Adverse effects of a single dose of (+)-sotalol in patients with mild stable asthma

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Aims To investigate the effect of (+)-sotalol, which is not thought to possess clinically significant β -adrenoceptor blocking activity, on airway responsiveness in subjects with mild asthma.

Methods A placebo controlled, double-blind, single dose, cross over study, evaluating the effects of oral (+)-sotalol 300 mg and oral ($\pm$)-sotalol 240 mg, on airway responsiveness, FEV₁, and heart rate in 18 asthmatic volunteers with quantifiable levels of airway responsiveness.

Results Compared with placebo, (+)-sotalol induced a significant increase in airway responsiveness, and a significant decrease in FEV₁, but there was no significant change in heart rate. Following ($\pm$)-sotalol there was no significant effect on airway responsiveness, but there were significant decreases in FEV₁ and heart rate. In one subject both (+)-sotalol and ($\pm$)-sotalol provoked a 49% decrement in FEV₁, and in another there were decrements of 20% and 18%, respectively.

Conclusions Despite theoretical considerations, it cannot be assumed that (+)-sotalol is safe in patients with asthma.

Keywords: (+)-sotalol, ($\pm$)-sotalol, airway responsiveness, asthma, ventilatory function

Introduction

Sotalol is used in the management of cardiac dysrhythmias because of its class II (β -adrenoceptor blockade) and class III (potassium channel inhibition) antiarrhythmic activity. It is a racemic mixture (($\pm$)-sotalol), with both (+)- and (–)-stereoisomers possessing similar class III antiarrhythmic activity. Its β -adrenoceptor blocking activity is, however, principally a property of (–)-sotalol [1–3]. Thus, (–)-sotalol is 32–40 times more potent than (+)-sotalol in antagonising the inotropic effect of isoprenaline in isolated mammalian atria (β_1 -adrenoceptor blockade), and 14–48 times more potent than (+)-sotalol in antagonising isoprenaline induced relaxation of tracheal smooth muscle (β_2 -adrenoceptor blockade). (+)-sotalol is said to have no β_1 -adrenoceptor binding activity [4–6]. The β -adrenoceptor blocking activity of ($\pm$)-sotalol precludes its use in asthmatic subjects, but because (+)-sotalol is considered to have clinically negligible β -adrenoceptor blocking activity, it should in theory be suitable for asthmatic subjects who need class III antiarrhythmic medication.

The severity of asthma correlates well with the level of airway responsiveness [7], and this has been shown to increase with β -adrenoceptor blockade [8, 9]. We consequently evaluated the respective effects of (+)-sotalol and ($\pm$)-sotalol compared with placebo on airway responsiveness, ventilatory function and heart rate in a group of subjects with mild asthma in a preliminary study designed to assess the safety of single doses. It was anticipated that

this would provide a basis for further investigations with regular dosing.

Methods

Subjects

Study participants were aged 18–65 years and all had an established diagnosis of asthma with a measured level of airway responsiveness from methacholine tests in the PD₂₀ (provoking dose responsible for a 20% decrement in FEV₁) range 50–3200 μ g. Their asthma had been stable for at least 3 months using no more than 1000 μ g inhaled beclomethasone dipropionate (or its equivalent) daily, and none had required oral or parenteral corticosteroids in that period. All gave written informed consent.

Study protocol

The investigation followed a placebo controlled, double-blind, single dose, cross over design, comparing oral (+)-sotalol 300 mg and oral ($\pm$)-sotalol 240 mg ((+)-sotalol 120 mg + (–)-sotalol 120 mg). The 300 mg dose of (+)-sotalol was chosen because the manufacturers anticipated that the recommended maximum daily dosage would be 300 mg twice daily (Bristol-Myers Squibb, personal communication). ($\pm$)-sotalol was chosen to provide a positive control with β -adrenoceptor blockade, and the 240 mg dose was chosen because it (unlike 300 mg) was conveniently available within the dose range currently recommended for use in Britain.

Each subject was assessed on five occasions, and each

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assessment commenced at about 09.00 h on a separate day at intervals of 7–10 days. For each study day, subjects were asked not to drink tea or coffee before the visit; not to use inhaled β_2 -adrenoceptor agonist or anticholinergic preparations for the preceding 12 h; and not to use long acting inhaled β_2 -adrenoceptor agonists, oral β_2 -adrenoceptor agonists or methylxanthines for the preceding 24 h.

On study day 1 entry criteria were validated; blood pressure and a 12 lead electrocardiogram (ECG) were recorded after 15 min of supine rest; a number of haematological, biochemical and urinary parameters were evaluated; ventilatory function was measured; and a methacholine test was performed.

On study days 2,3 and 4 all these investigations were repeated except, initially, the methacholine test. The subjects then swallowed the study medication of placebo, (+)-sotalol 300 mg, or ($\pm$)-sotalol 240 mg, providing that the predosing FEV₁ was $\geq 70\%$ of the predicted value. The study medications, which appeared identical, were administered in a balanced randomized sequence over study days 2–4. Heart rate, derived from a further ECG, was recorded 115 min after dosing (and after resting supine for the final 15 min), and then ventilatory function was remeasured. At 2 h after dosing a methacholine test was carried out. During the fifth and final visit, all investigations except the methacholine test were repeated. The study was approved by the local ethics committee.

Ventilatory function

Ventilatory function was measured using a pneumotachometer. 'Pre' and 'post' dosing FEV₁ were calculated as the mean of the best three from six forced expiratory manoeuvres.

Methacholine tests

Airway responsiveness was measured with optimal precision using a locally developed method [10]. Nebulised methacholine was administered in doubling cumulative doses at 5 min intervals over a maximum possible range of 3.125–6400 μg , and airway responsiveness was expressed conventionally as PD₂₀. A methacholine test was not performed 2 h after dosing if the FEV₁ had decreased by $\geq 20\%$, or if the FEV₁ was then $\leq 65\%$ of predicted. Methacholine induced bronchoconstriction was reversed by β_2 -adrenoceptor agonist medication.

Statistics

We calculated from previous experience that with 12 participants there would be 80% power to detect a 20% difference in geometric mean PD₂₀ (relative to placebo) at a 5% level of significance. To ensure adequate power we proposed to recruit 20 subjects in the expectation that 16–18 would complete the study. The primary response variable of interest was geometric mean PD₂₀, with FEV₁ and heart rate as secondary end points. The effects of (+)-sotalol and ($\pm$)-sotalol, compared with placebo, in each individual were assessed by paired *t*-tests; and all the

data were statistically modelled using a repeated measures analysis, with and without adjustment for baseline FEV₁ [11].

Results

Twenty subjects were recruited and 16 (eight men) completed all aspects of the study. Two subjects withdrew because of exacerbations of asthma, and two were unable to participate in all the methacholine tests because of the effects of the study medication on FEV₁: in one subject (+)-sotalol provoked a 20% decrease in FEV₁, and in the other, both (+)-sotalol and ($\pm$)-sotalol provoked a 49% decrement in FEV₁. The mean age of the 16 subjects was 38.8 years, (s.d. 10.6). The effects in these 16 subjects of single doses of placebo, (+)-sotalol, and ($\pm$)-sotalol on airway responsiveness, FEV₁, and heart rate are summarized in Table 1 and Figure 1.

Airway responsiveness (PD₂₀)

PD₂₀ measurements following placebo did not differ significantly from those on study day 1, when no study medications were administered (geometric mean PD₂₀.study day 1/geometric mean PD₂₀.Placebo = 1.05; 95% CI 0.60–1.85, *P* = 0.85). The geometric mean PD₂₀ after (+)-sotalol was reduced to 44% of that noted after placebo (95% CI 26–76%, *P* = 0.006). The geometric mean reduction after ($\pm$)-sotalol to 76% of that noted after placebo was much less and not significant (95% CI 44–128%, *P* = 0.3). Statistical modelling of the data confirmed this adverse effect of (+)-sotalol, and showed that it was independent of any confounding by postdose FEV₁.

FEV₁

There were no significant differences in predose mean FEV₁ on dosing study days. Two hours after placebo, mean FEV₁ had increased by 70 ml (95% CI 3–150 ml, *P* = 0.04), which was presumably a consequence of the characteristic circadian rhythm of asthma. Two hours after (+)-sotalol and ($\pm$)-sotalol there were small but significant decrements in mean FEV₁ compared with placebo of 140 ml (95% CI

Figure 1 Airway responsiveness as expressed by PD₂₀ to methacholine for placebo, (+)-sotalol, and ($\pm$)-sotalol in 16 subjects.

Table 1 Effects of placebo, (+)-sotalol 300 mg and (±)-sotalol 240 mg on airway responsiveness (PD₂₀), FEV₁ and heart rate in 16 subjects.

	Placebo	(+)-sotalol	(±)-sotalol
PD ₂₀ (µg methacholine)	271 (121–608)	120 (54.0–266)	206 (97.5–436)
FEV ₁ (l)			
Pre-dose	3.36 (2.78–3.93)	3.39 (2.85–3.93)	3.34 (2.78–3.90)
Post-dose	3.43 (2.85–4.01)	3.29 (2.75–3.82)	3.28 (2.69–3.86)
Heart rate (beats min ⁻¹)			
Pre-dose	69.4 (64.8–74.0)	69.7 (65.0–74.4)	68.3 (62.9–73.8)
Post-dose	62.1 (57.1–67.0)	58.4 (53.9–62.9)	54.1 (50.8–57.4)

Arithmetic means (95% confidence interval), except for PD₂₀ measurements, where geometric mean is given.

10–270 ml, $P=0.03$) and 150 ml (95% CI 10–300 ml, $P=0.04$), respectively.

Heart rate

There were no significant differences in predosing heart rates on dosing study days. Two hours after placebo, mean heart rate had decreased by 7.3 beats min⁻¹ (95% CI 4.4→10.3 beats min⁻¹, $P=0.001$). Compared with placebo both (+)-sotalol and (±)-sotalol induced further decreases in mean heart rate; this was highly significant for (±)-sotalol (−7.9 beats min⁻¹, 95% CI −12.3→ −3.6 beats min⁻¹, $P=0.001$), but not significant for (+)-sotalol (−3.7 beats min⁻¹, 95% CI −7.3→ +0.3 beats min⁻¹, $P=0.07$).

Haematological, biochemical, and urinary tests

Occasional values were outside the normal range, but there were no apparent patterns nor significant differences between study days 1 and 5. None of the abnormal values was clinically significant and no interventions were made.

Discussion

Both (+)-sotalol and (±)-sotalol differed significantly from placebo, each exerting potentially important adverse effects 2 h after single dose administration in these subjects with mild asthma. Both preparations provoked decrements in FEV₁; (±)-sotalol reduced heart rate; and (+)-sotalol increased airway responsiveness.

Studies of the repeatability of methacholine tests and hence PD₂₀ measurements have shown that the range may encompass a halving of PD₂₀ in the individual, but we have found that geometric mean levels from 20 subjects generally show very little variability when tests are repeated at intervals of only a few days [10, 12]. The (+)-sotalol induced decrease in geometric mean PD₂₀ to 44% of the comparable value following placebo consequently suggests a doubling of the level of airway responsiveness which could not be considered trivial. This effect was not expected, and it is not readily explained if the major threat to asthma from (±)-sotalol lies with the β-adrenoceptor blocking activity of (−)-sotalol.

The (+)-sotalol preparation used was >99.5% pure (Bristol-Myers Squibb, personal communication), and so it seems highly unlikely that (−)-sotalol contamination of the (+)-sotalol preparation was responsible for the observed increase in airway responsiveness—particularly as 120 mg (−)-sotalol in the (±)-sotalol preparation failed to produce such an increase. The class III (potassium channel inhibition) antiarrhythmic activities of (+)- and (−)-sotalol are thought to be very similar, as are their pharmacokinetic properties [13], and so the minor differences in dose (300 mg *vs* 240 mg) does not provide a convincing explanation either for the much clearer adverse effect on airway responsiveness of (+)-sotalol compared with (±)-sotalol.

A number of questions consequently arise: whether some other property of the (+)-isomer could explain these observations, whether β-adrenoceptor blockade may reduce the concomitant effect of potassium channel inhibition in the racemic (±)-sotalol mixture, or whether our results have been distorted by artefact. Statistical power considerations suggest that there was a 20% chance of a false negative result, a risk level normally deemed acceptable, but one which may have operated to produce no apparent effect of (±)-sotalol on airway responsiveness. We additionally noted rather more variability in PD₂₀ measurements following the use of either sotalol preparation than is usual with sequential measurements; only 16 subjects completed the study protocol; and the study period may have extended for as long as 40 days. Our usual limits of repeatability (and our initial power calculations) may not have been applicable therefore and the halving of geometric mean PD₂₀ associated with (+)-sotalol may not carry the usual degree of clinical importance. It is also conceivable that the relative effects of the two sotalol preparations were subjected to an additional source of variability, namely variability in resting adrenergic tone at the time the sotalol preparations were administered. The significant decrease in mean pulse rate identified 115 min after placebo is best explained by diminishing adrenergic tone from relative rest during the 100 min following dosing, and from the specific 15 min period of supine rest immediately before the ECG.

Whatever the mechanism and whatever its true magnitude, the adverse effect of (+)-sotalol on PD₂₀ was clearly significant in a statistical sense. Furthermore, there was a

clearly significant adverse mean effect on FEV₁. Again there was much variability, and one recruited subject experienced a 49% decrement which prevented him from undergoing the methacholine test and hence from completing the investigation. He experienced an identical decrement following (±)-sotalol. One other subject experienced a 20% decrement following (+)-sotalol and an 18% decrement with (±)-sotalol. The large decrements in FEV₁ in the two subjects most sensitive to (+)-and (±)-sotalol are likely to have exerted some bias and to have weakened the apparent effects on PD₂₀, since these subjects were excluded from the PD₂₀ analysis.

The adverse effects on airway responsiveness and ventilatory function were observed only 2 h after a single dose of the study medication, and in subjects with only mild asthma. Maximal blood concentration following the ingestion of a single dose of sotalol has been reported to occur at 3.4 h (95% CI, 2.7–4.1 h) and to be ≈30% greater after multiple compared to single dosing [13, 14]. As a consequence it might be anticipated that regular dosing of d-sotalol in order to control or prevent cardiac arrhythmias would have more serious consequences if it was to be used generally in subjects with asthma. Our study was designed as a preliminary to investigating this wider issue. We were anxious to establish that a single dose was as safe as theory would predict before investigating the safety of regular dosing, but our results suggest that (+)-sotalol is not likely to be safe if generally used in subjects with asthma.

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