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Resolution and Electrophysiological Effects of Mexiletine Enantiomers

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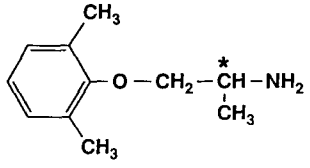
Abstract—Resolution of mexiletine enantiomers from the racemic mixture has been achieved by fractional crystallization through the formation of diastereoisomeric *p*-toluoyl tartrate salts. Following three crystallization steps in methanol, *R*-(−)- and *S*-(+)-mexiletine were resolved with an optical purity >98% (yield ≈30%) and their hydrochloride salts formed. Incremental doses of mexiletine enantiomers were administered to dogs with experimentally-induced arrhythmias to investigate the stereoselective antiarrhythmic and electrophysiological effects of these compounds. Using up to three extrastimuli, programmed electrical stimulation was performed in conscious animals 7–30 days after coronary ligation. *R*-(−)-Mexiletine prevented ventricular tachycardia in 3/6 dogs (2 after 0·5 mg kg^{-1}, 1 after 8 mg kg^{-1}); two animals died after 1 and 8 mg kg^{-1}, respectively; one remained unchanged even at the highest dosage (16 mg kg^{-1}). *S*-(+)-Mexiletine prevented ventricular tachycardia in only one dog (after 1 mg kg^{-1}); two died after 4 and 8 mg kg^{-1}, respectively; 2/5 remained unchanged even after the administration of 16 mg kg^{-1}. No significant changes in any electrocardiographic intervals (PR, QRS, QT_c) or refractory periods were induced by mexiletine enantiomers at any doses used (0·5–16·0 mg kg^{-1}). These results suggest that *R*-(−)-mexiletine possesses greater antiarrhythmic properties than the opposite enantiomer.

Clinically relevant problems may be encountered by administration of drugs as racemates since their optical isomers may have greatly different binding affinities (to a receptor site or plasma proteins), rates of elimination (metabolism or excretion), or toxicities (Williams & Lee 1985; Drayer 1986; Turgeon et al 1990). However, such knowledge does not implicitly mean that, for every racemate, a single enantiomer must be used clinically, but a rational approach to therapeutics with racemates requires a greater understanding of the pharmacokinetics, pharmacodynamics, and toxicity of the individual enantiomers.

Mexiletine, 1-(2,6-dimethylphenoxy)-2-aminopropane (Fig. 1), is an orally effective antiarrhythmic agent (Fenster & Comess 1986; Campbell 1987; Murray et al 1989). Inter-subject variability in both dose-concentration (pharmacokinetics) and concentration-effect (pharmacodynamics) relationships are observed during mexiletine therapy so that an overlap exists between therapeutic and toxic plasma levels (Prescott et al 1977; Campbell et al 1978; Vozeh et al 1982). Factors such as enzyme induction (Begg et al 1982; Pentikainen et al 1982; Grech-Bélanger et al 1985a) and inhibition (Klein et al 1985), genetics (Turgeon et al unpublished), or pathophysiological conditions (El Allaf et al 1982; Pentikainen et al 1983, 1984) alter mexiletine disposition and may be responsible (at least in part) for such variability in drug pharmacokinetics and efficacy.



Mexiletine

FIG. 1. Chemical structure of mexiletine (the star indicates the chiral centre).

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Mexiletine is available for clinical use as the racemic mixture and its disposition is stereoselective in man; mean serum concentrations, the unbound serum protein fraction, and urinary excretion of unchanged *S*-(+)-mexiletine are greater than those of *R*-(−)-mexiletine (Grech-Bélanger et al 1986; McErlane et al 1987; Igwemezie et al 1989). Mexiletine stereoselective disposition is related to the formation of a glucuronide conjugate although other metabolic pathways are most likely to be enantioselective (Grech-Bélanger et al 1986; Turgeon 1987). Overall, the role of stereoselective factors to explain inter-subject variability in drug response during mexiletine therapy is still unknown.

Radioligand competitive binding studies have shown that mexiletine interaction at the receptor site of cardiac sodium channels is stereoselective; the binding affinity of *R*-(−)-mexiletine is approximately twice that of the opposite enantiomer (Hill et al 1988). Despite this observation and the fact that mexiletine disposition is stereoselective, there are no reports in the literature on the relative antiarrhythmic potencies and clinical pharmacology of mexiletine optical isomers, which may be due to the non-availability of the pure enantiomers of the drug.

In this report, we describe a simple method for the resolution of racemic mexiletine. Using these products, we investigated the antiarrhythmic and electrophysiological effects of mexiletine enantiomers in dogs with experimentally-induced arrhythmias by programmed electrical stimulation.

Materials and Methods

Chemicals and reagents

The hydrochloride salt of *RS*-mexiletine and its enantiomers (50 mg; used as standards) were kindly provided by Boehringer Ingelheim Canada Ltd (Ontario, Canada). The optically active agents (+)-di-*p*-toluoyl-D- and (−)-di-*p*-toluoyl-L-tartaric acid monohydrate were purchased from Aldrich Chemical Co. (Milwaukee, WI). Diethyl ether (freshly distilled before use) and methanol were obtained from Fisher Scientific Co. (Fair Lawn, NJ). All other chemicals and reagents used were of analytical grade and obtained from usual commercial sources.

Resolution of mexiletine enantiomers

Fractional crystallization. Racemic mexiletine (free base) was extracted from an alkaline (pH 12) aqueous solution (250 mL) of the hydrochloride salt (3·4 g) with 2 vol diethyl ether. The diethyl ether fraction was dried with anhydrous magnesium sulphate (5 g) for 24 h, filtered and evaporated at 45°C. The residue consisting of racemic mexiletine free base was dissolved in boiling methanol (400 mL) and (−)-di-*p*-toluoyl-L-tartaric acid monohydrate (5·79 g; 15 μmol) was added with constant stirring. The precipitate (P1) formed almost instantaneously and was collected and redissolved in 1600 mL of boiling methanol, and the solution allowed to stand at room temperature (≈23°C) until the volume of methanol was reduced to 500 mL (≈72 h). The precipitate (P2) was collected and the procedure was repeated except that 1400 mL of methanol were used. *S*-(+)-Mexiletine tartrate salt (P3) was collected ≈72 h later.

To obtain the enantiomer as a free base, a 0·5 M sodium hydroxide solution (85 mL) was saturated with the tartrate salt (P3) and centrifuged to give mexiletine base as an oil in the upper phase. This was collected and dissolved in diethyl ether (E1). The aqueous phase was further diluted with 400 mL of water, the pH adjusted to 12 and extraction with diethyl ether (2 × 200 mL) was carried out. The combined ether extracts were added to solution E1 and dried with anhydrous magnesium sulphate. After filtration, the solvent was evaporated and *S*-(+)-mexiletine was obtained as a yellow oil. Treatment of *S*-(+)-mexiletine in dry diethyl ether with dry hydrogen chloride gave *S*-(+)-mexiletine hydrochloride as a white powder.

The tartrate and hydrochloride salt of *R*-(−)-mexiletine were prepared by the same procedure except that (+)-di-*p*-toluoyl-D-tartaric acid monohydrate was used as the resolving agent.

Optical purity determination. The optical purity of the precipitate obtained after each crystallization step was determined by a stereospecific high performance liquid chromatography assay (Grech-Bélanger et al 1985b). In summary, ≈ 1 mg of the precipitate was dissolved in 100 mL of water and 1 mL (≈ 10 μg) of this solution extracted twice at pH 12 with diethyl ether. The combined ether extracts were evaporated at 45°C and the residue derivatized with the chiral agent 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) (PolySciences Inc., Warrington, PA). Separation of the diastereoisomers was performed on an Apex ODS column (25 cm × 4·6 mm i.d.; 5 μm particle size; Rayonics Scientific, St-Laurent, Québec) using a mobile phase consisting of methanol: 10 mM phosphate buffer pH 5·5 (65:35).

Optical activity determination. The optical activity, [α], of mexiletine enantiomers was determined at 589 nm with a Carl Zeiss polarimeter. The hydrochloride salt of each enantiomer (20 mg) was dissolved in 10 mL of methanol (final concentration of the base form; 16·6 mg mL^{-1}) and the determination carried out at 28°C.

Assessment of the antiarrhythmic and electrophysiologic effects of mexiletine enantioners

Surgical and programmed electrical stimulation procedures used in this study were similar to those previously described in detail (Uprichard et al 1988; Uprichard & Harron 1989).

Coronary artery ligation. Adult greyhounds were anaesthetized by intravenous administration of sodium methohexitone (10 mg kg^{-1}) and their hearts exposed through a thoracotomy. A two-stage ligation procedure was performed on the anterior descending branch of the left coronary artery. Myocardial pacing wires were sutured onto the heart: one in the centre of the area supplied by the occluded artery and a second in an area jointly supplied by an adjacent branch of the anterior descending artery. Both pacing wires were brought out through skin anterior to the thoracotomy before the wound was closed in layers.

Programmed electrical stimulation (PES) protocol. Further observations were made on conscious dogs, 7 to 30 days after coronary ligation. The dogs were positioned on their left sides and remained in this position throughout the experiment. Using the myocardial pacing wires, ventricular pacing (S_1; basic cycle length 350 ms) was introduced by bipolar pulses of 4 ms duration at twice diastolic threshold. Burst pacing was then performed at different rates from 200 to 450 beats min^{-1}. If this failed to produce arrhythmia, an extrastimulus (S_2) was introduced at the end of a train (8 beats) of stimuli at a basic cycle length of 350 ms. The delay between S_1 and S_2 was sequentially reduced at 20 ms intervals from 350 ms until the extrastimulus failed to produce a ventricular response (R_2). S_2 was then set at the shortest delay (to the nearest 5 ms) which produced a ventricular response, and S_3 introduced with a delay of 350 ms after S_2. The procedure was repeated with S_3 and S_4 until an arrhythmia was produced or the protocol was exhausted.

Arrhythmia definition. Arrhythmias considered suitable for the continuation of the study were sustained ventricular tachycardia (VT_s; defined as a self-perpetuating arrhythmia of 5 min duration), and non-sustained ventricular tachycardia (VT_{ns}; defined as a reproducible arrhythmia of 4 or more ventricular ectopic beats at any given setting of S_2-S_3-S_4). Dogs that developed VT_s or VT_{ns} in response to PES were termed "inducible". Dogs that failed to produce an arrhythmia in response to PES were deemed "non-inducible".

Drug administration. Eleven animals with reproducible VT_{ns} were randomly allocated to receive intravenous doses (through a catheter in a foreleg vein) of either mexiletine

enantiomer obtained by fractional crystallization. Increasing doses of these drugs were administered in normal saline (0·9%) at 5 min intervals until the arrhythmia was abolished, side-effects were apparent or the dog died (ventricular fibrillation in response to stimulation; VF).

Antiarrhythmic efficacy definition. Dogs were rechallenged every 5 min with the stimulus setting that produced the arrhythmia. If stimulation failed to produce an arrhythmia after drug therapy, the protocol was continued as described above. Only if this failed to produce the required ectopic response was the arrhythmia considered abolished and the dog deemed non-inducible.

Electrocardiographic signal measurements. PR intervals and QRS duration were measured to the nearest 5 ms (paper speed 100 mm s^{-1}) before and after each treatment; QT intervals were measured and QT_c was calculated using the formula $QT_c = QT/\sqrt{RR}$ (Bazett 1920). The effective refractory period (ERP) was taken as the shortest S_1-S_2 interval (to the nearest 5 ms) that produced a ventricular response. Functional refractory period (FRP) was taken as the shortest R_1-R_2 interval measured during the pacing protocol.

Statistical analysis

Results of PES for each treatment group were ranked for abolition of arrhythmias, no change, or death, using the non-parametric Mann–Whitney U test or chi-square test. Statistical analysis of the electrocardiographic parameters was performed using Student's paired *t*-test and significance measured at the $P < 0{\cdot}05$ level. ERP and FRP were only available in dogs that survived PES, and were therefore compared with pretreatment values using an unpaired *t*-test.

Results and Discussion

Resolution of mexiletine enantiomers

Besides their specific optical activity, enantiomers of a drug have identical physical properties in symmetrical media. However, resolution of optical isomers from a racemic mixture can be achieved through the formation of diastereoisomers. In principle, addition of one of the enantiomers of an acid to a racemic amine in solution leads to the formation of two salts with different solubilities. Following several crystallizations, the diastereoisomeric salt of one of the enantiomers of the racemic amine is obtained as a precipitate. Using this principle, resolution of mexiletine enantiomers was achieved through the formation of *p*-toluoyl-tartrate salts.

The optically active agent *p*-toluoyl-tartaric acid was selected since both of its enantiomers were readily available through commercial sources. This made it an interesting

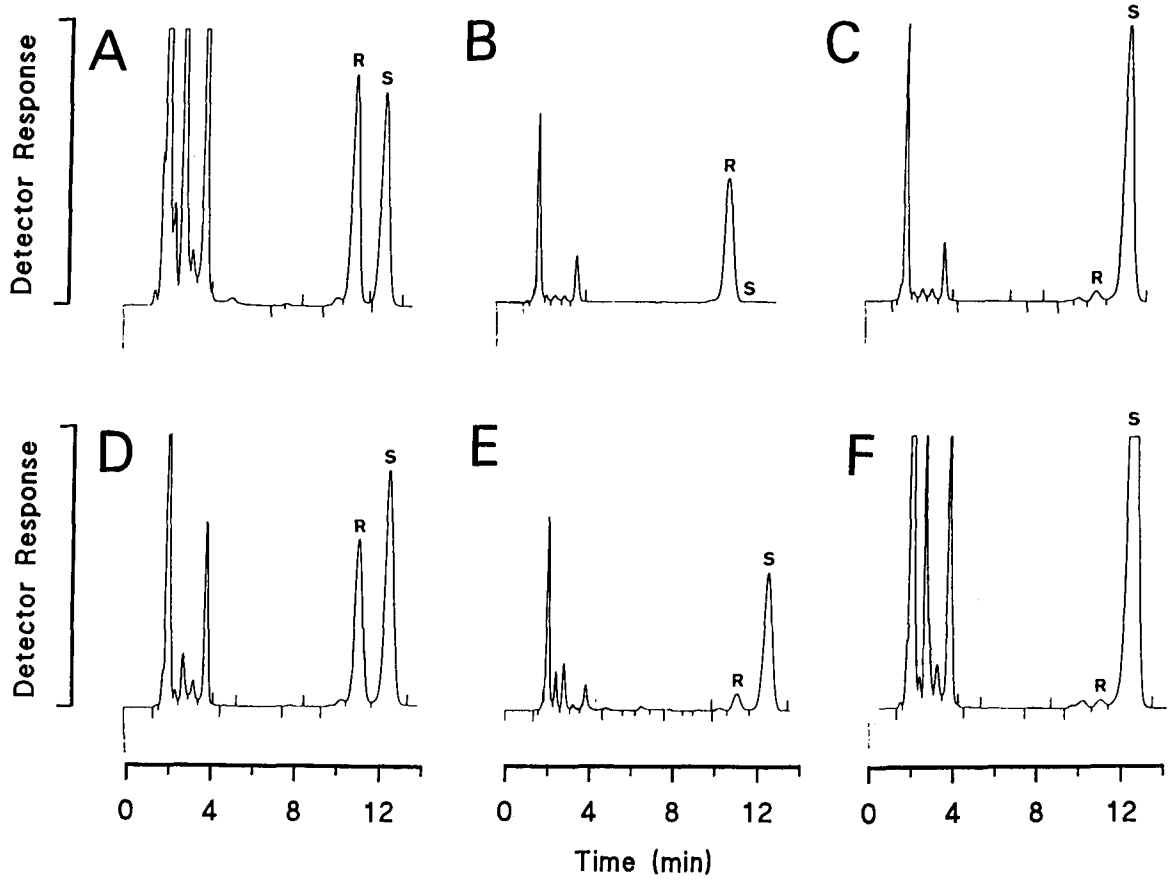

FIG. 2. Chromatograms of GITC derivatives obtained with *RS*-mexiletine standard (A), *R*-(−)-mexiletine standard (B), *S*-(+)-mexiletine standard (C), and precipitates obtained at successive crystallization steps during resolution of *S*-(+)-mexiletine with (−)-di-*p*-toluoyl L-tartaric acid: P1 (D), P2 (E), P3 (F).

Table 1. Physical properties, yield and optical purity of mexiletine enantiomers obtained by fractional crystallization.

	p-Toluoyl tartrate			Hydrochloride				
	Crystallization steps	Weight (mg)	Melting point[a] (°C)	Melting point[a] (°C)	Optical activity (α_D)	Yield[b] (%)	Optical purity *R*-(−)%	Optical purity *S*-(+)%
RS-Mexiletine	Standard	—	—	201·9 ± 0·2	NIL	—	51·9	48·7
R-(−)-Mexiletine	Standard	—	—	204·2 ± 0·5	−3·10[c]	—	100·0	0·0
	P1	4000	216·7 ± 0·5	—	—	—	72·1	27·9
	P2	2400	222·6 ± 0·7	—	—	—	89·9	10·1
	P3	1400	232·2 ± 0·1	203·7 ± 0·4	−3·07[d]	24·1	98·5	1·5
S-(+)-Mexiletine	Standard	—	—	203·3 ± 0·2	+3·50[c]	—	3·6	96·4
	P1	4500	212·4 ± 0·7	—	—	—	40·0	60·0
	P2	3000	223·3 ± 0·4	—	—	—	11·9	88·1
	P3	1800	233·5 ± 0·1	203·7 ± 0·6	+2·83[d]	32·7	1·6	98·4

[a]Mean ± s.d.; n = 3. [b]Based on a theoretical maximal yield of 7·5 mmol (1·618 g). [c]Determined at 20°C. [d]Determined at 28°C.

resolving agent since resolution of an enantiomer from the less soluble salt (precipitate) is often easier to achieve than from the more soluble one (Yost & Holtzman 1979). Therefore, both mexiletine enantiomers were resolved through the formation of precipitates by interchanging the optically active agent (*p*-toluoyl tartaric acid enantiomer).

Fig. 2 shows the optical purity determined by HPLC analysis of the precipitates obtained at each crystallization step during resolution of *S*-(+)-mexiletine with (−)-di-*p*-toluoyl L-tartaric acid. The retention times of the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) derivatives of *R*-(−)- and *S*-(+)-mexiletine were 10·50 and 12·25 min, respectively. Successive crystallizations produced an enrichment in *S*-(+)-mexiletine from 60% for P1 to 98·4% for P3 (Table 1). In addition, the melting point of the tartrate salt increased progressively with consecutive crystallizations. Similar results were obtained during the resolution of *R*-(−)-mexiletine with (+)-di-*p*-toluoyl D-tartaric acid. The optical purity and the melting point of the tartrate salt of P3 obtained for *R*-(−)- and *S*-(+)-mexiletine were almost identical, suggesting similar purity. The hydrochloride salts of the resolved enantiomers (P3) were formed to facilitate dissolution in aqueous medium. The melting point and optical activity of hydrochloride salts were similar to those of their respective standards.

When 15 mmol (3·236 g) of racemic mexiletine hydrochloride was used as the starting material, approximately 500 mg (≈ 30% yield) of the hydrochloride salt of one mexiletine enantiomer with an optical purity > 98% was obtained after three successive crystallizations (Table 1). Such yield is highly reproducible and the procedure has been used to prepare more than 7·5 g of each enantiomer. Further recrystallization slightly increased the optical purity but significantly decreased the yield. Solvent volume also appeared to be optimal to achieve an optical purity of 98·5% in three crystallization steps. A smaller volume provoked a faster crystallization of less pure products while a larger volume increased the interval between each crystallization step without significantly affecting the purity of the products. The crystals of P2 and P3 were in the form of long concentric needles while P1 consisted of a bulky white powder.

Assessment of the antiarrhythmic and electrophysiologic effects of mexiletine enantiomers

Pharmacological effects of class I antiarrhythmic agents are thought to be mediated via blockade of fast inward sodium currents (Vaughan Williams 1975). Although the molecular mode of these drugs is not completely understood, their mechanistic pharmacology is organized around the receptor concept (Hille 1977; Hondeghem & Katzung 1977; Grant et al 1984; Sheldon et al 1989). Therefore, relevant effects are observed following binding of class I antiarrhythmic drugs to a specific receptor site associated with cardiac sodium channels. Stereoselective binding to a cardiac sodium channel has been described for *R*-(−)-mexiletine using competitive radioligand binding (Hill et al 1988), consistent with the greater antiarrhythmic activity of this enantiomer found in this study.

Fig. 3 shows that arrhythmia was no longer inducible in 50% of the dogs treated with increasing doses of *R*-(−)-mexiletine compared with only 20% for *S*-(+)-mexiletine. Efficacy observed with the *R*-(−)-enantiomer appears to be superior not only to that of its opposite enantiomer but also to that of the racemic mixture or placebo. In fact, previous data obtained in dogs undergoing similar programmed electrical stimulation showed that 5/6 dogs treated with racemic mexiletine continued to exhibit ventricular tachycardia (VT) after 16 mg kg^{-1} of drug and 1/6 died after 4 mg kg^{-1}. In a matched placebo group, 4/6 dogs remained in VT throughout the study and the other 2 developed VF when stimulated five minutes after the first dose of placebo (Uprichard & Harron 1989).

The number of deaths (ventricular fibrillation) induced by PES in our study was ≈ 30% and may reflect heterogeneity in refractoriness, conduction and excitability in infarcted tissue caused by second and third extrastimuli (Moore et al 1986). However, such protocols are often required to produce reproducible and severe arrhythmias.

Mexiletine and other class IB antiarrhythmic agents shorten the APD, presumably through a decrease in inward sodium current but increase the ERP relative to the APD presumably through a slowed recovery from inactivation (Campbell 1979; Coraboeuf et al 1983). Table 2 reports the

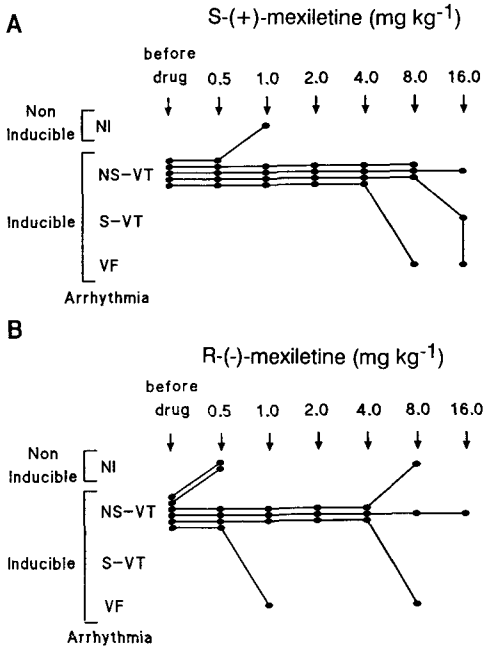

FIG. 3. Effects of *S*-(+)-mexiletine (A) and *R*-(−)-mexiletine (B) on the arrhythmias produced by programmed electrical stimulation.

Table 2. Effects of *S*-(+)-mexiletine and *R*-(−)-mexiletine on electrocardiographic intervals and refractory periods.

S-(+)-Mexiletine		
Parameter[1]	Before Drug[2]	After Drug
QT_c	0·300±0·015	0·285±0·005
QRS	0·070±0·005	0·070±0·005
ERP	0·110±0·005	0·110±0·005
PR	0·115±0·005	0·120±0·005
FRP	0·165±0·005	0·165±0·010
R-(−)-Mexiletine		
Parameter	Before Drug	After Drug
QT_c	0·305±0·010	0·310±0·015
QRS	0·080±0·005	0·075±0·005
PR	0·110±0·005	0·105±0·005
ERP	0·120±0·005	0·125±0·005
FRP	0·165±0·005	0·170±0·010

[1] Results in seconds. [2] Mean±s.e.

effects of *R*-(−)- and *S*-(+)-mexiletine on the electrocardiographic intervals and refractory periods. Neither the QT_c interval (related to APD) nor the ERP (which shows changes in refractory period at the site of stimulation) or the FRP (which is an index of the refractory period for conduction within the ventricular myocardium) exhibited any changes after therapy with mexiletine enantiomers. No significant changes in any other electrocardiographic parameters measured were observed following administration of *R*-(−)- or *S*-(+)-mexiletine. The magnitude of electrocardiographic interval changes induced by class IB agents is generally small.

In-vivo electrophysiological studies have not been previously conducted with mexiletine enantiomers due to the lack of significant amounts of pure products. Using fractional crystallization and the isomers of the optically active agent *p*-toluoyl tartaric acid, mexiletine enantiomers were resolved and some electrophysiologic and antiarrhythmic effects of the enantiomers determined. The *R*-(−)-enantiomer exhibited greater antiarrhythmic properties than the *S*-(+)-enantiomer while neither of the optical isomers (similarly to the racemic mixture) significantly affected electrocardiographic intervals and refractory periods. Stereoselective factors may partially explain inter-patient variability in drug efficacy during mexiletine therapy and their overall importance needs to be further established.

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