Oral xamoterol in patients with sinoatrial disease

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SUMMARY Twelve patients with sinoatrial disease were assessed while on oral xamoterol (200 mg twice daily) and placebo by a double blind randomised, crossover trial that lasted four weeks. Nine of the patients had been referred for permanent pacing. Xamoterol produced favourable changes in the number of pauses and the mean heart rate in six patients. Another patient deteriorated on xamoterol. Six patients were started on long term xamoterol.

Xamoterol produces short term electrocardiographic improvement in some, but not all, patients with symptomatic sinoatrial disease.

Drug treatment of sinoatrial disease has not been established. Although sustained release isoprenaline (Saventrine) has been used in some patients it has not been the subject of a controlled trial. Other agents that have been proposed include amidarone, theophylline, hydralazine, and pentalenol. But permanent cardiac pacing with adjuvant antiarrhythmic treatment remains the mainstay of treatment. Xamoterol (Corwin), 1-(+)-1-(4-hydroxyphenoxo)-3-(2-(4-morpholine carbonamido) ethylamino)-propan-2-ol fumerate is a β adrenoceptor partial agonist that is currently being evaluated for the treatment of mild to moderate heart failure. Xamoterol acts as a β, agonist at low levels of sympathetic tone and as a β blocker during period of excess sympathetic stimulation and therefore might provide a moderating influence on the heart rate of patients with sinoatrial disease.

Patients and methods

Twelve patients with sinoatrial disease were studied (table). This diagnosis included slow atrial fibrillation in the absence of other heart disease, a condition which is predominantly a disorder of the atria and the inflow to the atroventricular node. Patient 1 developed a junctional rhythm of 26 beats per minute and dizziness on gentle carotid sinus massage. Ambulatory monitoring showed P-P intervals of up to 2·05 s during the day and 2·10 s at night in patient 1. Patients 2, 4, and 12 had paroxysmal supraventricular tachycardias and maximum P-P intervals on ambulatory monitoring during the day of 1·85, 5·0, and 2·49 s respectively. Ambulatory monitoring showed 12 s of asystole during the day in patient 3. Patient 5 showed continuous slow atrial fibrillation with R-R intervals of up to 4·6 s during the day. Patients 6, 7, 9, and 11 had paroxysmal supraventricular tachycardias and sinus bradycardias of less than 45 beats per minute on a standard electrocardiogram. Patient 8, the only patient without symptoms of bradycardia, showed salvos (5-16 beats) of paroxysmal supraventricular tachycardias throughout 24 hours, with each paroxysm being followed by a pause (maximum 3·04 s during the day). Patient 10 had a sinus bradycardia of 44 beats per minute on a resting electrocardiogram and maximum P-P intervals of 2·13 s in the day and 3·54 s at night.

Eleven patients had symptoms (mean duration 51 months). Nine had been referred to the regional centre for consideration of permanent pacing. Patients whose predominant symptom was syncope were excluded from this study so that they would not be denied the immediate benefits of permanent pacing. Informed consent was obtained. None of the patients was taking drugs known to affect sinoatrial function. The study received the approval of the district ethics committee.

A double blind crossover study was carried out to compare the effects of oral xamoterol 200 mg twice daily with placebo. The study consisted of four one week periods (fig 1). Patients were randomised to receive xamoterol during either treatment periods A or B. On the sixth day of each period Holter monitoring was started and lasted for 24 hours after clinical review. The Holter tapes were recorded on
Oxford Medical Systems MR-2 recorders and played back on an Oxford Medical Systems PB-4 unit linked to the analyser mainframe incorporating a DDA-2 discriminator and HU3 histogram module. The following variables were analysed blindly on the tapes:—(a) modal R-R interval in each hour; (b) number of pauses >1.74 s in each hour; (c) duration of the longest pause in each hour; (d) mean heart rate over 24 hours.

A pause was defined as an R-R interval, excluding both atrioventricular and compensatory intervals after premature QRS complexes. Pauses lasting more than 1.74 s are found in <5% of the normal population of the age group studied. One of us visually checked the pauses during replay and the longer pauses were played out and measured directly. Module HU3 was used to update R-R interval information continuously as a histogram. This has 63 possible bin locations each having a width of 31.25 ms; the maximum interval which can be registered is 2-0 s. The bin with the largest number of beats determined the modal R-R interval. The Holter data were analysed by a repeated measures analysis of variance.

### Results

All 12 patients completed the protocol with no new symptoms while on xamoterol. One patient had a stroke while on placebo.

Xamoterol significantly shortened the modal R-R interval between the hours of midnight and 8 am (p < 0.01). This effect was less prominent at other times (fig 2). The result was a reduction in the diurnal range of modal R-R intervals. Figure 3 compares the number of pauses >1.74 s on placebo and xamoterol. Patients 3 and 9 did not have any prolonged pauses on either treatment. The pauses were abolished in three patients and substantially reduced in three others. Two patients had a slight increase in the number of pauses: the remaining two had a pronounced increase that was associated with symptomatic deterioration in one patient (case 4). In five patients the duration of the longest pause in the 24 hour period was considerably reduced (fig 4). This value showed little change in four patients. In patient 4 the longest pause was increased from 4.48 to 6.50 s. In 10 patients the mean heart rate was increased by xamoterol (fig 5). In six this was associ-
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Fig 2 Modal hourly R-R interval distribution over 24 hours for twelve patients.

ated with some reduction in both the number and duration of pauses; five of these patients had the bradycardia-tachycardia syndrome.

Six patients were started on long term xamoterol. Three, whose symptoms were still inadequately controlled, required permanent pacemakers. The three remaining patients were given no specific treatment.

Discussion

Six of 12 patients on short term xamoterol showed electrocardiographic improvement; one patient deteriorated. How reliable are these results? A cross-over trial is commonly used for drug assessment, but we are not aware that it has been used to assess the treatment of sinoatrial disease. There are no earlier studies to assess either the reproducibility of the results or the predictive ability for long term successful treatment.

The pharmacology of xamoterol is important to the assessment of this trial. Experiments in dogs have demonstrated that increasing doses of xamoterol produce 43% of the maximum increase in heart rate brought about by isoprenaline but have no direct effects on resistance to blood flow in the perfused hind leg. So xamoterol has a highly selective β₁ agonist effect. The experiments also demonstrated that xamoterol competitively inhibits the

Fig 3 Pauses in excess of 1.74 s while on xamoterol and placebo (log scale).

Fig 4 Duration of the longest pause (s) while on xamoterol and placebo.
effects of isoprenaline and noradrenaline on the heart rate. In doses that were 13 times higher, xamoterol also antagonised the vasodilator effect of isoprenaline on the perfused hind leg of a dog. Thus xamoterol has a partly selective $\beta_1$ antagonistic effect. Similar results have been demonstrated in normal volunteers, in whom xamoterol increased the heart rate at rest and reduced it during maximal exercise.$^8$ Xamoterol increases the minimum heart rate and reduces the maximum heart rate in patients with chronic atrial fibrillation on digoxin treatment.$^9$ Xamoterol also has positive inotropic effects and these are being evaluated for the treatment of heart failure.$^{10}$

The selection of two daily doses of 200 mg given for a week was determined by earlier studies. Oral doses of both 100 mg and 250 mg influenced the heart rate of healthy volunteers.$^9$ Data held by the manufacturer indicate that the mean elimination half life of 200 mg xamoterol in healthy volunteers is 13 hours (H M Snow, personal communication). In this study, the tape recordings of the placebo period were obtained before xamoterol treatment or 13 days after its discontinuation. Xamoterol has not been shown to have effects on the heart rate over this period of time, but such prolonged effects cannot be excluded with certainty; they are unlikely to be important, however.

Our study has some important limitations. Patients with severe symptoms could not be included because this would have denied them the immediate benefits of a pacemaker. The trial was designed for patients with mild-to-moderate symp-

toms, so it had to be completed reasonably quickly. Even patients with mild symptoms could not be kept on placebo for long periods. A longer study could have been carried out on asymptomatic patients with electrocardiographic evidence of sinoatrial disease; but the results would have been of little practical relevance.

The variable response of our patients to xamoterol is not surprising. Sinoatrial disease is a syndrome with several causes. This study does not give a clear indication as to which type of sinoatrial disease might be improved by xamoterol, though several responders had the tachycardia-bradycardia syndrome.

Xamoterol warrants further assessment as a potential alternative to pacing in some patients with sinoatrial disease.

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