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EFFECT OF CIMETIDINE ON RENAL FUNCTION IN MAN

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1 Renal function was studied in nine patients with chronic peptic ulcer before and at repeated intervals during treatment with cimetidine (1.6g daily).

2 Plasma creatinine concentration was significantly increased on the first day after starting cimetidine, and at 3 weeks, but not at 12 weeks. Blood urea concentration was unchanged.

3 Clearances of creatinine, ^{51}Cr EDTA and ^{125}I-hippuran were significantly reduced within 6 h of starting cimetidine. Clearances of ^{51}Cr EDTA and ^{125}I-hippuran returned to baseline within 3 weeks, and creatinine clearance within 12 weeks.

4 Urinary creatine excretion was significantly increased at 3 weeks, but there was no significant change in urinary creatinine excretion, or in serum creatine phosphokinase concentration.

5 These observations suggest that cimetidine causes an early but short-lived fall in glomerular filtration rate (GFR) and effective renal plasma flow. The later rise in plasma creatinine was unaccompanied by any change in GFR, and may have been due to competition by cimetidine for renal tubular handling.

6 Caution should be exercised when administering cimetidine to patients with pre-existing renal failure.

Introduction

Cimetidine is extensively used in the treatment of peptic ulceration, but is known to cause an increase in plasma creatinine concentration (Blackwood *et al.*, 1976; Haggie, Fermont & Wyllie, 1976). Possible mechanisms for this are: (1) An effect on the laboratory estimation of creatinine; (2) a reduction in glomerular filtration; (3) competition with creatinine for renal tubular handling; or (4) an increase in creatinine production. *In vitro* studies, using the Jaffé method for creatinine estimation, have ruled out the first explanation (Burland *et al.*, 1976). In order to investigate the other three mechanisms, we have studied nine patients receiving cimetidine for peptic ulcer. We have carried out repeated measurements of creatinine clearance and ^{51}Cr EDTA clearance as indices of glomerular filtration rate (GFR), and of ^{125}I-hippuran clearance as an index of effective renal plasma flow (ERPF). We have also measured urinary creatine excretion and serum creatine phosphokinase (CPK). Mechanism (2) would be expected to reduce clearances of both creatinine and ^{51}Cr EDTA. Mechanism (3) would be expected to reduce clearance of creatinine alone, and might increase urinary excretion of its immediate biochemical precursor, creatine. Mechanism (4) should increase the urinary creatine and creatinine excretion without any changes in the clearances. Active muscle damage would lead to a rise in serum CPK.

Methods

Nine patients with endoscopically proven peptic ulceration participated. All gave informed consent to

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the study. They received 400 mg cimetidine four times daily for 12 weeks. Studies were carried out on four occasions: before treatment, on the first day of treatment, and 3 and 12 weeks after starting treatment. Hydration and feeding were the same on all 4 days.

Creatinine clearance (Cannon, 1974) was estimated using the Jaffé method. GFR was also estimated from ^{51}Cr EDTA clearance (Chantler *et al.* 1969), using a technique of repeated plasma sampling following the injection of a bolus of ^{51}Cr EDTA. The ERPF was similarly measured following a bolus of ^{125}I-hippuran (Ramm, Evans & Chisholm, 1967). On each day of the study the above measurements were carried out over a 4 h period in the morning starting 2 h after the first dose of cimetidine (400 mg) and were repeated in the evening, 12 h after the first dose and 2 h after the last dose. In seven of the nine patients the serum CPK (Foster, Bernt & Bergmeyer, 1974) was estimated, and the urinary creatine was measured in the morning 4 h urine collection. Creatine was assayed by the alkaline diacetyl method (Tao-Wong, 1971), which is more sensitive than the standard Jaffé reaction usually used. All samples from any one patient for chemical analysis were stored frozen, and assayed together on completion of the study. Statistical evaluation was by the Wilcoxon Signed Rank Sum Test.

Results

Blood urea, plasma creatinine, urinary creatinine and urinary creatine

Mean blood urea concentration was 5.17 mmol/l before treatment and 4.78, 5.31 and 4.73 mmol/l on the first day and at 3 and 12 weeks respectively (NS).

Mean plasma creatinine (Figure 1) rose from 97 to 110 μmol/l on the first day ($P<0.05$), and to 122 μmol/l at 3 weeks ($P<0.01$). At 12 weeks, it was not significantly different from the pretreatment value. Mean urinary creatinine in the 4 h morning collection fell from 2.15 to 1.41 mmol on the first day ($P<0.01$). It was 2.0 and 2.35 at 3 and 12 weeks respectively (NS). In the 4 h evening collection it was 1.87 mmol before treatment, and 1.59, 1.59 and 2.13 mmol on the first day and at 3 and 12 weeks respectively (NS). Mean urinary creatine in the 4 h morning urine collection (Figure 1) rose from 62 to 114 μmol on the first day (NS), and to 139 μmol at 3 weeks ($P<0.05$). It was 99.5 μmol at 12 weeks (NS).

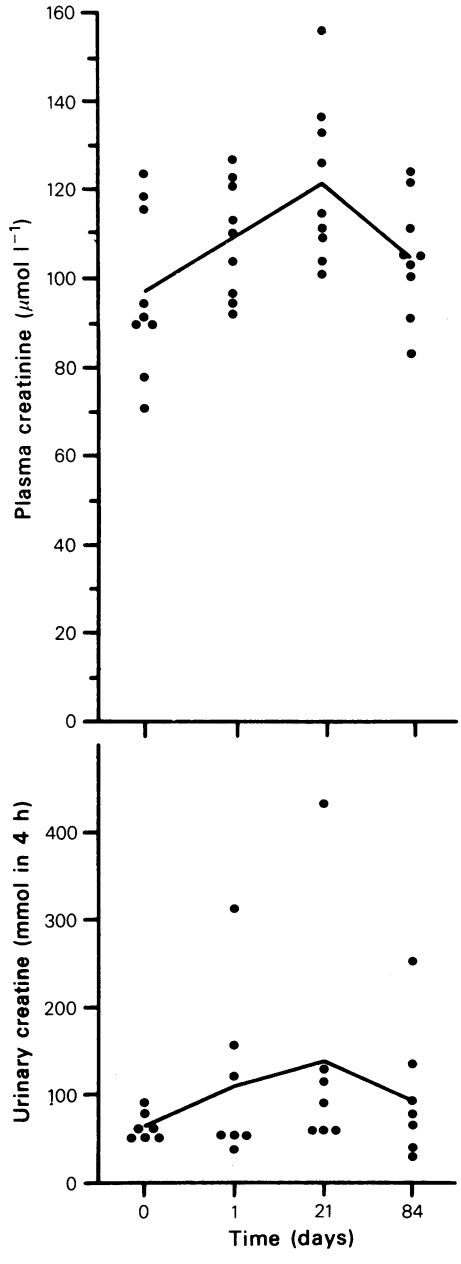

Figure 1 Plasma creatinine concentration and urinary creatine concentration (morning values only).

Clearances of creatinine, ^{51}Cr EDTA and ^{125}I-hippuran

Mean values are shown in Table 1 for both the morning and evening clearances. Individual data points are shown for morning clearances alone in Figure 2. All three clearances were reduced on day 1, and this reduction was statistically significant ($P<0.01$) for all three morning clearances. By day 21, the morning and evening clearances of ^{51}Cr

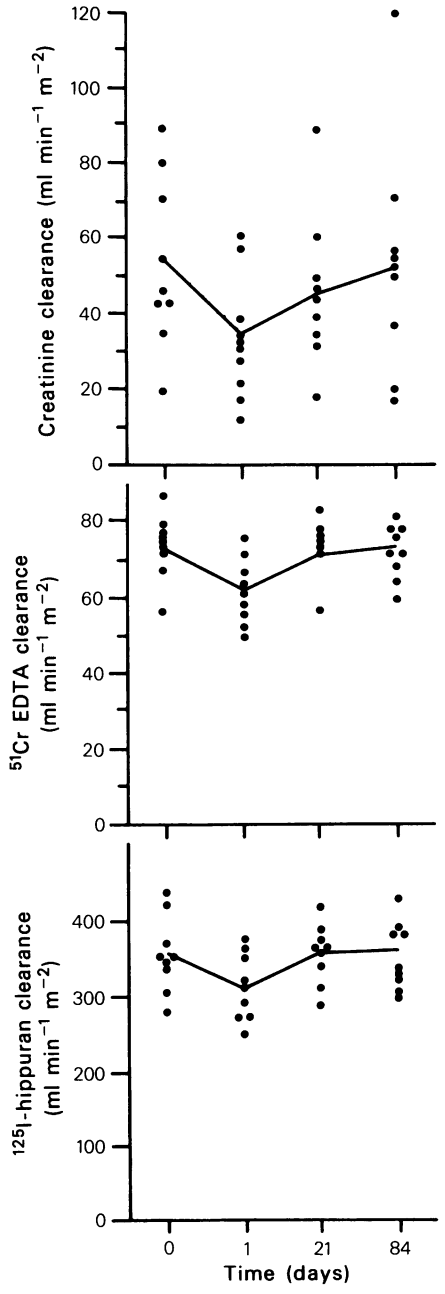

Figure 2 Creatinine clearance, ^{51}Cr EDTA clearance, and ^{125}I-hippuran clearance (morning values only).

EDTA and ^{125}I-hippuran had returned to baseline values. Morning and evening clearances of creatinine were still reduced, but these reductions were not significant. All clearances had returned to baseline by day 84.

Table 1 Mean clearances (ml min^{-1} m^{-2})

	Creatinine		*^{51}Cr EDTA*		*^{125}I-hippuran*	
	a.m.	*p.m.*	*a.m.*	*p.m.*	*a.m.*	*p.m.*
Day 0	54	40	78	68	335	340
Day 1	34*	33	62*	63	312*	310
Day 21	46	25	71	68	355	340
Day 84	53	37	73	73	360	360

*Significantly different from day 0 ($P<0.01$)

Serum CPK

Mean serum CPK was 81 iu/l before treatment, and 61, 64 and 79 iu/l on the first day and at 3 and 12 weeks respectively (NS).

Discussion

Burland *et al.* (1976) have previously demonstrated a fall in creatinine clearance following a single oral dose of cimetidine (800 mg). Our finding that this is accompanied by a fall in ^{51}Cr EDTA clearance demonstrates that it is due to a reduction in GFR (mechanism 2 in the introduction); and our finding that it is accompanied by a reduction in ^{125}I-hippuran clearance indicates that it is associated with a fall in ERPF. In order to detect transient changes, all our clearances were carried out over a short period of time. This may have introduced errors in creatinine clearance, because of difficulties in timing the urine collection, but it should not have affected the other clearances which showed exactly the same changes as creatinine clearance over the first 24 h. The expected normal diurnal variation in GFR was observed (Wesson & Lauler, 1961). Although all morning clearances were significantly reduced on the first day, within 2 h of the first dose of cimetidine, the reductions were less marked and no longer significant by the same evening despite continuing cimetidine. The fall in ERPF suggests that the mechanism underlying these alterations may involve transient renal vasoconstriction, but the cause for this is obscure. H_2 receptors have been detected in the renal vasculature of rabbits and dogs (Banks *et al.*, 1978; Bokesesay & Tutlies, 1974), but little is known about their presence and action in man.

The increased plasma creatinine at 3 weeks might still be related to the initial fall in GFR, but this seems unlikely since the afternoon ^{51}Cr EDTA and ^{125}I-hippuran clearances had returned to base line on day one, as did both morning and afternoon values at 3 weeks. Creatinine clearance, on the other hand, had not returned to baseline in either morning or evening collections. Although this reduction was no longer

statistically significant, it was similar in magnitude to the increase in serum creatinine, and was accompanied by a significant increase in urinary excretion of creatine but not of creatinine. These findings are consistent with competition for renal tubular handling (mechanism 3). The other possible mechanism, increased creatinine production (mechanism 4), is a less likely explanation in view of the absence of an increase in urinary creatinine excretion. The fact that all measurements had returned to baseline by the twelfth week suggests an adaptive process of some sort, possibly induction of an enzyme involved in tubular handling.

Our study suggests that an increase in plasma creatinine is not a harmful effect of cimetidine in those with normal renal function prior to treatment. It was not accompanied by a rise in blood urea concentration, although Langman *et al.* (1980) have reported a significant rise in blood urea after 4 weeks, cimetidine treatment. In our study, no abnormalities were detectable at 12 weeks. The initial fall in GFR and ERPF does, however, suggest that caution should be exercised when administering cimetidine to patients with pre-existing renal failure. There have been occasional case reports of deterioration in renal function in such patients during cimetidine treatment (McElligott, 1978) and in patients with moderate renal failure, Ma *et al.* (1978) found a rise in both plasma creatinine and blood urea concentration 1–2 days after a single intravenous dose of cimetidine (300 mg).

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