Stereoselective pharmacokinetics of disopyramide and interaction with cimetidine

J. BONDE¹, L. E. PEDERSEN², E. NYGAARD¹, T. RAMSING¹, H. R. ANGELO³ & J. P. KAMPMANN⁴

¹Department of Anaesthesiology and Intensive Care Medicine, KAS Herlev, ²The Royal Danish School of Pharmacy and

³Departments of Clinical Chemistry and ⁴Internal Medicine P, Bispebjerg Hospital, Copenhagen, Denmark

The pharmacokinetics of each of the enantiomers of disopyramide were examined after i.v. bolus administration of 150 mg racemic drug in a randomized cross-over study before and after the administration of cimetidine 400 mg twice daily orally. Clearance and volume of distribution (V_z) of total drug were significantly ($P < 0.001$) higher for the R-(–) enantiomer than the S-(+) enantiomer (7.9 vs 4.6 l h^{–1} and 89 vs 50 l, respectively), whereas no significant difference in half-life could be demonstrated. The clearance of free drug was significantly ($P < 0.05$) higher for the S-(+) enantiomer than that of the R-(–) enantiomer (34.6 ± 5.4 l h^{–1} vs 27.2 ± 5.6 l h^{–1}), whereas no significant enantioselective difference in unbound volumes of distribution (258 ± 38 l vs 226 ± 42 l) could be demonstrated. Coadministration of cimetidine did not alter the pharmacokinetics of disopyramide. A significant concentration- or time-related decrease in the renal clearance of each of the enantiomers measured with respect to total drug in serum was observed, whereas renal clearances of the free enantiomers were similar.

Keywords disopyramide pharmacokinetics stereoisomers cimetidine

Introduction

Disopyramide is a type IA antiarrhythmic drug used as a racemate. The enantiomers differ in their pharmacokinetic and pharmacodynamic characteristics (Giacomini *et al.*, 1986; Lima & Boudoulas, 1987; Lima *et al.*, 1990).

Cimetidine is an inhibitor of phase I drug metabolism and is known to inhibit hydroxylation and dealkylation processes in an apparently dose-dependent manner (Somogyi & Muirhead, 1987). Additionally, cimetidine is known to lower the clearance of many basic drugs including procainamide, ranitidine and flecainide, by competing for active secretion in the proximal tubule of the kidney.

The aims of this study were to examine the stereoselective disposition of disopyramide, with special reference to its renal handling, and to investigate the extent of any stereoselective interaction with cimetidine.

Methods

Seven healthy male volunteers aged 24–34 years (mean 29 years), with a mean weight of 78 kg (range 69–90 kg) entered the study. Each received an intravenous bolus dose of disopyramide (150 mg) in the absence of cimetidine and 1 h after the last dose of a 14 day treatment

with cimetidine (400 mg twice daily). The order of studies was randomised with three subjects receiving bolus doses of disopyramide prior to and 1 h after the period of cimetidine treatment and four subjects receiving bolus doses of disopyramide 1 h and 3 weeks after the period of cimetidine treatment.

Blood samples for the measurement of the enantiomers of disopyramide and its mono-dealkylated metabolite (MND) were obtained prior to and at 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 360, 420, 480, and 1440 min after dosage, which was given over a 3 min period. Urine was collected in the following periods: 0–1, 1–3, 3–6, 6–8 and 8–24 h.

The enantiomers of disopyramide and MND in serum and urine were measured by a modification of the h.p.l.c. method described by Corre *et al.* (1988). The limits of the assay for each isomer of disopyramide and MND were 0.2 $\mu\text{mol l}^{-1}$ and the intra-assay coefficients of variation (in the concentration range 0.5 – 7.6 $\mu\text{mol l}^{-1}$) were 2–6%.

Serum binding was measured by an ultrafiltration procedure. The ultrafiltration procedure underestimated the fraction unbound by approximately 5% when compared with a dialysis method (Pedersen *et al.*, 1986). pH was adjusted to 7.40 with a small volume of strong acid (HCl).

An open two-compartment model was fitted to the data for free as well as total drug concentrations using a

Gauss-Newton, non-linear least square iteration regression procedure on an HP-1000 computer.

Clearances of each enantiomer (free and total) were calculated from Dose/AUC. Half-lives ($t_{1/2}$) were estimated by linear regression of the log serum drug concentration-time curve. Volume of distribution (V_z) was calculated as $CL \times t_{1/2}/\ln 2$.

The data were analysed by paired/unpaired *t*-tests and ANOVA. Pearson's *r*-values were used in the regression analysis. A *P* value < 0.05 was considered significant.

Informed consent to the study, which was approved by the Local Ethics Committee, was obtained from all of the subjects.

Results

Disposition kinetics of the enantiomers of disopyramide measured in terms of total serum drug concentration

Clearance and V_z of the R(-) enantiomer of disopyramide were significantly greater than those of the S(+) enantiomer ($P < 0.001$), while no significant difference was observed in values of half-life (Table 1).

Coadministration of cimetidine did not change any of the pharmacokinetic parameters.

Disposition kinetics of the enantiomers of disopyramide measured in terms of unbound serum drug concentration

The clearance of the S(+) enantiomer was significantly greater than that of the R(-) enantiomer, whereas no significant differences were observed in Vu_z and $t_{1/2,z}$ (u) (Table 1). Cimetidine did not alter the disposition of disopyramide measured in terms of unbound drug.

By comparing the regression lines for concurrent values of serum concentrations of each of the enantiomers and the free fractions it was evident that the protein binding of the S(+) enantiomer was significantly ($P < 0.001$) higher at all serum concentrations than that of the R(-) enantiomer. A concentration-dependent protein binding was observed for both of the enantiomers (intercepts and slopes for the R(-) and S(+) enantiomers: 32.7 ± 9.2 ; -1.7 ± 7.1 and 6.7 ± 1.3 ; 5.7 ± 1.5 , respectively).

Comparing the differences between the intercepts and slopes from the individual regression lines of the total serum concentrations vs the free fraction of the R(-) and S(+) enantiomer, respectively (3.2 ± 11.3 ; 0.2 ± 9.2 and 1.0 ± 2.7 ; 0.1 ± 1.5 ; (NS)) it was evident that cimetidine does not alter the protein binding of either of the enantiomers.

The renal clearances of each of the enantiomers in terms of free and total drug without cimetidine administration are shown in Table 2. The renal clearance of total drug in the terminal urine collection period was significantly less than in the first period for both of the enantiomers, whereas no significant concentration or time-related decrease was evident in terms of free renal clearance.

Coadministration of cimetidine did not alter renal clearance values.

Table 1 Pharmacokinetic parameters of the enantiomers of disopyramide before and after 2 weeks treatment with cimetidine 400 mg twice daily orally

	<i>Before</i>		<i>After</i>	
	<i>R</i> -(-)	<i>S</i> -(+)	<i>R</i> -(-)	<i>S</i> -(+)
CL (l h ⁻¹)	7.9 ± 1.8	4.6 ± 1.1	8.2 ± 1.3	4.7 ± 1.0
	$P < 0.001$		$P < 0.001$	
CL _u (l h ⁻¹)	27.2 ± 5.6	34.6 ± 5.4	27.5 ± 3.7	35.3 ± 6.2
	$P < 0.05$		$P < 0.02$	
V _z (l)	89 ± 12	50 ± 13	90 ± 18	47 ± 8
	$P < 0.001$		$P < 0.001$	
Vu _z (l)	226 ± 42	258 ± 38	213 ± 33	244 ± 30
	NS		NS	
<i>t</i> _{1/2,z} (min)	452 (381–621)	447 (378–533)	442 (355–586)	420 (289–520)
	NS		NS	
<i>t</i> _{1/2,z} (u) (min)	378 (260–463)	297 (267–347)	320 (231–416)	297 (260–347)
	NS		NS	
	all NS			

Table 2 Renal clearances (total and free) of the R(-)- and S(+)-isomers of disopyramide (mean ± s.d.; ml min⁻¹)

Time (h)	CL _R (R)	CL _R (S)	CLu _R (R)	CLu _R (S)
0-1	119 ± 24	62 ± 15	359 ± 150	409 ± 120
1-3	97 ± 28	48 ± 12	321 ± 94	329 ± 72
3-6	81 ± 19	42 ± 11	280 ± 53	302 ± 86
6-8	81 ± 34	33 ± 12	235 ± 101	243 ± 30
8-24	60 ± 25	28 ± 11	277 ± 140	306 ± 144

Discussion

Our observations of a significantly higher clearance and volume of distribution (in terms of total drug) of the R(-) isomer, when disopyramide is administered as a racemate, are consistent with those of Giacomini *et al.* (1986).

Contradictory findings with respect to the kinetics of free drug have been reported (Giacomini *et al.*, 1986; Lima & Boudoulas, 1987). Our observation of a greater unbound clearance of the S(+) enantiomer is in accordance with the finding of Lima & Boudoulas (1987).

Coadministration of cimetidine administered orally 400 mg twice daily for 2 weeks did not alter the pharmacokinetics of disopyramide in terms of either bound or unbound drug after a single 150 mg i.v. dose.

Interactions with cimetidine have been demonstrated in studies with other antiarrhythmic drugs. Thus, significant decreases in the clearance of lignocaine (30%) (Bauer *et al.*, 1984) and procainamide (43% decrease in

renal clearance) and its major metabolite *N*-acetylprocainamide have been reported (Somogyi *et al.*, 1983). In contrast, no significant interactions were found between mexiletine and cimetidine (Klein *et al.*, 1985).

The present study should have disclosed any interaction, as the onset of a metabolic inhibition with cimetidine is generally rapid (24 h) and is expected to return to baseline values within 2–3 days after stopping cimetidine (Somogyi & Muirhead, 1987). Cimetidine does not seem to influence the kinetics of free disopyramide indicating that no inhibition of its hepatic metabolism or renal tubular secretion occurs.

Radioactive disopyramide was generously supplied by G. D. Searle.

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