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Stereoselective disposition of mexiletine in man

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1 The pharmacokinetics of S-(+)- and R-(−)-mexiletine and of the corresponding conjugates were investigated in six healthy young volunteers after administration of a single 200 mg oral dose of racemic mexiletine hydrochloride.

2 The values for the distribution rate constants as well as for the elimination half-lives of the two enantiomers were similar but the AUC of the S-(+)-enantiomer was always significantly higher ($P < 0.01$) than that of the opposite enantiomer. The mean R/S ratios for unchanged mexiletine in serum and in urine were 0.78 ± 0.12 (s.d.) and 0.80 ± 0.21, respectively.

3 Urinary excretion of mexiletine conjugates consisted mainly of the R-(−)-enantiomer; the mean R/S enantiomeric ratio over 48 h was 9.65 ± 3.10.

4 Serum concentrations of the conjugates were measured in three subjects. The mean R/S AUC ratio was 2.94 ± 0.48 and the renal clearance of the R-(−)-enantiomer was significantly higher ($P < 0.02$) than that of the S-(+)-enantiomer.

Keywords stereoselective disposition mexiletine mexiletine conjugates humans

Introduction

Mexiletine [1-(2,6-dimethylphenoxy)-2-aminopropane] is a class I orally effective antiarrhythmic agent (Campbell *et al.*, 1973; Talbot *et al.*, 1973). It is extensively metabolized in man by carbon and nitrogen oxidation, by reduction and by conjugation (Beckett & Chidomere, 1977a, b). The major metabolites are *p*-hydroxymexiletine, hydroxymethyl-mexiletine and their corresponding alcohols and a conjugate of mexiletine which is hydrolyzed by β-glucuronidase (Beckett & Chidomere, 1977b; Prescott *et al.*, 1977; Grech-Bélanger *et al.*, 1985a). Less than 10% of an administered dose is recovered unchanged in urine (Prescott *et al.*, 1977). An important correlation exists between the serum concentrations of the drug and both its antiarrhythmic and toxic effects (Talbot *et al.*, 1973; Campbell *et al.*, 1978a). However, considerable overlap has been observed between the therapeutic and toxic concentrations. The chemical structure of mexiletine contains an asymmetric carbon atom and the compound is employed clinically as the racemate. Several pharmacokinetic studies using this drug have been carried out both in healthy volunteers and in patients (Chew *et al.*, 1979; Gillis & Kates, 1984) but until now, calculations of the pharmacokinetic parameters have been based on total (R + S) mexiletine levels.

We recently measured the enantiomeric ratios of mexiletine in serum from patients stabilized on racemic mexiletine and found that in some subjects the R/S ratio was different from unity. This prompted us to investigate the disposition of mexiletine enantiomers and of their corres-

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ponding conjugates following administration of a single oral dose of racemic mexiletine to healthy young volunteers.

Methods

S-(+)-mexiletine hydrochloride (m.p. 202.5°; $[\alpha]_D^{20} = +3.5°$), R-(−)-mexiletine hydrochloride (m.p. 201.5°; $[\alpha]_D^{20} = -3.1°$), racemic mexiletine hydrochloride, hydroxymethylmexiletine oxalate, *p*-hydroxymexiletine hydrochloride and Mexitil® capsules were gifts from Boehringer Ingelheim Canada Ltd, Canada. Rimantadine hydrochloride was donated by Endo Laboratories, U.S.A. All the other chemicals and solvents were obtained from commercial sources.

Subjects, drug administration and sample collection

Subjects were six healthy Caucasian volunteers comprising three males and three females. Their mean age was 20.3 ± 1.4 (s.d.) years and their mean body weight was 66.9 ± 12.5 kg. They were all in good health as judged by a medical history, an electrocardiogram and normal values for serum albumin, SGOT, SGPT, total bilirubin, alkaline phosphatase and prothrombin time. All the subjects were non-smokers, none took drugs on a regular basis and they all abstained from alcohol, two days before and for the duration of the study.

Mexiletine hydrochloride (200 mg in capsule form, Mexitil®) was administered by the oral route with 100 ml of water after a minimum 9 h fast. No solid food intake was allowed during the first 4 h but liquids were allowed *ad libitum*. Blood samples were collected into heparin-free Vacu-tainers (Becton Dickinson, Ontario, Canada) prior to drug administration and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose. The first nine samples were withdrawn via a heparinized intravenous catheter maintained patent with heparin in physiological saline (100 units ml^{-1}). In this case, the first 3 ml of each sample was rejected to get rid of the heparin. The last sample was obtained by venous puncture. All blood samples were immediately centrifuged and the serum was stored at −20° C until analysed.

Pooled total urine was collected every 4 h until sleeping time the first day (14–16 h post-dose) and every 8 h up to 48 h post-dose. The volume and pH of each sample were recorded and 20 ml aliquots were stored at −20° C.

Drug analysis

The minimum measurable amounts of compounds reported for each chromatographic method represent the amount injected on column.

The concentrations of R-(−)- and S-(+)-mexiletine in each serum sample were analysed by h.p.l.c. after derivatization with the chiral agent 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) as already described by Grech-Bélanger *et al.* (1985b). The minimum measurable amount of each enantiomer was 50 ng.

Urinary concentrations of total (R + S) mexiletine in 4 ml aliquots of urine were analysed by gas–liquid chromatography as described by Grech-Bélanger (1984) except that the amount of the internal reference standard, rimantadine, was 50 μg. The minimum measurable amount of mexiletine was 500 ng. The enantiomeric ratios of mexiletine in urine were determined by gas–liquid chromatography and flame ionization detection after derivatization of the enantiomers with *N*-trifluoroacetyl S-(−)-prolyl chloride (TPC) which was prepared according to the method of Manius & Tscherne (1979). In brief, the method was as follows: mexiletine was extracted at alkaline pH from 4 ml aliquots of urine with diethyl ether. After the organic extracts were evaporated to dryness, the enantiomers of mexiletine were derivatized with *N*-trifluoracetyl S-(−)-prolyl chloride (TPC). Analysis was carried out on a glass column (2.4 m × 4 mm) packed with 2% Carbowax 20 M on Chromosorb W at an oven temperature of 200° C and a nitrogen flow rate of 60 ml min^{-1}. The retention times of R-(−)- and S-(+)-mexiletine were 38.4 and 41.1 min, respectively, and the minimum measurable amount of each enantiomer was 1 μg. The extent of racemization of the TPC reagent as prepared in our laboratory and stored at 0–4° C was never more than 1.5% using the reaction conditions described herein. The serum and urinary concentrations of the conjugates of both mexiletine enantiomers were obtained as the difference between the respective enantiomer concentration before and after hydrolysis of aliquots of either serum or urine with 1 ml HCl 4 N for 30 min at 100° C. These conditions for liberating mexiletine from the conjugate were chosen after preliminary studies revealed that acid hydrolysis using the conditions described herein did not cause any racemization of the samples and were equivalent to hydrolysis of serum and urine samples with 1000 Sigma units of β-glucuronidase (*E. coli*, Type VII) for 6 h. Furthermore, increasing the time of acid hydrolysis to 60 min or of the enzymic hydrolysis to 15 or 24 h did not increase the yield of mexiletine.

Data analysis

For each subject, the serum concentration of each enantiomer *vs* time data were fitted, using a one- or two-compartment model, by non linear least squares regression analysis with 1/c weighting. From the best-fit model, the disposition rate constants λ_1 and λ_z were calculated. In the case of the conjugates, λ_z was obtained by multiplying the slope of the terminal linear portion of a plot of log urinary excretion rate of each conjugate versus time by −2.303. The elimination half-life was calculated from the relationship $0.693/\lambda_z$ and the area under the serum concentration versus time curve (AUC) for each enantiomer was estimated by the trapezoidal rule from 0 to the last determined concentration and extrapolated to infinity by dividing the last determined concentration by λ_z. Renal clearance (CL_R) of each mexiletine enantiomer and corresponding conjugate was obtained from the equation Ae/AUC where Ae is the amount of each enantiomer or its corresponding conjugate eliminated in urine over 48 h. Differences in the pharmacokinetic parameters calculated for each enantiomer were assessed by using Student's two-tailed paired *t*-test. Probability values (*P*) smaller than 0.05 were considered to be significant.

Results

Results in the text and tables are given as mean ± s.d. The mean serum concentrations *vs* time profiles of R-(−)- and S-(+)-mexiletine obtained up to 24 h after administration of a single 200 mg oral dose of mexiletine hydrochloride are shown in Figure 1. In each subject, the concentrations of the R-(−)-enantiomer were lower than those of the other enantiomer at all times; the average

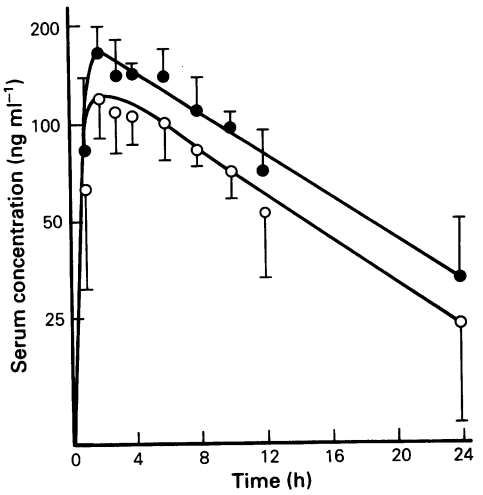

Figure 1 Mean serum concentrations ± s.d. *vs* time profile of (○) R-(−)- and (●) S-(+)-mexiletine obtained in six subjects after administration of a single oral 200 mg dose of racemic mexiletine hydrochloride.

R/S ratio for the six subjects over 24 h was 0.78 ± 0.12 (s.d.) which was significantly different from unity ($P < 0.001$). Mexiletine enantiomer kinetics were best described by a triexponential function in five out of six subjects. In subject 6, a distribution phase was not discernible and a bi-exponential equation was used. The pharmacokinetic parameters of each enantiomer as well as the mean urinary R/S ratios over 48 h are given in Table 1. The apparent absorption rate constants were not determined owing to insufficient sampling in the absorption phase. No significant differences were observed in the disposition (λ_1) rate constants, in the elimination half-lives and in the renal clearances of the two enantiomers. However, the area under the serum concentration

Table 1 Pharmacokinetic parameters and urinary ratios of mexiletine enantiomers

Subject	λ_1 ($X10^{-2}$) (h^{-1}) R-(−)-	S-(+)-	$t_{1/2,z}$ (h) R-(−)-	S-(+)-	AUC (μg ml^{-1} h^{-1}) R-(−)-	S-(+)-	CL_R (ml min^{-1} kg^{-1}) R-(−)-	S-(+)-	Urinary ratio R/S[a]
1	23.06	24.82	11.70	16.78	1.51	2.82	0.76	0.47	0.82 ± 0.15
2	27.67	78.99	12.81	13.78	2.87	4.15	0.44	0.30	1.03 ± 0.14
3	16.53	11.99	11.39	11.85	2.03	2.47	0.90	1.10	0.69 ± 0.05
4	53.68	30.50	10.12	9.85	1.66	2.16	0.50	0.48	0.63 ± 0.15
5	29.62	14.07	12.21	15.52	6.02	6.89	0.28	0.27	0.88 ± 0.10
6	[b]	[b]	8.22	7.05	1.37	1.76	0.28	0.34	0.78 ± 0.29
	NS		NS		$P < 0.01$		NS		$P < 0.001$[c]

[a] values are expressed as mean ± s.d. of R/S ratios obtained over 48 h.
[b] distribution phase not discernible.
[c] mean R/S ratio = 0.80 ± 0.21 (significantly different from unity; $P < 0.001$).

vs time curve of R-(−)-mexiletine was significantly less ($P < 0.01$) than that calculated for S-(+)-mexiletine. The mean amount (R + S) of unchanged drug excreted in urine over 48 h was 11.57 ± 5.02 mg which represented 7.04% of the administered dose and consisted mainly of the S-(+)-enantiomer, as indicated by the mean R/S ratio of 0.80 ± 0.21 (different from unity; $P < 0.001$).

Figure 2 shows the mean serum concentrations *vs* time curves for the conjugates of R-(−)- and S-(+)-mexiletine obtained from subjects 1, 2 and 3. In contrast to the profile of unchanged mexiletine, concentrations of R-(−)-mexiletine conjugate were always higher than those of S-(+)-mexiletine conjugate; the average R/S ratio over 24 h was 3.37 ± 0.99. The AUC, elimination half-life, renal clearance and the urinary R/S enantiomeric ratio calculated for each conjugate are given in Table 2. The AUC and renal clearance of the R-(−)-conjugate were significantly higher ($P < 0.05$ and $P < 0.02$, respectively) than those of the S-(+)-conjugate. However, no significant difference was observed in the elimination half-lives. The urinary excretion rates of the two enantiomeric conjugates decreased linearly with time and were independent of both the urinary pH and volume (Figure 3). The mean amount of total (R + S) conjugated mexiletine eliminated over 48 h by the six subjects was 20.06 ± 5.65 (s.d.) mg representing 14.8% of the administered dose. This consisted almost exclusively of the conjugate of R-(−)-mexiletine as indicated by the mean R/S ratio of 9.65 ± 3.10. The mean R/S ratio for the three subjects for whom serum mexiletine conjugate concentrations were measured was 9.01 ± 2.76.

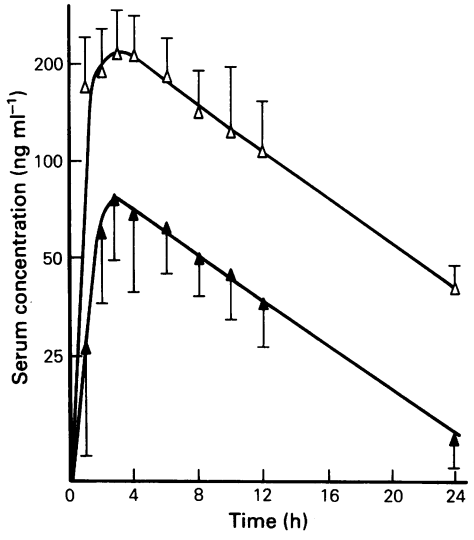

Figure 2 Mean serum concentrations ± s.d. *vs* time profile of (△) R-(−)- and (▲) S-(+)-mexiletine conjugates in three subjects after administration of a single oral 200 mg dose of racemic mexiletine hydrochloride.

Discussion

The mexiletine enantiomer serum concentration *vs* time data obtained from the six subjects shows that the rates of distribution and the elimination half-lives of the two enantiomers were similar but that of the AUC of the S-(+)-enantiomer was significantly greater ($P < 0.01$) than that of its antipode. It was not possible to calculate the volumes of distribution and the total body clearance of each enantiomer since the drug was administered orally. The bioavailability of racemic mexiletine has been reported by several workers to be about 0.8 (Prescott *et al.*, 1977; Campbell *et al.*, 1978b; Haselbärth *et al.*, 1981) but there are no data on the bioavailability of the

Table 2 Pharmacokinetic parameters and urinary ratios of R-(−)- and S-(+)-mexiletine conjugates

Subject	AUC (μg ml⁻¹ h⁻¹) R-(−)-	AUC (μg ml⁻¹ h⁻¹) S-(+)-	CL_R (ml min⁻¹ kg⁻¹) R-(−)-	CL_R (ml min⁻¹ kg⁻¹) S-(+)-	$t_{1/2,z}$ (h) R-(−)-	$t_{1/2,z}$ (h) S-(+)-	R/S urinary ratio[a]
1	2.62	1.04	1.97	0.71	7.32	[b]	7.54 ± 3.55
2	4.63	1.34	1.30	0.48	11.54	12.10	9.78 ± 2.16
3	4.14	1.46	1.29	0.25	8.12	14.39	9.71 ± 2.68
4	ND		ND		9.36	10.54	6.63 ± 4.26
5	ND		ND		15.48	23.34	13.94 ± 5.82
6	ND		ND		8.67	12.21	10.32 ± 4.12
	$P < 0.05$		$P < 0.02$		NS		$P < 0.001$[c]

[a] values are expressed as mean ± s.d. of R/S ratios obtained over 48 h.
[b] urinary excretion rate *v.* time plot was not linear.
[c] mean R/S ratio = 9.65 ± 3.10 (significantly different from unity; $P < 0.001$).

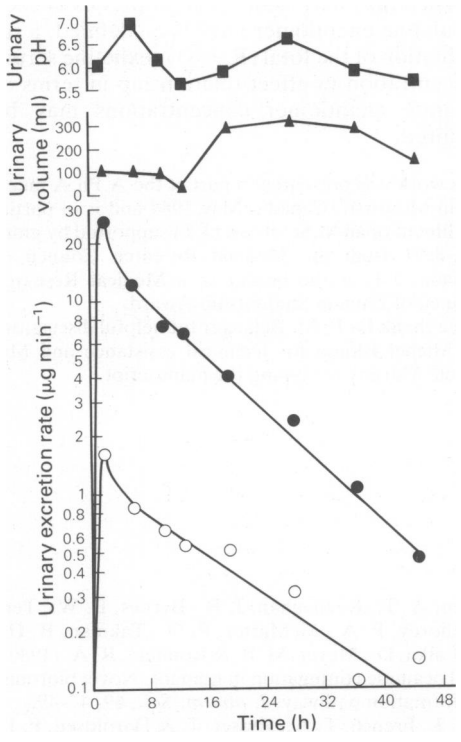

Figure 3 Urinary excretion rate *v.* time curves of (●) R-(−)- and (○) S-(+)-mexiletine conjugates in a representative subject. Variations in urine pH (■) and urine volume (▲) with time are also shown.

separate enantiomers. The difference in the AUC of the enantiomers is due to differences in their bioavailability, systemic clearance or plasma binding. Stereoselective differences in the pharmacokinetic properties of other drugs have been reported. The bioavailability of (+)-verapamil is more than double that of (−)-verapamil (Vogelgesang *et al.*, 1984) whereas the volume of distribution and the clearance of the latter enantiomer are higher than those of the former (Eichelbaum *et al.*, 1984). Stereoselective differences in volume of distribution and clearance have also been reported for the enantiomers of propranolol. In this case, the values of these two parameters are higher for the (+)-enantiomer than for its antipode (Olanoff *et al.*, 1984). Both for propranolol and verapamil, the stereoselective differences in the volume of distribution are due to differences in the degree of protein binding of the two enantiomers (Walle *et al.*, 1983; Eichelbaum *et al.*, 1984). Differences in the elimination half-lives of the enantiomers of tocainide (McErlane & Pillai, 1983; Hoffman *et al.*, 1984), warfarin (Hewick & McEwen, 1973; O'Reilly, 1974), indoprofen (Tamassia *et al.*, 1984) and propranolol (Silber *et al.*, 1982) have also been reported.

Both the urinary and serum data on the conjugates of mexiletine indicate stereoselectivity in the conjugation of mexiletine; the R-(−)-enantiomer being conjugated to a greater extent than the S-(+)-enantiomer. The difference in the ratios observed between the serum and urinary data indicates that the stereoselectivity is due to more than one mechanism, i.e. formation and/or distribution and renal excretion. Evidence for the stereoselectivity in renal excretion is obtained from the significant difference observed in the renal clearance of S-(+)- and R-(−)-mexiletine conjugates; the renal clearance of R-(−)-mexiletine conjugate is close to the value of the glomerular filtration rate whereas that for the (+)-enantiomer is far below this value. Tocainide, an analogue of mexiletine, has also been shown to undergo stereoselective conjugation in man with R-(−)-tocainide being more extensively conjugated to glucuronic acid than the S-(+)-enantiomer (Hoffman *et al.*, 1984). The structure proposed for this conjugate is tocainide carbomyl *O*-β-D-glucuronide (Elvin *et al.*, 1980). The structure of the conjugate of mexiletine has not been elucidated. Other examples of drugs that exhibit stereoselective conjugation are propranolol (Thompson *et al.*, 1981; Wilson *et al.*, 1984) and oxazepam (Sisenwine *et al.*, 1982) both of which are conjugated to glucuronic acid. According to studies carried out in animals, the stereoselective conjugation of propranolol is due to either involvement of different glucuronyltransferases or to different affinities of the enantiomers to the same enzyme or both. Stereoselective conjugation of 4-hydroxypropranolol to sulphate has been reported to occur in several species (Christ & Walle, 1985).

Although the serum concentrations of S-(+)-mexiletine were always higher than those of its antipode, the difference in the concentrations of the two enantiomers was never large enough to compensate for the amount of S-(+)-mexiletine that was not conjugated (see Figures 1 and 2). This suggests that part of the S-(+)-mexiletine that is not conjugated is metabolized via another pathway. Beckett & Chidomere (1977a) identified seven other metabolites, mostly obtained by oxidation reactions apart from the conjugate of mexiletine that is hydrolyzed by β-glucuronidase. Thus like warfarin (Kaminsky *et al.*, 1984) and propranolol (Walle *et al.*, 1984), stereoselective metabolism of mexiletine may take place via more than one pathway.

The clinical implications of the stereoselective disposition of mexiletine cannot be defined since the pharmacological effect of the separate isomers have not been studied. However, stereoisomers invariably do have distinct biological properties (Ariens, 1984). Therefore, it is unlikely that the enantiomers of mexiletine are identical in all of their effects. The enantiomers of tocainide, an analogue of mexiletine which differs from the latter in that it has an amide instead of an ether function connecting the aromatic ring to the asymmetric centre, have different antiarrhythmic potencies in mice and exhibit CNS toxicity at different doses in dogs (Byrnes *et al.*, 1979).

When the pharmacological properties of each mexiletine enantiomer have been defined, a re-evaluation of the total (R + S) mexiletine serum concentration *vs* effect relationship in terms of separate enantiomer concentrations may be required.

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