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Comparison of the Effects of Cimetidine and Ranitidine on the Pharmacokinetics of Disopyramide in Man

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Abstract

The widely prescribed antiulcer agents cimetidine and ranitidine have the potential to affect the absorption, metabolism or renal excretion of disopyramide. This study investigated the effect of a single oral dose of cimetidine or ranitidine on the pharmacokinetics of disopyramide and mono-*N*-dealkyldisopyramide in six healthy volunteers. The treatment was conducted in a randomized cross-over design. Serum levels and urinary recoveries of disopyramide and mono-*N*-dealkyldisopyramide were assayed by HPLC.

Cimetidine significantly elevated the maximum plasma concentration of disopyramide, the area under the plasma concentration–time curve and the total amount of disopyramide excreted unchanged in the urine, but the serum profile of mono-*N*-dealkyldisopyramide was not significantly affected. The effects of ranitidine on the pharmacokinetics of disopyramide and mono-*N*-dealkyldisopyramide were not significant. The interaction between cimetidine and disopyramide occurred mainly at the site of absorption.

The results indicate that cimetidine, but not ranitidine, significantly increased the absorption of orally administered disopyramide.

Disopyramide is an effective antiarrhythmic agent with a narrow therapeutic range (Yu 1979). About 50% of the drug is excreted unchanged in the urine and 25% is excreted as the major metabolite mono-*N*-Dealkyldiso-pyramide. *N*-Dealkylation is the major pathway of hepatic metabolism and is dependent on the microsomal mixed function oxidase system (Siddoway & Woosley 1986). Active secretion at proximal tubules is involved in the renal excretion of both disopyramide and mono-*N*-dealkyldisopyramide (Aitio et al 1982; Haughey & Lima 1983; Ito et al 1992).

Cimetidine is a widely prescribed H_2 antagonist which can affect the absorption, metabolism and renal excretion of other drugs (Sorkin & Darvey 1983; Nazario 1986; Iacona et al 1989; Reynolds 1990; Hansten 1991; Sorgel et al 1992; Fletcher et al 1995).

Ranitidine is another H_2 antagonist, but one which influences the pharmacokinetics of other drugs either not at all or to a lesser extent than does cimetidine. However, ranitidine is a more potent inhibitor of acid secretion than is cimetidine and also relies on tubular transport for renal excretion and therefore also has the potential to affect the absorption and renal excretion of other drugs (Brater et al 1982; Smith & Kendall 1988; Sudoh et al 1996).

On the basis of these properties, cimetidine and ranitidine both have the potential to affect the pharmacokinetics of disopyramide. This study has investigated the influence of single clinically prescribed doses of cimetidine (400 mg) or ranitidine (150 mg) on the pharmacokinetics of disopyramide (300 mg).

Materials and Methods

Subjects

Six healthy subjects (male), 22–25 years, 51–78 kg, consented to participate in the study after being fully informed of its purpose and risks. Appropriate biochemical tests indicated that their renal and hepatic functions were in good condition. They had not been taking any medication or alcohol for 2 weeks before the study. The protocol was approved by an ethical committee in our college.

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Dosage and biological fluid collection

For monotherapy, each subject after overnight fasting was administered 300 mg disopyramide (Rythmodan, Roussel) orally as commercially available 100-mg capsules. For combined therapy, each subject was administered 300 mg disopyramide orally together with a single dose of 400 mg cimetidine (Wintidine, Winston), as commercially available 200-mg tablets, or 150 mg ranitidine (Zantac, Glaxo). Treatment was conducted in a randomized cross-over design, with two weeks for wash-out. Each subject was supplied with 100 mL water for drug administration. Food intake was allowed 2 h after drug administration. Blood samples (3 mL) were drawn 0, 0·5, 1·0, 1·5, 2·0, 3·0, 5·0, 7·0, 9·0, 11·0 and 24·0 h after dosing. All blood samples were centrifuged for 10 min at 15 000 rev min^{-1} 30 min after collection and the serum was removed and frozen at −20°C until assay. Urine was collected in two-hourly periods up to 12 h, then between 12 and 24 h and between 24 and 48 h. The volumes were measured and samples from each fraction were frozen at −20°C for later assay.

Assays

Analysis of disopyramide and mono-*N*-dealkyldisopyramide in serum and urine were performed by the HPLC method described by Norris et al (1982) with modification. The mobile phase was 30:70 acetonitrile–0·05 M sodium dihydrogen orthophosphate, pH 3, at a flow rate of 1·5 mL min^{-1}. *p*-Chlorodisopyramide was used as internal standard and quantification was based on daily calibration.

Pharmacokinetic calculation and statistical analysis

Kinetic parameters were determined by conventional methods. K_e was obtained by linear regression of serum data during the elimination phase. The area under the serum concentration–time curve (AUC) was determined by the trapezoidal rule with extrapolation from the last point to infinity. Renal clearance (CL_r) was determined from $CL_r = D_u/C_p$ where D_u is the total amount of unchanged drug excreted in the urine in a given period and C_p is the serum level at the mid point. All data are reported as means ± s.e.m. Analysis of variance was used for statistical analysis.

Results

Fig. 1 shows the serum profiles of disopyramide and mono-*N*-dealkyldisopyramide after monotherapy by administration of a single oral dose of disopyramide (300 mg) and combined therapy by administration of disopyramide (300 mg) and cimetidine (400 mg). Table 1 lists the pharmacokinetic parameters of disopyramide and mono-*N*-dealkyldisopyramide after monotherapy and combined therapy. The results indicate that cimetidine significantly elevated C_{max} (19%), AUC (9%) and D_u (20%) of disopyramide. Renal clearance of disopyramide and the parameters for mono-*N*-dealkyldisopyramide were not significantly affected. The combined recovery of disopyramide and mono-*N*-dealkyldisopyramide in urine was significantly increased from 71% to 81% of the dose. However, the ratio of mono-*N*-dealkyldisopyramide to combined recovery of disopyramide and mono-*N*-dealkyldisopyramide was reduced, almost reaching statistical significance ($P = 0.075$).

Fig. 2 shows the serum profiles of disopyramide and mono-*N*-dealkyldisopyramide after monotherapy by administration of a single oral dose of disopyramide (300 mg) and combined therapy by administration of disopyramide (300 mg) with ranitidine (150 mg). The results indicate that ranitidine has a tendency to reduce serum levels of disopyramide and mono-*N*-dealkyldisopyramide, but the results did not reach statistical significance. Renal clearance of disopyramide and mono-*N*-dealkyldisopyramide was not significantly affected.

Individual values of C_{max} and AUC for disopyramide, administered with or without cimetidine or ranitidine, are compared in Figs 3 and 4.

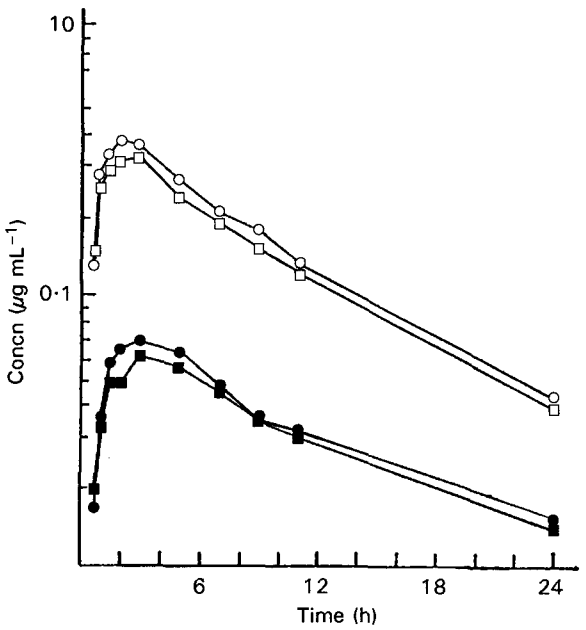

FIG. 1. Serum profiles of disopyramide (□, ○) and mono-*N*-dealkyldisopyramide (■, ●) after administration of disopyramide alone (300 mg) (□, ■) or after co-administration of disopyramide (300 mg) or cimetidine (400 mg) (○, ●).

Discussion

Disopyramide is a basic drug which undergoes almost no first-pass metabolism (Siddoway & Woosley 1986). Our data indicating that cimetidine significantly elevated C_{max}, AUC and D_u of disopyramide strongly suggest that absorption of disopyramide is increased in the presence of cimetidine. The literature reveals that cimetidine reduces the absorption of basic drugs such as antipyrine (Slusher & Vassell 1984) and ketoconazole (Van der Meer et al 1980) and increases the absorption of acidic drugs such as penicillin G (Fairfax et al 1978) and aspirin (Mackercher et al 1977; Khoury et al 1979), although the absorption of indomethacin, a water-soluble acidic drug, was inhibited by cimetidine (Howes et al 1983). There is little discussion of these diverse phenomena in the literature (Reynolds 1990). For drugs that are not water-soluble, cimetidine generally reduces the solubility of basic drugs in gastric juice and increases that of acidic drugs. Increased intragastric pH reduces the absorption of basic drugs, for example antipyrine (pK_a 1·4) and ketoconazole (pK_a 2·9) and enhances the absorption of acidic drugs, for example penicillin G (pK_a 2·8) and aspirin (pK_a 3·5; Vozeh et al 1988). For water-soluble drugs, on the other hand, dissolution in gastric juice might not be affected by pH change, although the ionization of these drugs could be influenced by the elevation of pH caused by cimetidine. For water-soluble acidic drugs, the ionization could be increased resulting in less of the non-ionized absorbable form. This could explain how cimetidine reduced the absorption of indomethacin (pK_a 4·5; Howes et al 1983). For water-soluble basic drugs, ionization could be reduced, resulting in more of the non-ionized absorbable form. Although disopyramide is a water-insoluble basic drug, its high basicity (pK_a 10·4; Vozeh et al 1988) makes it very soluble in gastric juice and dissolution might not be affected by cimetidine; however, the increased pH could significantly reduce the ionization of disopyramide and therefore increase the amount of non-ionized form, resulting in enhanced absorption. Together with previous reports, our current study further supports our proposal that solubility in water and pK_a are the two key physicochemical properties determining how cimetidine affects the absorption of a particular basic or acidic drug.

More absorption of disopyramide should result in more disopyramide in the circulation available for *N*-dealkylation. If hepatic *N*-dealkylation were not affected by cimetidine, a proportional increase in serum levels and urinary recovery of mono-*N*-dealkyldisopyramide should be observed. However, there was no significant increase in the serum profile and urinary recovery of mono-*N*-dealkyldisopyramide. Furthermore, the ratio of urinary recovery of mono-*N*-dealkyldisopyramide to total urinary recovery of disopyramide and mono-*N*-dealkyldisopyramide was reduced in combined therapy, but did not reach statistical significance ($P = 0.075$) indicating that *N*-demethylation was not significantly inhibited

Table 1. Pharmacokinetic parameters of disopyramide and mono-*N*-dealkyldisopyramide after administration of disopyramide alone (300 mg) or with cimetidine (400 mg) or ranitidine (150 mg).

Parameter	Disopyramide alone	Disopyramide + cimetidine	Disopyramide + ranitidine
Disopyramide			
Time to maximum concentration (h)	2·5 ± 0·2	2·3 ± 0·2	2·3 ± 0·3
Maximum concentration (μg mL^{-1})	3·35 ± 0·25	3·97 ± 0·22*	3·08 ± 0·41
Half-life (h)	7·2 ± 0·7	7·2 ± 0·7	6·9 ± 0·7
Area under the serum concentration–time curve (mg L^{-1} h)	38·8 ± 3·7	42·1 ± 3·10*	32·6 ± 5·8
0–8 hour clearance (mL min^{-1})	77 ± 3	95 ± 9	99 ± 12
0–12 hour clearance (mL min^{-1})	73 ± 4	84 ± 8	90 ± 12
Amount excreted unchanged in the urine (% of dose)	46 ± 2	55 ± 2**	43 ± 3
Mono-*N*-dealkyldisopyramide			
Time to maximum concentration (h)	3·2 ± 0·4	3·3 ± 0·3	3·2 ± 0·4
Maximum concentration (μg mL^{-1})	0·62 ± 0·04	0·66 ± 0·07	0·59 ± 0·06
Half-life (h)	10·7 ± 1·9	12·2 ± 1·8	9·7 ± 0·6
Area under the serum concentration-time curve (mg L^{-1} h)	10·8 ± 1·3	11·8 ± 1·1	8·1 ± 0·8
Clearance (mL min^{-1})	183 ± 12	187 ± 16	206 ± 8
Amount excreted in the urine (% of dose)	25 ± 2	27 ± 1	23 ± 1
Amount disopyramide + mono-*N*-dealkyldisopyramide excreted in the urine			
(Total amount of disopyramide and mono-*N*-dealkyldisopyramide excreted in the urine)/Dose	71 ± 2	81 ± 3**	66 ± 3 ($P = 0·083$)
(Amount of mono-*N*-dealkyldisopyramide excreted in the urine)/(Total amount of disopyramide and mono-*N*-dealkyldisopyramide excreted in the urine)	36 ± 2	33 ± 1 ($P = 0·075$)	35 ± 2

*$P < 0·05$, **$P < 0·01$, significantly different compared with disopyramide alone.

by cimetidine. The possibility of competition between cimetidine and disopyramide at the site of tubular secretion was not apparent from renal clearance data. In these respects our result is in good agreement with those of a previous study (Bonde 1991) which discovered that cimetidine given by intravenous bolus did not alter the pharmacokinetics of disopyramide.

The plasma-protein binding of disopyramide shows concentration-dependent variability within the assumed therapeutic range (Bredesen 1982). The unbound fraction increased as the concentration of disopyramide was increased. Therefore, the elevation of C_{max} of disopyramide might result in significant clinical consequence.

Combined therapy of ranitidine with disopyramide resulted in lower serum profiles of disopyramide and mono-*N*-dealkyldisopyramide than were observed for monotherapy. Interactions at hepatic or renal sites were not apparent from the data available from this study. The total recovery of disopyramide and mono-*N*-dealkyldisopyramide in urine was reduced from 71% to 66% of the dose ($P = 0·083$), indicating that ranitidine had no significant effect on the pharmacokinetics of disopyramide.

In summary, whereas cimetidine significantly increased the oral absorption of disopyramide, ranitidine had no significant effect on the pharmacokinetics of the drug.

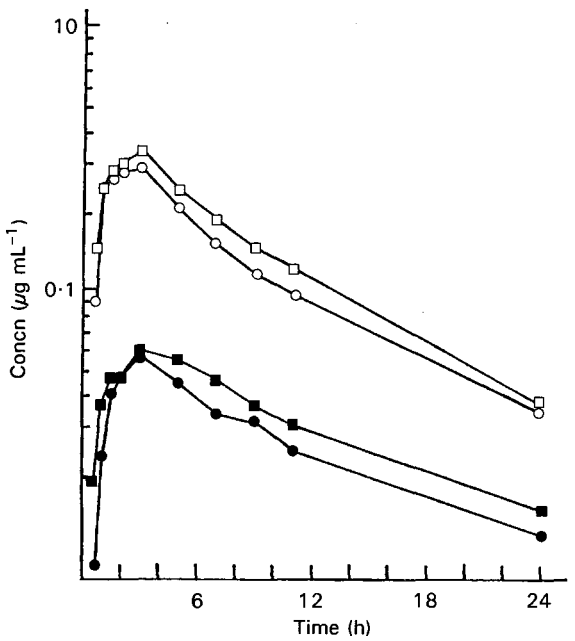

FIG. 2. Serum profiles of disopyramide (□, ○) and mono-*N*-dealkyldisopyramide (■, ●) after administration of disopyramide alone (300 mg) (□, ■) or after co-administration of disopyramide (300 mg) or ranitidine (400 mg) (○, ●).

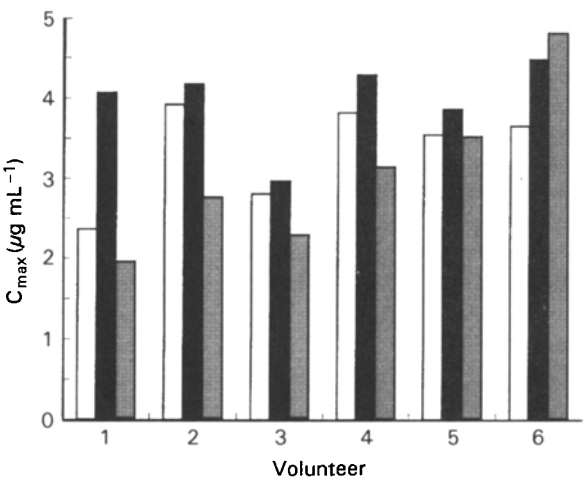

FIG. 3. Comparison of the individual disopyramide C_{max} values after administration with or without cimetidine or ranitidine. □ Disopyramide alone, ■ disopyramide + cimetidine, ■ disopyramide + ranitidine.

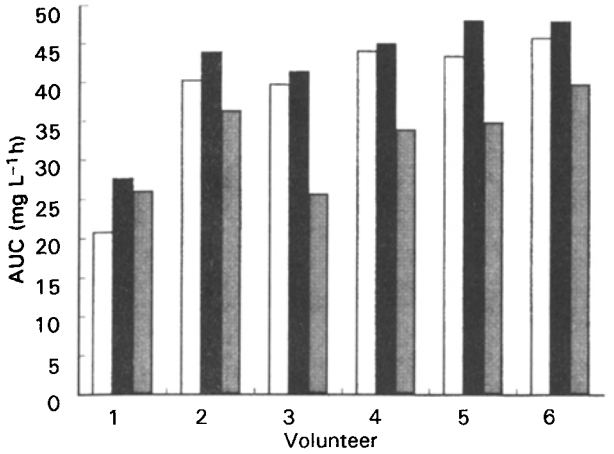

FIG. 4. Comparison of the individual disopyramide AUC values after administration with or without cimetidine or ranitidine. □ Disopyramide alone, ■ disopyramide + cimetidine, ■ disopyramide + ranitidine.

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