

# An Enantiomer-Enantiomer Interaction of (S)- and (R)-Propafenone Modifies the Effect of Racemic Drug Therapy

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**Background** Therapy with racemic compounds produces effects that can be attributed to both (S)- and (R)-enantiomers. Here we have tested the hypothesis that an enantiomer-enantiomer interaction would modulate the effects of treatment with a racemate, the antiarrhythmic propafenone. Previous studies have shown that while the enantiomers of propafenone exert similar sodium channel-blocking (QRS widening) effects, it is the (S)-enantiomer that produces  $\beta$ -blockade; moreover, we have demonstrated recently that (R)-propafenone inhibits the metabolism of (S)-propafenone in vitro.

**Methods and Results** This single-blind, randomized study compared the effects of (R/S)-, (S)-, and (R)-propafenone (150 mg q 6 hours for 4 days) and placebo on QRS duration ( $\Delta$ QRS) and on maximum exercise heart rate ( $\Delta$ HR<sub>max</sub>), an index of  $\beta$ -blockade. The clearance of (S)-propafenone was significantly lower ( $-55 \pm 24\%$ ,  $P < .001$ ) during treatment with

(R/S)-propafenone than with the (S)-enantiomer alone, and  $\Delta$ HR<sub>max</sub> was significantly altered during (R/S)-propafenone ( $-8.8 \pm 6.6$  beats per minute;  $P < .01$ ) and during (S)-propafenone ( $-4.3 \pm 4.8$  beats per minute;  $P < .01$ ) but not during (R)-propafenone ( $-1.8 \pm 6.4$  beats per minute) or placebo ( $0.3 \pm 7.1$  beats per minute). In contrast, (R/S)-, (S)-, and (R)-propafenone all prolonged QRS compared with placebo.

**Conclusions** These data indicate that (R)-propafenone impairs the disposition of (S)-propafenone in humans. As a result, the  $\beta$ -blocking effects of 150 mg of racemic propafenone (75 mg of the [S]-enantiomer) were more pronounced than those of 150 mg of (S)-propafenone alone. Thus, the effects of racemic drug therapy are not necessarily those predicted by summation of the effects of the individual enantiomers. (*Circulation*. 1994;89:2396-2400.)

**Key Words** • enantiomers • interactions • propafenone

Many drugs are marketed as racemates, which are defined as a mixture of equal amounts of (S)- and (R)-enantiomers.<sup>1</sup> For example, many of the  $\beta$ -adrenoceptor antagonists, calcium channel blockers, and class I antiarrhythmics are in clinical use as racemates.<sup>2</sup> If enantiomers differ in their pharmacological actions, then administration of racemates can be viewed as administration of a fixed combination of two agents with different pharmacological properties. The possibility of such stereoselectivity in drug action and drug disposition has led to further evaluation of the pharmacological properties of individual enantiomers during development of racemic compounds; moreover, it has been proposed that the development of racemic drugs should be avoided altogether.<sup>1</sup> However, if enantiomers interact with each other, then the effects of the racemate may differ from those predicted by the actions of the individual enantiomers. In this study, we used propafenone as a model drug to test the hypothesis that enantiomer-enantiomer interactions that modify the effect of racemic drug therapy can occur in humans.

The class I antiarrhythmic propafenone shares structural features with frequently used  $\beta$ -blockers (eg, metoprolol or propranolol) and is marketed as a racemate

((R/S)-propafenone<sup>3,4</sup>). Both enantiomers are equally potent sodium channel blockers.<sup>5</sup> In addition, the (S)-enantiomer exerts a modest degree of  $\beta$ -blockade.<sup>5-7</sup> Both enantiomers are extensively metabolized to 5-hydroxypropafenone, and in vitro experiments have indicated that metabolism of the  $\beta$ -blocking (S)-enantiomer is inhibited by (R)-propafenone.<sup>8</sup> These in vitro data predict that administration of racemic propafenone should lead to greater  $\beta$ -blockade compared with administration of the (S)-enantiomer alone, while the extent of sodium channel block should be identical after administration of the enantiomers or the racemate. In this study, we tested the hypothesis of such an interaction by comparing the effects of chronic treatment with (S)-, (R)-, and racemic propafenone in healthy volunteers.

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## Methods

### Study Population

Seven healthy male volunteers (age,  $29 \pm 5$  years; body weight,  $73 \pm 6$  kg [mean  $\pm$  SD]) were included in the study. They were informed by a participating physician about aim, course, and possible risks of the trial, which had been approved by an institutional ethics committee. All subjects gave their written informed consent. Before and after completion of the study, a physical examination and laboratory tests were carried out.

Metabolism of propafenone is in part catalyzed by the cytochrome P450 CYP2D6,<sup>9,10</sup> which is not active in 7% to 10% of a Caucasian population.<sup>11</sup> These "poor metabolizer" patients show aberrantly elevated plasma concentrations after administration of propafenone.<sup>9</sup> In this study, only volunteers with normal activity of CYP2D6 have been included. Individ-

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ual enzyme activity was assessed before study by genotyping (combination of restriction fragment length polymorphism and polymerase chain reaction<sup>12</sup>) and phenotyping (administration of the CYP2D6 substrate sparteine<sup>13</sup>).

### Study Design

The study design was single blind and placebo controlled, with a random order of the four treatments: (*R/S*)-propafenone, (*S*)-propafenone, (*R*)-propafenone (150 mg q 6 hours for 4 days), and placebo (1 tablet q 6 hours for 4 days). There was a drug-free interval of at least 7 days between each study part. Propafenone enantiomers were separated from racemic propafenone via diastereomeric salt formation using ditoluytartaric acid as a resolving agent and 2-butanone/water (98:2, vol/vol) as solvent for recrystallization.<sup>14</sup> The enantiomeric purity determined by chiral high-performance liquid chromatography (HPLC) using a Daicel Chiralpak AD column as stationary phase<sup>15</sup> was more than 99%. Racemic propafenone was a generous gift from Knoll AG, Ludwigshafen, Germany.

Blood samples were taken before the first dose and on day 4 before administration of the morning dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 hours. Urine was collected for 6 hours after the last dose (0 to 6 hours on day 4). In each arm, maximum exercise heart rate ( $HR_{max}$ ) was determined using the method described by Bailey et al (bicycle ergometer ERG 550 PS; Schiller AG)<sup>16</sup> before the first administration and on day 4 before administration of the morning dose and at 3, 6, and 24 hours. ECGs (12-channel ECG Cardiovit CS-6/12; Schiller AG) and blood pressure (automated Dinamap 1846SX; Critikon GmbH) were recorded at the same time.

### Determination of Propafenone, Its Enantiomers, and Metabolites

After administration of the individual enantiomers, a non-stereoselective HPLC assay was used for quantification of plasma propafenone.<sup>17</sup> In brief, 1 mL of plasma was spiked with 250 ng of internal standard [2'-(2-hydroxy-3-ethylamino-propoxy)-3-phenylpropiophenone hydrochloride], adjusted to pH 9 with 500  $\mu$ L of ammonium hydroxide/ammonium chloride buffer (1 mmol/L), and extracted with 5 mL of dichloromethane. After centrifugation, the organic phase was evaporated to dryness with a gentle stream of nitrogen. The residue was dissolved in 50  $\mu$ L of mobile phase, injected into the HPLC system, and quantified with UV detection ( $\lambda=220$  nm). A 5- $\mu$ m  $C_{18}$  reverse-phase column (15 $\times$ 0.46 cm) was used with a flow rate of 0.8 mL/min. The mobile phase consisted of aqueous tetrabutylammonium sulfate (0.01 mol/L) and methanol (56:44, vol/vol). After administration of the racemate propafenone, enantiomers in plasma were assayed by reverse-phase HPLC after derivatization with 2,3,4,5-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl-isothiocyanate, as previously described.<sup>5</sup> To exclude racemization (ie, transformation of [*S*]-propafenone to the [*R*]-enantiomer and vice versa), samples from one volunteer obtained after administration of the enantiomers were assayed in a stereoselective manner. Propafenone and 5-hydroxypropafenone in urine were determined using the method reported by Funck-Brentano et al.<sup>18</sup>

### Pharmacokinetic Evaluation

The area under the plasma concentration versus time curve (AUC) for the last dose interval ( $\tau$ , 0 to 6 hours on day 4, AUC <sub>$\tau$</sub> ) was calculated by the trapezoidal rule. Steady-state plasma concentrations ( $C_{ss}$ ) were derived from AUC <sub>$\tau$</sub> / $\tau$  and corrected for dose. The maximum concentration ( $C_{max}$ ) and the time of maximum concentration ( $t_{max}$ ) were obtained directly from the data. Elimination half-life ( $t_{1/2}$ ) was estimated by linear regression.<sup>19</sup> Apparent oral clearance was derived as dose/AUC <sub>$\tau$</sub> . For racemic propafenone, these calculations were performed separately for the (*R*)- and (*S*)-enantiomers. Relative absorption was calculated from cumulative urinary excretion of propafenone and its metabolite.

### Statistical Analysis

The effects of different treatments on  $HR_{max}$  and QRS intervals were analyzed by multifactor ANOVA.<sup>20</sup> Factors included were medication, patient, and part of the study. Effect at a given time point was defined as the difference of  $HR_{max}$  or QRS at that time point and the average  $HR_{max}$  or QRS before drug treatment ( $\Delta HR_{max}$  and  $\Delta QRS$  in beats per minute and milliseconds, respectively). A Duncan's post hoc test was performed to locate differences between treatments.<sup>20</sup> Pharmacokinetic parameters for (*S*)- and (*R*)-propafenone after administration of the individual enantiomers and the racemate were compared by paired *t* tests. All data are presented as mean  $\pm$  SD.

## Results

### Pharmacokinetics

Plasma concentrations as a function of time after the last dose of 150 mg of racemic propafenone and of the individual enantiomers in one subject are shown in Fig 1. With 150 mg of racemate (ie, 75 mg of each enantiomer, in combination), plasma concentrations of the (*S*)-enantiomer were higher than those of the (*R*)-enantiomer, as previously reported.<sup>5</sup> When 150 mg of the (*R*)-enantiomer was administered alone, plasma concentrations of (*R*)-propafenone were correspondingly higher. However, when 150 mg of the (*S*)-enantiomer was administered alone, plasma concentrations of (*S*)-propafenone were similar to those observed after administration of only 75 mg, as with racemate. Clearance of (*S*)-propafenone was significantly higher after administration of the individual enantiomer compared with clearance calculated after administration of racemate ( $2521 \pm 1450$  mL/min versus  $920 \pm 300$  mL/min,  $P < .02$ ). In contrast, clearance of the (*R*)-enantiomer was not different after administration of the (*R*)-enantiomer when compared with racemate ( $1279 \pm 348$  versus  $1460 \pm 480$  mL/min; NS). Elimination half-life of (*S*)-propafenone was significantly longer after administration of racemic propafenone when compared with that calculated after administration of the enantiomer alone ( $4.6 \pm 1.9$  versus  $2.7 \pm 0.9$  hours;  $P < .04$ ). No such effect was observed for the (*R*)-enantiomer ( $3.3 \pm 1.9$  versus  $4.2 \pm 1.0$  hours; NS). Cumulative urinary excretion of propafenone, expressed as a percentage of the dose administered, was not different after administration of racemate or individual enantiomers, arguing that altered absorption played no role. Pharmacokinetic data are summarized in Table 1.

### Pharmacodynamic Effects

Significant  $\beta$ -blockade occurred at the 3-hour time point ( $P < .01$ ) with racemate compared with placebo ( $\Delta HR_{max}$ ,  $-8.8 \pm 6.6$  versus  $0.3 \pm 7.1$  beats per minute;  $P < .01$ ) and with (*S*)-propafenone compared with placebo ( $\Delta HR_{max}$ ,  $-4.3 \pm 4.8$  versus  $0.3 \pm 7.1$  beats per minute;  $P < .01$ ). In contrast, (*R*)-propafenone had no effect on  $\Delta HR_{max}$  when compared with placebo ( $\Delta HR_{max}$ ,  $-1.8 \pm 6.4$  versus  $0.3 \pm 7.1$  beats per minute). Control heart rates were  $78 \pm 8$ ,  $79 \pm 6$ ,  $77 \pm 12$ , and  $75 \pm 8$  beats per minute for the racemate, (*R*)-propafenone, (*S*)-propafenone, and placebo legs, respectively. Control heart rates were not altered by  $\beta$ -blockade. The effects of treatments on  $\Delta HR_{max}$  are shown in Fig 2.

Significant effects of treatment on  $\Delta QRS$  were observed before the last dose ( $P < .001$ ) and 3 hours ( $P < .001$ ) and 6 hours ( $P < .001$ ) after the last dose. At the 3-hour time point,  $\Delta QRS$  was significantly pro-

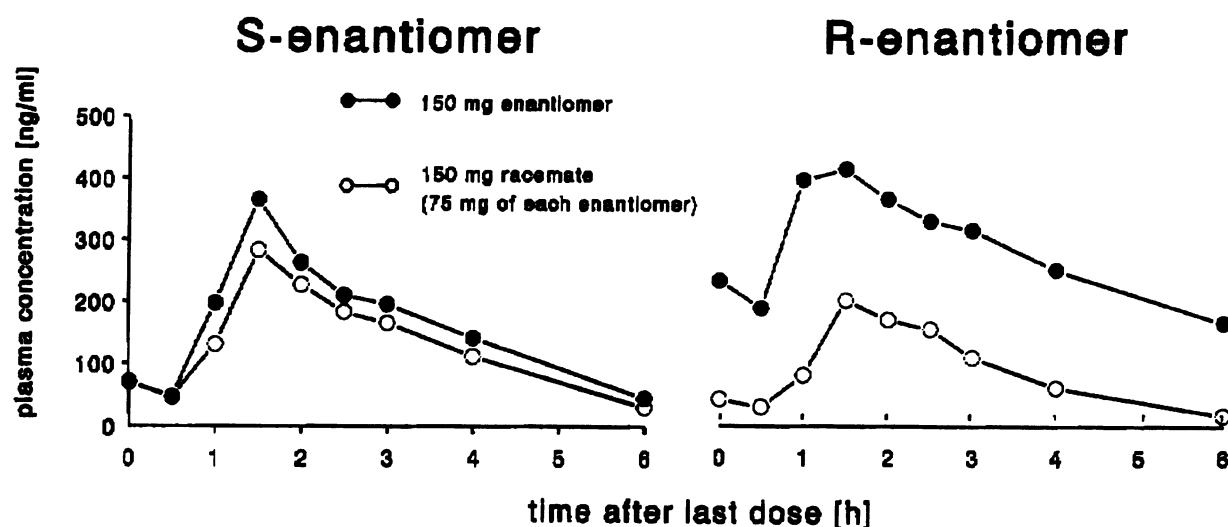


FIG 1. Graphs show steady-state plasma concentration vs time profile of (*S*)-propafenone (left) and (*R*)-propafenone (right) in one volunteer after administration of the enantiomers (150 mg [*S*]- or [*R*]-propafenone q 6 hours for 4 days) on two different occasions (●—●) or the racemate (150 mg [*R/S*]-propafenone q 6 hours for 4 days; ○—○).

longed for (*R/S*)-propafenone ( $\Delta\text{QRS } 10.4 \pm 7.6$  versus  $-0.9 \pm 4.5$  milliseconds;  $P < .01$ ), (*S*)-propafenone ( $\Delta\text{QRS } 8.9 \pm 6.3$  versus  $-0.9 \pm 4.5$  milliseconds;  $P < .01$ ) and (*R*)-propafenone ( $\Delta\text{QRS } 10.3 \pm 8.5$  versus  $-0.9 \pm 4.5$  milliseconds;  $P < .01$ ). No significant difference was detected for  $\Delta\text{QRS}$  between (*R/S*)-propafenone and the enantiomers. Control QRS intervals were  $100 \pm 9$ ,  $96 \pm 11$ ,  $97 \pm 10$ , and  $97 \pm 9$  milliseconds for the racemate, (*R*)-propafenone, (*S*)-propafenone, and placebo legs, respectively. The effects on  $\Delta\text{QRS}$  are shown in Fig 2. Electrophysiological data are summarized in Table 2.

No adverse effects were reported by the volunteers in either part of the study. Blood pressure was not affected by any of the treatments.

### Discussion

These pharmacokinetic data indicate that the clearance of the (*S*)-enantiomer of propafenone is considerably reduced when it is administered with the (*R*)-enantiomer in the racemic mixture. This reduced clearance resulted in significantly higher plasma concentrations of (*S*)-propafenone after administration of 150 mg of racemate than would be predicted based on

pharmacokinetic data obtained after administration of 150 mg of (*S*)-enantiomer. Steady-state plasma concentrations after administration of 150 mg of (*S*)-propafenone averaged  $196 \pm 105$  ng/mL. Thus, one would expect mean plasma concentrations after administration of racemate, which contains only 75 mg of the  $\beta$ -blocking (*S*)-enantiomer, to be no higher than 100 ng/mL. However, we observed plasma concentrations of  $224 \pm 76$  ng/mL, indicating that clearance of (*S*)-propafenone is reduced by  $55 \pm 24\%$  after administration of racemate.

The question arises as to the mechanism underlying this reduced clearance of (*S*)-propafenone in presence of the (*R*)-enantiomer. Our recent experiments in human liver microsomes indicated that cytochrome P450 2D6-mediated 5-hydroxylation of (*S*)-propafenone, which represents the major metabolic route in vivo, is inhibited by the (*R*)-enantiomer in a competitive manner.<sup>8</sup> Accordingly, we found a prolonged elimination half-life of (*S*)-propafenone after administration of racemate when compared with the (*S*)-enantiomer alone, which is compatible with reduced clearance of (*S*)-enantiomer due to the interaction with (*R*)-propafenone while volume of distribution remains constant.

TABLE 1. Pharmacokinetic Data of (*S*)- and (*R*)-Propafenone After Administration of (*R/S*)-Propafenone, (*S*)-Propafenone, and (*R*)-Propafenone (150 mg q 6 h for 4 days) to 7 Male Volunteers

	Administration of Racemate		Administration of Enantiomers	
	( <i>S</i> )-Propafenone	( <i>R</i> )-Propafenone	( <i>S</i> )-Propafenone	( <i>R</i> )-Propafenone
CL, mL/min	$920 \pm 300^{\dagger\ddagger}$	$1460 \pm 480$	$2521 \pm 1450^*$	$1279 \pm 348$
$t_{1/2}$ , h	$4.6 \pm 1.9^{\ddagger}$	$3.3 \pm 1.9$	$2.7 \pm 0.9^{\dagger}$	$4.2 \pm 1.0$
$C_{ss}/D$ , ng/mL $^{-1} \cdot \text{mg}^{-1}$	$3.3 \pm 1.1^{\ddagger\S}$	$2.1 \pm 0.8$	$1.4 \pm 0.8^{\dagger}$	$2.3 \pm 0.7$
$t_{max}$ , h	$1.9 \pm 0.5$	$2.0 \pm 1.0$	$2.0 \pm 1.0$	$1.6 \pm 0.5$
$C_{max}/D$ , ng/mL $^{-1} \cdot \text{mg}^{-1}$	$5.2 \pm 1.7^{\ddagger\S}$	$3.5 \pm 1.4$	$2.6 \pm 1.4^*$	$3.4 \pm 1.3$

CL indicates apparent oral clearance;  $t_{1/2}$ , terminal half-life;  $C_{ss}/D$ , dose-corrected, steady-state plasma concentration; and  $C_{max}/D$ , dose-corrected maximum plasma concentration. Mode of calculation is given in "Methods" section.

\* $P < .05$  (*S*)- vs (*R*)-propafenone;  $^{\dagger}P < .01$  (*S*)- vs (*R*)-propafenone;  $^{\ddagger}P < .05$  (*S*)-propafenone after administration of racemate vs (*S*)-propafenone after administration of the enantiomer;  $^{\S}P < .01$  (*S*)-propafenone after administration of the racemate vs (*S*)-propafenone after administration of the enantiomer.



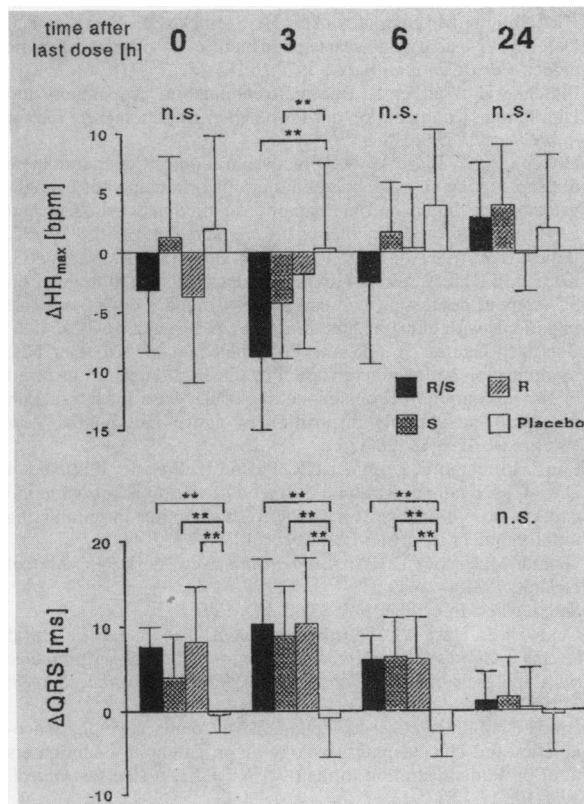


FIG 2. Bar graphs show effects of (R/S)-propafenone, (S)-propafenone, and (R)-propafenone (150 mg q 6 hours for 4 days) on maximum exercise heart rate ( $\Delta HR_{max}$ ) and QRS interval ( $\Delta QRS$ ) when compared with placebo (1 tablet q 6 hours for 4 days;  $**P < .01$ ). Time scale depicts hours after the last dose on day 4.

Another mechanism for this enantiomer-enantiomer interaction could be an interconversion from (R)-propafenone to (S)-enantiomer (such transformation has been described for 2-arylpropionic acid<sup>21</sup>). However, we observed no formation of the (S)-propafenone after administration of the (R)-enantiomer and vice versa; therefore, this possibility can be excluded. Enantioselectivity in absorption as a mechanism for the interaction appears to be unlikely, given the lack of difference in cumulative urinary excretion. The different clearance data after administration of the enantiomers are in agreement with a previous report by Brode et al,<sup>22</sup> who described decreased plasma concentrations of (S)-propafenone compared to the (R)-enantiomer after a single oral dose of 250 mg.

The  $\beta$ -blocking effects of propafenone are mediated exclusively by the (S)-enantiomer. (R)-propafenone and

the metabolites have low  $\beta$ -blocking activity and are not expected to contribute to  $\beta$ -blockade in vivo.<sup>5,23</sup> Therefore, increased plasma concentrations of (S)-propafenone as a consequence of the enantiomer-enantiomer interaction should lead to enhanced  $\beta$ -blockade. In fact, we observed a significant reduction of  $HR_{max}$  after administration of both 150 mg of the (S)-enantiomer and 150 mg of racemate, which contains only 75 mg of the (S)-enantiomer. These data indicate that the modest degree of  $\beta$ -blockade observed with racemic propafenone (eg, reduction in heart rate of 4.2% after long-term administration of 900 mg<sup>24</sup>) results largely from an enantiomer-enantiomer interaction.

Whether the  $\beta$ -blocking effects of propafenone are of any clinical relevance has been controversial. While  $\beta$ -adrenoceptor blockade can be readily demonstrated in in vitro experiments,<sup>5,25</sup> the in vivo effects are reported to be variable and inconsistent.<sup>24-28</sup> Genetically determined variability in drug metabolism has been shown to account for part of this variability with patients devoid of 5-hydroxylation activity exhibiting more pronounced  $\beta$ -blockade.<sup>23</sup> In that study as well as in the recent study by Boriani et al,<sup>24</sup>  $\beta$ -blockade was variable even among patients with normal enzyme function. We hypothesize that this variability may reflect interindividual variability in the extent of the enantiomer-enantiomer interaction described in our study.

The results obtained for prolongation of QRS interval by propafenone and its enantiomers stand in contrast to the situation described for  $\beta$ -blockade. In vitro, racemate and the 5-hydroxy-metabolite are equipotent in terms of electrophysiological activity, and other studies have shown the enantiomers to be equipotent.<sup>5,7,29,30</sup> Therefore, a metabolic interaction between the enantiomers is predicted to be of little relevance for electrophysiological effects of propafenone, the hallmark of which is prolongation of the QRS interval. Indeed, no differences were found between QRS prolongation by both enantiomers and the racemate (Fig 2). Again, these results highlight the fact that the consequences of interactions between enantiomers of a racemate depend on the individual pharmacological actions of the respective enantiomers. Moreover, as shown in the case of propafenone, these consequences pertain to the particular pharmacological activity being assessed and can be different for different types of drug action.

In summary, we present the first detailed evidence for an enantiomer-enantiomer interaction, which has implications for the effects of a racemic drug in humans. Previous reports concerning this type of interaction have been restricted to in vitro data.<sup>31-34</sup>

TABLE 2. ECG Data and Mean Arterial Pressure From 7 Male Volunteers Before and After Administration of (R/S)-Propafenone, (S)-Propafenone, (R)-Propafenone, and Placebo (150 mg q 6 hours for 4 Days)

	(R/S)-Propafenone		(S)-Propafenone		(R)-Propafenone		Placebo	
	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment
QRS, ms	100±9	109±10*	97±10	107±11†	96±11	108±14†	97±9	96±8
PQ, ms	147±15	169±14*	145±16	166±12†	148±8	172±12†	151±13	151±11
QT <sub>c</sub> , ms	403±19	401±16	402±23	399±17	410±24	406±16	394±12	398±14
MAP, mm Hg	89±8	90±12	91±9	92±6	87±11	86±11	87±7	87±6

MAP indicates mean arterial pressure.

\* $P < .05$  control vs treatment, † $P < .01$  control vs treatment.

Our findings have to be appreciated in a broader context. Forty percent of all synthetic drugs are chiral, and the vast majority (88%) is marketed as racemates.<sup>1</sup> A recent statement released from the FDA describes in detail requirements for future development of stereoisomeric drugs: pharmacokinetic and pharmacodynamic data have to be obtained for both the individual enantiomers and the racemate.<sup>35</sup> These regulatory efforts are paralleled by intense demands to market only enantiomerically pure drugs.<sup>1</sup> Consequently, considerable efforts are being undertaken by the pharmaceutical industry to develop such homochiral drugs from compounds that are already marketed as racemates (eg, *[R]*-fluoxetine, *[S]*-terfenadine, *[R]*-salbutamol, *[S]*-nitrendipine<sup>1</sup>).

Our data demonstrate that the pharmacological activity and toxicity profile of a racemate may be modulated by an enantiomer-enantiomer interaction. Therefore, the strategy of developing homochiral compounds from currently available racemates may not necessarily lead to drugs with target pharmacological effects. Our data indicate the need to consider enantiomer-enantiomer interactions in the evaluation of the pharmacological effects of any racemate.

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### References

- Ariens EJ. Nonchiral, homochiral and composite chiral drugs. *Trends Pharmacol Sci*. 1993;14:68-75.
- Turgeon J, Murray KT, Roden DM. Effects of drug metabolism, metabolites, and stereoselectivity on antiarrhythmic drug action. *J Cardiovasc Electrophysiol*. 1990;1:238-260.
- Funck-Brentano C, Kroemer HK, Lee JT, Roden DM. Propafenone. *N Engl J Med*. 1990;322:518-525.
- Bryson HM, Palmer KJ, Langtry HD, Fitton A. Propafenone. A reappraisal of its pharmacology, pharmacokinetics and therapeutic use in cardiac arrhythmias. *Drugs*. 1993;45:85-130.
- Kroemer HK, Funck-Brentano C, Silberstein DJ, Wood AJJ, Eichelbaum M, Woosley RL, Roden DM. Stereoselective disposition and pharmacological activity of propafenone enantiomers. *Circulation*. 1989;79:1068-1076.
- Burnett DM, Gal J, Zahnisser NR, Nies AS. Propafenone interacts stereoselectively with  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. *J Cardiovasc Pharmacol*. 1988;12:615-619.
- Stoschitzky K, Klein W, Stark G, Stark U, Zernig G, Graziadei I, Lindner W. Different stereoselective effects of (*R*)- and (*S*)-propafenone: clinical, pharmacologic, electrophysiologic, and radioligand binding studies. *Clin Pharmacol Ther*. 1990;47:740-746.
- Kroemer HK, Fischer C, Meese CO, Eichelbaum M. Enantiomer/enantiomer interaction of (*S*)- and (*R*)-propafenone for cytochrome P450IID6 catalyzed 5-hydroxylation: in vitro evaluation of the mechanism. *Mol Pharmacol*. 1991;40:135-142.
- Siddoway LA, Thompson KA, McAllister CB, Wang T, Wilkinson GR, Roden DM, Woosley RL. Polymorphism of propafenone metabolism and disposition in man: clinical and pharmacokinetic consequences. *Circulation*. 1987;75:785-791.
- Kroemer HK, Mikus G, Kronbach T, Meyer UA, Eichelbaum M. In vitro characterization of the human cytochrome P-450 involved in polymorphic oxidation of propafenone. *Clin Pharmacol Ther*. 1989;45:28-33.
- Eichelbaum M, Gross AS. The genetic polymorphism of debrisoquine/sparteine metabolism—clinical aspects. *Pharmacol Ther*. 1990;46:377-394.
- Heim M, Meyer UA. Genotyping of poor metabolisers of debrisoquine by allele-specific PCR amplification. *Lancet*. 1990;336:529-532.
- Eichelbaum M, Spannbrucker N, Steincke B, Dengler HJ. Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. *Eur J Clin Pharmacol*. 1979;16:183-187.
- Blaschke G, Walther B. Racemattrennung von Propafenon und Diprafenon, Konfiguration der Propafenon-Enantiomeren. *Liebigs Ann Chem*. 1987;561-563.
- Hollenhorst T, Blaschke G. Direct separation of the enantiomers of propafenone, diprafenone and their major metabolites by high-performance liquid chromatography on modified cellulose and amylose chiral stationary phases. *J Chromatogr*. 1991;585:329-332.
- Bailey IK, Anderson SD, Rozea PJ, Bernstein L, Nyberg G, Korner PI. Effect of beta-adrenergic blockade with alprenolol on ST-segment depression and circulatory dynamics during exercise in patients with effort angina. *Am Heart J*. 1976;92:416-426.
- Botsch S, Gautier JC, Beaune P, Eichelbaum M, Kroemer HK. Identification and characterization of the P450 enzymes involved in N-dealkylation of propafenone: molecular base for interaction potential and variable disposition of active metabolites. *Mol Pharmacol*. 1993;43:120-126.
- Funck-Brentano C, Kroemer HK, Pavlou H, Woosley RL, Roden DM. Genetically-determined interaction between propafenone and low-dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol*. 1989;27:435-444.
- Gibaldi M, Perrier D. *Pharmacokinetics*. New York, NY: Marcel Dekker; 1982:445-449.
- Statgraphics*. Rockville, Md: STSC Inc; 1991.
- Caldwell J, Hutt AJ, Fournel-Gigleux S. The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. *Biochem Pharmacol*. 1988;37:105-114.
- Brode E, Müller-Peltzer H, Hollmann M. Comparative pharmacokinetics and clinical pharmacology of propafenone enantiomers after oral administration to man. *Meth Find Exp Clin Pharmacol*. 1988;10:717-727.
- Lee JT, Kroemer HK, Silberstein DJ, Funck-Brentano C, Lineberry MD, Wood AJJ, Roden DM, Woosley RL. The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. *N Engl J Med*. 1990;322:1764-1768.
- Boriani G, Capucci A, Strocchi E, Marchesini B, Santarelli A, Biffi M, Magani B.  $\beta$ -Blocking properties of propafenone in extensive oxidisers: a study on heart rate behaviour during Holter monitoring. *Drug Invest*. 1993;6:25-32.
- McLeod AA, Stiles GL, Shand DG. Demonstration of beta-adrenoceptor blockade by propafenone hydrochloride: clinical pharmacologic, radioligand binding and adenylate cyclase activation studies. *J Pharmacol Exp Ther*. 1984;228:461-466.
- Hill MR, Gotz VP, Harman E, McLeod E, Hendeles L. Evaluation of asthmogenicity of propafenone, a new antiarrhythmic drug: comparison of spirometry with metacholine challenge. *Chest*. 1986;90:698-702.
- Müller-Peltzer H, Greger G, Neugebauer G, Hollmann M. Beta-blocking and electrophysiological effects of propafenone in volunteers. *Eur J Clin Pharmacol*. 1983;25:831-833.
- Cherix EC, Krijne R, Brugada P, Heymeriks J, Wellens HJJ. Lack of clinically significant beta-blocking effect of propafenone. *Eur Heart J*. 1987;8:53-56.
- Thompson KA, Iansmith DHS, Siddoway LA, Woosley RL, Roden DM. Potent electrophysiologic effects of the major metabolites of propafenone in canine Purkinje fibers. *J Pharmacol Exp Ther*. 1988;244:950-955.
- Malfatto G, Zaza A, Forster M, Sodowick B, Danilo P, Rosen MR. Electrophysiologic, inotropic and antiarrhythmic effects of propafenone, 5-hydroxypropafenone and N-depropylpropafenone. *J Pharmacol Exp Ther*. 1988;246:419-426.
- Nakano M, Chikai T, Matsubara T. Enantiomer/enantiomer interaction on N-monomethylation of diuretic in rat liver microsomes. *Drug Metab Dispos*. 1993;21:542-543.
- Wilson BK, Thompson JA. Glucuronidation of propranolol by dog liver microsomes: effects of enantiomeric inhibition and detergent treatment on stereoselectivity. *Drug Metab Dispos*. 1984;12:161-164.
- Wright JA, Cho AK, Gal J. The metabolism of amphetamine in vitro by rabbit liver preparations: a comparison of *R*(-) and *S*(+) enantiomers. *Xenobiotica*. 1977;7:257-266.
- Ames MM, Frank SK. Stereochemical aspects of para-chlor-amphetamine metabolism. *Biochem Pharmacol*. 1982;31:5-9.
- FDA. FDA's policy statement for the development of new stereoisomeric drugs. *Chirality*. 1992;4:338-340.

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