A mechanism of D-(+)-sotalol effects on heart rate not related to β -adrenoceptor antagonism

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1 In order to determine whether the effects of d- or (+)-sotalol on heart rate are mediated by β -adrenoceptor antagonism or might be due to other actions, we administered (+)-sotalol (400 mg every 12 h), atenolol (50 mg every 12 h) and placebo to eight healthy volunteers in a randomized, double-blind, crossover study. We also studied the affinity of human lymphocyte β_2 -adrenoceptor for (+)-sotalol, (–)-sotalol, and (±)-propranolol.

2 Compared with placebo, atenolol significantly reduced resting, standing and peak exercise heart rate whereas (+)-sotalol significantly reduced standing and peak exercise heart rate, but not resting heart rate. Atenolol significantly reduced resting, standing and peak exercise blood pressure while (+)-sotalol had no effect.

3 (+)-sotalol and atenolol both shifted the relationship between isoprenaline dose and heart rate to the right by similar degrees at the dosages tested.

4 (+)-sotalol but not atenolol significantly prolonged QTc interval. The degree of QTc prolongation due to (+)-sotalol, which has been shown to parallel action potential prolongation in the sinus node, correlated significantly with the reduction in peak exercise heart rate it produced ($r = 0.71$, $n = 8$, $P < 0.05$).

5 The affinity of the human lymphocyte β_2 -adrenoceptor was approximately 60-fold greater for (–)-sotalol (K_i , 108 ± 12 nM) than for (+)-sotalol (K_i , $6,410 \pm 1,020$ nM), and approximately 20,000-fold greater for (±)-propranolol (K_i , 0.33 ± 0.08 nM) than for (+)-sotalol.

6 The low affinity of (+)-sotalol for binding to the human β_2 -adrenoceptor and the contrasting effects of (+)-sotalol on heart rate and blood pressure, indicate that β -adrenoceptor antagonism is unlikely to contribute to the effect of (+)-sotalol on heart rate.

7 The relationship between (+)-sotalol's effects on repolarization and on exercise heart rate, suggest that class III activity of this enantiomer in the sinus node is responsible for its effects on heart rate in man.

Keywords sotalol atenolol enantiomer heart rate β_2 -adrenoceptor

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Introduction

Bradycardia can be due to alteration of sinus node action potential characteristics by one or more of five basic mechanisms: 1) decrease in the rate of spontaneous diastolic depolarization, 2) increase in the threshold potential at which action potential upstroke occurs, 3) decrease in upstroke velocity, 4) increase in the maximum diastolic potential, and 5) prolonged repolarization (Millar & Vaughan Williams, 1982). The first mechanism is the major explanation of the bradycardia induced by β -adrenoceptor antagonists whereas prolongation of action potential duration is responsible for the bradycardia induced by drugs such as melperone (Millar & Vaughan Williams, 1982).

Racemic sotalol is a non-selective β -adrenoceptor antagonist which also prolongs action potential duration (class III activity) in the sinus node and in the myocardium (Kato *et al.*, 1986; Singh & Nademanee, 1987). Either of these two properties might contribute to the bradycardia observed during sotalol therapy. Animal studies have shown that the ability of the d- or (+)-enantiomer of sotalol to antagonize the increase in heart rate produced by isoprenaline is approximately 20 times less than that of the l- or (-)-enantiomer (Gomoll & Bartek, 1986). However, both enantiomers share a similar ability to prolong action potential duration, in sinus node preparations as well as in atrial and ventricular myocardium, without altering other action potential characteristics (Hafner *et al.*, 1988; Kato *et al.*, 1986). Therefore, animal studies indicate that (-)-sotalol is responsible for twenty times as much of the β -adrenoceptor blocking properties of racemic sotalol as (+)-sotalol and that both enantiomers contribute to its class III activity. Studies in man have shown that administration of (+)-sotalol slows heart rate while it induces minimal changes in parameters, such as atrio-hissian conduction time and PR intervals, which are prolonged by β -adrenoceptor antagonists (Johnston *et al.*, 1985; McComb *et al.*, 1987; Schwartz *et al.*, 1987). Also, (+)-sotalol does not usually lower resting blood pressure. This discrepancy between the effects of (+)-sotalol on heart rate and its effects on other parameters usually altered by β -adrenoceptor antagonists suggest that a mechanism other than β -adrenoceptor blockade such as prolongation of action potential duration in the sinus node might contribute to its effects on heart rate.

The objective of the present study was to test the hypothesis that β -adrenoceptor blockade is not responsible for heart rate response to (+)-

sotalol in humans. This hypothesis was addressed by comparing the effects of (+)-sotalol, atenolol, and placebo on heart rate and blood pressure at rest, during exercise and during isoproterenol testing in normal volunteers and by comparing the affinity of human lymphocyte β_2 -adrenoceptor for (+)-sotalol, (-)-sotalol, and ($\pm$)-propranolol. The β_1 -selective adrenoceptor antagonist atenolol was chosen because its pharmacokinetic profile is similar to that of sotalol (Riddell *et al.*, 1987) and (+)-sotalol (Kato *et al.*, 1986; Poirier *et al.*, 1990) but lacks effects on repolarization. Also, it can be expected that the effects of a β_1 -selective adrenoceptor antagonist on the relationship between isoprenaline dose and heart rate increase are less than those produced by a non-selective agent (Pringle *et al.*, 1987). Therefore, by comparing the effects of (+)-sotalol with those of atenolol we would not minimize the effects of (+)-sotalol on heart rate by comparing it to a reference β -adrenoceptor antagonist with pronounced effects on this parameter. We correlated the extent of heart rate change during (+)-sotalol with the extent of its class III activity (QT interval). Non-invasive direct recording of sinus node action potential is not feasible in man. However, animal studies have shown that (+)-sotalol prolongs action potential duration in a concentration-dependent and similar manner in isolated sinus node and ventricular muscle preparations (Kato *et al.*, 1986). We therefore assessed the relationship between QT change and heart rate as an index of (+)-sotalol's effects on action potential in sinus node.

Methods

This was a randomized, double-blind, three period-crossover study performed in eight non-smoking healthy volunteers (six females and two males; mean $\pm$ s.d. age: 31 ± 4 years). The study was performed at the Vanderbilt University Clinical Research Center and was approved by the local Committee for the Protection of Human Subjects. All subjects gave written informed consent and showed no abnormality on routine medical examination, twelve lead electrocardiogram, chest X-ray and standard laboratory tests.

Study design

In order to familiarize volunteers with the procedures used in the study, two exercise tests and one isoprenaline test were performed by each subject less than 2 weeks prior to entry into the

active study. Subjects were then asked to take one of the three treatments, 1. (+)-sotalol (400 mg every 12 h) and a placebo of atenolol; 2. atenolol (50 mg every 12 h) and a placebo of (+)-sotalol; or 3. a placebo of atenolol and a placebo of (+)-sotalol, in a random order on three consecutive 1 week periods. The stereochemical purity of (+)-sotalol was > 99%. Commercially available tablets of atenolol were used. Each 1 week period was divided into a 3.5 day-treatment phase and a 3.5 day-wash-out phase. During the treatment phase, subjects were asked to take one of the treatments orally at 09.00 h and 21.00 h, starting one evening. Seven to seven and a half hours after the 6th dose, they were asked to come to the Clinical Research Center for an exercise test. This was a maximal treadmill exercise test performed according to the protocol of Bruce *et al.* (1973). Subjects were then discharged, took the 7th and last dose of their treatment at 21.00 h the same evening, and returned to the Clinical Research Center the following morning at 09.00 h for an isoprenaline test which was performed according to the protocol of Cleaveland *et al.* (1972). The next 3.5 days were a drug-free wash-out period. Subjects then entered the next 1 week period of the study during which the same tests were performed while the second treatment was administered. The third and last treatment was administered the following week.

Measurements of heart rate and blood pressure

The isoprenaline test was performed in a dark and silent room which was kept at a controlled and stable temperature. First, an intravenous line (Butterfly 19G or 20G) was inserted in a major forearm vein and a period of rest in the supine position was observed. During this period, heart rate (measured over a 60 s period), and systolic and diastolic blood pressures were measured every 2 min using the non-perfused arm. Resting heart rate, and resting systolic and diastolic blood pressures were obtained when three successive measurements showed no change. This typically occurred after 25 to 30 min. The dose of isoprenaline required to increase heart rate by 25 beats min^{-1} (CD_{25}) was calculated according to the simple linear regression method described by Jackson *et al.* (1987). Standing heart rate, and standing systolic and diastolic blood pressures were measured just prior to exercising, at the end of a 5 min period in the standing position. Peak exercise heart rate and peak systolic blood pressure were measured just before the end of exercise. Except for resting supine heart rate which

was measured by palpation of the radial artery over 1 min, all heart rate measurements were obtained by averaging the shortest five consecutive RR intervals of the electrocardiogram. Blood pressure was measured with a non random zero mercury sphygmomanometer using Korotkoff phase I and V for systolic and diastolic blood pressure measurements respectively. The same manometer was used throughout the study.

Measurements of QT interval and correction for heart rate

During maximal treadmill test, the electrocardiogram was recorded at a paper speed of 50 mm s^{-1} for 15 s every 1.5 min from a modified chest lead V_2 or V_3 using a Delmar Avionics Model 412 Recording Station linked to a Hewlett Packard model 7754A recorder. For a given subject, the electrodes were placed in the same anatomical site for each study period. Three QT and RR intervals were measured at each stage of exercise using a digitizing pad (Bitpad One, Summagraphics, Seymour, CT) linked to a microcomputer. The end of the T wave was defined according to the criterion of Lepeschkin & Surawicz (1952). All intervals were measured prior to breaking the medication code. Rather than using Bazett's formula, QT/RR data from each subject were separately fitted to the mono-exponential formula $\text{QT} = \text{A} - \text{B} \cdot \exp^{-\text{C} \cdot \text{RR}}$ (Puddu *et al.*, 1988; Sarma *et al.*, 1984) by a nonlinear regression analysis program based on a maximum likelihood least square estimation of nonlinear parameters. In this monoexponential formula, QT and RR are the measured electrocardiographic intervals and A, B and C are regression parameters obtained after iterative fitting to the data points using the equation. The QT interval normalized for a heart rate of 60 beats min^{-1} (QTc) was calculated from the best fit obtained with this exponential function.

Plasma concentrations of (+)-sotalol

Just prior to exercising, one blood sample was drawn in each subject. Plasma concentration of (+)-sotalol was determined by h.p.l.c. as previously described (Bartek *et al.*, 1987). This method is for quantification of sotalol and is not specific for (+)-sotalol. Use of this non-specific assay is based on studies, using a stereospecific assay, which demonstrated that racemization of (+)-sotalol does not occur in man (data on file at Bristol Myers Research and Development Corporation). The method gives linear results from 50 to 6000 ng of sotalol ml^{-1} and has a

Figure 1 Effects of placebo, (+)-sotalol and atenolol on heart rate. The mean $\pm$ s.d. resting (upper panel), standing (middle panel) heart rate, and % reduction in peak exercise heart rate (lower panel) is represented. *: $P < 0.05$; NS: not significant.

lower limit of quantification of 50 ng ml^{-1} . The accuracy and precision of the method ranges from 98 to 100% for concentrations of 200 to 4000 ng of sotalol ml^{-1} of plasma.

Affinity of β_2 -adrenoceptors for (+)-sotalol, (-)-sotalol, and ($\pm$)-propranolol

The affinity of human lymphocyte β_2 -adrenoceptor for (+)-sotalol, (-)-sotalol and ($\pm$)-propranolol was determined as previously described (Kroemer *et al.*, 1989). Atenolol was not used in the β_2 -adrenoceptor competition studies because it has already been shown that its affinity for β_2 -adrenoceptors is 30 to 40 times less than for β_1 -adrenoceptors (Abrahamsson *et al.*, 1988; Golf *et al.*, 1987) whereas sotalol and propranolol both are non-selective β -adrenoceptor blockers. Briefly, lymphocytes from five healthy, drug free, non-smoking volunteers were prepared. Competition binding studies were performed in duplicate with [^{125}I]-iodopindolol ($2,200 \text{ Ci mmol}^{-1}$; New England Nuclear, Boston, Massachusetts) as the radioligand (20 pmol) in presence of either (+)-sotalol, (-)-sotalol (both 10^{-4} to 10^{-9} M), or ($\pm$)-propranolol (10^{-7} to 10^{-12} M). Non-specific binding was

assessed in the presence of 0.1 mM isoprenaline and was between 5% and 10% of total binding. Displacement curves were analyzed with a four-parameter logistic equation that provides estimates for IC_{50} (the concentration of the competitor that displaced 50% of the specific binding) and the slope factor (pseudo-Hill coefficient) (De Lean *et al.*, 1978). A constant factor (K_i) describing the affinity of the β -adrenoceptor for each of the competitor ligands was determined by analysis of the binding data with the computer program LIGAND (Munson & Rodbard, 1980).

Statistical analysis

Data were analyzed in part by using the computer program MRTOD (Retriever Data Systems, Seattle, WA). Results obtained under the different treatments were compared by two-way analysis of variance after verification that data were normally distributed. When the null hypothesis of no difference could be rejected, multiple comparisons were then performed using Duncan's test (Steel & Torrie, 1980). Analysis of the relationship between peak heart rate reduction and QTc prolongation during (+)-sotalol therapy was performed using standard mean least square linear regression techniques. A difference was considered significant when the probability of a type I error was less than 5%. Unless otherwise specified, results are reported as mean $\pm$ one s.d.

Results

Effects of (+)-sotalol, atenolol and placebo on heart rate

Resting heart rate during (+)-sotalol administration was $54.4 \pm 7.5 \text{ beats min}^{-1}$. This value was not significantly different from the resting heart rate of $58.4 \pm 6.8 \text{ beats min}^{-1}$ observed during placebo. However, compared with (+)-sotalol and placebo, atenolol significantly decreased resting heart rate to $47.7 \pm 5.5 \text{ beats min}^{-1}$ ($P < 0.01$) (Figure 1, upper panel). Compared with placebo, (+)-sotalol significantly decreased standing heart rate from $85.4 \pm 9.3 \text{ beats min}^{-1}$ to $71.9 \pm 13.1 \text{ beats min}^{-1}$ ($P < 0.01$). Atenolol administration resulted in a further decrease in standing heart rate to $57.0 \pm 7.6 \text{ beats min}^{-1}$ ($P < 0.01$ vs (+)-sotalol) (Figure 1, middle panel). Similarly, both (+)-sotalol and atenolol significantly reduced peak exercise heart rate compared with placebo, but the $7.7 \pm 3.8\%$ reduction by (+)-sotalol was significantly less than the $15.9 \pm 3.0\%$ reduction by atenolol

Figure 2 Isoprenaline dose-response curves during placebo (●), (+)-sotalol (△) and atenolol (○). Each point represents the mean $\pm$ s.e. mean of the eight subjects. The dashed line corresponds to a 25 beats min^{-1} increase in heart rate from baseline.

($P < 0.001$) (Figure 1, lower panel). Finally, both atenolol and (+)-sotalol shifted the heart rate response vs dose of isoprenaline curve to the right (Figure 2). The CD_{25} was $0.99 \pm 0.51 \mu\text{g}$ during placebo, $1.77 \pm 1.05 \mu\text{g}$ during atenolol ($P < 0.01$) and $2.27 \pm 1.25 \mu\text{g}$ during (+)-sotalol ($P < 0.01$ vs placebo; $P = \text{not significant}$ vs atenolol).

Effects of (+)-sotalol, atenolol and placebo on blood pressure and QTc interval

(+)-sotalol did not significantly alter systolic and diastolic blood pressures, at rest or during standing, nor did it alter peak exercise systolic blood pressure (Table 1). In contrast, atenolol significantly decreased all these parameters (Table 1). Compared with placebo, (+)-sotalol but not atenolol prolonged QTc interval (Table 1). The percent reduction in peak exercise heart rate with (+)-sotalol compared with placebo was sig-

Figure 3 Correlation between percent reduction in peak exercise heart rate and percent QTc prolongation during (+)-sotalol therapy.

nificantly correlated with the % QTc prolongation ($r = 0.709$, $P < 0.05$) (Figure 3).

Plasma concentration of (+)-sotalol

Mean plasma concentration of (+)-sotalol prior to exercising was $2534 \pm 1058 \text{ ng ml}^{-1}$.

Affinity of β_2 -adrenoceptors for (+)-sotalol, (-)-sotalol, and ($\pm$)-propranolol

Each compound displaced [^{125}I]-iodopindolol from β_2 -adrenoceptors on human lymphocytes (Figure 4). The K_i values for (+)-sotalol, (-)-sotalol and ($\pm$)-propranolol were $6,410 \pm 1020 \text{ nM}$, $108 \pm 12 \text{ nM}$, and $0.33 \pm 0.08 \text{ nM}$ respectively. These values indicate that the affinity of β_2 -adrenoceptors was approximately 60-fold greater for (-)-sotalol than for (+)-sotalol and approximately 20,000-fold greater for ($\pm$)-propranolol than for (+)-sotalol.

Table 1 Effects of placebo (+)-sotalol, and atenolol on blood pressure and QTc interval

	Placebo	(+)-sotalol	Atenolol
Resting SBP (mm Hg)	110.5 ± 7.2	108.0 ± 8.6	$103.3 \pm 8.9^*$
Resting DBP (mm Hg)	68.0 ± 7.7	66.0 ± 3.7	$61.0 \pm 4.9^*$
Standing SBP (mm Hg)	115.8 ± 14.9	112.8 ± 1.35	$107.8 \pm 12.4^*$
Standing DBP (mm Hg)	79.3 ± 9.6	77.5 ± 9.0	$74.5 \pm 7.5^*$
Peak exercise SBP (mm Hg)	163.7 ± 22.7	159.0 ± 23.9	$147.5 \pm 10.3^*$
QTc interval (ms)	400 ± 31	$450 \pm 32^{**}$	398 ± 19

SBP: systolic blood pressure; DBP: diastolic blood pressure.

*: $P < 0.05$ vs placebo or (+)-sotalol; **: $P < 0.05$ vs placebo or atenolol.

Figure 4 Plot of displacement of [125 I]-iodopindolol (IPIN) from β_2 -adrenoceptors on human lymphocytes by ($\pm$)-propranolol ($\square$), ($-$)-sotalol ($\circ$) and ($+$)-sotalol ($\bullet$). Each point represents the mean of duplicate values from five experiments.

Discussion

Our results confirm those of previous studies which have shown that the significant effects of ($+$)-sotalol on heart rate contrast with its limited effects on other parameters usually altered by β -adrenoceptors antagonists (Gomoll & Bartek, 1986; McComb *et al.*, 1987; Schwartz *et al.*, 1987). Despite the use of a relatively high dose of ($+$)-sotalol, we were unable to detect any blood pressure lowering effect of this drug, even at peak exercise. Nevertheless, significant changes in standing and peak exercise heart rate were observed. Conversely, the β_1 -selective adrenoceptor antagonist atenolol induced consistent effects on heart rate and blood pressure under all our study conditions. These data therefore support the view that β -adrenoceptor blockade is not responsible for the effects of ($+$)-sotalol on heart rate. Several other arguments support this view and suggest that action potential prolongation in the sinus node contributes to the effects of ($+$)-sotalol on heart rate in man.

First, the affinity of human lymphocyte β_2 -adrenoceptors for ($+$)-sotalol was very low compared with ($-$)-sotalol and ($\pm$)-propranolol (Figure 4). Indeed, the large difference in affinity of β -adrenoceptors for ($+$)-sotalol and ($-$)-sotalol contrasts with the small difference the two enantiomers have shown in their ability to slow heart rate (Kato *et al.*, 1986; McComb *et al.*, 1987). Although no direct relationship between the K_i of ($+$)-sotalol or ($-$)-sotalol and their respective β -adrenoceptor activity has been established in man, the 60-fold smaller affinity of ($+$)-sotalol suggests that significant

β -adrenoceptor blockade does not occur with this enantiomer. Since the minimum propranolol plasma concentration associated with significant β -adrenoceptor blockade is 20 ng ml^{-1} (Coltart & Shand, 1970) and the drug is 90% protein bound (Riddell *et al.*, 1987), a free concentration of 2 ng ml^{-1} is required to produce significant β -adrenoceptor blockade. Therefore, our β -adrenoceptor binding data indicate that a concentration of ($-$)-sotalol of 650 ng ml^{-1} is required to produce significant β -adrenoceptor blockade. This is consistent with the concentrations of ($\pm$)-sotalol which have been found to be associated with β -adrenoceptor antagonism (Nattel *et al.*, 1989; Wang *et al.*, 1986). However, based on our β -adrenoceptor binding studies, the concentration of ($+$)-sotalol required to produce a significant β -adrenoceptor blocking effect is approximately $38,000 \text{ ng ml}^{-1}$, a concentration much above the concentrations we found prior to exercise testing in the present study. Although we cannot rule out that ($+$)-sotalol might bind to β_1 -adrenoceptors, the absence of blood pressure lowering effect of ($+$)-sotalol in our study suggests that clinically significant β_1 -adrenoceptor blockade does not occur with this drug. Second, if prolongation of repolarization in the sinus node, were to be one of the mechanisms which contribute to the relative bradycardia induced by ($+$)-sotalol, one would expect the effects of the drug to be most prominent when action potential duration is a significant fraction of sinus cycle length, i.e. at short cycle lengths. Indeed, ($+$)-sotalol slowed heart rate only when sinus cycle length was shortened by standing, by exercising or by isoproterenol infusion (Figures 1 and 2). Another result that supports the concept of a link between the class III activity of ($+$)-sotalol and its effects on heart rate, is the demonstration of a correlation between the extent of reduction in peak exercise heart rate and the degree of QTc prolongation (Figure 3). Caution should be observed when interpreting this correlation since it is based on the assumption that action potential prolongation in the ventricle reflects action potential prolongation in the sinus node. As mentioned earlier, *in vitro* studies support this assumption (Kato *et al.*, 1986). In fact, in the latter study, prolongation of action potential in the rabbit sinoatrial node with ($+$)-sotalol entirely accounted for the increase in sinus cycle length produced. This was not the case with ($-$)-sotalol, for which additional cycle length prolongation, presumably due to β -adrenoceptor blockade, was found.

A definite demonstration of the relationship between action potential prolongation and slow-

ing of heart rate with (+)-sotalol would require direct recording of sinus node activity. This is not currently possible using non-invasive techniques in man. The results of our study provide indirect evidence that the effects of (+)-sotalol on repolarization (i.e. its class III actions) are responsible for its effects on heart rate.

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This work was supported by grants HL-26782 and GM-31304 from the National Institutes of Health.

Dr Christian Funck-Brentano is the recipient of a Merck Sharp and Dohme International Fellowship in Clinical Pharmacology.

We thank Bristol Myers Laboratories for providing us with (+)-sotalol and its placebo, and for the determination of plasma concentrations of (+)-sotalol, ICI Pharma Laboratories for providing us with atenolol and its placebo.

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(Received 19 July 1989,
accepted 28 March 1990)