Pharmacokinetics of metronidazole in patients with varying degrees of renal failure

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1 Twenty-nine patients with varying degrees of renal insufficiency were given a single intravenous dose of metronidazole (500 mg). Plasma and urinary concentrations of metronidazole and two major metabolites were determined using a specific high performance liquid chromatographic assay.

2 The pharmacokinetic parameters of metronidazole elimination half-life, area under the metronidazole concentration against time curve, apparent volume of distribution, metronidazole clearance and predicted degree of accumulation of metronidazole on repeated dosing were not statistically significantly affected by renal inadequacy of any degree.

3 The urinary excretion of metronidazole in patients with moderate or severe renal insufficiency was approximately half the value in healthy volunteers. The renal clearance of metronidazole was significantly greater in healthy volunteers compared to renally insufficient patients, but accounted for less than 10% of the total metronidazole clearance in all groups.

4 The elimination half-life and predicted accumulation (on three times daily dosing) of metabolite I [1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole] were significantly increased with decreasing renal function from 9.2 h and 2.3, respectively, in healthy volunteers to 34 h and 6.7, respectively, in patients with total renal failure. The degree of accumulation of this metabolite on repeated dosing is probably of limited clinical significance in all patients except those with severe or total renal failure for reasons detailed in the text.

5 The elimination half-life and predicted accumulation on three times daily dosing of metabolite II, [2-methyl-5-nitroimidazole-1-acetic acid] increased rapidly with decreasing renal function. The average steady-state concentrations predicted for a dosing regimen of metronidazole (500 mg) every 8 h were 0.83 µg/ml and 17 µg/ml in patients with moderate and severe renal insufficiency, respectively.

6 In patients with creatinine clearances greater than 10 ml/min, the accumulation of metronidazole or its two major oxidative metabolites is unlikely to have any toxicological implications. Patients with creatinine clearances of less than 10 ml/min and not receiving dialysis will show marked accumulation of both metabolites on repeated dosing. Removal of these metabolites is achieved during haemodialysis.

Keywords metronidazole pharmacokinetics renal failure

Introduction

Metronidazole is used to treat a wide variety of anaerobic infections (Galgiani *et al.*, 1978) and is frequently used as a prophylactic in cases of elective gynaecological and bowel surgery (Willis *et al.*, 1977). Endotoxaemic renal failure is a possible complication of severe anaerobic infections. Patients with varying degrees of renal impairment may receive metronidazole therapy. The aim of this study was to determine any alterations in the pharmacokinetic parameters of metronidazole and its metabolites in patients with varying degrees of renal impairment and to attempt to correlate the observed variation with the degree of renal impairment.

Methods

Subjects

A total of 29 white Caucasian patients of either sex, aged 18 to 60 years and attending the Renal Unit of St Mary's Hospital, London, took part in the study. Ten patients were dialysis patients with residual creatinine clearance values below 1 ml/min. A further ten patients were defined as having severe renal insufficiency with creatinine clearance values between 2 and 10 ml/min (mean $\pm$ s.d. = 5.3 ± 2.5 ml/min). The final nine patients had moderate renal insufficiency with creatinine clearance between 10 and 50 ml/min (mean $\pm$ s.d. = 26 ± 10 ml/min).

The mean ages and weights of the three patient groups were closely matched and they had similar sex distributions. The healthy volunteer data included for comparative purposes was drawn from an all male group with an average age of 32 years compared to 45 years in patients and an average weight of 75 kg compared to 62 kg in patients.

The sex or age of subjects has been shown not to markedly alter the pharmacokinetics of intravenous metronidazole (Houghton *et al.*, 1979b). Weight differences may be expected to proportionately alter AUC and volume of distribution parameters in Table 1, but other parameters should remain unchanged.

All patients gave written informed consent of participation in this study. The study had been approved by the Ethics Committee of St Mary's Hospital. The patients were judged not to have any other disease process by clinical examination, analysis of biochemical and haematological variables, chest X-ray and electrocardiography. Primary renal disease was the cause of renal dysfunction in all. None had any infection at the time of the study, only aluminium hydroxide and synthetic analogues of Vitamin D were continued during the study.

Procedure

Each patient received a single intravenous infusion [0.5% w/v; Flagyl injection, May & Baker] of metronidazole (500 mg) over 20 min. The majority of patients received the infusion between 07.40 and 08.00 h. Blood was withdrawn by venepuncture prior to the start of the infusion and at 0.33, 1 or 2, 3 or 4, 6, 9, 12, 24, 33 and 48 h after the end of the infusion in all patients, and additionally at 57 h after dosing in those patients with renal failure. Urine was collected 0–12 h, 12–24 h and 24–48 h from those patients not on dialysis.

Plasma (obtained from blood by centrifugation) and urine were stored at -20°C until analysed by a specific high performance liquid chromatographic assay h.p.l.c. procedure (Gulaid *et al.*, 1978). Creatinine concentrations were determined at St Mary's Hospital by the Jaffe reaction, using a Technicon autoanalyser. Standard curves were prepared separately for metronidazole and each of the two major metabolites 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (metabolite I) and 2-methyl-5-nitroimidazole-1-acetic acid (metabolite II) in plasma and urine. Standard samples injected into the h.p.l.c. system on each day on which samples were assayed showed no systematic or major variations in the assay procedure, although the duration of the study was approximately 4 years. No samples used in the study were stored for more than 3 months, although metronidazole and both major metabolites were shown to be stable in frozen plasma or urine for over 1 year (Data on file, May & Baker).

The elimination half-life was calculated by the method of least squares, the area under the curve by the trapezoidal rule, plasma clearance from the ratio of dose to area under the curve, renal clearance from the ratio of material excreted in urine to area under the curve, volume of distribution using the formula $V = F.D./k.AUC$ and the accumulation ratio using the formula $R = 1/(1 - e^{-k\tau})$, where τ = dose interval (h), AUC = area under curve ($\text{mg l}^{-1}\text{h}$), k = elimination rate constant (h^{-1}), F = fraction of dose absorbed ($=1$), and D = dose (500 mg). Statistical comparisons were carried out using Student's *t*-test with a correction of unequal standard deviations.

Results

The mean plasma concentrations of metronidazole, metabolites I and II are shown in Figures 1, 2 and 3, respectively. Individual lines represent mean plasma concentrations for dialysis patients and those with severe and moderate

Figure 1 Plasma metronidazole concentrations in healthy volunteers (●) and patients with varying degrees of renal impairment (▲ severe, ■ moderate, ○ renal failure).

renal impairment. Additionally, data from nine healthy volunteers (Houghton *et al.*, 1979a) are superimposed on each graph for comparative purposes.

All pharmacokinetic parameters were calculated from individual plasma concentration or urinary data and mean results ($\pm$ s.d.) are given for each of the subgroups studied (Tables 1 and 2).

None of the pharmacokinetic parameters of unchanged metronidazole in patients with various degrees of renal impairment ranging from moderate to complete were statistically significantly different from those observed in healthy volunteers, except for renal clearance (Table 1).

The mean plasma elimination half-life of metabolite I in healthy volunteers was significantly shorter than that in patients with renal impairment (Table 1). Urinary excretion of metabolite I was similar in healthy volunteers to that in patients with moderate renal insufficiency, but was reduced in patients with severe renal insufficiency to only 25% of that observed in healthy volunteers (Table 2). This hydroxy

metabolite is eliminated by both renal and hepatic routes (Houghton *et al.*, 1979b), so that any decrease in the urinary excretion which is not compensated by an increase in hepatic elimination will extend the half-life of metabolite I.

The plasma elimination half-life of metabolite II was measurable in patients with moderate renal insufficiency in contrast to healthy volunteers whose plasma concentrations of this acidic metabolite were below the limit of detection of the assay. Metabolite II appears to be almost exclusively excreted in urine (Stambaugh *et al.*, 1968) and thus almost all metabolite II formed will eventually appear in urine, although the rate of elimination is very different between people with renal failure and normal individuals.

Discussion

The recommended dose of intravenous metronidazole is 500 mg every 8 h (Product data sheet).

Figure 2 Plasma metabolite I concentrations in healthy volunteers (●) and patients with varying degrees of renal impairment (▲ severe, ■ moderate, ○ renal failure).

During repeated dosing of healthy subjects accumulation of metronidazole occurs and steady-state plasma metronidazole concentrations rise to about twice the concentrations observed after a single dose (Houghton *et al.*, 1979b). The results of this study suggest that in patients with renal insufficiency, no further accumulation of metronidazole will occur.

The accumulation of metabolite I, increased with decreasing renal function, the mean accumulation ratio in dialysis patients being approximately three times that in healthy volunteers. Moreover the inter-subject variability of this parameter was greatly increased in those patients with severe or complete renal insufficiency. Metabolite I has a similar spectrum of antibacterial activity to metronidazole, but is either similar or less active against susceptible organisms (O'Keefe *et al.*, 1982). Therefore, the contribution to the total biological activity made by this metabolite will increase as renal function declines, but will remain less than that of metronidazole in all but a small proportion of patients with renal insufficiency.

Accumulation of metabolite II increases proportionate to the severity of renal failure. Steady-state conditions will not be achieved at all in patients with complete renal failure in the time available between twice-weekly haemodialyses. Since dialysis rapidly removed metabolite II from plasma (Gabriel *et al.*, 1980), exposure to this metabolite in patients with no renal function undergoing twice-weekly dialysis will be less than in patients with severe renal disease. In patients with acute renal failure when haemodialysis may be required daily, trivial accumulation of metabolite II will occur because of its rapid removal during dialysis. If acute renal failure were managed by using peritoneal dialysis the steady-state concentration of metabolite II would probably be of the order of that found in those patients studied with severe renal impairment. Peritoneal dialysis clears creatinine at about 5 ml/min (Rippe *et al.*, 1981). Metabolite II is almost inactive as an antibacterial agent (O'Keefe *et al.*, 1982) and has been dosed to dogs at the rate of 200 mg/kg every 8 h for 28 days with no apparent

Table 1 Plasma pharmacokinetic parameters. Mean ($\pm$ s.d.) value for each parameter after administration of a single intravenous dose (500 mg) of metronidazole.

Pharmacokinetic parameter	Healthy volunteers*	Moderate renal insufficiency	Severe renal insufficiency	Renal failure
<i>n</i>	9	9	10	10
Creatinine clearance (ml/min)	99 $\pm$ 34	26 $\pm$ 10	5.3 $\pm$ 2.5	<1
Metronidazole elimination half-life (h)	7.0 $\pm$ 0.80	7.4 $\pm$ 2.4	11 $\pm$ 5.7	7.2 $\pm$ 2.3
Hydroxy metabolite elimination half-life (h)	9.2 $\pm$ 1.4	16 $\pm$ 4.5**	28 $\pm$ 36	34 $\pm$ 43**
Acidic metabolite elimination half-life (h)	n.d.	13 $\pm$ 8.3	28 $\pm$ 23	140 $\pm$ 81
Area under plasma metronidazole concentration against time curve (mg l ⁻¹ h)	123 $\pm$ 35	159 $\pm$ 52	180 $\pm$ 82	99 $\pm$ 27
Area under plasma hydroxy metabolite concentration against time curve (mg l ⁻¹ h)	48 $\pm$ 8.6	131 $\pm$ 47**	136 $\pm$ 200	>79 +
Area under plasma acidic metabolite concentration against time curve (mg l ⁻¹ h)	n.d.	6.6 $\pm$ 3.8	135 $\pm$ 177	>67 +
Metronidazole clearance (ml/min)	72 $\pm$ 16	60 $\pm$ 20	68 $\pm$ 59	91 $\pm$ 29
Apparent volume of distribution of metronidazole (l)	43 $\pm$ 6.1	36 $\pm$ 9.4	48 $\pm$ 20	55 $\pm$ 21
Renal clearance of metronidazole (ml/min)	6.8 $\pm$ 2.5	2.7 $\pm$ 1.4	2.4 $\pm$ 1.1**	—
Renal clearance of hydroxy metabolite (ml/min)	28 $\pm$ 8.7	7.5 $\pm$ 4.7**	3.3 $\pm$ 2.2**	—
Renal clearance of acidic metabolite (ml/min)	>380++	272 $\pm$ 203	11.1 $\pm$ 11.8	—
Metronidazole accumulation ratio (three times daily treatment)	1.8 $\pm$ 0.15	1.9 $\pm$ 0.39	1.8 $\pm$ 0.15	1.9 $\pm$ 0.41
Hydroxy metabolite accumulation ratio (three times daily treatment)	2.3 $\pm$ 0.23	3.4 $\pm$ 0.80	5.5 $\pm$ 6.5	6.7 $\pm$ 7.7
Acidic metabolite accumulation ratio (three times daily treatment)	n.c.	2.9 $\pm$ 1.5	5.6 $\pm$ 4.2	26 $\pm$ 14.6

n. d. = no acidic metabolite detected.

n.c. = not calculable

+ = not accurately quantifiable due to long elimination half-life

++ = not accurately quantifiable due to low plasma metabolite concentrations

* = data from a previous publication (Houghton *et al.*, 1979a)** = statistically significantly different ($p < 0.05$) from data in healthy volunteers

— = no urine produced

Figure 3 Plasma metabolite II concentrations in patients with varying degrees of renal impairment (▲ severe, ■ moderate, ○ renal failure). Metabolite II is not found in the plasma of subjects with normal renal function.

toxicological complications (Tilson & Ward, 1983; personal communication).

We conclude that the dose of metronidazole should not be altered in patients with moderate degrees of renal impairment, and need not be changed, unless therapeutically acceptable, in

patients with severe or complete renal impairment. In the latter group, it should be noted that a further dose should be given after haemodialysis to replace metronidazole lost during dialysis (Gabriel *et al.*, 1980).

Table 2 Urinary excretion of metronidazole and its metabolites. Mean ($\pm$ s.d.) value for percentage of the dose excreted as each metabolic product after administration of a single intravenous dose (500 mg) of metronidazole

	Healthy volunteers	Moderate renal insufficiency	Severe renal insufficiency	Renal failure
Metronidazole	9.9 $\pm$ 1.7	5.0 $\pm$ 3.0	5.0 $\pm$ 1.7	n.u.
Hydroxy metabolite	15 $\pm$ 1.9	12 $\pm$ 10.2	2.9 $\pm$ 0.9	n.u.
Acidic metabolite	6.2 $\pm$ 1.4	11 $\pm$ 4.5	8.0 $\pm$ 4.7	n.u.
Total of above*	31	28	16	n.u.

*calculated as mean

n.u. = no urine produced.

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(Received April 30, 1984,
accepted October 8, 1984)