An open label, randomised, crossover study comparing sotalol and atenolol in the treatment of symptomatic paroxysmal atrial fibrillation

R P Steeds, A S Birchall, M Smith, K S Channer

Abstract

**Objective**—To compare sotalol and atenolol in the treatment of symptomatic paroxysmal atrial fibrillation.

**Design**—Prospective, randomised, open label, crossover study.

**Setting**—University hospital.

**Patients**—47 subjects aged over 50 years were recruited from the hospital outpatient department following ECG documentation of paroxysmal atrial fibrillation that coincided with symptoms. Six patients withdrew and 41 completed the trial.

**Interventions**—Patients were randomised to one month’s treatment with sotalol 80 mg twice daily or atenolol 50 mg once daily. Treatment arms were then crossed over. Patients underwent 72 hour Holter monitoring before randomisation and repeat studies were carried out at the end of both treatment periods. Symptom assessments were completed using linear analogue scales and the Nottingham health profile.

**Main outcome measure**—Frequency of paroxysmal atrial fibrillation; secondary outcome measures included average and total duration of paroxysmal atrial fibrillation, total ectopic count, and symptom assessments.

**Results**—A reduction in the number and duration of episodes of paroxysmal atrial fibrillation was noted following treatment with sotalol and atenolol. There was no difference in frequency of paroxysmal atrial fibrillation during treatment with sotalol or atenolol (median difference 0; 95% confidence interval (CI) 0 to 1; p = 0.47). There was no difference in total duration of paroxysmal atrial fibrillation (median difference 0 min; 95% CI −1 to 2; p = 0.51) or in average duration (median difference 0 min; 95% CI 0 to 1; p = 0.31). No difference was found in total ectopic count between sotalol and atenolol (median difference −123; 95% CI −362 to 135; p = 0.14). Treatments were equally tolerated with no difference in linear analogue scores for symptoms of paroxysmal atrial fibrillation (median difference −5; 95% CI −20 to 5; p = 0.26) or in all categories of the Nottingham health profile.

**Conclusions**—No difference was found in terms of ECG or symptomatic control of paroxysmal atrial fibrillation between prescribing sotalol 80 mg twice daily and atenolol 50 mg once daily. There was no improvement in paroxysmal atrial fibrillation from baseline following treatment with either sotalol or atenolol.

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Keywords: paroxysmal atrial fibrillation; sotalol; atenolol

Atrial fibrillation is an inefficient cardiac rhythm. The tachycardia combined with loss of atrioventricular synchrony causes an age related fall in systolic blood pressure and cardiac output of up to 50%. These changes are associated with symptoms of palpitation and effort intolerance. Compensatory mechanisms serve to minimise the haemodynamic effects so that symptoms abate with time. In paroxysmal atrial fibrillation, sudden repeated changes in rhythm cause symptoms which most patients find more debilitating than chronic atrial fibrillation. In addition, paroxysmal atrial fibrillation carries an intermediate risk of thromboembolic events, with a 1.3% annual risk of stroke, compared with 5.4% in those with chronic atrial fibrillation.

Treatment for paroxysmal atrial fibrillation is likely to last for a long time, as 80% continue to have paroxysms when followed up for six years. The morbidity imposed by this condition is clear and the need for effective and safe treatment evident. Class I (quinidine, flecainide, and propafenone) and class III agents (amiodarone) are effective in 50–70% of cases, yet concerns remain about their safety in long term use.

Support for the use of sotalol as a first line agent in the treatment of paroxysmal atrial fibrillation has grown owing to its ability to prolong action potentials recorded in cardiac tissue along with its β adrenoceptor activity (class II and III effects). However, the doses required to achieve β blockade and to prolong repolarisation are not equivalent. In patients with normal renal function, the minimal effective anti-arrhythmic dose of orally administered sotalol is 80 to 160 mg daily, given in two equal doses.

At low doses, β blockade predominates and it is possible that antiarrhythmic benefits merely reflect this action. Moreover, the risk of proarrhythmia with sotalol increases in a dose related manner.

Many patients fail to tolerate doses above 80 mg twice daily. Cardioselective β adrenoceptor antagonists such as atenolol are also used to treat paroxysmal atrial fibrillation, yet there are few trials comparing their efficacy with sotalol at doses in common usage.
This study was designed to compare the ability of sotalol 80 mg twice daily and atenolol 50 mg once daily to reduce the severity of symptomatic paroxysmal atrial fibrillation in an elderly population.

**Methods**

**PATIENT SELECTION**

Forty seven consecutive patients were recruited from the cardiology outpatient department of the Royal Hallamshire Hospital and 41 completed the trial. Those recruited were ambulatory outpatients of either sex, aged over 50 years, with recurrent paroxysmal atrial fibrillation documented on ECG monitoring which coincided with symptoms. The ECG criteria for paroxysmal atrial fibrillation were: absence of P waves when they had been identifiable on ECGs during sinus rhythm; atrial activity chaotic or absent both in amplitude and rate; variable successive RR intervals; QRS complexes with the form usual for the subject and lead; episodic occurrence (each paroxysm consisting of more than three consecutive beats).

Exclusion criteria were: uncompensated congestive cardiac failure; asthma or chronic obstructive airways disease requiring regular bronchodilator treatment; second or third degree atrioventricular block; recent myocardial infarction (< 1 month); recent surgery (< 3 months); unstable angina; bradycardia (< 50 beats/min); sick sinus syndrome; prolonged QT interval (> 0.45 s); uncontrolled hypertension (diastolic > 105 mm Hg); thyroid dysfunction; and patients requiring concomitant antiarrhythmic drugs likely to interfere with the activity of the study drugs (class I, II, and III antiarrhythmic agents of the Vaughan-Williams classification, digoxin, diltiazem, and verapamil).

**STUDY DESIGN**

The study was a randomised, open label crossover comparison of sotalol 80 mg twice daily and atenolol 50 mg once daily. Initially, a full history was obtained followed by a physical examination, 12 lead ECG, chest radiograph, and screening biochemistry (which included thyroid function, renal function, and liver function tests). Cross sectional ultrasound Doppler echocardiography was performed using a Toshiba SS130A (Toshiba Ltd, Tokyo, Japan). Left atrial diameter was recorded from the M mode image obtained in the long axis left para-sternal view through the aortic leaflets. Left ventricular ejection fraction was calculated by the Teicholz method from left ventricular dimensions measured from M mode recordings taken at the level of the papillary muscles. All echocardiographic recordings were reviewed by an experienced echocardiographer and consultant cardiologist.

All antiarrhythmic treatment was withdrawn before entry into the study. During the baseline period, patients were monitored using a continuous 72 hour Holter recorder (Tracker, Reynolds Medical, Hertford, UK) to establish a summary measure of the frequency and duration of symptomatic episodes of paroxysmal atrial fibrillation, together with total ectopic count for each patient. Patients were then randomised to receive either sotalol or atenolol for one month, at the end of which the Holter monitoring was repeated. Following crossover to the alternate drug, patients received a further month of antiarrhythmic treatment before final Holter recordings were carried out.

Treatment of underlying heart disease was optimised before entry into the study and kept constant in all patients throughout the study. Holter recordings were visually analysed using a Reynolds (UK) professional semiautomatic analyser by a single, experienced observer who was blinded to the treatment period of the tape under analysis (that is, baseline, sotalol, or atenolol) and to the patient details. On each tape the total number and duration (in minutes) of episodes of paroxysmal atrial fibrillation were measured.

“Quality of life” was monitored during the study by the use of the Nottingham health profile, providing information on changes in six categories—sleep, energy, emotional reactions, pain, physical mobility, and social isolation. In addition, symptom scores relating specifically to paroxysmal atrial fibrillation (severity of palpitation, dizziness, or breathlessness) were measured using visual analogue scales 0–100 mm in length, where zero represented absence of symptoms and 100 reflected maximum severity. Patients were asked to complete a visual analogue rating and Nottingham health proforma at baseline and at the end of each treatment period. At the end of the trial, patients were asked whether they had felt better on sotalol or atenolol, or whether they felt the same on both treatments.

**STATISTICAL ANALYSIS**

The primary end point of the trial was a comparison of the effect of sotalol and atenolol on the frequency of episodes of paroxysmal atrial fibrillation. A power calculation assuming normal distribution of data was performed at the outset of the trial, which indicated that a sample size of 40 patients was required to give a power of 87% to detect a difference between treatments of three episodes over the period of Holter recording at the 5% significance level. However, analysis at the end of the trial indicated that the non-normal nature of the data precluded formal power estimation, which should be remembered when interpreting the results. Secondary end points included: alteration in the average duration of episodes of paroxysmal atrial fibrillation, alteration in the total duration of episodes of paroxysmal atrial fibrillation, change in total ectopic count, and change in symptom scores. The distribution of values for all these measured variables was non-normal and therefore non-parametric methods were used for the analysis.

Data comparing sotalol with atenolol were considered in the manner of a crossover study, and Mann–Whitney U tests were carried out as recommended by Altman1 to examine the possibility of a period effect, a treatment–period interaction, and for the treatment effect itself. In addition, Wilcoxon signed rank tests...
were performed to examine the reduction in frequency and duration of paroxysmal atrial fibrillation from baseline when patients received atenolol and sotalol. Confidence intervals were calculated for differences between group medians using a universal definition of the interval for a difference between two measures of location, as described by Conover,\(^\text{12}\) within the Arcus Pro-Stat 3.01 statistical package. Patient data for age and echocardiographic variables were analysed assuming normal distributions and are described using mean (SD). Statistical significance was assumed with an \(\alpha\) level of 0.05.

### Results

**CLINICAL CHARACTERISTICS OF STUDY PATIENTS**

Forty one consecutive patients meeting inclusion and exclusion criteria completed the trial. Two patients withdrew during the first month of active treatment when receiving sotalol (one with diarrhoea and one with depression). Two other patients withdrew during the first month of active treatment following randomisation to atenolol (both with malaise). A further two patients withdrew consent during randomisation (one because of an impending holiday and one without specifying a reason). Data from these patients were not included in the analysis.

Twenty one patients started treatment with sotalol and 20 started treatment with atenolol. There were 24 men and 17 women with a mean (SD) age of 67 (9.5) years. The average time from onset of symptoms was 683 (432) days. The origin of the paroxysmal atrial fibrillation was considered to be ischaemic heart disease in 13 patients, hypertensive heart disease in eight, valvar heart disease in four, pulmonary disease in three, and alcohol related in one. In 12 patients, no known aetiology was identified.

Most patients (32) described palpitations, seven complained of dizziness, and two complained of episodic breathlessness during episodes of paroxysmal atrial fibrillation. Antiarrhythmic treatment was withdrawn before randomisation in only four of the 41 patients (two were receiving digoxin, one quinidine, and one flecainide). Medication was withdrawn in these patients by the equivalent of at least five half lives before the time of entry for each drug. The remainder of the study population was not currently taking antiarrhythmic treatment.

Mean (SD) left atrial diameter was 37.5 (7.6) mm, left ventricular end diastolic diameter 51 (8) mm, and left ventricular ejection fraction 70 (9)%. PR and QT intervals were within normal limits for all patients during sinus rhythm.

**CROSSOVER STUDY RESULTS FOR SOTALOL AND ATENOLOL**

No period effect and no treatment–period interaction were found on analysis of the crossover data, although there was a trend towards a reduction in frequency of episodes with time. This analysis for period effect and treatment–period interaction was repeated for each of the measured variables and results are presented in table 1. There was no difference in frequency of episodes of paroxysmal atrial fibrillation documented on Holter monitoring, during treatment with sotalol or atenolol (median difference 0, 95% confidence interval (CI) 0 to 1, \(p = 0.46\)).

Complete data for the study on the primary end point of frequency of paroxysmal atrial fibrillation are presented in fig 1. There was no difference in average duration of episodes of paroxysmal atrial fibrillation (median difference 0 min, 95% CI 0 to 1, \(p = 0.31\)) or in total duration of episodes of paroxysmal atrial fibrillation (median difference 0 min, 95% CI −1 to 2, \(p = 0.51\)). There was no difference in total ectopic count (median difference −123, 95% CI −362 to 135, \(p = 0.14\)) during either treatment period (table 1). Differences are presented so that positive numbers reflect an improvement on atenolol and negative numbers an improvement on sotalol. However, 15
of the 41 patients did not have any episodes of paroxysmal atrial fibrillation at all during either period of active treatment. This affected the ability of our study to detect superiority of one drug over the other. However, even on removal of these 15 patients from the analysis, there were no differences in the frequencies of any of the Holter outcome measures during treatment with sotalol or atenolol (table 2).

As treatment for paroxysmal atrial fibrillation is given primarily for the amelioration of symptoms, treatment effects on symptoms as such are of independent interest. There was no difference between treatments in the severity of symptoms during paroxysmal atrial fibrillation as recorded on linear analogue scales (median difference −5 mm, 95% CI −20 to 5, p = 0.26). In terms of quality of life as graded by the Nottingham health profile, there were no differences in scores for energy, emotional reactions, physical mobility, pain, social isolation, and sleep (table 3). In terms of patient preference, 20 patients preferred treatment with sotalol, 15 patients preferred atenolol, and six patients expressed no preference. Using a binomial test for proportions, no difference was found between the number of patients expressing a preference for sotalol and the number expressing a preference for atenolol (p = 0.50).

Table 4 Treatment differences compared with baseline

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline − sotalol</th>
<th>Baseline − atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>−6.5</td>
<td>−6.5</td>
</tr>
<tr>
<td>CI</td>
<td>−3.5 to −13</td>
<td>−4 to −12</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Average duration</td>
<td>−2.24</td>
<td>−2.5</td>
</tr>
<tr>
<td>CI</td>
<td>−1 to −13.9</td>
<td>−0.75 to −15</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total duration</td>
<td>−60.75</td>
<td>−64.25</td>
</tr>
<tr>
<td>CI</td>
<td>−16 to −424</td>
<td>−18.5 to −385</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TEC</td>
<td>−478</td>
<td>−434</td>
</tr>
<tr>
<td>CI</td>
<td>−208 to −882</td>
<td>−99 to −860</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0017</td>
<td>0.012</td>
</tr>
<tr>
<td>Analogue</td>
<td>−12.5</td>
<td>−10</td>
</tr>
<tr>
<td>CI</td>
<td>−5 to −22.5</td>
<td>0 to −15</td>
</tr>
<tr>
<td>p Value</td>
<td>0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Negative numbers represent a reduction with respect to baseline. TEC, total ectopic count.

Discussion

In this randomised, open label, crossover trial comparing the prophylactic use of sotalol with response to drug treatment compared with baseline

A reduction in the frequency of episodes of paroxysmal atrial fibrillation was seen after treatment with sotalol in comparison with the baseline period (median difference −6.5, 95% CI −3.5 to −13, p < 0.0001). Differences are presented so that negative numbers represent fewer episodes, a shorter duration, or lower ectopic count on sotalol compared with baseline. A reduction was seen in the average duration (median difference −2.24 min, 95% CI −1 to −13.9, p = 0.0002) and total duration of episodes of paroxysmal atrial fibrillation after treatment with sotalol compared with the baseline period (median difference −60.75 min, 95% CI −16 to −424, p < 0.0001). There was a reduction in total ectopic count after treatment with sotalol (median difference −478, 95% CI −208 to −882, p = 0.002). Symptom scores recorded on linear analogue scales fell following sotalol treatment (median difference −12.5 mm, 95% CI −5 to −22.5, p = 0.001). Data for the reduction in paroxysmal atrial fibrillation are given in table 4. There were no differences in the quality of life scores from the Nottingham health profile during treatment with sotalol compared with baseline.

Changes in response to atenolol compared with baseline were of similar significance and are expressed in the same manner. A reduction in the frequency of paroxysmal atrial fibrillation was seen after treatment with atenolol compared with the baseline period (median difference −478, 95% CI −208 to −882, p = 0.002). Symptom scores recorded on linear analogue scales fell following sotalol treatment (median difference −12.5 mm, 95% CI −5 to −22.5, p = 0.001). Data for the reduction in paroxysmal atrial fibrillation are given in table 4. There were no alterations in overall quality of life according to the Nottingham health profile for the two periods.
atenolol in paroxysmal atrial fibrillation, we found no difference in the frequency and duration of paroxysmal atrial fibrillation as recorded on ambulatory ECG. Furthermore, no difference in symptomatic efficacy was found between the drugs. There was a reduction in the frequency and duration of paroxysmal atrial fibrillation in comparison with baseline following treatment with either sotalol or atenolol. In addition, there was a reduction in total ectopic count and symptoms related to paroxysmal atrial fibrillation during both active treatments compared with baseline.

There has only been one previous comparison of sotalol with atenolol in the treatment of atrial arrhythmia in ambulatory outpatients. In that study, sotalol (120–240 mg) was found to reduce the frequency and duration of episodes of paroxysmal supraventricular tachycardia when compared with atenolol (50–100 mg) in 13 patients. Three of these patients did not suffer any episodes of arrhythmia during either treatment period. Our study was larger, but still 15 of the 41 patients did not have any episodes of arrhythmia during active treatment, which makes it more difficult to show superiority of one treatment over the other. Patients in the study by Schofield and Bennett used hand held devices to record the cardiac rhythm at the time of symptoms, whereas in our study both symptomatic and asymptomatic episodes were recorded by continuous ECG monitoring. Asymptomatic patients may continue to have up to 27% of the episodes of paroxysmal atrial fibrillation suffered before treatment after receiving drug therapy and these episodes would be missed by any study using self activated recordings.

Other studies have compared sotalol with β adrenoceptor antagonists in the treatment of supraventricular tachyarrhythmias (including atrial fibrillation) following coronary artery bypass surgery. Jasssen et al showed that sotalol was superior to both placebo and metoprolol in the post-surgical setting, although both drugs were given intravenously. Suttrop et al found no difference between sotalol and the non-cardioselective β adrenoceptor antagonist propranolol. However, atrial fibrillation following surgery is a particular form of arrhythmia with a distinct pathophysiology, driven by high catecholamine levels and frequent ectopy. β Adrenoceptor antagonists are known to improve outcome after surgery and it may be that the response to antiarrhythmic agents under those circumstances is different from that expected in an ambulatory population. Thus there is little support from other studies to document a clear difference in efficacy between sotalol and other β adrenoceptor antagonists in the treatment of paroxysmal atrial fibrillation in an ambulatory outpatient population.

The rationale for the preferential use of sotalol in the prevention of supraventricular arrhythmias lies in the presence of its class III antiarrhythmic activity in addition to class II β adrenoceptor antagonism. Why was there no difference in efficacy shown between the two drugs in our study? Electrophysiological studies of sotalol have confirmed the presence of these additional properties over and above those of other β adrenoceptor antagonists. Sotalol lengthens the duration of monophasic action potentials in the atria and ventricles, and increases the ventricular effective refractory period. It also prolongs refractoriness in the atioventricular node and the His–Purkinje system. However, higher doses of sotalol are required to prolong cardiac repolarisation than to achieve β adrenoceptor antagonism. Dosages have varied in clinical trials investigating the use of sotalol in supraventricular arrhythmias. Sotalol was effective in maintaining sinus rhythm after direct current cardioversion of chronic atrial fibrillation when used in a dose of 160–320 mg/day, although 11% of subjects withdrew owing to side effects. A 40 mg dose given six hourly reduced the incidence of atrial fibrillation and flutter when given after coronary artery bypass surgery in a placebo controlled trial. Sotalol was found to be more effective than propafenone in a double blind trial in ambulatory patients with paroxysmal atrial fibrillation at a daily oral dose of 3 mg/kg. There has been only one clinical trial investigating the relative efficacy of two dose regimens of sotalol in the prophylactic treatment of supraventricular arrhythmias. Primary efficacy analysis was carried out on 95 patients with symptomatic paroxysmal supraventricular tachycardia in a randomised double blind trial of placebo compared with sotalol 80 mg twice daily and 160 mg twice daily. Fewer patients in both sotalol groups had recurrence of paroxysmal supraventricular tachycardia, but no significant difference was observed between the two dosages. Analysis on the basis of intention to treat showed efficacy of sotalol in paroxysmal atrial fibrillation only at the higher dose. However, it is of some concern that each upward dose increment increases the proarrhythmic effects of sotalol.

Following the baseline period, there was a reduction in the frequency and duration of paroxysmal atrial fibrillation on treatment with either sotalol or atenolol. There was a significant decrease in total ectopic count and an improvement in symptoms directly related to paroxysmal atrial fibrillation with both drug interventions. Our trial was designed with the primary aim of comparing sotalol with atenolol. The comparison between active treatment and the preceding drug-free state must be treated with caution as it is not in randomised order. No control group was included. It is conceivable that patients may improve spontaneously after first presenting with paroxysmal atrial fibrillation, so that the effect of any subsequent intervention is overemphasised. Atrial electrophysiological studies have not shown a consistent benefit of β adrenoceptor antagonists on the inducibility of paroxysmal atrial fibrillation. However, there have been no placebo controlled studies of the efficacy of β adrenoceptor antagonists other than sotalol for preventing these arrhythmias. The only clinical trials of β adrenoceptor antagonists have been in the context of preventing perioperative supraventricular arrhythmia which, as has been
mentioned, is a specific subset of paroxysmal atrial fibrillation. Atenolol has been found to decrease the frequency of supraventricular arrhythmias following coronary artery surgery in two studies of up to 60 patients.\textsuperscript{26, 28} The finding of this study that the frequency of paroxysmal atrial fibrillation fell after the baseline period following treatment with atenolol is interesting but raises the question as to whether a randomised, double blind, placebo controlled trial of cardioselective \(\beta\) adrenoceptor antagonists should be performed for the prophylaxis of paroxysmal supraventricular tachycardia.\textsuperscript{29}

There are methodological considerations in any study designed to compare the efficacy of two antiarrhythmic agents in paroxysmal arrhythmias. Investigating the efficacy of drugs in the treatment of paroxysmal atrial fibrillation is difficult because of the sporadic nature of the condition. Prolonged baseline Holter monitoring has previously been recommended as a method of defining the frequency of supraventricular arrhythmia.\textsuperscript{30} We found that patients tolerated 72 hour Holter monitors well and that recording was complete over this period. However, there was considerable resistance among subjects in our study to the idea of prolonging the Holter monitoring any further. Thus by definition our results are limited to patients with recurrence over three days. Moreover, limiting the recording period in our study to 72 hours resulted in data with a large variance, partly because of the inclusion of patients suffering from long bursts of atrial fibrillation alongside others who have multiple short episodes. Subjects were not monitored for as long as is possible with hand held transthoracic systems, although Holter recording does have the advantage of monitoring both symptomatic and asymptomatic episodes. We believe our approach would be important in any future assessment of cardioselective \(\beta\) adrenoceptor antagonists as antiarrhythmic agents in paroxysmal atrial fibrillation, because symptoms would be suppressed by the reduction in ventricular rate during episodes of fibrillation.

In conclusion, we have not shown an objective or subjective difference in efficacy between sotalol 80 mg twice daily and atenolol 50 mg once daily in the treatment of paroxysmal atrial fibrillation. However, there was a reduction in the ECG and symptomatic occurrence of paroxysmal atrial fibrillation compared with baseline following treatment with either sotalol or atenolol.

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