THE PHARMACOKINETICS OF CIMETIDINE AND ITS SULPHOXIDE METABOLITE IN PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

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1 The pharmacokinetics of cimetidine and its sulphoxide metabolite were studied after a single intravenous dose of 200 mg cimetidine in nine patients with normal renal function and ten patients with severe renal failure on regular haemodialysis and during continuous oral cimetidine treatment in ten patients with normal renal function and 31 patients with different degrees of renal failure.

2 In normal renal function a mean of 47.3% of the single intravenous dose was excreted as unchanged drug and 12.8% as cimetidine sulphoxide. The mean plasma elimination half-life ($T_{1/2}$) of cimetidine was 2.0 h and of cimetidine sulphoxide 1.7 h.

3 In severe renal failure a mean of 2.2% of the single intravenous dose was excreted as unchanged drug and 0.5% as cimetidine sulphoxide. The mean plasma $T_{1/2}$ of cimetidine was 3.9 h. The plasma concentrations of the sulphoxide metabolite increased successively with time after dosing and no elimination phase was observed still 9 h after dose. The mean non-renal clearance of cimetidine was 210 ml/min and lower than in normal renal function, suggesting decreased metabolism of cimetidine in uraemia.

4 During continuous oral cimetidine treatment in patients with normal renal function and in patients with different degrees of renal failure given reduced doses of cimetidine the plasma concentrations of the sulphoxide metabolite were higher with decreasing renal function. The mean plasma $T_{1/2}$ of cimetidine was 3.1 h in mild renal dysfunction (creatinine clearance 50–75 ml/min) and 4.5 h in severe renal failure (creatinine clearance 5–15 ml/min) and of cimetidine sulphoxide 5.3 and 14.4 h respectively.

5 Toxicity studies of cimetidine sulphoxide may be needed to assess if high plasma concentrations of the sulphoxide metabolite in severe renal failure are of clinical significance.

Introduction

The histamine H_2 -receptor antagonist, cimetidine (Tagamet®) has been reported to be effective in the treatment of peptic ulcer disease in patients with renal failure on regular haemodialysis treatment (Doherty *et al.*, 1977; Jones *et al.*, 1979) and in the prophylactic treatment of upper gastrointestinal haemorrhage in renal transplant recipients (Jones *et al.*, 1978).

Of the parent drug, between 58–77% is excreted as unchanged drug after intravenous administration of single doses (Walkenstein *et al.*, 1978; Somogyi *et al.*, 1980). Reduced daily doses of cimetidine according to the degree of renal failure have therefore been advocated (Ma *et al.*, 1978; Larsson *et al.*, 1979; Bjaeldager *et al.*, 1980).

Thin layer chromatography examinations of urine samples after administration of single intravenous

doses of isotope-labelled cimetidine to two healthy subjects have shown that the main metabolite of cimetidine is a sulphoxide which, however, only accounted for 10.1 and 11.9% of the total radioactivity in the urine (Taylor *et al.*, 1978). During treatment with cimetidine 1.0 g/day, Lee & Osborne (1978) could not detect measurable amounts of the sulphoxide metabolite in plasma in patients with normal renal function. In patients with unspecified degrees of renal failure given the same dose they found a plasma level of about 0.5 $\mu\text{g/ml}$ 2–3 h after a dose of 200 mg.

The aim of the present study was to investigate the plasma elimination and urinary excretion of the sulphoxide metabolite in relation to cimetidine after single intravenous doses of cimetidine in patients with

normal renal function and severe renal failure. We also wanted to study the plasma levels of the sulphoxide metabolite during continuous treatment with cimetidine in patients with normal renal function and with different degrees of renal failure given reduced doses according to the degree of renal impairment.

Methods

Intravenous single dose studies

Two groups of patients participated in this study. The first group consisted of nine patients (six men), mean age 52 years (range 27–66 years), with peptic ulcer disease and normal renal function (mean creatinine clearance 90 ml/min, range 79–110 ml/min). The second group consisted of ten patients (seven men), mean age 59 years (range 44–78 years), with severe renal failure (creatinine clearance < 5 ml/min) on regular haemodialysis treatment.

Cimetidine was given as a single intravenous dose of 200 mg at 8.00 h. In the patients with normal renal function blood samples for analyses of cimetidine and its sulphoxide metabolite were taken immediately before dosing, every 5 min during the first 15 min, every 15 min until 2 h, every 30 min between 2 and 6 h and 7, 8, 9 and 24 h after dose. Urine was collected between 0–9 and 9–24 h after the dose. In the patients with severe renal failure blood samples were taken before and 5, 15, 30, 45 min, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 9.0 h after dosing. An additional blood sample was taken at the start of haemodialysis, 14–38 h after dose. Urine was collected 0–9 h and from 9 h after dosing until the start of haemodialysis.

Oral continuous treatment studies

During continuous treatment with cimetidine blood samples for analysis of cimetidine and cimetidine sulphoxide were taken at the following times in three groups of patients:

One blood sample was taken at 09.00 h before the morning dose (10 h after an evening dose of cimetidine 400 mg) in ten patients (six men) mean age 45 years (range 29–58 years) with peptic ulcer disease and normal renal function (mean creatinine clearance 82 ml/min, range 72–124 ml/min). They had been treated with cimetidine 200 mg three times daily and 400 mg at bedtime for at least a week. The plasma concentrations and excretion of unchanged drug in the urine followed for 24 h in this group of patients have previously been reported (Bodemar *et al.*, 1981).

One blood sample was taken at 08.00 h (10 or 12 h after an evening dose of cimetidine 200 mg or 400 mg) before a final morning dose of 200 mg was given on day 7 after cimetidine treatment for 6 days in 25 patients, 7 women and 18 men, mean age 55 years

(range 26–77 years), with renal impairment (creatinine clearance 5–75 ml/min). Eight patients with creatinine clearances of 50–75 ml/min were given the standard dose of cimetidine 1.0 g/day. The other 17 patients with creatinine clearances of 5–50 ml/min received reduced doses of cimetidine according to the degree of renal impairment (Table 2). Blood samples were taken at 1.5, 2.5, 3.5, 5.0, 6.0, 7.0, 8.0 and 9.0 h after the final morning dose of 200 mg on day 7. The steady state plasma concentrations and urinary excretion of cimetidine in this pharmacokinetic study have been reported previously (Larsson *et al.*, 1981).

One plasma sample was taken at 08.00 h before the morning dose of 200 mg (two patients) or 6 h after the morning dose (four patients) at 2 and 4 weeks during continuous treatment with cimetidine 200 mg twice daily in six patients with severe renal failure (creatinine clearance 0–5 ml/min), when they arrived for haemodialysis. These six patients, four women and two men with mean age 63 years (range 55–71), participated in a trial concerning the effect of cimetidine on hypercalcaemia.

None of the patients with normal or impaired renal function had liver disease assessed by conventional laboratory tests. None of the patients with renal insufficiency had gastrointestinal disease. These patients were treated with one or more of the following drugs: digoxin, frusemide, β -adrenoceptor blocking agents, hydralazine, calcium lactate, 1- α -hydroxyvitamin-D₃, warfarin and antacids. In patients with normal renal function only antacids were given apart from cimetidine.

The nature of the trial was fully explained to the patients in each group and his/her consent obtained prior to entry to the trial, in accordance with the Declarations of Helsinki and Tokyo. The studies were conducted with the approval of the Hospital Ethical Committee.

Drug analyses

The samples of plasma and urine were frozen within 2 h until analysed. All plasma and urine samples were analysed in duplicate. The analyses of the cimetidine sulphoxide metabolite in plasma and urine were performed with a recently developed high pressure liquid chromatography (h.p.l.c.) method, which allowed simultaneous analysis of cimetidine (Larsson *et al.*, 1981). The coefficients of variation were 2.0 and 2.4%, respectively, for the analyses of cimetidine and cimetidine sulphoxide in plasma. The minimum detection limit of cimetidine and the sulphoxide metabolite was 0.05 μ g/ml. The concentration of cimetidine in plasma in the previously reported groups of patients with normal renal function and different degrees of renal failure during continuous treatment with cimetidine was determined by the h.p.l.c. method described by Bodemar *et al.* (1979).

Calculations

Intravenous single dose studies The elimination rate constant (β) of cimetidine in patients with normal renal function and severe renal failure was calculated from the final linear parts of the elimination curve (β -slope) 2.5–9.0 h after dose. The β of cimetidine sulphoxide in patients with normal renal function was calculated from the mean plasma concentration curve 1–4 h after dose. The plasma elimination half-life ($T_{1/2}$) was calculated from β according to the formula:

$$T_{1/2} = \frac{0.693}{\beta}$$

The total plasma clearance (Cl_{tot}) of cimetidine was calculated according to the formula:

$$Cl_{tot} = \frac{\text{Dose}}{AUC_{0-\infty}}$$

$AUC_{0-\infty}$ is the total area under the plasma concentration curve calculated by the trapezoidal rule from the plasma concentration curve and the last concentration divided by β .

The renal clearance (Cl_{renal}) of cimetidine in patients with normal renal function and with renal failure, and of cimetidine sulphoxide in normal renal function, was calculated:

$$Cl_{renal} = \frac{X_{0-24\text{ h}}}{AUC_{0-24\text{ h}}}$$

and of cimetidine sulphoxide in renal failure:

$$Cl_{renal} = \frac{X_{0-9\text{ h}}}{AUC_{0-9\text{ h}}}$$

X is the urinary excretion of cimetidine or cimetidine sulphoxide determined in urine 0–24 h or 0–9 h after dose.

The apparent volume of distribution ($V_{d\text{ area}}$) of cimetidine in the two groups of patients was calculated:

$$V_{d\text{ area}} = \frac{\text{Dose}}{\beta \times AUC_{0-\infty}}$$

Oral continuous treatment studies. The elimination rate constants (β) of cimetidine and cimetidine sulphoxide in the subgroups of patients with different degrees of renal failure treated with cimetidine for 6 days were determined from the β -slope of the plasma concentration curve 5–9 h after the final oral dose given on the morning of day 7.

The differences in the patients with normal renal function and renal failure are evaluated by the Student's t -test for independent samples. The results are given as mean $\pm$ s.e. mean.

Results

Intravenous single dose studies

The mean plasma concentration curves of the sulphoxide metabolite and cimetidine after the administration of the single intravenous dose of cimetidine 200 mg in normal renal function and severe renal failure are presented in Figure 1. In normal renal

Figure 1 Plasma concentrations (mean $\pm$ s.e. mean) of cimetidine — and cimetidine sulphoxide - - - - - in normal renal function (Group I, $n = 9$, Δ) and severe renal failure (Group II, $n = 10$, $\bullet$) after a single intravenous dose of 200 mg cimetidine.

function the plasma concentrations of the sulphoxide metabolite were low. The mean maximum value appeared 15 min after dosing and was 0.18 ± 0.03 $\mu\text{g/ml}$ (range 0.10–0.31) and after 4.5 h the sulphoxide metabolite could not be detected in plasma. In severe renal failure the plasma concentrations of cimetidine sulphoxide increased with time and 6 h after dosing the plasma concentrations of cimetidine and the sulphoxide were similar. The concentration of the sulphoxide then remained constant up to 9 h after dose (mean $\pm$ s.e. mean 0.95 ± 0.15 $\mu\text{g/ml}$ (range 0.56–2.06). After 24 h the mean plasma concentration of the sulphoxide metabolite determined in six of the ten patients was still 0.59 ± 0.09 $\mu\text{g/ml}$ compared to that of cimetidine 0.05 ± 0.03 $\mu\text{g/ml}$. Thirty-eight hours post dose the plasma concentrations of cimetidine sulphoxide in two patients were 0.91 and 1.42 $\mu\text{g/ml}$, respectively. At that time cimetidine could not be detected in plasma in these two patients.

In Table 1 some pharmacokinetic parameters of cimetidine sulphoxide and cimetidine are given. From the mean plasma concentration curve of cimetidine sulphoxide in the patients with normal renal function the apparent mean plasma $T_{1/2}$ was

Table 1 Pharmacokinetic parameters of cimetidine and cimetidine sulphoxide after a single intravenous dose of 200 mg cimetidine in nine patients with normal renal function and ten patients with severe renal failure (creatinine clearance 0–5 ml/min). (Mean $\pm$ s.e. mean, figures in parentheses denote range).

	Cimetidine						
	$V_d \text{ area}$ (l/kg)	β (h^{-1})	$T_{1/2}$ (h)	AUC_{0-24h} ($\mu g \text{ ml}^{-1} h$)	Total plasma clearance (ml/min)	24 h urine excretion (mg)	Renal clearance (ml/min)
Normal renal function	1.69 $\pm$ 0.16 (1.06–2.54)	0.36 $\pm$ 0.03 (0.27–0.46)	2.00 $\pm$ 0.15 (1.49–2.61)	5.04 $\pm$ 0.47 (2.66–6.81)	718 $\pm$ 80 (489–1254)	94.5 $\pm$ 10.0 (42.8–144.1)	326 $\pm$ 40 (181–584)
Severe renal failure	0.99 $\pm$ 0.04 (0.81–1.18)	0.18 $\pm$ 0.01 (0.12–0.27)	3.90 $\pm$ 0.22 (2.59–5.28)	17.63 $\pm$ 2.80 (11.85–41.83)	214 $\pm$ 19 (80–281)	4.4 $\pm$ 0.4 ¹ (1.1–11.7)	2.5 $\pm$ 0.8 ¹ (0–5.8)
<i>Cimetidine sulphoxide</i>							
Normal renal function	β (h^{-1})	$T_{1/2}$ (h)	AUC_{0-24h} ($\mu g \text{ ml}^{-1} h$)	24 h urine excretion (mg)	Renal clearance (ml/min)		
	0.41 ²	1.73 ²	0.49 ²	25.5 $\pm$ 5.0 (8.7–51.2)	873 ³		
Severe renal failure	⁴	⁴	7.74 $\pm$ 1.13 ⁵ (3.99–15.46)	0.9 $\pm$ 0.5 ¹ (0–3.2)	1.9 $\pm$ 0.7 (0–7.8)		

¹Determined in six patients.

²Calculated from the mean plasma concentration curve.

³Calculated from the mean values of AUC_{0-24h} and 24 h urine excretion.

⁴Not possible to calculate (see text).

⁵ AUC_{0-9h}

calculated to be 1.73 h. In the group of patients with severe renal failure, it was not possible to calculate the plasma $T_{1/2}$ of the metabolite, because a true elimination phase had not appeared, when the last blood sample of the day 9 h post-dose was taken. In normal renal function a mean of 47.3% (range 21.4–72.1) of the intravenous dose was recovered in 24 h urine as cimetidine and a mean of 12.8% (range 4.4–25.6) as the sulphoxide metabolite. The corresponding mean values in the patients with severe renal failure were 2.2% (range 0.6–5.9) and 0.5% (range 0.3–1.6), respectively. The mean renal clearance of cimetidine sulphoxide was 873 ml/min in normal renal function and 1.9 ml/min in severe renal failure.

Pharmacokinetic parameters for the parent drug, cimetidine, are also given in Table 1. Compared to the values in the patients with normal renal function the plasma $T_{1/2}$ of cimetidine was longer ($P < 0.001$), the apparent volume of distribution smaller ($P < 0.01$) and the total plasma clearance lower ($P < 0.001$) in the patients with severe renal failure. However, the non-renal clearance of cimetidine calculated as the difference between the total plasma clearance and renal clearance was also lower ($P < 0.05$) in severe renal failure than in normal renal function.

Oral continuous treatment studies

The plasma concentrations of cimetidine sulphoxide and of the parent drug before the morning dose during continuous treatment with cimetidine in patients with normal renal function and varying degrees of renal failure are given in Table 2. In the

groups of patients with renal failure the plasma concentrations 6 h after the morning dose are also given. The mean morning plasma concentration of cimetidine sulphoxide in normal renal function was about 1/3 and in patients with creatinine clearance 50–75 ml/min 1/2 of the mean plasma concentration of cimetidine achieved at the same time. In moderate and severe renal failure the mean plasma concentrations of cimetidine sulphoxide before and 6 h after the morning dose were progressively higher with decreasing renal function, even though the daily doses of cimetidine were reduced. In the patients on regular haemodialysis treated with cimetidine 200 mg twice daily the mean morning plasma concentrations of cimetidine sulphoxide in two patients were 5 and 10 times higher than those of cimetidine and about 14 and 20 times higher than the plasma concentrations of the sulphoxide metabolite in normal renal function. The values of cimetidine sulphoxide after treatment for 2 weeks in these patients with severe renal failure (Table 2) were about the same as those obtained after treatment for 4 weeks: 1.70 and 3.10 before the morning dose (2 patients) and 4.86 ± 1.27 6 h after the morning dose (4 patients).

The mean plasma concentration curves of cimetidine sulphoxide and of cimetidine after the final dose of cimetidine in the morning of day 7 in two subgroups of patients with creatinine clearance 5–15 ml/min and 50–75 ml/min are presented in Figure 2. The plasma $T_{1/2}$ of cimetidine sulphoxide were 14.4 ± 1.4 h (range 10.3–15.9) and 5.3 ± 0.8 h (range 1.8–8.4), and of the parent drug 4.5 ± 0.3 h (range 3.9–5.4) and 3.1 ± 0.1 h (range 2.3–5.3) in these two groups respectively.

Table 2 Steady state plasma concentrations of the cimetidine sulphoxide metabolite and the parent drug before and 6 h after the morning dose in patients with normal renal function and different degrees of renal failure. (Mean $\pm$ s.e. mean, figures in parentheses denote range).

n	Treatment period (weeks)	Creatinine clearance (ml/min)	Dose (mg)	Plasma concentration before dose (μ g/ml)		Time interval after dose (h)	Plasma concentration 6 h after dose (μ g/ml)	
				sulphoxide	cimetidine		sulphoxide	cimetidine
10	1–4	> 75	200 $\times$ 3 + 400	0.12 ± 0.02 (0.07–0.21)	0.38 ± 0.05 (0.26–0.80)	10		
8	1	50–75	200 $\times$ 3 + 400	0.44 ± 0.09 (0.20–1.00)	0.83 ± 0.06 (0.55–1.06)	10	0.35 ± 0.06 (0.21–0.82)	0.84 ± 0.07 (0.47–1.16)
6	1	30–50	200 $\times$ 4	0.62 ± 0.09 (0.39–0.67)	0.58 ± 0.05 (0.38–0.73)	10	0.69 ± 0.06 (0.43–0.75)	1.03 ± 0.12 (0.80–1.58)
6	1	15–30	200 $\times$ 3	0.86 ± 0.20 (0.46–1.60)	0.70 ± 0.06 (0.47–0.93)	10	0.83 ± 0.15 (0.37–1.05)	1.15 ± 0.11 (0.93–1.39)
5	1	5–15	200 $\times$ 2	0.82 ± 0.25 (0.55–1.83)	0.45 ± 0.06 (0.31–0.68)	12	1.09 ± 0.23 (0.84–2.00)	1.01 ± 0.09 (0.73–1.20)
2	2	0–5	200 $\times$ 2	1.66 and 2.37	0.17 and 0.47	12	—	—
4	2			—	—	—	4.97 ± 1.05 (3.47–7.98)	1.34 ± 0.23 (0.89–1.79)

Discussion

In the present single dose studies, the values of the plasma half-lives and total plasma and renal clearances of cimetidine are in agreement with those previously reported in normal renal function (Burland *et al.*, 1975; Walkenstein *et al.*, 1978; Somogyi *et al.*, 1980). The non-renal clearance of cimetidine calculated as the difference between the total plasma clearance and renal clearance was in normal renal function about 55% and in severe renal failure 98% of the total plasma clearance of the drug. Since only small amounts of given intravenous doses of cimetidine are eliminated via the bile (Spence *et al.*, 1977) and faeces (Griffiths *et al.*, 1977; Taylor *et al.*, 1978), the non-renal clearance of cimetidine probably mainly represents the capacity to metabolise the drug. The significantly lower non-renal clearance of the drug in severe renal failure compared to normal renal function suggests that the metabolism of cimetidine is decreased in uraemia.

Figure 2 Plasma concentrations (mean $\pm$ s.e. mean) of cimetidine (—) and cimetidine sulphoxide (-----) in patients with creatinine clearance 5–15 ml/min ($n = 5$) (a) and 50–75 ml/min (b) after a single oral dose of 200 mg cimetidine on day 7 after continuous treatment for 6 days with cimetidine 200 mg twice daily and 200 mg three times daily and 400 mg at bedtime respectively.

Since cimetidine has been reported to inhibit the metabolism of antipyrine (Puurunen *et al.*, 1980) and warfarin (Silver & Bell, 1979), it might be metabolised by the same metabolic system, the cytochrome-P-450-linked monooxygenase system in the liver. Activity of this enzyme system has recently been reported in renal tissue (Anders, 1980). The decreased rate of metabolism of cimetidine in severe renal failure may be explained either by the fact that uraemic toxins inhibit the cytochrome P-450 enzyme system or by lack of activity of this enzyme system in the damaged kidneys. Another possible explanation would be product inhibition (Wagner, 1975), i.e. accumulation of a metabolite would inhibit the metabolic rate of the parent drug.

In the present study a significantly lower apparent distribution volume ($V_{d \text{ area}}$) of cimetidine was found in severe renal failure compared to normal renal function. Gibaldi & Perrier (1972) stated that $V_{d \text{ area}}$ is a hybrid pharmacokinetic parameter depending on the complex relationships between $V_{d \text{ area}}$, β and AUC in the calculations. They showed, that reduced $V_{d \text{ area}}$ is a general phenomenon associated with renal failure for drugs with short plasma $T_{1/2}$, which are predominantly eliminated by the kidneys. They concluded, that changes in $V_{d \text{ area}}$ do not reflect actual changes in physiologic space occupied by a given drug, but merely the degree of equilibration of the drug between the central and peripheral compartments during the β -slope after single doses. The clinical significance of a decrease in $V_{d \text{ area}}$ of cimetidine in renal failure is unclear.

The low plasma concentrations and high renal clearance of cimetidine sulphoxide in normal renal function and high plasma concentrations in the patients with severe renal failure suggest that the metabolite is mainly eliminated unchanged via the kidneys. The values of the renal clearances of cimetidine sulphoxide and the parent drug are considerably higher than the glomerular filtration rate, which suggests that these two substances are eliminated in the urine predominantly by tubular secretion. The considerably higher renal clearance of cimetidine sulphoxide compared to cimetidine in normal renal function could not be explained by the small difference in molecular weight (268.35 and 252.35, respectively), but possibly by differences in physicochemical properties, e.g. polarity. The plasma $T_{1/2}$ of the sulphoxide metabolite after administration of cimetidine represents both continuous synthesis of the metabolite from cimetidine and elimination by the kidneys. It was clearly prolonged after the final dose in the continuous oral treatment study in the patients with creatinine clearance 5–15 and 50–75 ml/min compared to that in the patients with normal renal function after a single intravenous dose. The plasma $T_{1/2}$ of the sulphoxide could not be calculated in the patients with severe renal failure on

regular haemodialysis treatment in our single dose study, but has recently been reported to be about 27 h after administration of single intravenous doses to a similar group of patients (Randolph *et al.*, 1980). In that study the plasma $T_{1/2}$ of the sulphoxide was reported to be 10.52 h in moderate and 4.91 h in mild dysfunction, which is in agreement with the results obtained in the present study.

During continuous treatment the standard dose of cimetidine 1.0 g/day gave more than two times higher mean morning cimetidine plasma concentration in patients with mild renal dysfunction (creatinine clearance 50–75 ml/min) compared to that in patients with normal renal function (Table 2), which made us recommend a reduced dose of cimetidine 200 mg four times daily in mild renal dysfunction (Larsson *et al.*, 1981). In this group of patients with mild renal dysfunction the mean plasma cimetidine sulphoxide concentration was more than three times higher than in the group of patients with normal renal function. The reduced doses of cimetidine according to the degree of renal failure in the subgroups of patients with creatinine clearance < 50 ml/min gave similar plasma cimetidine concentrations in these groups compared to those in patients with normal renal function given the standard dose (Table 2). However, the mean plasma concentrations of cimetidine sulphoxide were successively higher with decreasing renal function in these subgroups of patients and were especially high in relation to the mean cimetidine plasma concentration in patients requiring regular haemodialysis treatment.

Cimetidine sulphoxide is the main identified metabolite of cimetidine. However, it represents probably only a minor part of the total metabolites, as only 12.8% of the given dose was recovered as the sulphoxide metabolite in the 24 h urine in normal renal function. This is in agreement with the results reported by Taylor *et al.* (1978) in two healthy subjects given a single intravenous dose of isotope-labelled cimetidine. Besides cimetidine sulphoxide, these authors identified another metabolite, a compound with a hydroxylated methyl group in the imidazole ring, which, however, only accounted for 4.0–4.3% of the total radioactivity in urine. A considerable part of the total radioactivity in urine (14.2–19.8%) re-

mained unidentified. Recent pharmacological studies in guinea pigs have shown, that the sulphoxide metabolite does not inhibit gastric acid secretion and thus seems to lack histamine- H_2 -receptor antagonist activity (Mills, Smith, Kline & French Research Ltd, personal communication, 1981).

Considering the present wide use of cimetidine, serious side-effects are rare (McGuigan, 1981). However, cimetidine does have the potential to cause a variety of central nervous system symptoms, especially mental confusion. These often appear to be dose-related and are more common in the elderly, with or without known renal insufficiency (Delaney & Ravey, 1977; Menzies-Gow, 1978; Vickery, 1978; Wood *et al.*, 1978). In 6 of 36 critically ill patients with hepatic and/or renal dysfunction, mental confusion appeared during cimetidine treatment and was associated with high plasma levels of the drug (Schentag *et al.* 1979). None of the patients in the present studies given reduced doses of cimetidine according to the degree of renal dysfunction had any side-effects during continuous treatment, even though the plasma concentrations of the sulphoxide were high in relation to those of cimetidine especially in severe renal failure. In a recent trial on the effect of cimetidine in secondary hyperparathyroidism in severe uraemia, three of seven patients treated with cimetidine 400 mg/day on days of dialysis and 600 mg/day on nondialysis days had to discontinue treatment due to somnolence and dizziness (Ahlmén, personal communication, 1981). All patients had high plasma sulphoxide concentrations, but there was no apparent difference in the plasma concentrations of the sulphoxide or the parent drug between the patients with and without side-effects.

Toxicity studies of cimetidine sulphoxide need to be performed to assess if high plasma levels of the metabolite in renal failure may be of significance for development of side effects.

This study was partly supported by the Swedish Medical Research Council. We are indebted to Mrs Ingrid Pettersson and Miss Sonja Tunek for skillful technical assistance.

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(Received April 22, 1981)