A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers

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In a placebo controlled open study in six healthy male volunteers (+)-sotalol in the dose range 0.125 mg kg⁻¹–2.0 mg kg⁻¹ intravenously, was found to have little or no β -adrenoceptor blocking activity in comparison to the racemic mixture (±)-sotalol. The repolarization effects of (+)- and (±)-sotalol on the QT_c interval however were comparable over the same dose range. The β -adrenoceptor blocking activity and repolarization effects of sotalol appear to be unrelated.

Keywords (+)-sotalol (±)-sotalol β -adrenoceptor antagonist QT_c interval

Introduction

Racemic (±)-sotalol is a non-selective β -adrenoceptor blocking drug without partial agonist or membrane stabilizing activity (Fitzgerald, 1969). In addition to its β -adrenoceptor blocking activity, (±)-sotalol has been shown to prolong the duration of the action potential and effective refractory period of cardiac muscle cells, features which are consistent with type III anti-arrhythmic activity (Strauss *et al.*, 1970; Laasko *et al.*, 1981). Evidence in animals suggests that while the (–)-isomer is responsible for the drug's β -adrenoceptor blocking activity, the (+) form is almost devoid of this effect on the β -adrenoceptors but accounts for some of the electrophysiological effects of sotalol on cardiac muscle cells (Kato *et al.*, 1984). The present study was therefore undertaken to compare the β -adrenoceptor blocking activity and cardiac repolarisation effects of (±)- and (+)-sotalol in man. A direct comparison of the two enantiomers was not possible as (–)-sotalol was not available for use in man.

Methods

Six healthy male volunteers aged 18–27 years and weighing 63–78 kg were studied after a full clinical examination and having given informed consent. The protocol of the study had been approved by the Ethics Committee of The Queen's University, Belfast. On three separate occasions the subjects received cumulative doses of (+)-sotalol (0.125, 0.25, 0.5, 1.0 and 2.0 mg kg⁻¹), (±)-sotalol (0.125, 0.25, 0.5, 1.0 and 2.0 mg kg⁻¹) or placebo as 20 ml normal saline. Each intravenous injection was administered as a 20 ml volume and given over a 5 min period. There was at least 1 week between each treatment.

On each study day the subject rested for a 30 min period in the supine position, at the end of which blood pressure, resting heart rate and QT_c interval were recorded. The subjects then stood erect for 3 min, blood pressure recorded, and a blood sample taken from an intravenous cannula. Exercise, consisting of stepping on and off a box 46 cm high at a rate of 32 steps min⁻¹ for 3 min, was performed immediately after blood sampling.

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Blood pressure was measured using a Hawksley random zero sphygmomanometer (Wright & Dore, 1970) and heart rate from a direct writing electrocardiograph as the mean of five consecutive R-R intervals at the end of the resting period and immediately after completing the exercise test. The QT_c was calculated from the electrocardiographic tracing run at a paper speed of 25 mm s^{-1} and corrected for heart rate using the formula $QT_c = QT (60/\text{HR})^{-1/2}$ (Bazett 1920). After a 30 min period in the supine position, the first dose of (+)-sotalol, (±)-sotalol or placebo was given by intravenous injection over 5 min. Twenty minutes after starting the injection repeat observations on heart rate, QT_c interval and blood pressure were made and a blood sample taken. Subsequent doses of each treatment were given at 40 min intervals with observations and blood sampling 20 min after each administration and at 5 and 7 h (resting only). Blood samples for measurement of plasma concentrations of sotalol were centrifuged and the plasma stored at -20°C until analysis. Plasma concentrations of sotalol were determined by high performance liquid chromatography (Lefebvre *et al.*, 1980). Total sotalol concentrations were measured and there was no attempt to distinguish between the two enantiomers in the assay. Comparisons of multiple data were made using analysis of variance and Duncan's multiple range test. Individual comparisons were made with the corresponding placebo values. The relationships between data were also made using product moment correlations. Results are expressed as the mean $\pm$ s.e. mean and the level of significance chosen as $P < 0.05$.

Results

Resting heart rate was significantly reduced by all but the lowest doses of (±)-sotalol and during the post-treatment period ($P < 0.05$) (Figure 1). Exercise heart rate was significantly reduced by all doses of (±)-sotalol (Figure 1). (+)-Sotalol reduced resting (67.5 ± 1.8 – $61.3 \pm 3.0 \text{ beats min}^{-1}$) and exercise (160.5 ± 7.1 → $142.9 \pm 3.1 \text{ beats min}^{-1}$) heart rate only after the highest cumulative dose of 2.0 mg kg^{-1} ($P < 0.05$). The effect of (+)-sotalol on resting heart rate persisted throughout the post-treatment period (Figure 1). During the dose escalation phase, exercise heart rate correlated with log plasma concentrations of both (±)- ($n = 30$, $r = 0.56$; $P < 0.01$) and (+)-sotalol ($n = 30$, $r = 0.43$; $P < 0.05$). No significant changes in blood pressure (erect or supine) were observed with (+)-sotalol or placebo in the six subjects. (±)-Sotalol re-

duced supine systolic blood pressure throughout the course of the study ($P < 0.01$) reaching a maximum 5 h after the administration of the first dose (118.0 ± 4.6 → $103.3 \pm 2.6 \text{ mm Hg}$; $P < 0.01$). During the period of drug administration but not in the post-treatment phase, (±)-sotalol reduced standing systolic ($P < 0.01$) and diastolic ($P < 0.05$) blood pressures. Maximum changes were seen at 180 min after drug administration for both systolic (114.3 ± 2.5 → $103.7 \pm 3.0 \text{ mm Hg}$; $P < 0.01$) and diastolic (77.3 ± 2.5 → $72.0 \pm 4.2 \text{ mm Hg}$; $P < 0.05$) blood pressures. A significant correlation between the log plasma concentration of (±)-sotalol and supine systolic blood pressure was apparent ($n = 45$, $r = 0.52$; $P < 0.01$).

The QT_c interval was significantly longer after (±) ($P < 0.01$) and (+) ($P < 0.01$) than after placebo in the dose escalating phase (Figure 2). During this period the repolarization effects appeared to be greater with (±)-sotalol than (+)-sotalol ($P < 0.05$) but in the post-dosing phase no differences between the two drugs could be determined (Figure 2). Log plasma concentrations of (+)-sotalol and (±)-sotalol were linearly correlated with the QT_c intervals ($P < 0.05$).

Discussion

This study confirms previous observations that (±)-sotalol is an effective β -adrenoceptor blocking agent in man which causes prolongation of the QT_c interval which cannot be explained in terms of its effects on β -adrenoceptors alone. There is evidence that this repolarization effect is probably due to Type III anti-arrhythmic activity and it has been shown that (±)-sotalol reduces the frequency and complexity of ventricular ectopic beats in patients with ischaemic heart disease (Burckhardt *et al.*, 1983) and decreases the ventricular response to atrial fibrillation in the Wolff-Parkinson-White syndrome (Bennet, 1982), a feature not normally seen with other β -adrenoceptor blocking agents.

This present study demonstrates that the repolarisation effects on the QT_c interval do not depend on the presence of β -adrenoceptor blocking activity. (+)-Sotalol produced prolongation of the QT_c interval comparable to (±)-sotalol but β -adrenoceptor blocking activity was seen only at the highest dose of (+)-sotalol. These observations with (+)-sotalol are similar to those of Rowland *et al.* (1984) who described an anti-arrhythmic effect in patients with supra-ventricular arrhythmias consistent with type III activity and independent of β -adrenoceptor

Figure 1 Changes in resting (0–420 min) and exercise heart rate 0–180 min following cumulative doses of (±)-sotalol (●.....●), (+)-sotalol (---●) compared with placebo (●—●) (individual rather than cumulative doses are illustrated).

Figure 2 Changes in QT_c (0–420 min) following cumulative doses of (±)-sotalol (●.....●), (+)-sotalol (---●) compared with placebo (●—●) (individual rather than cumulative doses are illustrated).

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blockade. It is possible in this experiment that the β -adrenoceptor blocking activity seen with (+)-sotalol was due to incomplete separation of the enantiomers and that a small amount of (–)-sotalol present in the sample resulted in the reduction of exercise heart rate at the highest dose. The β -adrenoceptor blocking activity therefore resides almost entirely on the (–)-isomer while the (+)-form is devoid of this property or has weak β -adrenoceptor blocking effect. The drug effects on the QT_c interval would appear to be due to both the (+) and the (–)-enantiomer. The repolarization effects cannot be due to the (+)-isomer alone since the racemate produced changes in the QT_c which were comparable or even greater than (+)-sotalol alone even though it only formed 50% of the racemic mixture. The reasons why (±)-sotalol produced greater electrophysiological effects during the dose escalation period but not in the post-treatment period are unclear but could relate to differences in the speed of onset of the antiarrhythmic activity of the two enantiomers.

In conclusion this study confirms results from animals (Kato *et al.*, 1984) that the β -adrenoceptor blocking activity of sotalol is principally due to the (–)-enantiomer. The electrophysiological effects appear to be due to both the (+) and the (–) enantiomers which are probably equally potent but may differ in the rate of onset of their repolarization effects. These observations suggest that the effect of sotalol on the QT interval is unrelated to its β -adrenoceptor blocking activity.

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