Stereoselective Disposition and Pharmacologic Activity of Propafenone Enantiomers

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Propafenone is an antiarrhythmic drug that produces a variable degree of β-blockade in humans and is administered as a racemate. To examine the relative contribution of the individual enantiomers to pharmacologic effects seen during treatment with propafenone, we assessed the steady-state plasma concentrations of (+)-S-propafenone and (-)-R-propafenone in seven patients who were on long-term oral therapy, and we evaluated the electrophysiologic and β-blocking properties of both enantiomers in vitro. The metabolism of propafenone is known to be polymorphic and to cosegregate with that of debrisoquine-4-hydroxylation. Among five patients with the extensive metabolizer phenotype (EM), the ratio of the area under the plasma concentration–time curve of (+)-S-propafenone to (-)-R-propafenone was 1.73±0.15 (mean±SD). In the other two patients, who had the poor metabolizer phenotype (PM), the concentrations of both enantiomers were elevated but the S/R ratios were similar to those seen in patients with EM. In canine cardiac Purkinje fibers, both enantiomers produced similar frequency-dependent depression of maximum upstroke of phase 0. In contrast, the affinity of the human lymphocyte β2-adrenoreceptor was approximately 100-fold greater for (+)-S-propafenone (Kᵦ, 7.2±2.9 nM) than for the (-)-R-enantiomer (Kᵦ, 571±141 nM). We conclude that during long-term oral therapy, propafenone undergoes stereoselective disposition in patients with either EM or PM. β-Blockade during propafenone therapy is likely related to accumulation of (+)-S-propafenone. The lower β-blocking activity of the (-)-R-enantiomer without significant difference in sodium channel blockade suggests that administration of this enantiomer rather than the racemic mixture may be of advantage in patients intolerant of β-blockade. (Circulation 1989;79:1068–1076)

Propafenone is a recently developed antiarrhythmic agent that has proven to be effective in a variety of arrhythmias, including frequent ventricular ectopic depolarizations,1 sustained ventricular tachyarrhythmias,2 and arrhythmias related to accessory atrioventricular pathways.3 The drug produces sodium channel– and β-blocking actions as well as weak calcium channel antagonism.4 Propafenone undergoes extensive and saturable hepatic metabolism in humans.5 In addition, considerable variability in the dose-plasma concentration

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Supported in part by a grant from the US Public Health Service (GM-31304). H.K.K. was supported by a Fellowship of the Scientific Committee of NATO received through the Deutshe Akademische Austauschdienst. C.F-B. was a recipient of a Merck, Sharp & Dohme International Fellowship in Clinical Pharmacology.

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relation has been reported. One explanation for this variability is the genetically determined impairment in approximately 7% of the Caucasian population to metabolize propafenone.6 This polymorphism cosegregates with the ability to 4-hydroxylate the antihypertensive debrisoquine and correlates with the functional presence or absence of the hepatic cytochrome P-450d1.6 Patients with the extensive metabolizer phenotype (EM) or the poor metabolizer phenotype (PM) can be distinguished,4 and the metabolic pathway affected by polymorphic oxidation is the formation of the active metabolite 5-hydroxy propafenone.7,8

Propafenone is administered as a racemic mixture of (+)-S- and (-)-R-enantiomers. Pharmacokinetic differences between the enantiomers of other racemic drugs, such as metoprolol and N-propylajmaline, which are substrates for P-450d1, have been found in EM but not in PM subjects, indicating the potential for stereoselective metabolism of substrates for this cytochrome P-450.9,10 The in vitro electrophys-
iologic actions of antiarrhythmic drugs can also be dependent on stereochemical conformations. For example, S-disopyramide and quinidine increase action potential duration, while R-disopyramide and quinine shorten it.\textsuperscript{11,12} Also, S-disopyramide is a more potent anticholinergic agent than the R-enantiomer.\textsuperscript{13} In contrast, \textit{l}-sotalol and \textit{d}-sotalol are equipotent as action potential–prolonging agents.\textsuperscript{14} Interestingly, despite their effects on action potential duration, quinidine and quinine as well as the enantiomers of disopyramide exert similar depressant effects on the maximum upstroke velocity of phase 0 ($V_{\text{max}}$), an index of sodium current. Presumably, such differences reflect important stereospecific conformations that impact on drug interactions with transmembrane ion channel proteins.

Similarly, many agents exhibit stereoselectivity in the $\beta$-blocking actions of their enantiomers. For example, Barrett and Cullum\textsuperscript{15} showed that $\beta$-blockade by propranolol is related to the S-isomer. Propafenone (Figure 1) has some structural features in common with propranolol and has been reported to produce variable $\beta$-blocking actions. The relative potency was estimated to be about 2:5th to 2:4th of that obtained with propranolol,\textsuperscript{16–18} and propafenone can produce $\beta$-blockade in patients. Hill et al\textsuperscript{19} demonstrated an increased airway reactivity in patients with mild asthma after administration of propafenone. Recently, Lee et al\textsuperscript{20} found dose-related decreases in maximum heart rate and isoproterenol sensitivity during steady-state administration of propafenone in normal subjects, with the effect being greater in the PM subset. Interestingly, combination therapy with sodium channel blockers plus $\beta$-blockers can result in increased clinical antiarrhythmic efficacy.\textsuperscript{21} Thus, block of both sodium channels and $\beta$-receptors by propafenone may be a desirable combination of attributes. On the other hand, $\beta$-blockade appears to cause at least some of the side effects seen during propafenone therapy. To investigate differences in the pharmacokinetic, pharmacodynamic, or combined properties of propafenone for both enantiomers, three different experimental approaches have been used in the present study.

First, the disposition of propafenone enantiomers during long-term oral administration was investigated in patients with either EM or PM phenotypes. Second, the ability of propafenone enantiomers to depress $V_{\text{max}}$ and to modify action potential characteristics was assessed in isolated canine Purkinje fibers. And third, the affinity of propafenone enantiomers for the $\beta_1$-adrenergic receptor was determined in human lymphocytes.

Analysis of these experiments should determine whether one of the enantiomers is predominant in plasma and whether sodium channel blockade and $\beta$-blockade due to propafenone are related to one particular enantiomer. A prediction can then be made whether administration of a single enantiomer rather than the racemic mixture might lead to fewer side effects without reducing clinical efficacy.

\textbf{Methods}

\textbf{Disposition Kinetics of Propafenone Enantiomers}

\textbf{Patients.} Data were obtained in seven patients (three men and four women) who were receiving long-term oral propafenone therapy (150 mg/8 hr) for treatment of symptomatic and frequent isolated ventricular ectopic depolarizations.

The phenotype of five patients for debrisoquine 4-hydroxylation had been previously determined according to the method of Wedlund et al.\textsuperscript{22} Three patients had the EM phenotype and two had the PM phenotype based on an antimode of 12.6 for the amount of debrisoquine versus 4-hydroxy debrisoquine excreted in urine within 8 hours after the oral administration of 10 mg debrisoquine. Two other patients were classified as EM subjects based on the clearance of propafenone and plasma concentrations of metabolites.\textsuperscript{1} Blood samples were collected during an 8-hour interval at 0, 1, 2, 3, 4, 6, and 8 hours after the 8:00 AM dose. No food intake was allowed 2 hours before and after the administration of propafenone.

Patients participated as part of a protocol approved by the Committee for the Protection of Human Subjects at Vanderbilt University, and written informed consent was obtained from each patient.

\textbf{High-Performance Liquid Chromatography Determination of Propafenone Enantiomers}

The concentrations of (+)-S-propafenone and (-)-R-propafenone were determined by a high-performance liquid chromatography assay. One milliliter of plasma was spiked with 500 ng internal standard (2′-(2-hydroxy-3-ethylamino-propoxy)-3-phenyl-propiophenone hydrochloride, Knoll Pharmaceuticals, Whippany, New Jersey), alkalinized with 0.1 M Tris buffer (pH 12.0), and shaken with 6 ml diethylether for 10 minutes. After centrifugation, the organic layer was transferred to a conical tube, and 200 $\mu$1 0.5N phosphoric acid was added. The tube was shaken for 10 minutes and centrifuged, and the organic layer was removed. The acid phase was alkalinized again with 2N NaOH, and 5 ml dichloromethane was added. The mixture was shaken for 10 minutes and centrifuged. The organic layer was transferred to a conical tube and again
evaporated under vacuum at 40°C. Subsequently, 40 μl of a solution of 2,3,4,5-tetra-O-acetyl-
β-D-glucopyranosyl-isothiocyanate (GITC; Polyscience Inc) solution in toluene (1 mg/ml) and 60 μl
toluene were added. The mixture was allowed to
react for 30 minutes and then evaporated at 40°C
under vacuum. The residue was dissolved in 30 μl
acetonitrile and injected to a high-performance liq-
uid chromatography system. The mobile phase con-
sisted of 60% acetonitrile, 40% water, and 0.01% glacial acetic acid, and the peaks were monitored by
ultraviolet detection at a wavelength of 208 nm after
separation on a reverse-phase column (Altex Ultra-
sphere ODS, 4.6×250 mm, 5 μm). The retention
times were 8.1 and 8.9 minutes for the diaste-
romers of the internal standard, 10.0 minutes for the
GITC derivative of (+)-S-propafenone, and 11.5
minutes for derivatized (−)-R-propafenone. Calibration
curves were established in plasma for each individu-
al enantiomer and were linear in a range of 0 to 1,000 ng/ml (r=0.99) for the (+)-S-propafenone and the (−)-R-enantiomer (r=0.99). The purity of the
enantiomers exceeded 98%. Recovery averaged 40%, presumably reflecting the multistep extrac-
tion. The detection limit was 100 ng/ml.

The area under the concentration versus time
curve during one dosing interval (AUC), was cal-
bulated by the trapezoidal rule. The apparent
oral clearance was determined by dose/AUC, 
where the dose is 67.85 mg of the base of the individual enantiomer.

Electrophysiologic Studies

Studies were conducted in isolated canine Pur-
kinje fibers using methods described recently by
Thompson et al,7 which consisted of removal of the
hearts of mongrel dogs through a thoracotomy after
deep anesthesia with pentobarbital (30 mg/kg i.v.).
The hearts were rinsed with cold Tyrode’s solution
(NaCl 137 mM, NaHCO3 12 mM, dextrose 5.5 mM,
MgCl2 0.5 mM, NaH2PO4 1.8 mM, KCl 4 mM, and
CaCl2 2.7 mM). The Tyrode’s had been gassed with
95% O2-5% CO2. Free running false tendons were
discharged, stored in oxygenated Tyrode’s solution
at room temperature for 30 minutes to allow recover-
y from dissection, and then placed in a Lucite
bath and perfused with warm oxygenated
Tyrode’s solution (15 ml/min). The preparations
were stimulated using two Teflon-coated silver wires
placed above one end of the preparation (current
pulses <2 msec delivered at 1.5–2 times threshold).
Machine-pulled glass capillary microelectrodes (tip
resistance, 10–20 MΩ) filled with 3 M KCl were
used to impale single Purkinje cells, and transmem-
brane potential was measured with respect to an
extracellular ground in the tissue bath. Both the
ground and the microelectrode were connected
through 3 M KCl silver-silver chloride junctions to
a high input impedance amplifier with variable input capacitance. The action potential was displayed with a Tektronix 5113 dual time base multichannel
oscilloscope. The action potential signal was also
processed by a differentiator having a linear output
between 100 and 1,000 V/sec, and the differentiated
phase 0 upstroke was displayed on a second chan-
el of the oscilloscope with a different time base.
This oscilloscopic display of $V_{\text{max}}$ was calibrated
with a 200 V/sec signal from a sawtooth signal
generator. Before each impalement, the action poten-
tial signal was zeroed and calibrated with a 100 mV
signal on the oscilloscope.

Before each study, the preparation was stimu-
lated at a basic cycle length of 1,000 msec for 30
minutes to ensure stability of the impalement. The
preparation was then stimulated over a wide range
of frequencies (300–8,000 msec), and a Polaroid
photograph was taken of the oscilloscope screen
once action potentials had stabilized at each fre-
quency. After baseline data were obtained, the prep-
paration was superfused for 30 minutes with Tyrode’s
solution containing 1 μM of either (+)-S-propafenone
or (−)-R-propafenone and the entire baseline proto-
col was repeated. Action potential characteristics,
including action potential amplitude, takeoff poten-
tial, overshoot, and action potential duration at 50%
and 90% repolarization (APD50 and APD90, respec-
tively), were measured from each photograph with a
digitizing board (Bit Pad One, Summagraphic Corp,
Fairfield, Connecticut) connected to a microcom-
puter. $V_{\text{max}}$ was measured directly with the differen-
tiated 200 V/sec signal and a permanent measure-
ment scale on the oscilloscope, both of which were
present on each photograph.

Affinity of β2-Adrenoceptors for
Propafenone Enantiomers

Blood was drawn from five healthy, drug-free,
nonsmoking male volunteers (age, 22–29 years)
using ethylendiamine tetaacetic acid (EDTA) as the
anticoagulant. Mononuclear leukocyte (MNL)
membranes were prepared according to a modifica-
tion of a previously described method. Competition
binding studies were performed with 125I-
iodopindolol (2,200 Ci/mmol; New England Nuclear,
Boston, Massachusetts) as the radioligand (20 pmol)
in presence of either (+)-propafenone, (+)-S-
propafenone, or (−)-R-propafenone (10−4 to 10−10
M). MNL membranes were incubated at 37°C for 60
minutes in a final volume of 250 μl containing 12 mM
Tris-HCl (pH 7.6 at 37°C), 60 mM NaCl, 9 mM
MgCl2, 1.8 mM EDTA, 3.6 mM sucrose, 4 ng/ml
BSA, and 0.5 mM ascorbic acid. The binding reac-
tion was stopped by the addition of 10 ml wash buffer
containing 10 mM Tris-HCl (pH 7.6 at 37°C), 90 mM
NaCl, 15 mM MgCl2, and 3 mM EDTA. Samples
were filtered through Whatman GF/C filters, and
filters were then washed with an additional 10 ml
wash buffer and dried by vacuum filtration at a
pressure of 15–20 psi. Radioactivity retained on the
filters was determined in a gamma counter (Beck-
mann Gamma 5500). Duplicate values were obtained
at each concentration of displacing drug. Nonspe-
specific binding was assessed in the presence of 0.1 mM isoproterenol and was between 5% and 10% of total binding. Displacement curves were analyzed with a four-parameter logistic equation that provided estimates for IC₅₀ (the concentration of the competitor that displaced 50% of the specific binding) and the slope factor (pseudo–Hill coefficient). A constant factor (Kₛ) describing the affinity of the β-adrenoceptor for each of the competing ligands was determined by analysis of the binding data with the computer program LIGAND.

Statistic Calculation

All values are given as mean±1 SD. The statistic analysis of predrug and drug data derived from Purkinje fibers was performed using paired Student’s t test after confirming normal distribution of the data. Other comparisons were performed by Student’s t test for unpaired data after confirming normal distribution of the data. Correlation between metabolic ratio and clearance was evaluated by Spearman’s rank correlation test.

Results

Stereoselective Disposition of Propafenone Enantiomers

Typical chromatograms using the HPLC system described above are shown in Figure 2. A baseline separation between the enantiomers was achieved.

Figure 3 shows the time versus plasma concentration profile for one patient with EM. During the 8 hours of interdose sampling, plasma concentrations of (+)-S-propafenone were greater than those of (-)-R-propafenone. The results of the pharmacokinetic calculations are summarized in Table 1. The AUC, for (+)-S-propafenone was 1.73±0.15 (range, 1.56–1.92) times greater than that of the (-)-R-propafenone (p<0.002) in the EM group, indicating that the latter compound is cleared 1.7 times faster than (+)-S-propafenone. Clearance of both enantiomers was reduced in the two patients with PM (Table 1) but remained stereoselective. The clearance of both enantiomers correlated well with the metabolic ratio of debrisoquine/4-hydroxy debrisoquine in the five patients in whom an accurate metabolic ratio was obtained (Figure 4).

Electrophysiologic Studies

(+)-S-Propafenone and (-)-R-propafenone (n=6 each) both depressed V max in a frequency-dependent manner (Figure 5). The effect was significantly different from baseline at the shorter basic cycle lengths—300, 500, and 1,000 msec. A comparison between the enantiomers showed a trend toward a greater effect of (+)-S-propafenone (V max, 80.2±8.8% of baseline) compared with (-)-R-propafenone (88.4±4.5% of baseline) at fast rates (basic cycle length, 300 msec), but the difference was not statistically significant (p<0.069).
Table 1. Area Under the Time Versus Concentration Curve During an 8-hour Dosage Interval (AUC) and Apparent Oral Clearance (Cl) of (+)-S-Propafenone and (−)-R-Propafenone During Long-term Oral Therapy With Racemic Propafenone HCl (150 mg q8h) in Five Extensive Metabolizers (EM) and Two Poor Metabolizers (PM1 and PM2)

<table>
<thead>
<tr>
<th></th>
<th>EM (n=5)</th>
<th>PM1</th>
<th>PM2</th>
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<tbody>
<tr>
<td></td>
<td>(+)-S</td>
<td>(-)-R</td>
<td>(+)-S</td>
</tr>
<tr>
<td>AUC, (ng/ml/hr)</td>
<td>2,905±1,010</td>
<td>1,698±670</td>
<td>6,895</td>
</tr>
<tr>
<td>S/R ratio of AUC</td>
<td>1.73±0.15</td>
<td>1.48</td>
<td>2.12</td>
</tr>
<tr>
<td>Cl (ml/min)</td>
<td>424±126</td>
<td>735±226</td>
<td>164</td>
</tr>
</tbody>
</table>

Figures 6 illustrates the changes in action potential duration at 50% repolarization (APD50). (−)-R-Propafenone significantly reduced APD50 at basic cycle lengths of 300, 500, and 8,000 msec, while (+)-S-propafenone had no effect. Comparison of the two groups showed significant differences at 300 msec (95.4±8.2% of baseline for (+)-S-propafenone versus 84.4±7.9% of baseline for (−)-R-propafenone; p<0.04), at 500 msec (96.9±6.9% of baseline for (+)-S-propafenone versus 83.2±6.5% of baseline for (−)-R-propafenone; p<0.005), and at 8,000 msec (100.4±7.1% of baseline for (+)-S-propafenone versus 87.1±9.6% of baseline for (−)-R-propafenone; p<0.021). Typical tracings, which illustrate the changes in APD50 by propafenone enantiomers, are shown in Figure 7.

Propafenone enantiomers did not alter action potential duration at 90% repolarization, action potential amplitude, overshoot, and the takeoff potential.

Affinity of β2-Adrenoceptors for Propafenone Enantiomers

Each compound displaced 125I-iodopindolol from β2-adrenoceptors on MNL membranes. The displacement curve of (+)-S-propafenone was shifted to the left compared with the (−)-R-enantiomer (Figure 8). The values of Ki and IC50 indicated that the affinity of (+)-S-propafenone for the β2-adrenoceptor was about 100 times greater than that for (−)-R-propafenone (Table 2). Differences between the enantiomers for both IC50 and Ki were highly significant (p<0.005).

Discussion

Pharmacokinetic and pharmacodynamic profiles of drug enantiomers have gained increasing attention in the clinical evaluation of new compounds. Several consequences of stereoselective drug metabolism that might have important implications for the therapeutic effect of a drug have been described by Eichelbaum. First, stereoselective first-pass metabolism can cause different concentration-response relations depending on the route of administration (e.g., verapamil). Second, stereoselective drug interactions may have important therapeutic implications if the enantiomers have substantially differing potencies (e.g., warfarin). Third, stereoselective drug oxidation may be phenotype dependent. This has been investigated in detail for metoprolol and N-propylajmaline. Both drugs undergo polymorphic oxidation of the debrisoquine type. Differences in the pharmacokinetics of the enantiomers were shown in patients with EM, while patients with PM were characterized by a loss of stereoselectivity. In the present study, we have shown that (−)-R-propafenone is cleared faster than (+)-S-propafenone in patients with EM, leading to a higher concentration of the (−)-S-enantiomer in plasma. In contrast to metoprolol and N-propylajmaline, the two patients with PM included in our study exhibited a similar degree of enantioselective disposition as those with EM. The major oxidative metabolic pathways of propafenone during long-term oral therapy in humans are 5-hydroxylation and N-dealkylation. In PMs of propafenone, 5-hydroxylation is impaired and the apparent oral clearance of propafenone is dramatically reduced. Thus, routes of metabolism other than 5-hydroxylation contribute to the stereoselective disposition of propafenone during long-term oral therapy. This conclusion is further supported by the fact that we did not observe significant changes in stereoselective steady-state disposition of propafenone after coadministration of quinidine (H. Kroemer, unpublished results), an inhibitor of propafenone 5-hydroxylation.

However, stereoselective drug disposition is of little consequence if the enantiomers produce similar pharmacologic actions. Consequently, the other
aim of our study was to determine whether electrophysiologic or β-blocking effects of propafenone are stereoselective. Several groups have previously reported that racemic propafenone depresses $V_{\text{max}}$, and this depressive effect is due to both enantiomers and is, like the effect produced by virtually all Class I antiarrhythmic drugs, frequency dependent (Figure 5). Thus, the depression of the fast inward sodium channel is not sensitive for steric differences of propafenone enantiomers, suggesting that the putative binding site of propafenone to the channel is distant from the chiral center of the drug.

In agreement with previous reports, we found that APD$_{90}$ was not altered by propafenone concentrations of 1 μM. The APD$_{90}$ prolongation reported by Dukes and Vaughan Williams occurred at propafenone concentrations of 3.96 μM, whereas no change was observed at 1 μM. In contrast, the action potential duration at 50% repolarization (APD$_{50}$) was reduced only by (-)-R-propafenone (Figures 6 and 7). Changes in APD$_{50}$ indicate alterations in the phases 2 and 3 of the action potential.
and changes in multiple ion currents may be responsible. One possible explanation is blockade of the plateau or "window" sodium current previously described by Attwell et al.\textsuperscript{36} with action potential shortening in analogy to that produced by tetrodotoxin.\textsuperscript{37} The contribution of the APD\textsubscript{90} reduction to the clinical effects of the drug remains to be evaluated.

Finally, we demonstrated that (+)-S-propafenone is a much more potent \(\beta\)-blocker than (−)-R-propafenone when measured as binding to \(\beta_2\)-adrenoceptors on human lymphocytes. Changes in lymphocyte \(\beta_2\)-adrenoceptors have been shown to correlate with changes in cardiac sensitivity to the \(\beta\)-adrenergic agonist isoproterenol.\textsuperscript{38} Moreover, data obtained using rat lung membranes and human left ventricular membranes\textsuperscript{18} have indicated that propafenone-induced \(\beta\)-blockade is nonselective. Thus, binding data obtained in the present study also provide an indication of propafenone interaction with \(\beta_1\)-adrenoceptors. In our study, we observed a large disparity in the ability of the compounds to displace the radioligand iodopindolol from the \(\beta_2\)-adrenoceptor on human lymphocytes. The IC\textsubscript{50} found for racemic propafenone (31.6 ± 18.7 nM) was in the same range as reported by McLeod et al.\textsuperscript{18} Because (+)-S-propafenone was found to be about 100 times more potent than (−)-R-propafenone, we conclude that (+)-S-propafenone is responsible for the \(\beta\)-blocking properties of propafenone. This is in contrast to propranolol where the (−)-enantiomer is the more potent \(\beta\)-blocker.\textsuperscript{15} However, determination of the configuration has shown that the (+)-enantiomer of propafenone has the S-configuration,\textsuperscript{39} whereas the (−)-enantiomer of propranolol has the R-configuration. Therefore, for both agents, the S-configured enantiomer appears responsible for \(\beta\)-blockade.

Integration of the three parts of our study allows us to make some inferences on the role of propafenone enantiomers in man. Regardless of phenotype, (+)-S-propafenone is predominant in plasma. As a consequence of their impaired metabolism, subjects with PM have a decreased clearance and substantially higher plasma levels than those with EM for (−)-R-propafenone and (+)-S-propafenone. Thus, the PM subset is more likely to develop \(\beta\)-blocking effects because the latter compound is responsible for \(\beta\)-blocking effects of propafenone. In agreement are recent findings of Lee et al.,\textsuperscript{20} who described a greater degree of \(\beta\)-blockade in those with PM. A simple reduction of the propafenone dose in those with PM may lead to reduced therapeutic effect because those with PM lack the ability to form 5-hydroxy propafenone, which contributes to the sodium channel-blocking effect.\textsuperscript{7,32} Therefore, higher plasma levels of the parent compound are required in those with PM than in those with EM to achieve similar suppression of arrhythmias.

![Figure 7](image1.png)  
**Figure 7.** Tracings of action potentials (basic cycle length, 500 msec) before (-----) and after superfusion with 1 μM (+)-S-propafenone (upper panel) or (−)-R-propafenone (lower panel).

![Figure 8](image2.png)  
**Figure 8.** Plot of displacement of \(^{125}\text{I}\)-iodopindolol from \(\beta_2\)-adrenoceptors on human lymphocytes by (+)-S-propafenone and (−)-R-propafenone. Each point represents the mean of duplicate values from five experiments.

<table>
<thead>
<tr>
<th>Type of Propafenone</th>
<th>IC\textsubscript{50} (nM)</th>
<th>K\textsubscript{i} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-S-Propafenone</td>
<td>31.6 ± 18.7</td>
<td>11.7 ± 4.4</td>
</tr>
<tr>
<td>(−)-R-Propafenone</td>
<td>1,538 ± 422</td>
<td>571 ± 141</td>
</tr>
</tbody>
</table>

TABLE 2. Competition of (±)-Propafenone, (+)-S-Propafenone, and (−)-R-Propafenone With \(^{125}\text{I}\)-Iodopindolol for \(\beta_2\)-Adrenoceptors on Human Lymphocytes (n=5)
Because (+)-S-propafenone and (-)-R-propafenone have comparable sodium channel-blocking activities, the (-)-R-propafenone may suppress arrhythmias without blocking β-adrenoceptors and may be of advantage for therapy in those at risk for β-mediated side effects. Conversely, therapy with the (+)-S-enantiomer may produce greater arrhythmia suppression in those patients in whom a combined sodium channel and β-blocking effect is desirable.

Acknowledgments

The authors are grateful to Professor G. Blaschke, Münster, FRG, and Dr. C.O. Meese, Stuttgart, FRG, for providing the propafenone enantiomers.

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**KEY WORDS** *propafenone* • sodium channel blockade • enantiomers • $\beta$-blockade
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Circulation. 1989;79:1068-1076
doi: 10.1161/01.CIR.79.5.1068

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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