Dose and concentration dependent effect of ranitidine on procainamide disposition and renal clearance in man

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1 The pharmacokinetics of oral procainamide (1 g) were investigated in six healthy subjects during chronic dosing with ranitidine 150 mg twice daily, and in three of the subjects when ranitidine 750 mg was administered over 12 h.

2 The procainamide area under the plasma concentration-time curve was significantly ($P < 0.02$) increased by ranitidine (27.761.5 vs 31.561.8 mg l⁻¹ h) with a significant reduction in renal clearance (379632 vs 309630 ml/min, $P < 0.02$). There was no change in half-life. The *N*-acetylprocainamide (NAPA) area under the plasma concentration-time curve was also significantly ($P < 0.02$) elevated by ranitidine (8.661.2 vs 9.761.3 mg l⁻¹ h) due to a reduction in renal clearance from 187630 to 168628 ml/min. The larger dose of ranitidine produced greater alterations in the procainamide and NAPA pharmacokinetics. Ranitidine reduced the absorption of procainamide by 10% and by 24% at the higher dose level.

3 Two-hourly renal clearance values of procainamide were significantly ($P < 0.05$) reduced in the 2 to 10 h period and for NAPA between 0 to 6 and 8 to 10 h. The larger ranitidine dose reduced the renal clearances of procainamide and NAPA over the control period at each 2-hourly time period. The reductions in renal clearance are most likely mediated by competition for the renal tubular cationic secretory pathway.

4 Clinical implications arising from this study suggest a reduction in procainamide dosage may be necessary in a small, select number of patients with high plasma ranitidine concentrations, e.g., the elderly; furthermore, failure of therapeutic response for some drugs may be due to ranitidine-induced impaired gastrointestinal absorption.

Keywords ranitidine procainamide renal clearance pharmacokinetics

Introduction

In therapeutics, a criterion for the selection of an histamine H₂-receptor antagonist may be the knowledge that a clinically important drug interaction is probable. Whereas cimetidine reduces hepatic drug metabolism by inhibition of cytochrome P-450 mixed function oxidases leading to reduced drug clearance (for review see Somogyi & Gugler, 1982), the recently released

more potent antagonist, ranitidine, appears not to have this property (Breen *et al.*, 1982; Feely & Guy, 1983; Reimann *et al.*, 1982; Watts *et al.*, 1983). More recent drug interactions involving the kidney have shown that cimetidine reduces the renal clearances of creatinine (Burgess *et al.*, 1982), procainamide and *N*-acetylprocainamide (NAPA) (Somogyi *et al.*, 1983) in man. The

mechanism for this interaction has been postulated to be inhibition of cationic tubular secretion of creatinine and procainamide/NAPA, the latter of which has been confirmed by the use of rabbit isolated proximal tubules (McKinney & Speeg, 1982). Ranitidine is also a base (pK_a 8.2) and has a high renal clearance (500 ml/min, McNeil *et al.*, 1981; van Hecken *et al.*, 1982) in man which is three to five times the glomerular filtration rate; hence active tubular secretion is an important mechanism for its overall elimination from the body.

The aim of this study was to investigate the influence of ranitidine on the disposition and, in particular, the renal clearance of procainamide in man, and to determine if it is an inhibitor of the active tubular cationic transport pathway.

Methods

Subjects

Six healthy subjects (five male, one female), ranging in age from 18 to 32 years and weighing between 52 and 73 kg, consented to participate in the study after being fully informed of its purpose and risks. They were judged to be in good health as assessed by physical examination and appropriate laboratory tests including ECG. They had not been taking any medication for 2 weeks prior to the study, and alcohol intake was ceased at least 3 days prior to and throughout the study period. The study was approved by the Research Review and Ethics Committees of the Royal Adelaide Hospital.

Dosage and biological fluid collection

After an overnight fast, the subjects received on two occasions, separated by 7 days, a 1 g oral dose of procainamide hydrochloride (Pro-nestyl® capsules; E. R. Squibb & Sons). On the second occasion, they received oral doses of 150 mg ranitidine (Zantac®; Glaxo Australia Ltd) 12-hourly, commencing 13 h prior to the procainamide dose. In a subsequent study, three of the previously studied subjects took oral doses of ranitidine as 300 mg 1 h prior to the procainamide dose, then 150 mg 4-hourly for 12 h (total dose 750 mg). In both studies, all subjects remained supine or seated for the first 2 h following the procainamide dose, and thereafter were either seated or ambulant but confined to the laboratory. Both blood pressure and pulse rate were recorded at frequent intervals during each of the study periods. Food was permitted after 3 h and liquids hourly to maintain an adequate urine flow rate.

Blood samples (5 ml) were taken from an intravenous indwelling catheter placed in a forearm vein at the following times: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after the procainamide dose. Urine was collected in 2-hourly periods up to 12 h, then 12 to 24 and 24 to 48 h. The volume and pH of urine were recorded and stored with the plasma samples at -20°C prior to analysis.

Assays

Procainamide and NAPA were analysed in plasma and urine by the h.p.l.c. method of Stearns (1981). Minor modifications of the mobile phase allowed separation of procainamide, NAPA and internal standard (*N*-propionyl-procainamide) from the potentially interfering compound, caffeine. Ranitidine did not interfere with the assay. Intra- and inter-day assay coefficients of variation were less than 5% for both procainamide and NAPA. Ranitidine was measured in the plasma samples by a slight modification of a cimetidine h.p.l.c. assay (Cohen *et al.*, 1980). Conversion factors to S.I. units are procainamide 4.25, NAPA 3.61, and ranitidine 3.18.

Pharmacokinetic calculations and statistical analyses

Pharmacokinetic symbols and calculations were based upon those suggested by Rowland & Tucker (1982). The maximum plasma concentration ($C_{\max}$) and the time of its occurrence ($t_{\max}$) were taken from the measured values. The area under the plasma concentration-time curve up to the last sampling time (AUC^{12}_0) was calculated by the linear trapezoidal method, and the area to infinity (AUC) was calculated as AUC^{12}_0 plus C_{12}/λ , where C_{12} is the plasma concentration at 12 h and λ , the slope of the terminal exponential phase which was determined by linear regression analysis of the terminal data points. The half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda$. Renal clearance was determined by the amount excreted divided by the area under curve for each of the six 2-hourly periods and also from zero to 12 h. The parameter CL_H/F was assigned as the ratio of the metabolic clearance of procainamide (CL_H) to the fraction (F) of dose absorbed. This was calculated as dose (D) divided by AUC minus CL_R , with F being assigned the value of the combined cumulative excretion of procainamide and NAPA.

Differences in pharmacokinetic parameters between study periods were analysed for statistical significance by the non-parametric

Wilcoxon matched-pairs signed-ranks test (Daniel, 1978), and correlations between pharmacokinetic parameters and urine flow rate and pH were determined by the Spearman rank correlation coefficient (Daniel, 1978). All data are tabulated as mean $\pm$ s.d.

Results

Ranitidine induced alterations in the pharmacokinetics of procainamide. Figure 1 shows the mean plasma concentrations of procainamide and NAPA when procainamide was given alone and when co-administered with the 150 mg twice daily dose of ranitidine. Table 1 summarises the effects of this dose of ranitidine on the calculated pharmacokinetic parameters of procainamide. There was no difference in maximum concentration, time to maximum and half-life ($P > 0.05$); however, the AUC^{12}_0 and AUC were significantly ($P = 0.016$) increased by 14.4 ± 8.6 and $13.9 \pm 7.9\%$, respectively. The overall renal clearance between 0 and 12 h was reduced by

Figure 1 Mean plasma concentration-time profiles for procainamide (O ●) and NAPA (□ ■) when procainamide was given alone (O □) and when co-administered with 150 mg ranitidine (● ■) in six subjects.

$18.6 \pm 4.5\%$ ($P = 0.016$) and the parameter CL_H/F was also significantly ($P = 0.016$) reduced by $21.6 \pm 18.5\%$ by ranitidine. Commensurate with these reductions in clearance, both the amounts of procainamide excreted to 12 and to 48 h were significantly reduced ($P = 0.016$) by ranitidine, the latter by a mean of $9.1 \pm 2.8\%$ (Table 1). Table 2 lists the effects of ranitidine on the pharmacokinetic parameters of NAPA generated from procainamide. The AUC^{12}_0 was significantly ($P = 0.016$) increased by $14.0 \pm 13.0\%$ and renal clearance of NAPA over the 12 h period was reduced by $11.1 \pm 6.2\%$ ($P = 0.016$). The combined urinary excretion of procainamide and NAPA decreased from 77.8 ± 7.8 to $70.8 \pm 6.9\%$ of dose ($P = 0.016$). In this part of the study, the average ranitidine plasma concentration over the 12 h blood sampling period was 0.18 ± 0.04 mg/l (range 0.12 to 0.22 mg/l).

In the three subjects subsequently studied on the much higher ranitidine dose, the AUC of procainamide increased by an average of $20.8 \pm 5.4\%$ and its renal clearance was reduced from 366 ± 43 to 236 ± 10 ml/min, an average reduction of 35%. As well, the amount of procainamide excreted in urine to 48 h was reduced from 62 ± 9 to $48 \pm 4\%$. The NAPA AUC^{12}_0 increased from 8.3 ± 0.5 to 9.3 ± 1.6 mg l⁻¹ h and its renal clearance was reduced from 189 ± 46 to 118 ± 15 ml/min. With this dose of ranitidine the combined urinary excretion of procainamide and NAPA fell from 76.0 ± 11.4 to $57.8 \pm 5.5\%$. The average concentration of ranitidine in plasma was 0.59 ± 0.14 mg/l (range 0.43 to 0.67 mg/l).

Table 3 summarises the influence of ranitidine 150 mg twice daily on the 2-hourly renal clearance values of both procainamide and NAPA. Statistically significant ($P < 0.05$) reductions in procainamide renal clearance occurred in the four periods between 2 and 10 h, and for NAPA they occurred between 0 and 6 h and in the 8 to 10 h period. When ranitidine was administered at the higher dose, the renal clearance values for both procainamide and NAPA were lower at each 2-hourly time period in each of the three subjects.

There was no statistically significant ($P > 0.05$) difference in urine flow rate between the control state and when ranitidine was administered. However, urine pH increased by an average of 0.40 pH units, from a mean of 6.11 to 6.54 pH units ($P = 0.002$). During the higher ranitidine dose there was no difference in urine flow rate or urine pH compared with the control period ($P > 0.05$). There was no statistically significant correlation ($P > 0.05$) between the renal clearances of procainamide and NAPA and

Table 1 Comparison of pharmacokinetic data for procainamide when given alone and when co-administered with 150 mg ranitidine in six subjects.

<i>Parameter</i>	<i>Procainamide</i>	<i>+ Ranitidine</i>	<i>Statistical significance (P)</i>
$t_{\max}$ (h)	1.6 ± 0.5	1.4 ± 0.5	N.S.
$C_{\max}$ (mg/l)	5.7 ± 1.0	6.6 ± 1.1	0.078
AUC^{12}_0 (mg l ⁻¹ h)	25.7 ± 0.9	29.3 ± 1.4	0.016
AUC (mg l ⁻¹ h)	27.7 ± 1.5	31.5 ± 1.8	0.016
Half-life (h)	2.76*	2.81*	N.S.
Renal clearance (ml/min)	379 ± 32	309 ± 30	0.016
CL _H /F (ml/min)	90 ± 31	67 ± 20	0.016
% Dose in urine (0–12 h)	60 ± 5	54 ± 6	0.016
% Dose in urine (0–48 h)	64 ± 6	58 ± 6	0.016

*Harmonic mean.

Table 2 Comparison of pharmacokinetic data for NAPA generated from procainamide when given alone and when co-administered with 150 mg ranitidine in six subjects.

<i>Parameter</i>	<i>NAPA</i>	<i>+ Ranitidine</i>	<i>Statistical significance (P)</i>
AUC^{12}_0 (mg l ⁻¹ h)	8.6 ± 1.2	9.7 ± 1.3	0.016
Renal clearance (ml/min)	187 ± 30	168 ± 28	0.016
% Dose in urine (0–12 h)	8 ± 1	8 ± 1	N.S.
% Dose in urine (0–48 h)	14 ± 3	13 ± 2	N.S.

Table 3. Comparison of 2-hourly renal clearance values for procainamide and NAPA when procainamide was given alone and when co-administered with 150 mg ranitidine in six subjects.

<i>Time period (h)</i>	<i>Procainamide renal clearance (ml/min)</i>		<i>NAPA renal clearance (ml/min)</i>	
	<i>Alone</i>	<i>With ranitidine</i>	<i>Alone</i>	<i>With ranitidine</i>
0–2	436 ± 94	346 ± 110	204 ± 31	$146 \pm 22^*$
2–4	366 ± 55	$279 \pm 49^*$	181 ± 29	$150 \pm 22^*$
4–6	368 ± 61	$311 \pm 50^*$	187 ± 32	$155 \pm 20^*$
6–8	418 ± 60	$331 \pm 70^*$	192 ± 36	181 ± 44
8–10	378 ± 111	$312 \pm 130^*$	189 ± 50	$171 \pm 44^*$
10–12	328 ± 79	336 ± 132	202 ± 60	188 ± 42

* $P < 0.05$

urine flow rate ($r_s = 0.0$ and 0.24 , respectively) in the 0 to 12 h period. However, in three of the subjects there were statistically significant ($P < 0.05$) correlations between procainamide renal clearance and urine flow rate ($r_s = -0.45$ to $+0.57$) and in one of the subjects between NAPA renal clearance and urine flow rate ($r_s = +0.73$). There was no statistically significant ($P > 0.05$) correlation between procainamide renal clearance and urine pH in any of the six subjects, and in only one of the subjects was there an association between NAPA renal clearance and urine pH ($r_s = 0.73$, $P < 0.05$).

There were no untoward effects experienced by the subjects arising from the study.

Discussion

This study highlights the importance of measuring ranitidine plasma concentrations when conducting drug interaction studies with ranitidine and in general for other histamine H_2 -receptor antagonists.

There appear to be two mechanisms involved in the alterations of oral procainamide disposition by ranitidine. Firstly, the renal clearance component of procainamide total clearance was reduced by ranitidine in a dose- and concentration-dependent manner. Secondly, the parameter metabolic clearance/bioavailability was also reduced in a dose-dependent manner. The change in this parameter appeared to be due to a reduction in the fraction of dose absorbed rather than a reduction in metabolic clearance. This is based upon the observation of a 10% reduction in the combined urinary excretion of procainamide and NAPA by a single dose of ranitidine and a 24% reduction when the larger dose of ranitidine was administered. Reduced acetylation of procainamide, which accounts for between 10 and 30% of its total clearance (Dutcher *et al.*, 1977; Galeazzi *et al.*, 1976) is most unlikely, as the increase in NAPA's AUC was of the same order as the reduction in its renal clearance, which accounts for 85% of NAPA total plasma clearance (Stec *et al.*, 1980). Commensurate with this hypothesis, if F were reduced by 10%, then the parameter hepatic clearance/bioavailability would decrease by 21%, which is exactly the value found. As well, if the reported procainamide bioavailability of 83% (Manion *et al.*, 1977) is used, then a 10% reduction would also lead to a 21% decrease in the hepatic clearance/bioavailability parameter. However, it is conceded that definite proof of reduced procainamide absorption can only be determined by the use of the intravenous dosage formulation; nevertheless, the available data

strongly suggests a reduction in procainamide absorption by ranitidine. This interaction in the gastrointestinal tract is dose dependent, as the reduction in absorption increased from 10 to 24% when the initial ranitidine dose was increased from 150 to 300 mg. Procainamide absorption is generally believed not to be perturbed by pharmacological or food intervention (McKnight & Murphy, 1976), although pathophysiological perturbations (e.g., elderly, heart failure) can reduce both the rate and extent of absorption (Koch-Weser, 1974; Lima, 1980). In this context, Klotz *et al.* (1983) reported a 26% reduction in diazepam absorption by ranitidine, whereas Elwood *et al.* (1983) showed an almost 70% increase in midazolam absorption, although an effect on midazolam clearance cannot be excluded. The exact mechanism by which ranitidine alters drug absorption remains unknown. Although it reduces the gastric emptying of solids in man (Scarpignato *et al.*, 1983), this would be expected to reduce the rate but perhaps not the extent of absorption. The other possibility resides in the pharmacological activity of ranitidine, in that a 150 mg dose reduced basal acid secretion by 99% (Bianchi Porro *et al.*, 1980) and nocturnal acid secretion by 90% (Walt *et al.*, 1981). It can therefore be envisaged that this and larger doses of ranitidine in healthy volunteer subjects would reduce both the volume and acidity of gastric juice to less than 10% of normal, hence potentially retarding the disintegration and dissolution of solid oral dosage formulations, leading to impaired gastrointestinal absorption. It is possible that ranitidine may reduce the absorption of a number of drugs, especially those whose absorption is formulation or pH dependent (e.g., ketoconazole; van der Meer *et al.*, 1980).

The central aim of this study was to determine whether ranitidine reduced the renal clearances of procainamide and NAPA in a similar manner to that observed for cimetidine (Somogyi *et al.*, 1983). The cimetidine induced reduction in procainamide renal clearance was on average 42% and the 150 mg dose of ranitidine produced a 19% reduction. However, when the ranitidine blood level was elevated 3.3-fold by administering 750 mg over 12 h, the reduction in procainamide renal clearance was 35%. The mechanism proposed for this interaction is postulated to be a competition for renal proximal tubular cationic transport (Somogyi *et al.*, 1983). McKinney & Speeg (1982) showed cimetidine to be a potent inhibitor of procainamide tubular secretion using a rabbit isolated perfused proximal tubule model. It is most likely that ranitidine also competes with procainamide for this secretory process, since it is a base (pK_a 8.2)

and has a renal clearance of 500 ml/min in healthy young adults (McNeil *et al.*, 1981; van Hecken *et al.*, 1982); hence it must undergo extensive proximal tubule cationic secretion, in common with other basic substances (Rennick, 1981). Although it was only the larger dose of ranitidine which produced a similar degree of reduction in procainamide renal clearance, this may be explained by the fact that at blood pH, 86% of ranitidine is in the ionized form, whereas for cimetidine it is only 20% (pKa 6.8). This working hypothesis assumes that it is the ionized form of the base which is actively transported across both the basolateral (McKinney, 1983) and apical cell (Kinsella *et al.*, 1979) membrane of the proximal tubule. If this is the case, then ranitidine is a weaker inhibitor of this (these) process(es).

Although the specificity of the organic cation secretory pathway in the kidney has been well documented (Peters, 1960; Rennick, 1981) using chemical substrates such as tetraethylammonium, there is still a paucity of data involving clinically used drugs. Cimetidine has been shown to block the tubular secretion of creatinine (Burgess *et al.*, 1982) and procainamide/NAPA in humans (Somogyi *et al.*, 1983) and animals (McKinney & Speeg, 1982). Ranitidine can now be added to this short list, although it has no influence on plasma creatinine levels in man (Langman *et al.*, 1980; Simon *et al.*, 1982).

During ranitidine administration, urine pH increased by a mean of 0.4 units, a similar phenomenon being observed for cimetidine (Somogyi *et al.*, 1983). However, there was no relationship between urine pH or flow rate and either procainamide or NAPA renal clearance. Nevertheless, in three of the subjects there were statistically significant, both positive and negative, associations between procainamide renal clearance and urine flow rate. Because of the complexity of the associations, i.e., negative and positive, and because of the low coefficient of

determination ($r^2 = 0.32$), these may have occurred by chance rather than being causative relationships. Galeazzi *et al.* (1976) demonstrated a lack of change of procainamide renal clearance under both acid and alkali load states and under varying urine flow rates.

Since the population was small and consisted of healthy volunteers, extrapolation of the data to patients needs to be made with caution. Nevertheless, ranitidine could impair the gastrointestinal absorption of some drugs, which may lead to less than optimal therapeutic response. Further, because of the narrow therapeutic indices of procainamide (Koch-Weser, 1977) and NAPA (Rodén *et al.*, 1980) in a small, select group of patients with elevated blood ranitidine concentrations — e.g., the elderly and those with liver cirrhosis (Young *et al.*, 1982) — the combination of intravenous procainamide and ranitidine could possibly result in toxic antiarrhythmic blood concentrations, necessitating dosage reduction.

In conclusion, this study demonstrates the existence of drug-drug interactions with ranitidine at the sites of the gastrointestinal tract and kidney. In future drug interaction studies involving basic drugs, it is proposed that procainamide, given as a single dose, can be used as a model substrate for investigating the clinical potential of competition for the cationic tubular secretory process in the human kidney.

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