·1 respectively) and plasma clearance less (p 0·27) in cirrhotics than in British controls. Cirrhotics also had slightly lower AUCs of metabolite of metronidazole. These changes did not, however, reach statistical significance at the p<0·05 level. Values for C_{max} were 9·9±1·6 μg/ml and 10·1±0·9 μg/ml, and for T_{max} 2·25±0·5 hours and 1·5±0·5 hours in cirrhotics and controls respectively.
   Mean antipyrine clearance was 0·23±0·04 ml/min/

kg (mean ± SEM) in cirrhotics and 0·64±0·03 ml/min/kg in British normal subjects (p<0·0001).

INTERSTUDY COMPARISONS
There were no statistically significant differences in metronidazole pharmacokinetics when comparisons were made between Sudanese normal subjects, British normal subjects, cirrhotics, and patients with schistosomiasis. Significant differences were, however, noted in the mean AUC of metabolite of metronidazole which were 34% (p 0·01) and 24% (p 0·04) lower in patients with schistosomiasis and normal Sudanese subjects respectively as compared with normal British subjects. The differences in T_{max} between the groups were almost certainly due to the effect of food in delaying absorption and were not

Table 3 *Disposition of oral metronidazole in patients with schistosomiasis and in Sudanese normal controls (mean ± SEM)*

	Metronidazole				Metabolite
	AUC (μg/ml/h)	Half-life (h)	Volume of distribution (l/kg)	Plasma clearance (ml/min/kg)	AUC (μg/ml/h)
Patients (n=6)	128·7±18·0	8·4±1·3	0·79±0·05	1·21±0·15	26·1±4·1
Normal subjects (n=8)	132·2±22·0	7·8±0·6	0·76±0·07	1·21±0·16	29·9±3·4

Table 4 *Disposition of oral metronidazole in patients with cirrhosis and in British normal controls (mean ± SEM)*

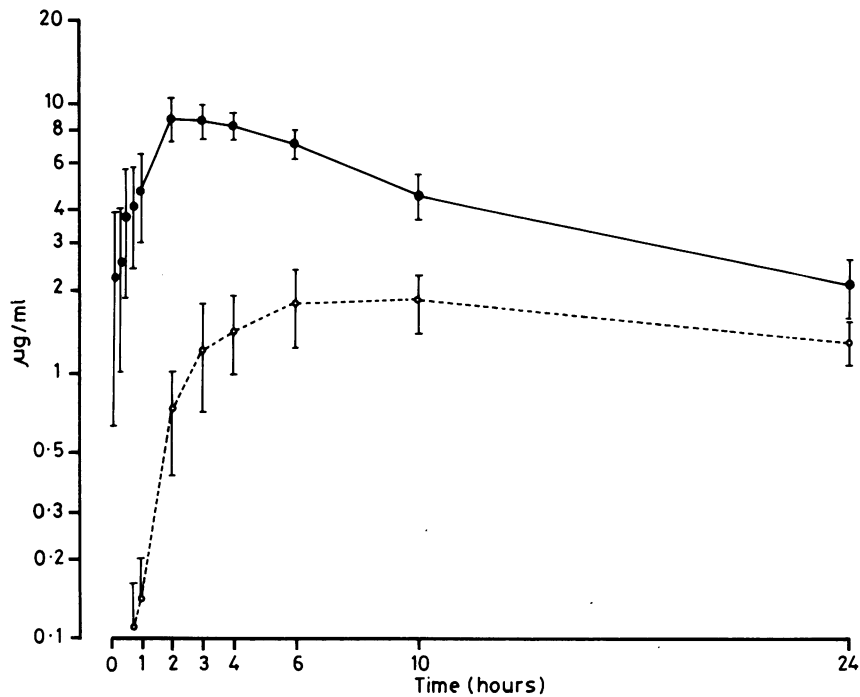|	Metronidazole				Metabolite
	AUC (μg/ml/h)	Half-life (h)	Volume of distribution (l/kg)	Plasma clearance (ml/min/kg)	AUC (μg/ml/h)
Patients (n=6)	157·8±36·6	10·8±2·4	0·74±0·04	1·15±0·26	35·3±8·9
Normal subjects (n=5)	114·6±7·8	7·4±0·3	0·60±0·01	1·06±0·04	39·5±3·1

Fig. 3   *Mean ± SEM plasma concentrations of metronidazole and its oxidative metabolite in six patients with liver cirrhosis after metronidazole 500 mg orally.* ● *Metronidazole.* ○ *Metabolite.*

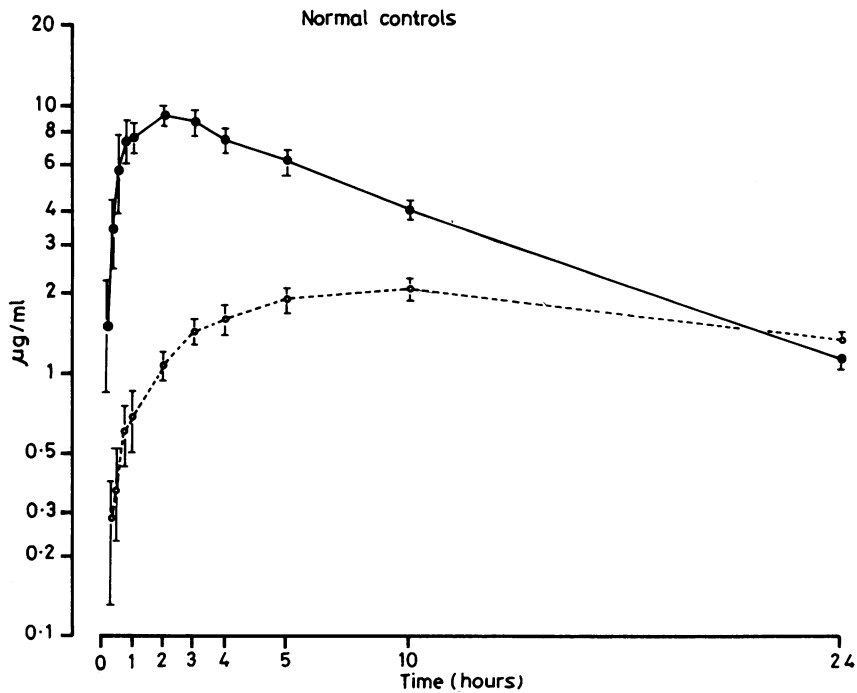Fig. 4   *Mean ± SEM plasma concentrations of metronidazole and its oxidative metabolite in five normal British control subjects after metronidazole 500 mg orally.* ● *Metronidazole.* ○ *Metabolite.*

significant. Values for C_{max} were similar in both studies.

No adverse effects to metronidazole or antipyrine were noted.

Discussion

Our major observation from these studies is that decompensated liver disease due either to cirrhosis or hepatosplenic schistosomiasis does not markedly influence the disposition of oral metronidazole. Mean metronidazole concentrations at 10 hours post-dose were between 4 μg/ml and 4·6 μg/ml in all four groups. Twenty-four hours post-dose cirrhotics, however, had a mean metronidazole concentration of 2·2 μg/ml compared with 1·2 μg/ml in normal British subjects (p 0·1). This difference is reflected in the prolongation of metronidazole half-life in cirrhotics as compared with normal British subjects and there was a trend towards statistical significance (p 0·1). It is possible that these minor differences could be of clinical significance in that chronic oral dosing in cirrhotics may lead to higher steady state metronidazole concentrations.

It should be pointed out that patients with cirrhosis in this study were selected if they had creatinine clearances within the normal range. Some unchanged metronidazole is excreted in urine, and renal disease is known to raise plasma concentrations of metronidazole and its metabolites.[8] [9] Consequently, cirrhotics with renal impairment may show further increases in steady state concentrations of metronidazole. No such differences in mean metronidazole concentrations at 24 hours were noted between patients with schistosomal liver disease and normal Sudanese subjects.

Interestingly, the mean AUC of the oxidative metabolite of metronidazole was significantly lower in patients with schistosomal liver disease and normal Sudanese subjects than in normal British subjects. Though differences may reflect variability between the groups in hepatic oxidative activity, these results should be interpreted with caution. Plasma samples would need to be collected for at least 48 hours to provide meaningful kinetic analysis. In addition, cumulative urinary excretion of the metabolite over at least 48 hours would have been desirable. In the present study the blood sampling ended at 24 hours when the metabolite concentrations were still at the plateau phase.

The pharmacological profile of metronidazole is in many respects similar to that of the model drug antipyrine. Like antipyrine, metronidazole is rapidly and completely absorbed after oral administration, is only slightly bound to plasma proteins, has a volume of distribution that approximates to body water, is eliminated in man largely by hepatic metabolism, and its pharmacokinetics appear to fit a one-compartment model.[1] [5] It is interesting that metronidazole pharmacokinetics are normal in patients with impaired antipyrine clearance, as it is known that metronidazole is oxidatively metabolised in the rat[10] and in man.[11] [12] A substantial non-oxidative metabolic pathway for metronidazole, however, involving glucuronide and sulphate conjugation has also been demonstrated in the rat[10] [13] [14] and in man,[11] [12] and the drug is known to redistribute from the systemic circulation to the gut lumen.[10] Hence it is possible that existing non-oxidative routes of elimination of metronidazole become increasingly important in a compensatory manner as hepatic oxidative enzyme activity falls.

Clinically compensated schistosomal liver disease in the Sudan does not appear to significantly decrease the clearance of antipyrine.[15] The effects of decompensated schistosomal liver disease on antipyrine clearance are not known. Marked reductions have been noted in hepatic concentrations of the drug metabolising enzymes cytochrome P_{450} and cytochrome P_{450} reductase, and of drug metabolising activity in mice.[16] It is therefore probable that decompensated schistosomal liver disease is accompanied by some reduction in the activity of microsomal oxidative enzymes. The normal disposition of oral metronidazole in such patients is another unexpected finding. Clinically it would appear that no dosage adjustment appears necessary when metronidazole is given to patients with schistosomal liver disease.

It has previously been shown[17] that food does not alter the bioavailability of metronidazole. In our study, however, we noted a delay of about one hour in the mean time to peak concentration associated with food in patients and normal subjects in Bristol. Mean peak concentrations of metronidazole were also somewhat lower in this group. All subjects achieved peak concentrations of most susceptible anaerobic bacteria (about 6·2 μg/ml)[18] and maintained an inhibitory concentration of metronidazole in plasma for four to six hours post-dose.

The present study shows that liver disease of differing aetiology does not adversely affect the disposition of single doses of metronidazole, and in the absence of renal impairment the dose of metronidazole need not be adjusted. The effects of liver disease on chronic oral dosing of metronidazole – for example, 400 mg four times a day – remain unknown and predictions based on the present single dose studies may not be applicable.

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