Stereoselective steady state disposition and action of propafenone in Chinese subjects

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Aims To investigate the steady state disposition and action of racemic propafenone and its enantiomers and the potential for an enantiomer-enantiomer interaction in Chinese subjects.

Methods Eight healthy male Chinese individuals received in a double-blind, randomized, cross-over study racemic propafenone (150 mg every 6 h), (S)-, and (R)-propafenone (150 mg each every 6 h) and placebo orally for 4 days. During the last dosing interval the plasma concentrations of both enantiomers of propafenone were measured and ECG, blood pressure (MAP) and heart rate were monitored.

Results Whereas the apparent elimination half-life ($t_{1/2,z}$), mean residence time (MRT) and time to reach peak concentrations (t_{max}) of (S)- and (R)-propafenone were similar and independent of the administered agent, significant differences were observed in the apparent oral clearance (CL_O) of the enantiomers. During dosing with racemic propafenone CL_O of (S)- and (R)-propafenone averaged ($\pm$ s.d.) 1226 ± 751 and 1678 ± 625 ml min⁻¹, respectively ($P=0.024$). Following the administration of the pure enantiomers CL_O of (S)-propafenone increased ($P=0.007$) to 2028 ± 959 ml min⁻¹ and that of (R)-propafenone was reduced ($P=0.042$) to 1318 ± 867 ml min⁻¹. Both enantiomers and the racemate caused about a 10% increase in the QRS duration ($P<0.05$) and PR-interval ($P<0.01$) when compared with placebo. The increase in maximum exercise heart rate was significantly ($P<0.05$) attenuated only at 3 h following the administration of the racemate and the S-enantiomer. MAP and QT_C were not affected significantly.

Conclusions These data indicate that the stereoselective disposition of propafenone is similar in Chinese and Caucasian subjects (previously published findings), the (R)-enantiomer being cleared more rapidly. A similar enantiomer-enantiomer interaction also occurred. Thus, when the racemate was given, the elimination of (S)-propafenone was impaired and that of the (R)-form accelerated compared with single enantiomer administration. The results indicate that dosage adjustments are probably not required in Chinese patients receiving propafenone.

Keywords: propafenone, enantiomers, interactions, pharmacokinetics, pharmacodynamics, racial differences

Introduction

Many drugs are given as racemates to various populations of different ethnic origin. Therefore stereoselective and ethnic aspects have to be considered in assessing drug disposition and response as both factors might contribute to interindividual variability in drug action [1]. Recently racial differences between Caucasian and Chinese subjects both in the pharmacokinetics and pharmacodynamics of morphine [2], atropine [3] and propranolol [4] have been reported. For the latter, differences in its stereoselective disposition between Caucasians and Chinese have also been observed [5].

Propafenone used widely for the treatment of arrhythmias, represents another important racemic drug which is structur-

ally related to β -adrenoceptor antagonists and which possesses β -adrenoceptor antagonistic activity residing mainly in the (S)-enantiomer [6, 7]. Therefore it could be speculated that the pharmacokinetics and pharmacodynamics of propafenone might exhibit interethnic differences similar to those of propranolol. In addition, it was recently demonstrated in Caucasians (Germans) that the clearance of (S)-propafenone was significantly lower during treatment with racemic propafenone compared with when the (S)-enantiomer was given alone [8]. Therefore, the present study was performed: 1) to determine whether the enantiomers of propafenone interact in Chinese subjects in a similar manner to Caucasians, and 2) to evaluate whether the stereoselective disposition and action of propafenone differs between Chinese and Caucasian subjects.

Methods

Subjects

After written informed consent was obtained, eight healthy, nonsmoking, drug-free male volunteers (19–22 years, 60–80 kg) participated in the double-blind, placebo controlled study which had been approved by the institutional ethics committee of the university hospital. The study was designed to detect a 30% difference (80% power at $P < 0.05$) in the principle parameters of interest (oral CL and AUC). All subjects were phenotyped with metoprolol [10] and only extensive metabolisers with respect to CYP2D6, which partially metabolises propafenone [11], were included. Basal heart rate averaged ($\pm$ s.d.) 69 ± 10 beats min^{-1} (placebo trial), 73 ± 13 beats min^{-1} (racemic trial), 73 ± 8 and 70 ± 8 beats min^{-1} ((S)- and (R)-propafenone respectively). 12-channel ECG-recordings exhibited no abnormalities.

Study design

All subjects received in random order racemic propafenone, (S)-propafenone, (R)-propafenone (150 mg every 6 h) and placebo (1 tablet every 6 h) orally for 4 days. There was a wash-out period of at least 7 days between each study phase. Blood samples were taken before the first dose and on day 4 before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 24 h after drug administration. ECG, blood pressure (MAP) and exercise heart rate (HR_{max}) [12] were monitored and recorded at 0, 3, 6 and 24 h.

Preparation of study medication

Racemic propafenone HCl (Tai Cang Pharmaceutical Company China) was separated into R- and S-enantiomers according to Blaschke & Walther [13] with some modifications. In brief, the racemate was suspended in a mixture of 25% ammonia solution and dichloromethane (1:3 v/v). In order to ensure a complete dissolution and extraction of the propafenone base, the pH of the aqueous phase was increased to ≥ 12 by addition of more ammonia and the mixture was vigorously shaken. The organic phase was separated, dried over sodium sulfate, filtered and evaporated to dryness. The racemic propafenone base and an equimolar amount of (-)-ditoluyll tartaric acid were dissolved in 2-butanone/ H_2O (98:2 v/v) and allowed to crystallize overnight at room temperature. After the colourless crystals were filtered, dried and purified with 2-butanone/ H_2O (98:2 v/v), the diastereomeric salt was obtained and subsequently suspended in a mixture of 25% ammonia solution and dichloromethane (1:6 v/v). The organic phase was separated and dried. (R)-propafenone base was obtained as an oil which was recrystallized from n-hexane. (S)-propafenone base was resolved from racemic propafenone and treated analogously with (+)-ditoluyll tartaric acid. The optical purities of R- and S-propafenone as determined by the described h.p.l.c.-assay were greater than 99.8%.

To avoid confounding galenic effects on oral bioavailability, tablets containing (R/S)-, (R)- and (S)-propafenone were prepared by identical pharmaceutical procedures and their *in vitro* dissolution rates were determined by the

rotating basket method according to standardized test criteria (Chinese Pharmacopoeia, Chinese Health Ministry 1995, second section, appendix 66). For comparison, racemic propafenone tablets (Knoll AG, Ludwigshafen, Germany) used in a previous study [8], were also tested.

Determination of the enantiomers of propafenone in plasma

Plasma concentrations of (S)- and (R)-propafenone were measured by a recently described stereoselective h.p.l.c. assay [8, 14] with slight modifications. A 250×4.6 mm ODS II column and acetonitrile: water: glacial acetic acid (600:400:0.1 by volume) as eluent (1.0 ml min^{-1}) were used with u.v. detection at 208 nm. The limit of quantification was 10 ng ml^{-1} and the day to day coefficient of variation averaged 3.5% for (S)-propafenone and 4.6% for (R)-propafenone. Standard curves were linear ($r \geq 0.998$) between 10 and 1000 ng ml^{-1} . After derivatisation acetonitrile was used as solvent and samples were protected from light. Recoveries of (S)- and (R)-propafenone from plasma were 70.1 and 69.1%, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated model-independently by the TopFit programme [15]. The area under the curve (AUC) for the last dosing interval (0–6 h) on day 4 was calculated by the trapezoidal rule and mean steady state plasma concentrations ($C_{\text{ss}} = \text{AUC}/\tau$) were corrected for the administered dose (C_{ss}/D). Peak concentrations (C_{max}) and the time of C_{max} (t_{max}) were obtained directly from the data. Apparent elimination half-life ($t_{1/2}$) was estimated from the four last measurable time points (2.5–6 h). Mean residence time (MRT) was calculated according to the standard equation AUMC/AUC where AUMC represents the first moment curve. Oral clearance (CL_0) was derived from D/AUC .

Pharmacodynamic analyses

ECG data (QRS, PR, QT_c , HR and HR_{max}) were calculated from 10 recorded intervals and mean values taken.

Statistics

All data are presented as mean $\pm$ s.d. Pharmacokinetic parameters of (S)- and (R)-propafenone after administration of the individual enantiomers and the racemate were compared using a paired *t*-test. Pharmacodynamic effects were analyzed by multifactor ANOVA (Statgraphics; Rockville, MD).

Results

Pharmacokinetics

Racemic propafenone and its two enantiomers were administered in identical galenic formulations to prevent any confounding influence of absorption on drug elimination. As can be seen from Figure 1 the dissolution of the tablets and the liberation of the active ingredients occurred

Figure 1 *In vitro* dissolution time profiles of (S)-propafenone ($\square$), (R)-propafenone ($\triangle$) and the racemate ($\circ$). For comparison, data for the racemic drug (racemate Knoll® ($\diamond$)) used in previous study of healthy Caucasian men [8] are included.

Figure 2 Dose corrected mean steady state plasma concentrations of a) (S)- and b) (R)-propafenone after treatment of eight male Chinese for 4 days with the racemic drug ($\circ$) or the two individual enantiomers ($\bullet$).

rapidly *in vitro* and with a very similar pattern. Within 12 min $\geq 90\%$ of the active drugs had dissolved from all three preparations and from the German reference product used previously, [8].

In vivo peak concentrations ($C_{\max}$) were reached at the same time ($t_{\max}$) which is consistent with active drug from each preparation being absorbed at about the same rate (Figure 2). Following $C_{\max}$ in most individuals a mono-exponential decline in the plasma concentration was evident and the resulting $t_{1/2}$ did not differ significantly between the two enantiomers. Likewise, MRT was similar for (S)- and (R)-propafenone and independent of the preparation administered (Table 1).

The most striking differences were seen in the AUC and the derived parameters CL_O and dose-corrected mean steady state plasma concentrations (C_{ss}/D). Following racemic drug administration the mean plasma concentrations of (S)-propafenone were higher and consequently CL_O was lower than the corresponding values for (R)-propafenone (see Table 1,). However, when both enantiomers were administered alone, the dose-corrected steady-state concentrations of (S)-propafenone decreased and CL_O increased significantly when compared to the values after racemic administration (95% C.I. for the difference in CL_O 304 to

1300 ml min⁻¹). In contrast plasma concentrations of (R)-propafenone increased and CL_O decreased (95% C.I. for the difference ranged from -17 to -704 ml min⁻¹) when compared with the data from racemic drug administration (see Table 1). Thus, during steady state conditions the elimination of each enantiomer was affected by the presence of its optical antipode. This is also evident from the S/R-ratio of the AUC which changed ($P < 0.001$) from 1.49 (administration of racemate) to 0.64 (administration of individual enantiomers).

Pharmacodynamics

As expected from a sodium channel blocking drug racemic propafenone caused a modest (10–15%) but significant prolongation of the QRS and PR intervals particularly 3 and 6 h post-dose. Similar but less pronounced effects were seen after dosing with both enantiomers. A minor increase in the QT_C interval was observed, which did not reach statistical significance (Table 2).

As (S)-propafenone also has weak β -adrenoceptor blocking properties some changes in maximum exercise heart rate ($HR_{\max}$) might have been anticipated following individual enantiomer and racemate administration. The attenuation of $HR_{\max}$ was significant ($P < 0.05$) but only at 3 h following racemic and (S)-propafenone dosing.

Blood pressure was not affected by any of the treatments and no adverse events were reported by the healthy volunteers during any part of the study.

Discussion

The pharmacokinetic data clearly demonstrate that the disposition of (R)- and (S)- propafenone depends on whether they are administered as pure enantiomers or as racemate. No differences were observed in MRT and $t_{\max}$, indicating that absorption was not affected. However, there were significant differences in the mean AUCs and derived kinetic parameters C_{ss}/D and CL_O (Table 1).

The decreased elimination of the (S)-enantiomer when given as a racemate compared to the single enantiomer is consistent with the inhibition of its hepatic elimination by (R)-propafenone, which has already been shown *in vitro* [16]. If identical enzymes are involved in the metabolism of the two enantiomers this would mean that (R)-propafenone can serve both as substrate and inhibitor.

In contrast, the elimination of (R)-propafenone was increased in the presence of (S)-propafenone compared with when only (R)-propafenone was administered. This finding is difficult to explain but may have a basis in the non-linear and saturable first pass metabolism of propafenone [17–20]. If elimination is dose-dependent, the CL_O of (R)-propafenone may be greater for the lower dose of 75 mg present in the racemate than at the higher dose of 150 mg when it was given alone. Furthermore, the smaller *in vitro* $V_{\max}$ of (R)-propafenone (5.5 pmol μg^{-1} h⁻¹), [16] compared to that of the (S)-form (10.2 pmol μg^{-1} h⁻¹) would suggest that the first pass metabolism of (R)-propafenone would be saturated at a lower dose than that of its antipode.

Isomerisation could not explain these enantiomeric

Table 1 Mean ($\pm$ s.d.) pharmacokinetic data for (S)- and (R)-propafenone after administration of racemic propafenone (150 mg every 6 h), S-propafenone and R-propafenone (150 mg every 6 h) to eight male Chinese subjects (for comparison brackets contain mean $\pm$ s.d. data from seven Caucasians [8]).

	Enantiomer <i>S</i> -propafenone	Racemate <i>S</i> -propafenone	<i>R</i> -propafenone	Enantiomer <i>R</i> -propafenone
CL _O (ml min ⁻¹)	2028 $\pm$ 959 ^{1,4} (2521 $\pm$ 1450)	1226 $\pm$ 751 ^{1,2} (920 $\pm$ 300)	1678 $\pm$ 625 ^{2,3} (1460 $\pm$ 480)	1318 $\pm$ 867 ^{3,4} (1270 $\pm$ 348)
C _{ss} /D (ng ml ⁻¹ mg ⁻¹)	1.90 $\pm$ 1.50 ^{5,8} (1.4 $\pm$ 0.8)	2.92 $\pm$ 1.48 ^{5,6} (3.3 $\pm$ 1.1)	1.97 $\pm$ 1.07 ^{6,7} (2.1 $\pm$ 0.8)	2.98 $\pm$ 1.70 ^{7,8} (2.3 $\pm$ 0.7)
t _{1/2} (h)	2.3 $\pm$ 1.1 (2.7 $\pm$ 0.9)	3.3 $\pm$ 1.6 (4.6 $\pm$ 1.9)	3.0 $\pm$ 0.7 (3.3 $\pm$ 1.9)	2.9 $\pm$ 1.5 (4.2 $\pm$ 1.0)
MRT (h)	4.5 $\pm$ 1.4	5.8 $\pm$ 2.4	5.4 $\pm$ 1.0	5.4 $\pm$ 2.5
T _{max} (h)*	2.0(1.5–2.5)	2.3 (1.5–3.0)	2.3 (1.5–3.0)	2.0 (0.5–3.0)
S/R-AUC	0.64 $\pm$ 0.18	1.49 $\pm$ 0.34 (<i>P</i> = 0.001)		

*Median (range) ¹*P* = 0.0066 ²*P* = 0.0237 ³*P* = 0.0422 ⁴*P* = 0.0009 ⁵*P* = 0.0011 ⁶*P* = 0.0023 ⁷*P* = 0.0147 ⁸*P* = 0.0073 (the corresponding numbers refer to the differences of the compared data).

Table 2 Mean ($\pm$ s.d.) ECG-data, arterial blood pressure (MAP), decrease in heart rate (Δ HR_{max}) from eight healthy male Chinese at various times following the last dose of racemic propafenone (150 mg every 6 h), propafenone enantiomers (150 mg every 6 h), and placebo.

Mean $\pm$ s.d.	Time	Racemate	<i>S</i> -Enantiomer	<i>R</i> -Enantiomer	Placebo
QRS (ms)	0 h	84 $\pm$ 14*	80 $\pm$ 13	83 $\pm$ 10*	79 $\pm$ 5
	3 h	90 $\pm$ 6**	85 $\pm$ 5**	86 $\pm$ 10**	78 $\pm$ 4
	6 h	87 $\pm$ 5**	83 $\pm$ 8**	83 $\pm$ 5**	79 $\pm$ 6
	24 h	81 $\pm$ 13	79 $\pm$ 13	79 $\pm$ 10	79 $\pm$ 9
PR (ms)	0 h	168 $\pm$ 8**	163 $\pm$ 14**	168 $\pm$ 8**	152 $\pm$ 10
	3 h	168 $\pm$ 7**	160 $\pm$ 9**	160 $\pm$ 9**	153 $\pm$ 10
	6 h	170 $\pm$ 9**	157 $\pm$ 19	162 $\pm$ 16*	155 $\pm$ 13
	24 h	147 $\pm$ 24	155 $\pm$ 8	152 $\pm$ 13	153 $\pm$ 18
QT _c (ms)	0 h	373 $\pm$ 11	372 $\pm$ 21	375 $\pm$ 17*	372 $\pm$ 10
	3 h	384 $\pm$ 20	381 $\pm$ 19	380 $\pm$ 13	372 $\pm$ 12
	6 h	373 $\pm$ 22	367 $\pm$ 20	376 $\pm$ 13	374 $\pm$ 10
	24 h	369 $\pm$ 22	360 $\pm$ 24	362 $\pm$ 23	365 $\pm$ 13
MAP (mmHg)	0 h	87 $\pm$ 4	85 $\pm$ 6	87 $\pm$ 3	85 $\pm$ 3
	3 h	84 $\pm$ 5	82 $\pm$ 4	87 $\pm$ 3	83 $\pm$ 2
	6 h	86 $\pm$ 6	82 $\pm$ 6	85 $\pm$ 5	84 $\pm$ 6
	24 h	84 $\pm$ 3	81 $\pm$ 4	85 $\pm$ 6	84 $\pm$ 6
Δ HR _{max} (beats min ⁻¹)	0 h	-6.4 $\pm$ 10.8	-4.0 $\pm$ 4.6	0.5 $\pm$ 8.1	2.3 $\pm$ 7.7
	3 h	-9.8 $\pm$ 7.5*	-8.6 $\pm$ 6.3*	0.5 $\pm$ 11.9	1.5 $\pm$ 13.0
	6 h	-4.9 $\pm$ 9.7	-2.1 $\pm$ 5.5	-2.5 $\pm$ 8.6	5.6 $\pm$ 9.4
	24 h	-2.3 $\pm$ 4.0	-0.9 $\pm$ 4.0	-1.8 $\pm$ 9.6	3.5 $\pm$ 7.3

P* < 0.05, *P* < 0.01 (*verum* vs placebo).

interactions, since following the administration of each enantiomer, the antipode was not detected in blood.

As the β -adrenoceptor antagonistic property of propafenone resides mainly in the (S)-enantiomer significant attenuation of HR_{max} was only observed following the administration of racemic and (S)-propafenone. Owing to the elevated plasma concentrations of (S)-propafenone in the presence of (R-) propafenone, the racemic drug (containing 75 mg of (S)-propafenone) was about equieffective as 150 mg of (S)-propafenone (Table 2). In contrast, sodium channel blocking effects, measured as prolongation of PR- and QRS-intervals, were observed to a similar extent (7–14%) with all three agents.

The pharmacodynamic effects induced by racemic propafenone and its two enantiomers in Chinese subjects were

qualitatively and quantitatively similar to those seen in young male Caucasians [8]. This indicates that there are no clinically relevant differences in responsiveness to propafenone between these two ethnic groups.

In addition, the derived pharmacokinetic parameters (e.g. CL_O, C_{ss}/D, t_{1/2}, t_{max}) and the enantiomeric interaction observed in our population was similar to that observed in Caucasians [8]. Thus, racial differences between these populations in the disposition of propafenone, which is metabolized mainly by CYP2D6 in EM [9, 21] and to a lesser extent by CYP3A4, appear to be absent. Based on two case reports of an interaction between theophylline and propafenone [22, 23], it could be speculated that CYP1A2 might also be involved in the metabolism of propafenone. If this is the case, our results would indicate that CYP1A2

has similar activities in Chinese and Caucasian subjects. Because of the small differences observed between both populations and the large interindividual variability of the data, a type II error cannot be completely ruled out; however an unrealistic sample size of 60 to 100 subjects in each group would be necessary to proof this theoretical possibility.

In conclusion, the mutual interaction between the enantiomers of propafenone is also present in Chinese subjects. Since the pharmacokinetics and pharmacodynamics of propafenone does not differ between Caucasians and Chinese, dosage modifications are probably not required for this class I antiarrhythmic drug in oriental populations.

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