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Metronidazole Elimination is Preserved in the Elderly

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1 The disposition of metronidazole and its major metabolites was compared in 11 subjects aged 86 ± 6 years and 8 aged 30 ± 6 years.

2 The plasma clearance of metronidazole was 1.20 ± 0.53 and 1.25 ± 0.22 ml min^{-1} kg^{-1}, the volume of distribution 0.77 ± 0.27 and 0.77 ± 0.09 l kg^{-1} and the half-life 7.8 ± 1.9 and 7.2 ± 0.9 h in elderly and young subjects, respectively ($P > 0.05$).

3 The area under the plasma concentration–time curve of the hydroxy metabolite was 32 ± 14 and 21 ± 3 mM min^{-1} ($P < 0.05$) whereas its half-life was 21 ± 14 and 12 ± 2 h ($P < 0.05$) in the elderly and young subjects, respectively.

4 The recovery in the urine of metronidazole and its metabolites was 42 ± 21% and 87 ± 6% of dose in elderly and young subjects, respectively ($P < 0.05$). With this reservation the only elimination pathways of metronidazole affected by old age were the renal excretion of unchanged compound and the hydroxy metabolite.

5 It is concluded that the ability to eliminate metronidazole is preserved in old age and that age-related dose adjustments are not necessary.

Introduction

The rate of drug elimination by oxidative processes in the liver is generally considered to decrease with advancing age.[1,2] The widely used antimicrobial, metronidazole, is eliminated mainly by hydroxylation and oxidation of its alcohol moiety, whereas glucuronidation and renal excretion of unchanged compound are minor pathways.[3,4] For treatment of anaerobic infections metronidazole may be administered intravenously at high dosage and impaired elimination could thus result in accumulation and neurotoxicity.[5] Indeed, the plasma clearance of total nitroimidazoles (i.e. metronidazole and its metabolites), has been reported to be decreased in elderly patients compared to young controls.[6] However, this could very well reflect a decreased renal clearance of hydroxymetronidazole which has a longer plasma half-life than the mother compound. In a study of 119 healthy subjects from 18 to 62 years old there was no correlation between age and the clearance of metronidazole.[7]

In the present study the effect of extreme age on the disposition of metronidazole and its major metabolites was investigated.

Materials and methods

The subjects were recruited among patients aged at least 74 years from a mixed medical unit. The patients were considered eligible after their convalescence from an acute ailment and while waiting for discharge to their own home or a nursing home. Eleven patients (four women) participated in the study (age 86 ± 6 years; weight 61 ± 14 kg; mean ± s.d.). All patients were in a stable condition without signs of cardiac incompensation, pulmonary insufficiency, or liver or renal disease, as judged by clinical examination, and clinical chemistry tests, including plasma creatinine, aspartate aminotransferase, alkaline phosphatase, bilirubin and prothrombin index

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within the normal range. Seven of the elderly subjects had bladder catheters for various reasons, such as hypertrophy of the prostate or incontinence. Most of the aged patients received one or more drugs. The treatments were digoxin and frusemide or bendroflumethiazide in seven, oxazepam in four, salicylates in two and theophylline and terbutaline in two, one of whom also received spironolactone. Eight healthy volunteers (two women) below the age of 40 years served as controls (age 30 ± 6 years; weight 68 ± 11 kg). None of the controls smoked or took any drugs. All subjects gave their informed consent. The study protocol was approved by the Ethics Committee of Copenhagen County.

Metronidazole 500 mg was administered as an intravenous infusion over 20 min. Blood was sampled into heparinized tubes before metronidazole administration and at timed intervals for 72 h (patients) or 60 h (controls) afterwards. Urine was collected for the same time periods. Plasma and urine was stored at −20°C until analysed by HPLC.[4]

Before excretion into the urine, part of the hydroxylated metronidazole is oxidized to a carboxylic acid.[3] After incubation in acid at 37°C for 48 h this carboxylic acid was decarboxylated, quantitated by HPLC analysis and the amount added to the excreted amount of hydroxymetronidazole. Reference compounds for the carboxylic acid and the decarboxylation product were kindly provided by Dumex Ltd, Copenhagen.

The area of metronidazole and hydroxymetronidazole under the concentration–time curve was calculated by the logarithmic trapezoidal method and extrapolated to infinity. The clearance of metronidazole was calculated as the dose divided by the area under the curve. The elimination rate constant was determined from the terminal linear part of the log concentration–time curve. The apparent volume of distribution was calculated as the clearance divided by the elimination rate constant.

For statistical analysis the *t*-test was used. The level of statistical significance was set at 0.05.

Results

There were no significant differences between elderly and young subjects regarding the pharmacokinetics of metronidazole in plasma (Figure 1; Table 1). In most of the subjects from both groups hydroxymetronidazole was measured in plasma throughout the sampling period and its half-life exceeded that of the mother compound. The area under the curve and the half-life of the hydroxy metabolite and the total nitroimidazoles

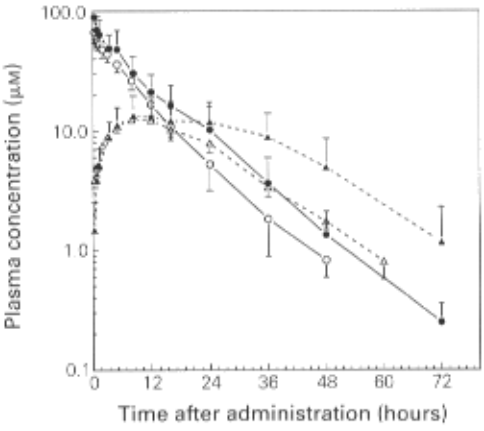

Figure 1 Concentration–time profiles of metronidazole (●—○) and its hydroxy metabolite (▲---△) after intravenous administration of 500 mg to 11 elderly (filled symbols) and 8 young (open symbols) subjects. The values are the mean plus s.d.

were larger in the elderly ($P < 0.05$; Figure 1; Table 1). The acetic acid metabolite of metronidazole was detected in plasma only in trace amounts.

In the elderly subjects the average recovery of metronidazole and metabolites in the urine was less than half that of the young subjects ($P \pm 0.05$; Table 2). If the urinary excretion of each compound was expressed as a percentage of the total recovered amount, only that of the mother compound was lower in the elderly ($P \pm 0.05$; Table 2).

Discussion

The present study has demonstrated that the elimination of metronidazole is preserved in the extreme age. However, the elimination from plasma of the hydroxy metabolite was slightly compromised in the elderly. With the reservations regarding the poor recovery in the urine the only elimination pathway of metronidazole particularly affected by old age was the renal excretion of unchanged compound.

The decreased renal excretion of unchanged metronidazole and of the elimination rate of the hydroxy metabolite from plasma in the elderly was probably caused by the age-related reduction of renal function, in some patients aggravated by the presence of a bladder catheter *per se* or the indication for it.[2] The decreased renal function in the elderly was not reflected in plasma creatinine concentrations above the normal range.

Table 1 Plasma pharmacokinetics of metronidazole, hydroxymetronidazole and the total nitroimidazoles after administration of metronidazole 500 mg to 11 elderly and 8 young subjects.

	metronidazole						*hydroxymetronidazole*		*nitroimidazoles*	
	Clearance (renal) *ml min^{-1}*		*Clearance* *ml min^{-1} kg^{-1}*	*V_{area}* *l*	*V_{area}* *l kg^{-1}*	*half-life* *hours*	*AUC* *mM min^{-1}*	*half-life* *hours*	*AUC* *mM min^{-1}*	*half-life* *hours*
Elderly										
no 1	71.3	(1.6)	1.10	51.2	0.79	8.30	19.0	14.4	60.1	11.5
no 2	86.0	(4.2)	1.15	57.6	0.77	7.74	16.9	14.4	50.9	10.4
no 3	53.5	(2.5)	1.03	26.4	0.51	5.70	22.5	10.6	77.2	8.96
no 4	139	(0.1)	2.70	75.9	1.47	6.30	8.99	15.1	30.0	8.47
no 5	94.5	(1.7)	1.18	49.2	0.61	6.01	35.8	10.5	66.7	10.3
no 6	95.9	(3.0)	1.07	61.8	0.69	7.44	56.0	20.0	86.5	16.6
no 7	43.7	(2.6)	0.80	36.3	0.66	9.58	33.3	20.1	100	13.5
no 8	35.9	(2.5)	0.87	22.9	0.56	7.38	44.9	30.9	127	12.7
no 9	46.8	(3.1)	0.82	38.3	0.67	9.45	41.0	23.7	104	14.9
no 10	80.4	(2.3)	1.46	42.4	0.77	6.09	43.2	12.7	79.6	12.6
no 11	54.6	(1.1)	0.99	55.6	1.01	11.8	28.7	58.1	82.3	20.8
mean ± s.d.	73 ± 30	(2.2 ± 1.1*)	1.20 0.53	47 ± 16	0.77 ± 0.27	7.8 ± 1.9	31.9 ± 14.1*	20.9 ± 13.7*	78 ± 27*	12.8 ± 3.6*
Young										
no 1	71.2	(8.9)	1.15	48.2	0.78	7.82	20.7	12.1	61.7	9.90
no 2	82.8	(13.2)	1.27	47.1	0.72	6.58	17.5	10.5	52.8	8.44
no 3	74.6	(13.8)	1.29	46.0	0.79	7.12	23.2	11.8	62.4	9.72
no 4	96.9	(14.2)	1.38	63.9	0.91	7.62	19.5	8.97	49.7	8.97
no 5	107	(12.5)	1.26	59.8	0.70	6.44	18.6	12.0	45.9	9.39
no 6	107	(16.5)	1.57	57.7	0.85	6.25	21.0	11.9	48.4	9.71
no 7	68.7	(12.4)	0.81	53.8	0.63	9.04	27.6	15.3	70.2	11.6
no 8	91.0	(10.9)	1.30	55.3	0.79	7.02	22.8	13.0	55.0	10.2
mean ± s.d.	87 ± 15	(12.8 ± 2.3)	1.25 ± 0.22	54 ± 6	0.77 ± 0.09	7.2 ± 0.9	21.4 ± 3.2	12.0 ± 1.7	56 ± 8	9.7 ± 0.9

*$P < 0.05$ *vs* young subjects; the renal clearance was calculated as the amount of unchanged metronidazole recovered in the urine collected for 60 or 72 h divided by the AUC.

Table 2 Recovery of metronidazole 500 mg as mother compound and metabolites in urine collected for 72 and 60 h after administration to 11 elderly and 8 young subjects, respectively.

	Metronidazole acetic acid	*Hydroxy-metronidazole*[§]	*Metronidazole glucuronide*	*Unchanged metronidazole*	*All nitro-imidazoles*
Elderly					
no 1	9.4 (29.0)	18.2 (56)	2.7 (8.2)	2.2 (6.8)	32 (100)
no 2	9.0 (28.9)	15.6 (50)	1.9 (6.1)	49 (15.5)	31 (100)
no 3	9.7 (33.8)	13.7 (48)	0.5 (1.9)	4.7 (16.5)	29 (100)
no 4	27.7 (69.8)	11.0 (28)	0.9 (2.4)	0.1 (0.3)	40 (100)
no 5	7.0 (20.2)	25.3 (72)	0.8 (2.2)	1.8 (5.2)	35 (100)
no 6	21.5 (21.7)	69.0 (70)	5.3 (5.4)	3.1 (3.1)	99 (100)
no 7	15.8 (25.2)	38.9 (62)	2.1 (3.3)	6.0 (9.6)	63 (100)
no 8	6.5 (15.6)	25.0 (59)	4.0 (9.4)	7.0 (16.6)	42 (100)
no 9	4.4 (11.5)	27.4 (71)	0.0 (0.0)	6.6 (17.1)	38 (100)
no 10	3. (14.2)	14.4 (64)	1.9 (8.4)	2.9 (13.0)	22 (100)
no 11	2.5 (7.2)	26.6 (77)	3.3 (9.5)	2.0 (5.8)	34 (100)
mean ± s.d.					
% of dose	10.6 ± 8.0*	25.2 ± 16.7*	2.1 ± 1.6*	3.7 ± 2.2*	42 ± 21*
% of recovered	25.5 ± 18.3	58.9 ± 22.8	5.4 ± 3.4	10.3 ± 6.3*	100
Young					
no 1	9.9 (13.9)	44.0 (58)	3.8 (5.4)	8.9 (12.5)	76 (100)
no 2	16.5 (17.5)	45.2 (55)	6.1 (7.3)	13.2 (16.0)	94 (100)
no 3	20.0 (22.8)	44.9 (58)	6.1 (7.3)	13.8 (18.5)	88 (100)
no 4	14.8 (15.3)	48.9 (50)	4.9 (5.1)	14.2 (14.7)	85 (100)
no 5	16.1 (18.8)	48.6 (57)	9.7 (9.0)	12.5 (11.6)	85 (100)
no 6	19.4 (20.5)	54.2 (57)	5.4 (5.8)	15.5 (16.4)	95 (100)
no 7	12.9 (14.4)	51.2 (52)	7.6 (8.5)	18.0 (20.1)	90 (100)
no 8	15.2 (18.3)	50.2 (61)	5.5 (6.7)	12.0 (14.5)	83 (100)
mean ± s.d.					
% of dose	16.1 ± 2.5	49.7 ± 3.9	6.2 ± 1.6	14.8 ± 2.7	87 ± 6
% of recovered	18.6 ± 2.4	57.3 ± 2.7	7.2 ± 1.8	17.0 ± 2.5	100

* < 0.05 *vs* young subjects; [§]includes further metabolized compound; individual values are a percentage of dose (percentage of recovered).

Ludwig *et al.*[6] reported that the area under the concentration–time curve of metronidazole was almost doubled in patients aged 75 years compared with control subjects in their mid-twenties. However, an unspecific method not discriminating mother compound and metabolites was employed.[6] Thus, in that study at least part of the difference was related to retention of the hydroxy metabolite in the elderly. It was also reported that the volume of distribution was decreased in the elderly.[6] By contrast, in the present material there was no difference between young and aged subjects regarding the volume of distribution. Moreover, in the elderly the area under the curve and the half-life of the combined nitroimidazoles were increased to the same extent and a volume of distribution calculated from these data would not have differed between the two age groups.

Despite the fact that metronidazole is mainly eliminated by low clearance oxidative reactions the rate was not impaired by extreme age. It is recognized that advancing age slows the oxidative elimination of many, but not all, drugs.[1] This may reflect a differential effect of age on the various cytochrome P450 forms catalysing the oxidation of drugs with variable substrate specificity. Thus, the well known decrease in the clearance of antipyrine with increasing age was related only to the N-demethylation pathway while the clearance reflecting the two other pathways was preserved.[8] Similarly, in a population of 119 18–62-year-old healthy subjects the clearance of metronidazole was independent of age whereas that of antipyrine showed the expected decrease with advancing age.[7]

Generally, it is believed that drug elimination by conjugation reactions is less sensitive to advancing age than by oxidative reactions.[1,2] Nevertheless, with the reservation regarding the poor recovery of material in elderly subjects in this study, the possible effects of age on metronidazole metabolism did not seem to favour glucuronidation.

Most of the aged subjects received drugs, some of which may have modified the capacity of the hepatic drug metabolizing enzymes. Theophylline

given to two patients may induce its own metabolism but not that of antipyrine.[9,10] Spironolactone given to one of these two patients may induce the metabolism of antipyrine.[11] However, these two patients had metronidazole clearance values at or below the average of the group. The other drugs received are not known to alter drug metabolism. Unfortunately, the smoking history of the patients was not available but the clearance of metronidazole has been shown not to be affected by smoking.[7]

The poor recovery of metronidazole and metabolites in the urine of the elderly may have several explanations. Frequently, permanent bladder catheters are colonized with various bacteria. The urine was collected from the catheter in plastic bags for up to 24 h without refrigeration. In rat urine collected in a cage where minimal faecal contamination was unavoidable metronidazole and its metabolites were degraded during 24 h unless the sampling vial was refrigerated to 0°C (unpublished observations). Thus, in patients with bladder catheters the low recovery could have been caused by decomposition. In the remaining patients without a bladder catheter the collection of urine may have been incomplete. Due to the low recovery in aged subjects no attempt was made to calculate the clearance rates representing each elimination pathway for comparison between the two age groups.

The elderly participants of this study were taken from a mixed medical ward and were in a stable condition. They should thus be representative of a hospital setting. The results from a single injection may not always predict the kinetics of chronic administration. Nevertheless, from the present results it should not be necessary to reduce the dosage of metronidazole in elderly patients unless overt renal insufficiency is present.

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