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Stereoselective disposition of flecainide in relation to the sparteine/debrisoquine metaboliser phenotype

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1 The disposition of the enantiomers of the antiarrhythmic drug flecainide has been studied in five extensive (EM) and five poor (PM) metabolisers of sparteine/debrisoquine after administration of 50 mg of racemic flecainide acetate under conditions of high urinary flow rate and acidic urinary pH.

2 In the EM subjects there were no significant differences in the oral clearance, half-life or urinary excretion of (+)-S- and (−)-R-flecainide.

3 In the PM subjects differences in the pharmacokinetics of S- and R-flecainide were observed. The oral clearance of R-flecainide (467 ± 109 ml min^{-1}) was less ($P < 0.03$) than that of the S-enantiomer (620 ± 172 ml min^{-1}). The half-life of R-flecainide (12.9 h) was longer ($P < 0.03$) than that of S-flecainide (9.8 h). The renal clearance of the two enantiomers was, however, comparable and similar to that observed in the EM subjects. The urinary recovery of R-flecainide (15.6 ± 3.7 mg) was greater ($P < 0.03$) than that of the S-enantiomer (12.0 ± 3.7 mg). The enantioselective disposition observed in PMs is therefore due to greater impairment in the metabolism of R- than S-flecainide.

4 The urinary recoveries of two major metabolites of flecainide, *meta-O*-dealkylated flecainide (MODF) and the *meta-O*-dealkylated lactam of flecainide (MODLF) were lower ($P < 0.05$) in PMs, 12.0% ± 3.1% and 8.2% ± 3.2% of the dose administered, respectively, than in EMs of 17.7% ± 3.3% and 16.5% ± 3.3%, respectively.

5 One PM subject had a greatly diminished flecainide metabolic capacity and a rare genotype, as assigned by XbaI RFLP analysis.

Keywords flecainide enantiomers sparteine polymorphism pharmacokinetics metabolism

Introduction

Flecainide is a Class 1C antiarrhythmic agent which is being used increasingly in the treatment of ventricular and various supraventricular arrhythmias (Holmes & Heel, 1985; Roden & Woosley, 1986). In up to 20% of patients, pro-arrhythmic effects occur which in some cases are associated with very high flecainide plasma concentrations (Salerno *et al.*, 1986). Flecainide elimination is impaired in patients with renal failure (Braun *et al.*, 1987; Forland *et al.*, 1988), hepatic disease (McQuinn *et al.*, 1988) and congestive heart failure (Nitsch *et al.*, 1987; Cavalli *et al.*, 1988). It has been established recently that the metabolism of flecainide cosegregates with that of sparteine/debrisoquine (Beckmann *et al.*, 1988; Mikus *et al.*, 1989), and it may be concluded that flecainide is metabolised by cytochrome P450IID6. A genetic polymorphism has

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been observed in the oxidative metabolism of drugs catalysed by this isoenzyme, and 5–10% of the Caucasian population, known as poor metabolisers (PMs), have a deficiency of hepatic P450IID6 (Zanger *et al.*, 1988; Gonzalez *et al.*, 1988). Compared with the remainder of the population, who are termed extensive metabolisers (EMs), the PMs have an impaired ability to metabolise more than 20 drugs which have been identified as substrates for this isoenzyme (Eichelbaum, 1988a). At least three mutant alleles for the gene encoding for the synthesis of cytochrome P450IID6 have been identified in PMs (Gonzalez *et al.*, 1988). The alleles of the P450IID6 gene associated with the PM phenotype have been defined using restriction fragment length polymorphism analysis (RFLP) of genomic DNA (Skoda *et al.*, 1988).

Flecainide is marketed as a racemic mixture of (−)-R- and (+)-S-enantiomers (Blaschke *et al.*, 1985). No differences in the antiarrhythmic activity of the enantiomers of flecainide have been observed in animal models (Banitt *et al.*, 1986). However no information on whether other pharmacological effects or side effects show stereoselectivity has been published. Poor metabolisers, in addition to showing deficient metabolism, can also exhibit diminished substrate or product enantioselectivity for the metabolic reactions catalysed by cytochrome P450IID6. For example, after administration of racemic metoprolol in extensive metabolisers plasma concentrations of the more active S-enantiomer are appreciably higher than those of R-metoprolol, whereas in PMs S-metoprolol concentrations are slightly lower than those of the R-enantiomer (Lennard *et al.*, 1983). The stereoselective disposition observed in EMs for *N*-propylajmaline is also absent in poor metabolisers (Zekorn *et al.*, 1985). Metabolism to 4-hydroxydebrisoquine after debrisoquine administration in EMs results almost exclusively in formation of the S-enantiomer. In PMs there is not only a greatly diminished synthesis of this metabolite, but also a substantial proportion of the 4-hydroxydebrisoquine is excreted as the R-enantiomer (Eichelbaum *et al.*, 1988). Our study of flecainide disposition in EMs and PMs has been extended to determine whether the disposition of flecainide is stereoselective and if there are differences in enantioselectivity between the two oxidation phenotypes as has been observed for other P450IID6 substrates. In addition the RFLP XbaI genotype of the PM and EM subjects has been determined to examine whether genotype differences can account for some of the interindividual variation in flecainide disposition observed in PMs.

The metabolism of flecainide in humans has been studied by McQuinn *et al.* (1984). The most important routes of metabolism identified are shown in Figure 1. Up to 50% of the dose is excreted in the urine as unchanged drug, the rate of urinary excretion being dependent on urinary pH (Muhiddin *et al.*, 1984). The major urinary metabolites identified in humans are *meta-O*-dealkylated flecainide (MODF), and the *meta-O*-dealkylated lactam of flecainide (MODLF). Both oxidative metabolites are excreted in the urine as conjugates. As poor metabolisers of

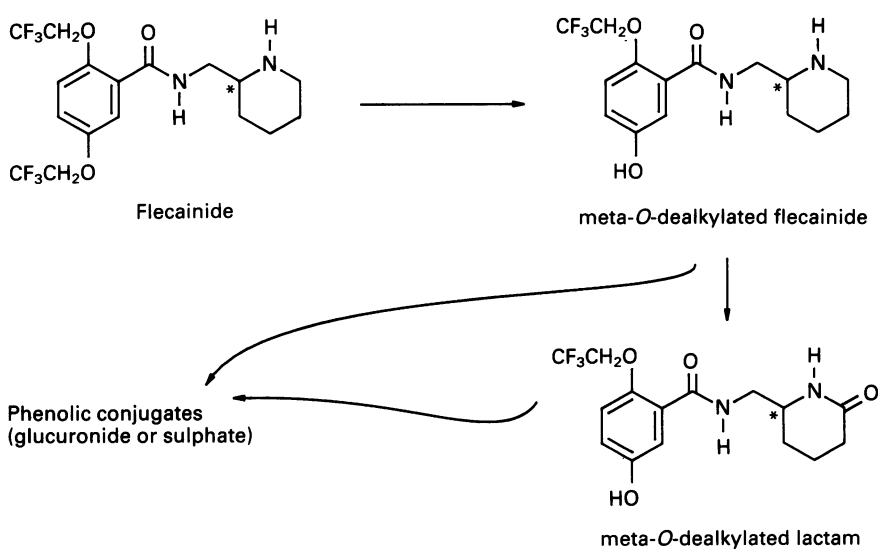

Figure 1 The major routes of metabolism of flecainide. The asterisk denotes the centre of chirality.

sparteine have an impaired nonrenal clearance of flecainide, at least one of the pathways of oxidative flecainide metabolism must be impaired in PMs. In order to examine which routes of flecainide metabolism are catalysed by cytochrome P450IID6 and thus impaired in poor metabolisers of sparteine relative to extensive metabolisers, the urinary excretion of MODF and MODLF has been measured in the subjects studied.

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Methods

Subjects and sample collection

Ten young healthy volunteers, five extensive and five poor metabolisers of sparteine, were administered a 50 mg dose of racemic flecainide acetate orally in solution (Tambocor®) 1 h after a normal breakfast. A high urinary flow rate and low urinary pH were maintained for 12 h prior to and 60 h following flecainide by administration of 500 ml fluid and 2 g of ammonium chloride every 4 h. The study protocol was approved by the local ethics committee and has been described in detail previously (Mikus *et al.*, 1989). Characteristics of the individual subjects are given in Tables 1 and 2. Blood samples were withdrawn at timed intervals for 60 h after flecainide administration and the plasma was stored frozen at −20° C until assayed. Urine samples were also collected at timed intervals over 60 h, the pH measured and aliquots stored frozen pending analysis. Blood pressure, heart rate and ECG were monitored for 0.5 h prior to and 4 h following flecainide administration. However, no significant changes were observed.

Flecainide plasma assay

The plasma concentrations of (−)-R- and (+)-S-flecainide were measured by gas chromatography-mass spectrometry (Fischer *et al.*, 1989). Briefly, the enantiomers of flecainide were resolved as their PFPA derivatives using chiral gas chromatography and detection by mass spectrometry in negative ion chemical ionisation mode. A resolution factor of 1.1 was achieved using the Chirasil Val Capillary column (25 m, Chrompack, Netherlands).

Table 1 Pharmacokinetic parameters of (−)-R- and (+)-S-flecainide acetate (50 mg oral racemic solution) in five extensive metabolisers of sparteine/debrisoquine

Subject	*Sex*	*Weight (kg)*	*Ae (mg)*	$t_{1/2,ur}$ *(h)*	*AUC (ng ml^{-1} h)*	$t_{1/2z}$ *(h)*	*CL_o (ml min^{-1})*	*CL_R (ml min^{-1})*
(−)-R-Flecainide								
1	M	60	7.9	8.9	384	8.1	952	344
2	M	63	6.0	6.1	452	7.4	809	223
3	M	74	8.2	7.6	439	7.8	833	313
4	M	61	7.6	8.8	630	8.3	581	202
5	M	63	9.4	8.2	550	6.5	666	287
Mean		64	7.9	7.8*	491	7.5*	768	274
± s.d.		6	1.2		98		146	60
(+)-S-Flecainide								
1			7.4	8.9	435	7.4	842	285
2			6.4	6.8	452	6.9	810	236
3			8.6	8.4	356	8.1	1027	403
4			9.2	9.6	565	8.7	648	273
5			8.6	8.1	571	6.5	641	252
Mean			8.1	8.3*	476	7.4*	793	290
± s.d.			1.1		91		159	66
P value**			0.655	0.317	0.655	0.655	0.655	0.655

* harmonic mean.
** Friedman two way analysis of variance: R *vs* S.
Ae = amount excreted in urine; $t_{1/2,ur}$ = elimination half-life in urine; AUC = area under the plasma concentration-time curve; $t_{1/2z}$ = elimination half-life in plasma; CL_o = oral clearance; CL_R = renal clearance.

Table 2 Pharmacokinetic parameters of (−)-R- and (+)-S-flecainide acetate (50 mg oral racemic solution) in five poor metabolisers of sparteine/debrisoquine

Subject	Sex	Weight (kg)	Ae (mg)	$t_{1/2,ur}$ (h)	AUC (ng ml^{-1} h)	$t_{1/2z}$ (h)	CL_o (ml min^{-1})	CL_R (ml min^{-1})
(−)-R-Flecainide								
1	F	52	13.2	14.2	863	12.9	424	255
2	F	69	20.8	14.9	1133	12.4	323	307
3	F	71	16.5	9.3	839	12.8	436	329
4	M	71	16.3	12.3	617	10.5	593	439
5	M	75	11.1	17.2	656	18.1	557	281
Mean		68	15.6	13.0*	822	12.9*	467	322
± s.d.		9	3.7		205		109	71
(+)-S-Flecainide								
1			10.2	11.6	626	8.8	585	271
2			17.8	12.7	985	11.2	371	301
3			12.7	8.1	627	9.0	584	338
4			11.7	10.3	492	8.4	743	395
5			7.8	13.1	449	12.5	816	289
Mean			12.0	10.8*	636	9.8*	620	319
± s.d.			3.7		211		172	49
P value**			0.025	0.025	0.025	0.025	0.025	0.655

* harmonic mean.
** Friedman two way analysis of variance: R *vs* S.
Ae = amount excreted in urine; $t_{1/2,ur}$ = elimination half-life in urine; AUC = area under the plasma concentration-time curve; $t_{1/2z}$ = elimination half-life in plasma; CL_o = oral clearance; CL_R = renal clearance.

Flecainide metabolites in urine

Meta-O-*dealkylated flecainide and* meta-O-*dealkylated lactam of flecainide* A common extraction and GC/MS analysis was developed for the measurement of both metabolites (Fischer *et al.*, 1989). The PFPA derivatives of MODF and MODLF were assayed as the racemates using a SE 52 capillary column (CS-Chromatographic Service, GmbH, FRG).

Flecainide urine assay

The flecainide enantiomers were measured in urine by normal phase h.p.l.c. after formation of diastereoisomers with (−)-menthyl chloroformate. The chromatographic system comprised a silica gel 250 × 4.6 mm column (Hypersil 3 μm, Shandon, England). The mobile phase was hexane 98.75:2-butanol 1:acetonitrile 0.25 (flow rate 1.0 ml min^{-1}). The native fluorescence of the flecainide diastereoisomers was utilised for measurement (RF 530 Fluorescence Detector, Shimadzu Corporation, Kyoto Japan; excitation wavelength 290 nm, emission wavelength 340 nm). Aliquots (200–500 μl) of urine samples were mixed with 300 ng of the internal standard *N*-(2-piperidyl-methyl)-2,5,-bisethoxybenzamide acetate (S 15277), a nonfluorinated analogue of flecainide, 500 μl 2.5 N NaOH saturated with NaCl and extracted on a head-to-tail mixer with 5 ml ethyl acetate for 10 min. The organic phase was transferred to glass conical tubes and evaporated to dryness under N_2. The residue was reconstituted in 10 μl pyridine and 1 μmol (200 μl) of (−)-menthyl chloroformate (Aldrich GmbH, FRG) in toluene was added. After mixing thoroughly the reaction mixture was allowed to stand overnight at room temperature. Distilled water (1 ml) and hexane (3 ml) were then added and after extraction for 10 min and centrifugation (2000 rev min^{-1}, 10 min), the organic phase was evaporated to dryness under nitrogen. The residue was reconstituted in 300 μl of mobile phase and 100 μl was injected into the chromatographic system. The retention times of the R- and S-flecainide derivatives were 18.5 and 20.3 min, respectively. The derivatives of the racemic internal standard eluted at 41.0 and 43.4 min. For each enantiomer standard curves were linear over the range 250 to 5000 ng ml^{-1} and the limit of sensitivity of the assay was

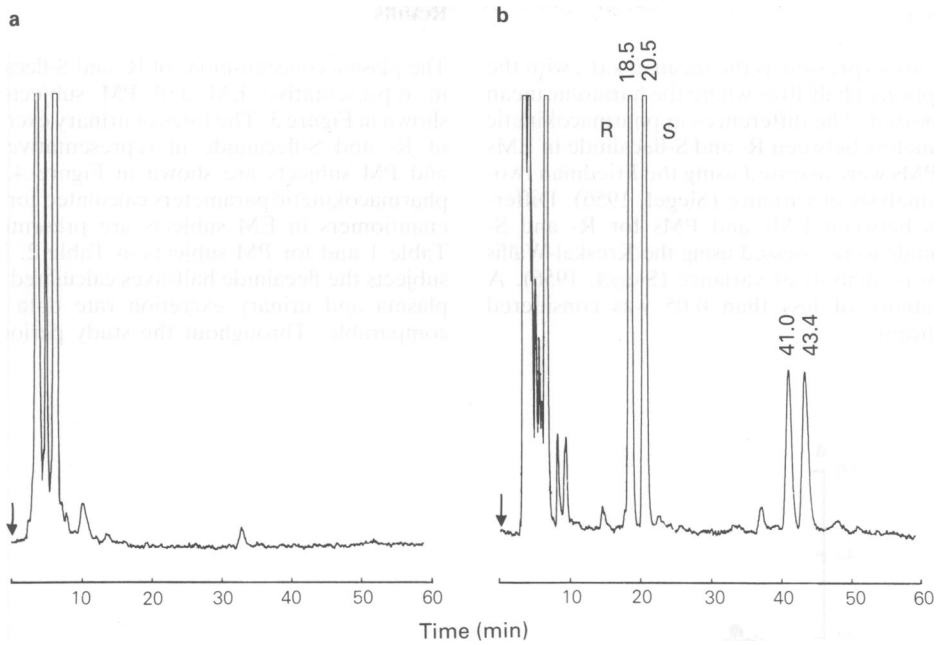

Figure 2 Typical chromatograms of urine samples from a PM subject (a) before and (b) after flecainide administration, containing 603 ng ml^{-1} R-flecainide and 562 ng ml^{-1} S-flecainide. The derivatives of R- and S-flecainide eluted with retention times of 18.5 and 20.5 min, respectively, and the derivatives of the racemic internal standard eluted at 41.0 and 43.4 min.

25 ng ml^{-1}. At a concentration of 1000 ng ml^{-1} racemic flecainide, the within-day reproducibilities (n = 10) of the assay of R- and S-flecainide were 502 ± 12 ng ml^{-1}, C.V. 2.3% and 486 ± 8.0 ng ml^{-1}, C.V. 1.7%, respectively. The between-day reproducibility of the determination of flecainide at a concentration of 500 ng ml^{-1} was 498 ± 14 ng ml^{-1}, C.V. 2.7% (n = 9), and at a concentration of 5000 ng ml^{-1} was 4849 ± 192 ng ml^{-1}, C.V. 3.9% (n = 8). This method has been verified against both h.p.l.c. and GC/MS techniques for racemic flecainide. Representative chromatograms of urine samples from a PM subject before and after flecainide administration are shown in Figure 2.

Genotype assignment

Genomic DNA was isolated from peripheral leukocytes obtained from whole blood samples from each subject. The DNA was digested to completion with the restriction endonuclease XbaI, and the method of Skoda *et al.* (1988) was used to determine the restriction fragment length polymorphism utilising the cDNA of cytochrome P450IID6. Genotype was assigned according to the presence of fragments of differing kilobase length.

Data treatment

The plasma concentration-time data of R- and S-flecainide in each subject were fitted by a one compartment open model with first order absorption using nonlinear least squares regression (Peck & Barrett, 1979). The area under the curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to infinity. The urinary half-life ($t_{½ur}$) was calculated by least squares regression analysis of the terminal slope of the log of the rate of urinary excretion *vs* time data. Flecainide bioavailability was assumed to be 1 (Conard & Ober, 1984). Oral clearance (CL_o) was calculated as the dose divided by AUC. Flecainide renal clearance (CL_R) and the clearance to the sum of the metabolites MODF and MODLF (CL_m) were calculated as the amount of flecainide or metabolites excreted in the urine divided by the AUC. Nonrenal clearance (CL_{NR}) was calculated as the difference between oral clearance and renal clearance.

Statistics

Data are expressed as the mean ± s.d., with the exception of half-lives where the harmonic mean is reported. The differences in pharmacokinetic parameters between R- and S-flecainide in EMs and PMs were assessed using the Friedman two-way analysis of variance (Siegel, 1956). Differences between EMs and PMs for R- and S-flecainide were assessed using the Kruskal-Wallis one way analysis of variance (Siegel, 1956). A probability of less than 0.05 was considered significant.

Results

The plasma concentrations of R- and S-flecainide in representative EM and PM subjects are shown in Figure 3. The rates of urinary excretion of R- and S-flecainide in representative EM and PM subjects are shown in Figure 4. The pharmacokinetic parameters calculated for both enantiomers in EM subjects are presented in Table 1 and for PM subjects in Table 2. In all subjects the flecainide half-lives calculated from plasma and urinary excretion rate data were comparable. Throughout the study period the

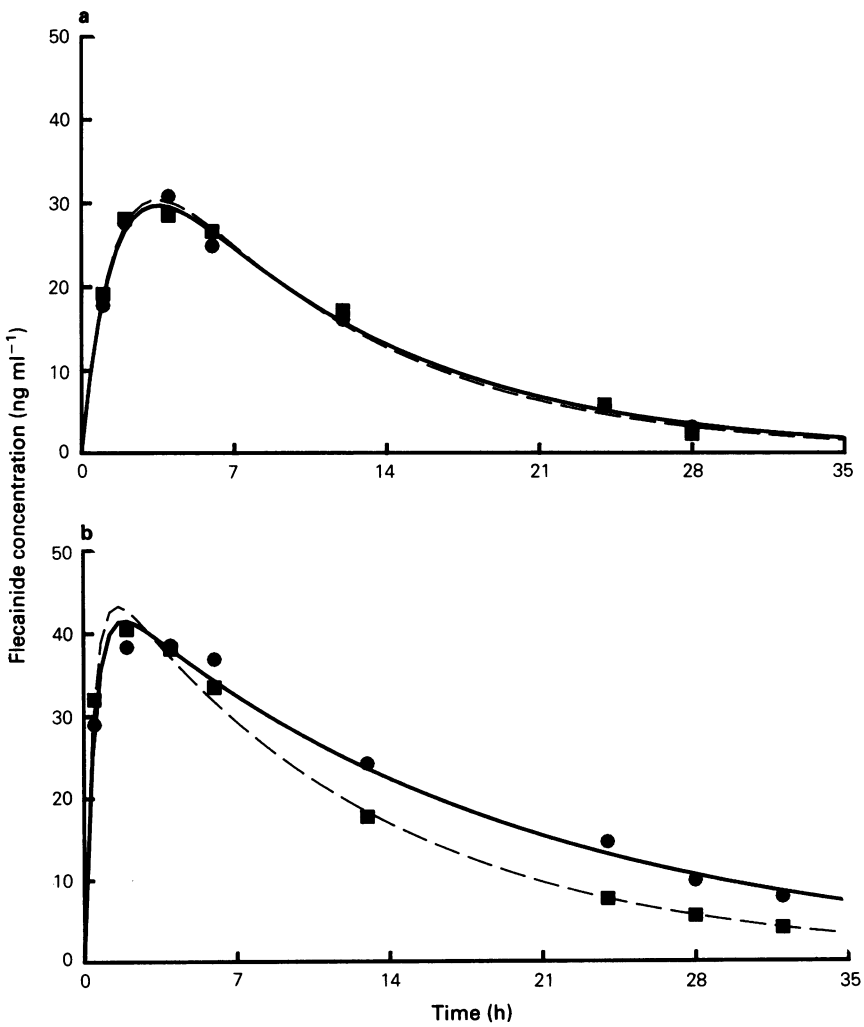

Figure 3 R-(●) —— and S-(■) ---- plasma flecainide concentrations in (a) an EM and (b) a PM subject following oral administration of 50 mg R/S flecainide acetate under conditions of high urinary flow and acidic urinary pH.

concentrations of the enantiomers of flecainide were comparable in EM subjects. Consequently the AUC, oral clearance and terminal half-life values were not significantly different for R- and S-flecainide (Table 1). Over the 60 h urine collection interval 31.6% of the dose of R-flecainide and 32.4% of the dose of the S-enantiomer were recovered in EM subjects. The renal clearance of the two enantiomers did not differ in the extensive metabolisers.

In poor metabolisers the initial plasma concentrations of both enantiomers were comparable, however, with time in each subject higher concentrations of the R-enantiomer were found. The AUC for R-flecainide was greater ($P < 0.05$) than that of S-flecainide, and the oral clearance of the R-enantiomer was lower than that of the S-enantiomer (Table 2). In each PM subject the urinary recovery of unchanged R-flecainide was greater than that of S-flecainide. The half-life of R-flecainide was longer ($P < 0.03$) than that of S-flecainide. The renal clearance of both flecainide enantiomers was comparable in the PMs (R: 322 ± 71 ml min^{-1}, S: 319 ± 49 ml min^{-1}).

Significant differences in the disposition of the flecainide enantiomers were observed between the extensive and poor metabolisers. Greater differences between EMs and PMs were observed for R- than S-flecainide. For R-flecainide the AUC was lower ($P < 0.02$) in EMs (491 ± 98 ng ml^{-1} h) than in PMs (822 ± 205 ng ml^{-1} h).

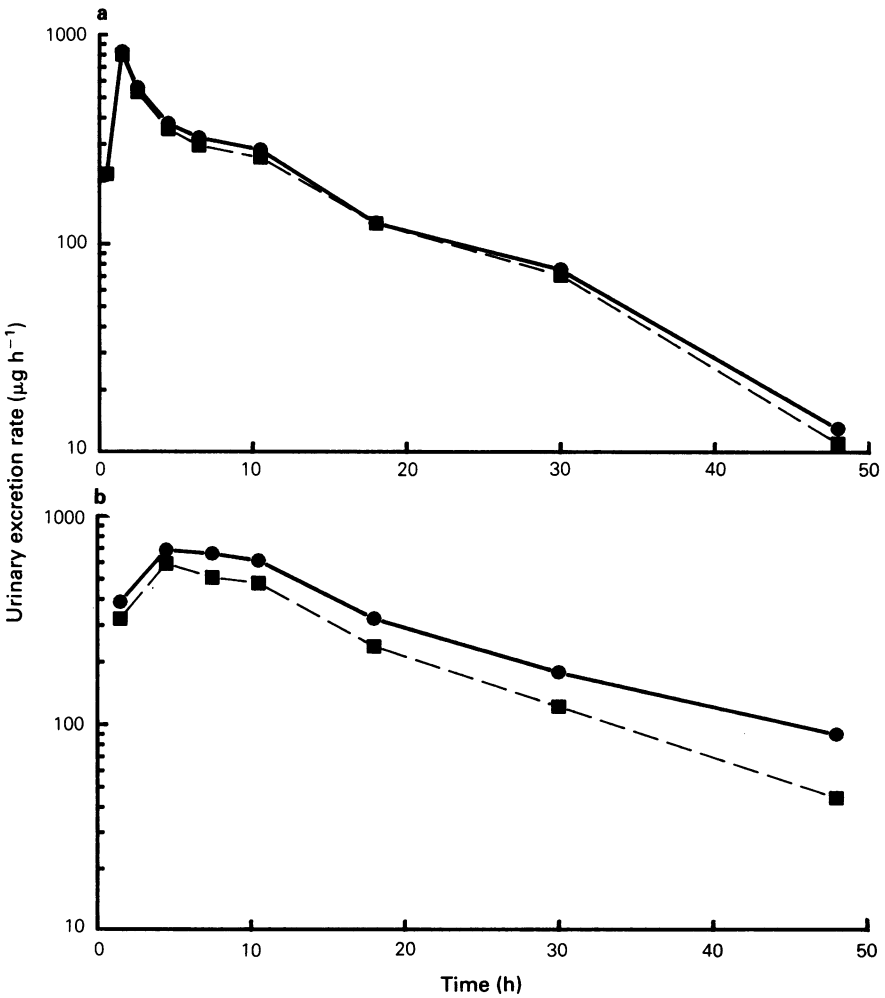

Figure 4 Rate of urinary excretion of R-(●) —— and S-(■) ---- flecainide in representative (a) EM and (b) PM subjects following oral administration of 50 mg R/S flecainide acetate under conditions of high urinary flow rate and acidic urinary pH.

Table 3 Nonrenal clearances of (−)-R- and (+)-S-flecainide acetate (50 mg oral racemic solution) in five poor and five extensive metabolisers of sparteine/debrisoquine in relation to their metabolic ratio and genotype assigned using XbaI RFLP analysis

Subject	*MR*	*XbaI (kb)*	CL_{NR} *(ml min^{-1})* (−)-*R-flecainide*	(+)-*S-flecainide*
EM subjects				
1	0.54	29/29	609	556
2	0.52	29/29	586	574
3	0.24	29/29	520	624
4	0.40	29/29	379	376
5	0.73	29/29	379	389
Mean			495	504
± s.d.			110	114
PM subjects				
1	38.6	44/29	169	314
2	129.8	11.5/11.5	16	70
3	80.0	44/29	107	246
4	173.3	44/29	154	349
5	85.2	29/29	276	527
Mean			144	301
± s.d.			95	166
P value*			0.009	0.028

* Kruskal-Wallis analysis of variance: EM *vs* PM.
MR = metabolic ratio of sparteine; XbaI = result of RFLP analysis with XbaI; CL_{NR} = nonrenal clearance.

For S-flecainide the difference in AUC was not significant ($P > 0.1$). Consequently the oral clearance of R-flecainide was lower ($P < 0.02$) in PMs than EMs, but for S-flecainide the difference was not significant. The half-life of both enantiomers was prolonged significantly in PMs relative to EMs (R: $P < 0.01$; S: $P < 0.02$). A greater proportion of the dose was recovered in the urine as flecainide in the PMs than in the EMs (R: $P < 0.01$, S: $P < 0.05$). No difference ($P > 0.05$) in the renal clearance of either enantiomer was apparent between EMs and PMs.

The nonrenal clearances of both R- and S-flecainide in EMs and PMs are shown in Table 3. In addition, the metabolic ratio for sparteine used to assign oxidative phenotype is indicated. Substantial interindividual variation in the nonrenal clearance of both S- and R-flecainide was observed in both phenotypes. In extensive metabolisers no difference in nonrenal clearance was observed for the two enantiomers (R: 495 ± 110 ml min^{-1}, S: 504 ± 114 ml min^{-1}). In poor metabolisers the nonrenal clearance of each enantiomer was less (R: $P < 0.01$, S: $P < 0.03$) than the respective values observed in EMs. In PMs the nonrenal clearance of R-flecainide was only half the value for S-flecainide ($P < 0.03$).

The results of the XbaI RFLP analysis are also shown in Table 3. All extensive metabolisers had only 29 kilobase (kb) DNA fragments. The poor metabolisers studied displayed three different RFLP patterns. Three poor metabolisers were heterozygous for the mutant recessive 29 kb and the recessive 44 kb fragment. PM5 was homozygous for the mutant 29 kb fragment and PM2 was homozygous for the 11.5 kb fragment.

The urinary recoveries of flecainide, MODF and MODLF in all subjects, expressed as a percentage of the dose administered, are shown in Table 4. The proportion of the total dose accounted for by these three compounds and the partial clearance to the sum of MODF and MODLF are also given. A greater ($P < 0.01$) proportion of the dose was recovered as unchanged drug in PMs than EMs. Both flecainide metabolites were recovered in appreciable quantities in subjects of both phenotypes. However significantly greater amounts of MODF and MODLF were recovered from the EMs than the PMs. The clearance of flecainide to the sum of MODF and MODLF was lower ($P < 0.01$) in the

Table 4 Urinary recovery of flecainide, *meta-O*-dealkylated flecainide (MODF) and *meta-O*-dealkylated lactam metabolite of flecainide (MODLF), as percent of the dose administered (50 mg), in the poor and extensive metabolisers. The partial clearance to the sum of the two metabolites (CL_m) is shown

Subject	*Flecainide (%)*	*MODF (%)*	*MODLF (%)*	*Total recovered (%)*	*CL_m (ml min^{-1})*
EM subjects					
1	30.4	20.7	21.0	72.1	425
2	24.6	20.6	18.9	64.1	364
3	33.5	13.0	13.6	60.1	279
4	33.5	15.8	14.8	64.1	214
5	35.8	18.2	14.1	68.1	241
Mean	31.6	17.7	16.5	65.7	305
± s.d.	4.3	3.3	3.3	4.6	79
PM subjects					
1	46.8	10.0	6.4	63.2	92
2	77.2	8.4	4.6	90.2	52
3	58.4	11.1	6.9	76.4	103
4	56.0	16.0	11.6	83.6	207
5	37.8	14.3	11.7	63.8	196
Mean	55.2	12.0	8.2	75.4	130
± s.d.	14.7	3.1	3.2	11.9	61
P value*	0.009	0.047	0.009	0.346	0.009

* Kruskal-Wallis analysis of variance: EM *vs* PM.

PM subjects than in the EM subjects (Table 4). The percentage of the dose recovered as flecainide, MODF and MODLF was not significantly different ($P > 0.3$) in the PMs (75.4 ± 11.9%) and EMs (65.7 ± 46%).

Discussion

Differences in the pharmacokinetics and pharmacodynamics of the individual enantiomers of a large number of drugs administered as racemates have been observed (Drayer, 1988; Eichelbaum, 1988b). An increasing number of compounds are also being identified whose oxidative metabolism cosegregates with the polymorphic oxidation of probe drugs such as sparteine or mephenytoin, and where the degree of enantioselectivity of drug disposition differs between the phenotypes (Eichelbaum, 1988a). It was observed recently that the metabolic clearance of flecainide is impaired in poor metabolisers of sparteine (Beckmann *et al.*, 1988). Using stereoselective assay methodology, it has been possible in the present study to describe the pharmacokinetics of the individual enantiomers of flecainide in poor and extensive metabolisers of sparteine/debrisoquine.

No significant differences in the pharmacokinetic parameters for R- and S-flecainide in the extensive metabolisers, who comprise 93% of the German population, were observed. By contrast in the PM subjects, the oral clearance of R-flecainide was impaired relative to that of the S-enantiomer, resulting in significant differences in pharmacokinetic parameters. The renal clearance of flecainide, however, was not enantioselective in the PMs, nor impaired relative to EMs. The study described was conducted under conditions of accelerated urinary flow rate and acidic urinary pH, which hasten flecainide renal excretion. The total and renal clearances of flecainide in the EMs are similar to values reported for the racemate in healthy volunteers under similar conditions of urinary flow and pH (Muhiddin *et al.*, 1984). In patients where urine flow rate and pH are uncontrolled, the contribution of metabolism to the overall elimination of flecainide would be greater, and the relative impairment in the nonrenal clearance of R-flecainide in PMs would be even more pro-

nounced. During chronic administration in these subjects, R-flecainide may be expected to accumulate to higher concentrations than the S-enantiomer. In experimentally induced arrhythmias in animals, the enantiomers of flecainide were essentially equipotent (Banitt *et al.*, 1986). Consequently no enantioselective differences in flecainide antiarrhythmic effects are expected, even in PM patients. It is, therefore, probably of little or no significance for the antiarrhythmic efficacy of flecainide that the drug is administered as a racemate. However, it may be possible that other pharmacological effects or side effects, for example negative inotropy, exhibit enantioselectivity.

In order to investigate which routes of flecainide metabolism are impaired in PMs relative to EMs, the two major metabolites of flecainide, MODF and MODLF, were measured in the urine of each subject. All PM and EM subjects metabolised an appreciable proportion of the dose to both metabolites. The recovery in EMs of MODF (17.6 ± 3.3% of the dose) and MODLF (16.5 ± 3.3%) was similar to that reported by McQuinn *et al.* (1984) after administration of 200 mg of [^{14}C]-labelled flecainide (12 ± 3% and 12 ± 4%, respectively). PMs excreted significantly smaller amounts of both MODF (11.9 ± 3.1%) and MODLF (8.2 ± 3.2%). The impairment of flecainide metabolism in PMs results in higher serum concentrations of flecainide and therefore a greater proportion of the dose is excreted unchanged in the urine in the PM subjects (Table 2). The lower recovery, but not total absence, of flecainide metabolites in PMs suggests that enzymes other than P450IID6, which have overlapping substrate specificities, compensate for some of the lower metabolic capacity due to a deficiency of P450IID6 in PMs. The difference in flecainide disposition between EMs and PMs, however, cannot be wholly explained by the lack of formation of MODF and MODLF. Assuming total bioavailability of racemic flecainide ($F = 1$), and taking into consideration that up to 5% of the dose is excreted in the faeces (McQuinn *et al.*, 1984; Conard & Ober, 1984), 95% of the flecainide dose should be accounted for. Indeed in PM2 90% of the dose can be recovered as flecainide, MODF and MODLF. However in PM1 and PM5 and in the EM subjects, only 60% of the dose was found. Other flecainide metabolites must therefore be formed in these subjects. The additional metabolic pathway(s) must consequently be impaired in some PM individuals, such as PM2.

The enantioselectivity of flecainide disposition in PMs, but not in EMs, is worthy of discussion. The renal excretion of the flecainide enantiomers is not enantioselective in either EMs or PMs, and the stereoselectivity observed must therefore be due to metabolism. It may be postulated that the different pathways of flecainide biotransformation may each preferentially metabolise either R- or S-flecainide. In the extensive metabolisers, the enantioselectivity of the multiple routes of metabolism is balanced, and no differences in disposition are noted between R- and S-flecainide. The PMs lack at least one step of oxidative metabolism which must preferentially eliminate the R-enantiomer and, therefore, stereoselective pharmacokinetics are observed. It is interesting to compare the disposition of flecainide with that of other P450IID6 substrates. In contrast to flecainide, the stereoselective disposition of metoprolol and *N*-propylajmaline noted in EMs is diminished in PMs (Lennard *et al.*, 1983; Zekorn *et al.*, 1985).

Pronounced interindividual variation was observed in the nonrenal clearance of both R- and S-flecainide. Relative to the other PMs the CL_{NR} of R-flecainide in PM2 was extremely low. In this subject the lack of metabolic capacity was compensated for by renal excretion of a very high proportion of the dose as unchanged drug. Were this subject to develop renal failure during flecainide administration, both routes of elimination would be impaired. Consequently at standard doses of flecainide, very high plasma concentrations may be attained, which could in turn have proarrhythmic effects (Salerno *et al.*, 1986).

All extensive metabolisers studied had a XbaI restriction fragment length polymorphic pattern of 29/29, and must therefore be at least heterozygous for the dominant 29 kb fragment. This EM genotype was observed in 90% of 29 EMs examined by Skoda *et al.* (1988). The frequency of mutant XbaI RFLP patterns in 51 unrelated PMs has been determined recently (Gaedigk & Eichelbaum, 1989). This sample represents in turn a population of 785 individuals. The 44/29 pattern, present in three of the PMs administered flecainide, is found in 33% of PMs. Twenty-five percent of PMs are homozygous for the recessive 29 kb fragment as seen in PM5. The RFLP pattern 11.5/11.5 noted in PM2 is present in only 4% of PMs. This corresponds to a frequency in the general population of approximately 1 in 500 individuals. It is tempting to speculate that a cause and effect relationship may exist between the rare RFLP genotype observed in PM2 and the greatly impaired metabolic clearance of flecainide noted in this subject. Further studies in larger numbers of individuals of each genotype are necessary to test this hypothesis.

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