Reduction of metformin renal tubular secretion by cimetidine in man

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1 To determine whether cimetidine altered the renal handling of metformin, seven subjects took 0.25 g metformin daily with and without cimetidine 0.4 g twice daily. Blood and urine samples were collected and assayed for metformin, cimetidine and creatinine by h.p.l.c.

2 Cimetidine significantly increased the area under the plasma metformin concentration-time curve by an average of 50% and reduced its renal clearance over 24 h by 27% ($P < 0.008$). There was no alteration in the total urinary recovery of metformin when cimetidine was co-administered.

3 The effect of cimetidine on the renal clearance of metformin was time dependent, being significantly reduced up to 6 h following cimetidine. These results appeared to be consistent with competitive inhibition of renal tubular secretion.

4 Cimetidine had no effect on the renal clearance of creatinine, but time-dependent variations in both metformin and creatinine renal clearance were observed. Metformin had no effect on cimetidine disposition.

5 It is concluded that cimetidine inhibits the renal tubular secretion of metformin in man, resulting in higher circulating plasma concentrations. Because of its propensity for causing dose and concentration-dependent adverse effects, the dose of metformin should be reduced when cimetidine is co-prescribed.

Keywords metformin cimetidine drug interaction renal clearance tubular secretion

Introduction

The most frequently described mechanisms for drug-drug pharmacokinetic interactions are displacement from plasma protein binding sites and induction or inhibition of hepatic metabolism. Interactions occurring in the kidney have not been systematically studied; although, the major mechanisms would focus on tubular secretion. Whereas interactions in the proximal tubule involving organic anions such as probenecid and the cephalosporins (Welling *et al.*, 1979) have

been widely documented, those involving the organic cations have been poorly studied. Recently, Somogyi *et al.* (1983) demonstrated that the histamine H_2 -receptor antagonist cimetidine reduced the renal clearance in man of procainamide and its active metabolite, *N*-acetylprocainamide, by inhibition of their tubular secretion via the organic cation transport system. The disposition in man of the biguanide hypoglycaemic drug metformin has not been well

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documented, mainly due to chemical analytical difficulties. However, the available evidence indicates that the kidney is the major route for its elimination, with renal clearance being much higher than the glomerular filtration rate, indicating secretion by the proximal tubules (Tucker *et al.*, 1981; Sirtori *et al.*, 1978; Pentikainen *et al.*, 1979). Metformin has the propensity for causing adverse effects, especially lactic acidosis, which may be related to high circulating concentrations of the drug (Phillips *et al.*, 1978). The purpose of this study was to examine whether the renal handling of metformin could be altered by cimetidine. This would enable the relative importance of the renal secretory system for metformin elimination to be confirmed; the likelihood of a clinically important interaction between drugs involving the kidney would also be ascertained.

Methods

Subjects

Seven healthy subjects agreed to participate in the study after being fully informed of the purpose and risks involved. The study was approved by the Research Review Committee of the Royal Adelaide Hospital, and the Committee on the Ethics of Human Experimentation, University of Adelaide. The subjects (three male, four female) were aged between 19 and 23 years and weighed between 55 and 78 kg. They were in good health as judged by physical examination and biochemical screening tests. They had no evidence of renal, hepatic, haematologic or cardiovascular dysfunction. The subjects received a single daily oral dose of 250 mg metformin HCl (half a Glucophage® tablet; Riker Laboratories Australia Pty Ltd) each day for 10 days, and between days 6 and 10 received, in addition, 400 mg cimetidine twice daily (2×200 mg Tagamet®; Smith, Kline and French Laboratories). The subjects were studied on days 5 and 10. On a separate occasion, the subjects took cimetidine 400 mg twice daily for 2 days before being studied on the third day for cimetidine disposition.

Biological fluid collection

On each of the 3 study days, the subjects presented to the laboratory where an intravenous cannula and stylet (Jelco®; Critikon, Tampa, U.S.A.) were placed in a forearm vein. They then took their medication following a light breakfast, and 5 ml venous blood samples were

collected at 0 (just prior to drug administration), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h, and in the case of metformin, a sample was collected by venepuncture at 24 h. The blood was immediately centrifuged and the plasma stored at -20°C prior to analysis. In addition, 2 ml blood samples were collected at 0, 4, 8 and 12 h for the determination of lactic and pyruvic acid concentrations. Urine was collected at 3 hourly intervals to 12 h, then 12–24 h. The volume and pH were recorded and an aliquot retained at -20°C prior to analysis.

The subjects were instructed to drink dilute fruit juice in order to maintain an even urine flow rate. They were either seated or ambulant in the laboratory. Physical exercise was not permitted.

Chemical analyses

Metformin was measured in plasma and urine samples by a recently described h.p.l.c. method (Keal & Somogyi, 1986) which has a detection limit of 10 ng ml^{-1} and inter-day coefficient of variation of less than 5%. Cimetidine did not interfere with this assay. Cimetidine was measured in plasma and urine by a slight modification to the h.p.l.c. method of Cohen *et al.* (1980). Metformin did not interfere with this assay. Creatinine in plasma and urine was analysed by minor modifications to the h.p.l.c. method of Huang & Chiou (1983). The variability of this assay was less than 6.7%. Pyruvic acid and lactic acid concentrations in the blood samples were analysed by commercially available enzymatic assays (Diagnostic Kit No. 726-UV and 826-UV; Sigma Chemical Co., St Louis, U.S.A.). Cimetidine did not interfere with these assays. Conversion factors to S.I. units are metformin 7.74 and cimetidine 3.96.

Pharmacokinetic analyses

Pharmacokinetic symbols and calculations were based upon those recommended by Rowland & Tucker (1982). The maximum attained plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were obtained from the measured data points. The area under the plasma concentration–time curve during the dosing interval (AUC_0^{24}) was calculated by the linear trapezoidal method. The fraction of the dose excreted in urine unchanged during the dosing interval (f_e^{24}) was calculated directly from the data. Renal clearance (CL_R) was calculated as

$$\text{CL}_R = \frac{Ae}{\text{AUC}}$$

where A_e is the amount of drug excreted unchanged in urine and AUC the area under the plasma concentration-time curve during a time interval. This was calculated for the time intervals 0–3, 3–6, 6–9, 9–12, 12–24 and 0–24 h for metformin, creatinine (0–24 h omitted), and cimetidine (12–24 h and 0–24 h omitted, 0–12 h included). The ratio of the renal clearance of metformin to the renal clearance of creatinine and the blood lactate to pyruvate ratio were also calculated.

Differences between the study periods were analysed for statistical significance by the non-parametric Wilcoxon matched-pairs signed-ranks test or the Friedman two-way analysis of variance by ranks (Daniel, 1978), and within study periods by analysis of variance (Daniel, 1983). Correlations between renal clearance and urine flow rate or pH were determined by linear regression analysis. All data are tabulated as mean $\pm$ s.d.

Results

Cimetidine produced substantial alterations to the disposition of metformin. Figure 1 shows the mean plasma metformin concentrations when given alone and when combined with cimetidine and Table 1 lists the resultant pharmacokinetic analyses. Although there was no alteration in the time to achieve the maximum plasma metformin concentration, the concentration itself was increased by cimetidine by an average of 81% ($P < 0.008$). The area under the plasma metformin concentration-time curve during the dosing interval was increased by an average of 50% (range 11 to 76%; $P < 0.008$). During the first 12 h, the fractional excretion of unchanged metformin was 0.47 ± 0.12 and 0.49 ± 0.11 when combined with cimetidine ($P > 0.05$). During the 12–24 h time period, approximately 3% of the dose was excreted in urine, so that throughout the entire dosing interval there was no dif-

Figure 1 Mean plasma concentration-time profile for metformin when given alone as 0.25 g daily ($\circ$) and when co-administered with cimetidine 0.4 g twice daily ($\bullet$) in seven subjects.

ference in the fraction of the dose recovered in urine (Table 1). Metformin renal clearance was significantly ($P < 0.008$) reduced by cimetidine by an average of 27%. Table 2 summarises several renal disposition parameters for metformin and creatinine. Metformin renal clearance was significantly reduced by cimetidine in the 0–3 and 3–6 h time periods only. However, metformin renal clearances differed ($P < 0.05$) between time periods. When given alone, the 12–24 h renal clearance was significantly smaller than the 3–6 and 9–12 h periods, and when

Table 1 Comparison of pharmacokinetic data for metformin when given alone (250 mg day⁻¹) and when combined with cimetidine in seven subjects

Parameter	Metformin	Metformin + cimetidine	Significance (P)
$C_{\max}$ (mg l ⁻¹)	0.59 ± 0.24	1.02 ± 0.39	0.008
$t_{\max}$ (h)	3.3 ± 0.8	2.5 ± 0.6	0.078
AUC ₀₋₂₄ (mg l ⁻¹ h)	4.26 ± 1.64	6.23 ± 2.09	0.008
fe_0^{24}	0.50 ± 0.13	0.52 ± 0.11	NS
CL _R (0–24) (ml min ⁻¹)	527 ± 165	378 ± 122	0.008

NS— $P > 0.05$.

Table 2 The effect of cimetidine (C) on the renal disposition of metformin (M) and creatinine

Time period (h)	Metformin renal clearance (ml min ⁻¹)		Creatinine renal clearance (ml min ⁻¹)			Metformin to creatinine renal clearance ratio	
	M	M + C	M	M + C	C	M	M + C
0-3	498 ± 260 ^a	221 ± 147 ^{*b}	124 ± 37 ^c	149 ± 34 ^d	121 ± 36	4.2 ± 2.4	1.4 ± 1.0 ^{*e}
3-6	726 ± 386	400 ± 192 ^{**}	97 ± 21	105 ± 8	111 ± 51	7.8 ± 4.6	3.8 ± 1.9 [*]
6-9	568 ± 227	678 ± 349	88 ± 43	108 ± 17	93 ± 58	7.5 ± 3.9	5.4 ± 1.6 ^{***}
9-12	694 ± 361	715 ± 295	113 ± 23	131 ± 26	110 ± 24	6.3 ± 3.7	5.6 ± 2.6
12-24	284 ± 189	146 ± 73	87 ± 13	77 ± 23		3.5 ± 3.0	2.5 ± 1.2

P* = 0.008 M vs M + C*P* = 0.016 M vs M + C****P* = 0.078 M vs M + Ca—*P* < 0.025: 3-6, 9-12 vs 12-24b—*P* < 0.005: 0-3, 12-24 vs 6-9, 9-12c—*P* < 0.025: 0-3 vs 6-9, 12-24d—*P* < 0.005: 0-3 vs 3-6, 6-9, 12-24e—*P* < 0.005: 0-3 vs 6-9, 9-12

12-24 vs 6-9, 9-12

combined with cimetidine, the 6-9 and 9-12 h values were significantly greater than the 0-3 and 12-24 h periods. Creatinine renal clearance was not significantly different (*P* > 0.05) between the three study occasions; however, within each study significant differences (*P* < 0.05) were found. When metformin was given by itself, the 0-3 h creatinine clearance was significantly larger than the 6-9 and 12-24 h values. This was also the case when metformin was combined with cimetidine, but, in addition, the 0-3 h values were larger than the 3-6 h values and the 9-12 h values were greater than the 12-24 h values. When cimetidine was given by itself, there were no differences in creatinine renal clearance between the various time periods. The ratio of metformin to creatinine renal clearances is also summarised in Table 2. Cimetidine significantly (*P* < 0.05) reduced this ratio at the 0-3 and 3-6 h time periods, whereas between 6-9 h it just failed to reach statistical significance (*P* = 0.078). This ratio remained constant throughout the various time periods when metformin was given alone; however, when combined with cimetidine, the 0-3 h values were significantly smaller (*P* < 0.05) than the 6-9 and 9-12 h values. In addition, the 12-24 h ratio was less than the 6-9 and 9-12 h values. There was no statistically significant (*P* > 0.05) correlation between metformin renal clearance and urine flow rate or hydrogen ion concentration, and metformin did not influence either of these two variables.

Table 3 summarises the results of the cimetidine disposition data. Metformin had negligible effects on the disposition of cimetidine, including the 3 hourly renal clearance values. The single difference occurred in the 6-9 h renal clearance

value, which was significantly smaller (*P* = 0.039) when cimetidine was given alone. However, two subjects had exceptionally low renal clearance values (63 and 56 ml min⁻¹) which were also associated with low creatinine values (37 and 27 ml min⁻¹); it is likely that incomplete urine collection in two subjects may have been the cause of this statistically significant finding. There was no difference in cimetidine renal clearance between the various time intervals during the two study periods.

Figure 2 shows the blood lactate to pyruvate ratios between the three occasions. Although not different at the 0 h time point, thereafter, at 4, 8 and 12 h, the ratio was much higher when metformin was administered either alone (except at 8 h) or with cimetidine, compared with cimetidine alone. At 8 h, the ratio was significantly higher (*P* = 0.023) when metformin was combined with cimetidine, compared with metformin alone. No subject experienced any adverse effects.

Discussion

The results from this study indicate a significant drug interaction between cimetidine and metformin. Cimetidine increased the plasma concentrations of metformin in all subjects. This was not due to an increase in the absorption of metformin, as the total urinary recovery was the same on both occasions. Recovery of only 50% of the dose has been reported by others (38%, Sirtori *et al.*, 1978; 52%, Pentikainen *et al.*, 1979; 50%, Tucker *et al.*, 1981; 40%, Karttunen *et al.*, 1983), although Tucker *et al.* (1981) reported

Table 3 Comparison of pharmacokinetic data for cimetidine when given alone and when combined with metformin in seven subjects

Parameter	Cimetidine	Cimetidine + metformin	Significance (P)
$C_{\max}$ (mg l ⁻¹)	2.36 ± 0.70	2.41 ± 0.61	NS
$t_{\max}$ (h)	1.71 ± 0.59	1.29 ± 0.45	NS
AUC ₀ ¹² (mg l ⁻¹ h)	10.08 ± 1.56	10.14 ± 1.20	NS
fe_{12}^{12}	0.51 ± 0.17	0.65 ± 0.13	NS
Renal clearance (ml min ⁻¹)			
0-3 h	361 ± 150	402 ± 151	NS
3-6 h	370 ± 69	410 ± 122	NS
6-9 h	322 ± 213	511 ± 174	0.039
9-12 h	422 ± 161	519 ± 252	NS
0-12 h	320 ± 108	436 ± 105	NS

NS— $P > 0.05$ **Figure 2** Mean blood lactate to pyruvate ratios in seven subjects following cimetidine (▲), metformin (○) and metformin plus cimetidine (■). *Significantly different ($P < 0.05$) compared with cimetidine; **significantly different ($P < 0.05$) compared with metformin alone. The bars indicate 1 s.d.

that by increasing the metformin dose, absorption decreased. The remainder of the dose represents unabsorbed drug (about 30%, Tucker *et al.*, 1981; Pentikainen *et al.*, 1979). Although Pentikainen *et al.* (1979) could find no metformin metabolites, Tucker *et al.* (1981) proposed that about 20% of the dose may be metabolised. However, this represents a minor fraction of total clearance with the major clearance organ

being the kidney. Cimetidine reduced the overall renal clearance of metformin by almost 150 ml min⁻¹, indicating that the interaction involved tubular secretion. Cimetidine reduces the renal clearances of procainamide/*N*-acetylprocainamide (Somogyi *et al.*, 1983; Christian *et al.*, 1984), ranitidine (Van Crugten *et al.*, 1986), and triamterene (Muirhead *et al.*, 1986) in man. The mechanism is considered to be competition for proximal tubular secretion by the organic cation transport system. McKinney & Speeg (1982) have demonstrated *in vitro* that this is a competitive process, although this has not been confirmed in man. Metformin can be added to the list of drugs which interact with cimetidine in the kidney. The renal clearance of cimetidine was not altered by metformin, implying that the former has a higher affinity for the transporting system.

The inhibitory effect of cimetidine on metformin renal clearance was time dependent, being significant up to 6 h after cimetidine administration. This observation strengthens the hypothesis that the interaction has a competitive, rather than a noncompetitive basis. In addition, metformin renal clearance was time dependent, being significantly lower during the night period (12-24 h). This may be a reflection of lower renal blood flow in the supine position, or circadian variations in renal blood flow or proximal tubular transport. Concentration-dependent metformin renal clearance can be excluded, as the observation was also noted during cimetidine administration.

A number of previous studies have indicated that cimetidine reduces the renal clearance of creatinine towards but not below the glomerular

filtration rate (Burgess *et al.*, 1982; Ochs *et al.*, 1984). The mechanism is considered to be inhibition of the proximal tubular secretion of creatinine via the organic cation transport system. In this study, using a specific h.p.l.c. method, cimetidine appeared to have no effect on creatinine clearance, although, unfortunately, a control period where no drug was given was not included. This may indicate that metformin also reduces creatinine clearance or the glomerular filtration rate; however, documented evidence for this is lacking. Nevertheless, time dependent variations in creatinine clearance were observed, in which the 0–3 h values were much higher than at other time periods (often reaching statistical significance). This is a reflection of the circadian variation of creatinine clearance (Sirota *et al.*, 1950), although the relative changes found were much larger than those observed by Sirota and co-workers. It is of interest that when cimetidine was administered alone, this variation was blunted. More studies are required in this area of renal pharmacology.

The ratio of metformin to creatinine renal clearance appeared to parallel metformin renal clearance with regard to the inhibitory effects of cimetidine. There was no time-dependent variation in the ratio when metformin was given alone, suggesting a common mechanism for the time-dependent variation observed for each substrate. However, when cimetidine was administered, there were marked time-dependent variations, with the initial 0–3 h ratio being significantly less than at other time points. This reflects the marked inhibitory effect of cimetidine on metformin renal clearance associated with the highest circulating cimetidine concentrations during the dosing interval. The renal clearance of metformin was almost reduced to the glomerular filtration clearance in the first 3 h.

Although only a low dose of metformin was used, so as not to provoke side effects during the

study, there was an increase in the pharmacodynamic response as measured by an increased blood lactate to pyruvate ratio. When cimetidine was co-administered, with its resultant increase in circulating metformin concentrations, the ratio was increased at the 8 h time point only. This data indicates an association between plasma concentration and response which may be more evident in the patient population taking larger doses of metformin.

Phillips *et al.* (1978) noted that high doses of metformin in patients with declining renal function were risk factors in metformin associated lactic acidosis. Cimetidine, and potentially other organic cations, by reducing the tubular secretion of metformin and hence elevating metformin plasma concentrations, should be considered as a previously unrecognised risk factor. Patients being prescribed both should have the dose of metformin reduced or an alternative to cimetidine, in this instance, prescribed. The interaction would be more significant in patients with multiple pathology (e.g., the elderly), and because of the severity of the adverse effects, this represents a clinically important drug interaction.

In conclusion, cimetidine reduces the renal clearance of metformin by inhibiting tubular secretion via the organic cation system. This results in elevated blood metformin concentrations and the possibility of contributing to adverse effects. Physicians ought to be made aware of this interaction and take appropriate measures.

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