

Placebo controlled trial of xamoterol versus digoxin in chronic atrial fibrillation

Eng L Ang, Wan L Chan, John G F Cleland, David Moore, Shirley J Krikler, Neal D E Alexander, Celia M Oakley

Abstract

Thirteen patients in chronic atrial fibrillation with a normal resting heart rate but with exercise tachycardia and episodes of bradycardia were randomised to treatment periods of two weeks on xamoterol (200 mg twice daily), low dose digoxin, or placebo, in a blind crossover study. The results (mean SEM) of symptom scores, a treadmill exercise test, and 24 hour ambulatory electrocardiographic monitoring were obtained. Xamoterol improved symptom scores and controlled exercise heart rate better than digoxin. Xamoterol was better than digoxin or placebo in reducing the heart rate response to exercise and tended to improve exercise duration. Xamoterol, by reducing the daytime maximum hourly heart rate and increasing the night time minimum hourly heart rate, significantly reduced the difference between the two compared with placebo. In contrast, digoxin tended to reduce both the maximum and minimum hourly heart rates through day and night. Both the frequency and duration of ventricular pauses were reduced by xamoterol but tended to increase with digoxin.

Xamoterol reduced both the circadian variation in ventricular response to atrial fibrillation and exercise tachycardia by modulating the heart rate according to the prevailing level of sympathetic activity. These changes were translated into symptomatic benefit for the patients studied.

Medical treatment of chronic atrial fibrillation has largely concentrated on the control of tachycardia. However, recent 24 hour ambulatory electrocardiographic studies emphasised the wide circadian variation in heart rate in chronic atrial fibrillation,¹ and the importance of episodic ventricular standstill.² Tachycardia of more than 140 beats/min associated with bradycardia of less than 50/min and nocturnal pauses of up to 4.0 s are commonly found in patients thought to be optimally treated.¹ In fact, digoxin, the most widely used treatment, tends to provoke or aggravate bradycardia by its vagomimetic effect.³

Xamoterol is a selective β_1 adrenoceptor partial agonist that has 43% of the stimulant activity of the full agonist isoprenaline.⁴ At low levels of sympathetic activity, it occupies

the β_1 receptors to produce both positive inotropic and chronotropic effects on the heart.⁵ When sympathetic activity increases, it behaves as a competitive antagonist at the β_1 receptor.⁶ This ability of xamoterol to stabilise activation of the β_1 receptor may be of use in modulating the ventricular response to atrial fibrillation in patients whose heart rate shows considerable circadian variation. We investigated the effects of xamoterol, digoxin, and placebo on symptoms, exercise performance, and 24 hour control of heart rate in patients with chronic atrial fibrillation and normal resting heart rate who showed exercise tachycardia during the day and episodes of bradycardia, especially at night.

Patients and methods

PATIENTS

We studied 13 patients (seven women) aged 55-84 years (mean 67). All had chronic atrial fibrillation and electrocardiographic evidence of bradycardia at rest that had caused the attending physician to reduce or stop specific treatment. Patients had a documented resting heart rate of <50 beats/min before the dose of digoxin was reduced. All patients had at least one ventricular pause of 1.5 s after digoxin was stopped. Ten patients had conduction abnormalities on the electrocardiogram: three had bifascicular block, two had right bundle branch block, two had right axis deviation, and three had non-specific intraventricular conduction defects. No patient complained of syncope but ten patients reported dizziness and six palpitation. All patients experienced some degree of breathlessness or fatigue on exertion. Eight were in the New York Heart Association class I category, and five in class II (who needed diuretics). The aetiology was non-rheumatic valvar heart disease in four patients; rheumatic valvar heart disease in three; two were "lone" fibrillators; and there was one case each of ischaemic heart disease, constrictive pericarditis, post-thyroidectomy, and hypertrophic cardiomyopathy. Six patients took no specific treatment for atrial fibrillation, six were taking digoxin 0.125 mg daily (5) or 0.0625 mg daily (1); one patient was taking atenolol 50 mg daily. Other important medications were frusemide, warfarin, thyroxine, captopril, and bendrofluzide. We obtained informed consent from each patient after a full explanation of the study.

DESIGN

Treatment with digoxin and atenolol was

Department of
Medicine (Clinical
Cardiology),
Hammersmith
Hospital, London

E L Ang
W L Chan
J G F Cleland
D Moore
S J Krikler
C M Oakley

Medical Physics
Department,
Hammersmith
Hospital, London
N D E Alexander

Correspondence to
Dr John G F Cleland,
Department of Medicine
(Clinical Cardiology),
Hammersmith Hospital,
London W12 0NN

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stopped in the six patients who were taking it; these patients were then observed and assessed for at least two weeks before entry into the study. Each patient underwent three treatment periods—one each of xamoterol, digoxin, and placebo—in a randomised cross-over fashion. Each treatment period lasted two weeks and was followed by a two week wash out period before the next treatment. Xamoterol (200 mg) and its matching placebo were given twice daily. Digoxin tablets were started at 0.5 mg on the first day of the treatment period, then the maintenance dosage was adjusted from 0.0625 mg daily to achieve a low therapeutic serum concentration.

The treatments were administered by an investigator who was not involved in the assessment. The other investigators and technicians conducting the investigations were not aware of the current treatment phase. Patients were assessed at entry into the study and reassessed at the end of each treatment period. The assessment comprised symptomatic evaluation, a treadmill exercise stress test, and 24 hour ambulatory electrocardiograph monitoring. Dizziness, palpitation, and breathlessness were rated for frequency on a descriptive 5 point scale. We assessed heart rate variability with 24 hour ambulatory electrocardiography on Reynolds Tracker recorders and analysis by a visually assisted Reynolds Pathfinder 3 system. We measured the maximum and minimum hourly heart rates, the number of ventricular pauses > 1.5 s, and the longest ventricular pause in 24 hours. (The heart rate was calculated from 15 s electrocardiographic strips.) A symptom limited treadmill exercise test was performed according to the modified Bruce protocol. The resting heart rate before the exercise was measured after the patient had sat down for five minutes. During the exercise, heart rate was monitored continuously and blood pressure was measured every minute. The maximum heart rate, maximum blood pressure, and exercise duration were recorded.

STATISTICAL ANALYSIS

To assess the differential effect of xamoterol on the circadian control of heart rate, the 24 hour data on heart rate were analysed over two 12 hour periods: 10 am to 9 pm (day) and 10 pm to 9 am (night). The area under the curve (AUC) of the plot of heart rate against time, calculated by the trapezoidal rule, reflects the mean heart rate over the time measured. For the day period, each area under curve of the maximum and minimum heart rates, termed AUC (day max) and AUC (day min) respectively, was calculated. AUC (night max) and AUC (night min) were similarly

derived for the night period. The overall difference between the three treatment groups was determined by two way analysis of variance for the heart rate and exercise data, after we had checked for normality and equality of variance. If the variance ratio obtained was significant at the 5% level, we performed multiple paired comparisons between treatment groups using contrasts. Symptom scores and the number of ventricular pauses in 24 hours were analysed by Friedman two way analysis of variance by ranks. When the Friedman analysis showed a significant treatment effect, individual paired comparisons were carried out by the critical range method.⁷ Results are given as mean (SEM). The 95% confidence intervals (95% CI) were calculated where appropriate. A *p* value of < 0.05 was regarded as significant.

Results

Statistical analysis was carried out on the results from 12 patients who completed all phases of the study. In one patient, a 58 year old woman with valvar heart disease and symptoms (New York Heart Association class II), nausea, vomiting, and increased dyspnoea developed with two days of the start of xamoterol treatment. When xamoterol was stopped she improved but continued to feel unwell. Further investigations did not show an organic cause. During the digoxin treatment phase, five patients were given digoxin 0.0625 mg daily, the other seven patients were given 0.125 mg daily, and a mean serum concentration of 0.7 (0.1) nmol/l was achieved at completion of the treatment phase, when assessment took place. Analysis for possible period effect based on the exercise test results showed no significant differences between the three treatment periods.

SYMPTOM SCORES

Table 1 shows the comparative data on symptom scores based on a descriptive 5 point frequency scale. The symptom scores for the three treatments for palpitation, dizziness, and breathlessness were similar, although the scores for xamoterol seemed to be consistently lower than those for digoxin or placebo. Digoxin tended to produce less palpitation than placebo but more dizziness and breathlessness. Although there were no significant differences between individual symptoms during any treatment phase, a combined symptom score showed that patients had significantly more symptoms on digoxin than on xamoterol (*p* < 0.05).

EXERCISE TEST

Table 2 shows the comparative data on exercise test for the three treatments. The resting heart rate before the exercise test was significantly lower with digoxin treatment than with xamoterol (*p* < 0.005) or placebo (*p* < 0.01). There was no significant difference between xamoterol and placebo. The maximum heart rate on exercise was significantly lower with xamoterol treatment than with placebo or

Table 1 Comparative data on scores for symptom frequency (mean (interquartile range))

Symptom	Placebo	Xamoterol	Digoxin
Palpitation	2.0 (1.0-3.0)	1.5 (1.0-1.8)	1.8 (1.0-2.8)
Dizziness	1.6 (1.0-1.7)	1.2 (1.0-1.3)	1.7 (1.0-2.3)
Breathlessness	2.6 (1.3-3.8)	2.2 (1.3-3.0)	2.7 (2.0-3.8)

Table 2 Comparative data obtained from exercise test (mean (SEM))

	Placebo (Pl)	<i>p</i> (Pl v X)	Xamoterol (X)	<i>p</i> (X v D)	Digoxin (D)	<i>p</i> (D v Pl)
Resting HR (beats/min)	70 (5)	NS	72 (5)	<0.005	62 (5)	<0.01
Peak HR (beats/min)	159 (12)	<0.001	136 (10)	<0.005	150 (10)	NS
Peak SAP (mm Hg)	181 (10)	NS	174 (8)	NS	170 (9)	NS
Peak DAP (mm Hg)	83 (3)	NS	87 (4)	NS	84 (2)	NS
PR product (mm Hg × min)	28612 (2545)	<0.001	23668 (2110)	NS	25786 (2412)	<0.05
Exercise duration (min)	9.7 (1.1)	NS	10.7 (0.9)	NS	10.2 (1.0)	NS

HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; PR, pressure × rate.

digoxin; the values for placebo and digoxin were not significantly different from each other ($p = 0.45$). There were no significant differences between the three treatments in the peak exercise systolic or diastolic blood pressure. The maximum pressure-rate product was significantly reduced by xamoterol and digoxin compared with placebo; but there was no significant difference between the two active treatments ($p = 0.17$). The patients tended to exercise longer on xamoterol treatment (95% CI: 10.0–11.4 min) than placebo (95% CI: 9.0–10.4 min) or digoxin (95% CI: 9.5–10.9 min), though this difference did not achieve statistical significance ($p = 0.20$).

HOURLY HEART RATE DATA

Figure 1A shows the effects of the three treatments on the maximum hourly heart rate over a 24 hour period, and fig 1B similarly shows the minimum hourly heart rate. Figure 2A shows the area-under-curve analysis of the data on maximum and minimum hourly heart rate from 10 am to 9 pm (day), and figure 2B the data from 10 pm to 9 am (night). Compared with placebo, xamoterol tended to reduce both AUC (day max) and AUC (day min) but

increase both AUC (night max) and AUC (night min). Digoxin, in contrast, tended to reduce the values of all four variables compared with placebo or xamoterol. The difference between the areas under the curves of the plots of maximum and minimum hourly heart rate reflects the variability of the heart rate within the hour. Table 3 shows that the heart rate variability within the hour was similar in the three treatment groups. However, the circadian variability as indicated by AUC (day max)–AUC (night min) was significantly lower with xamoterol treatment than with either digoxin ($p < 0.05$) or placebo ($p < 0.01$). Compared with placebo, xamoterol increased the lowest minimum hourly heart rate from 50 (4) beats/min to 59 (5) beats/min ($p < 0.05$) but reduced the highest maximum hourly heart rate from 139 (8) beats/min to 132 (8) beats/min ($p = 0.30$) (table 4). Digoxin produced lower values for both the variables (45 (3) and 131 (8) beats/min respectively) than either xamoterol or placebo; the lowest minimum hourly heart rate was significantly different from the xamoterol value ($p < 0.001$).

VENTRICULAR PAUSES

Table 4 shows that xamoterol reduced the number of ventricular pauses (> 1.5 s) in 24 hours compared with placebo or digoxin; the comparison with digoxin was significant ($p < 0.05$). The pauses were most frequent between 1 am and 6 am and least common between 1 pm and 6 pm. The maximum ventricular pause in 24 hours was the longest with digoxin treatment (95% CI: 2.2 to 2.8 s),

Figure 1 (A) Maximum hourly heart rate over a 24 hour period. (B) Minimum hourly heart rate over a 24 hour period.

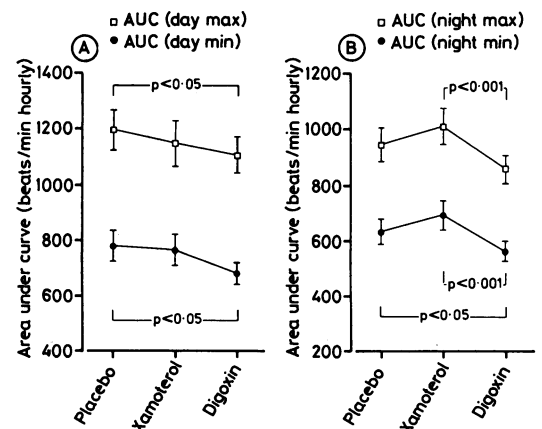
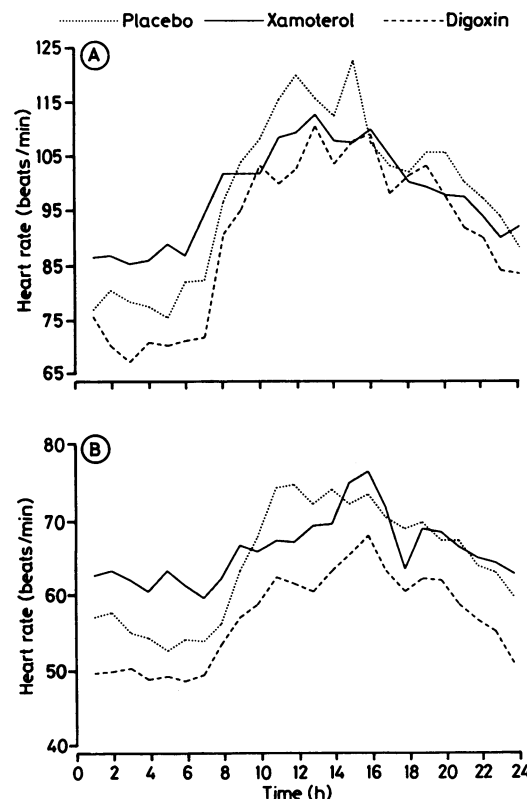


Figure 2 (A) Area-under-curve analysis of hourly heart rate data from 10 am to 9 pm. Results are given as mean (SEM). (B) Area-under-curve analysis of hourly heart rate data from 10 pm to 9 am.

Table 3 Comparative data on variability of heart rate by area-under-curve analysis (mean (SEM))

	Placebo	Xamoterol	Digoxin
AUC (day max)—AUC (day min) (beats/min hourly)	417 (27)	386 (37)	427 (32)
AUC (night max)—AUC (night min) (beats/min hourly)	312 (18)	319 (39)	296 (22)
AUC (day max)—AUC (night min) (beats/min hourly)	565 (39)	458* (47)	546 (35)

*Xamoterol v placebo, $p < 0.01$; xamoterol v digoxin, $p < 0.04$.

unaltered by placebo (95% CI: 2.0 to 2.6 s), but reduced significantly by xamoterol (95% CI: 1.5 to 2.1 s).

Discussion

In a placebo controlled study of patients with chronic atrial fibrillation characterised by normal resting heart rate, but with both exercise induced tachycardia and episodes of bradycardia, xamoterol seemed to be better than digoxin. Xamoterol treatment was more effective than digoxin in reducing exercise tachycardia and was accompanied by an improvement in exercise duration. Compared with digoxin, xamoterol reduced the frequency and duration of ventricular pauses and restored the minimum hourly heart rates to the normal range (fig 1B).

An important limitation in our selection of patients was that ethical considerations prevented us from recruiting patients with obvious symptomatic bradycardia or from placing them on conventional doses of digoxin. Only a few studies of the medical treatment of chronic atrial fibrillation have addressed the problem of bradycardia.⁸⁻¹⁰ While the importance of symptomatic bradycardia is widely recognised, the significance of recurrent ventricular pauses in bradycardiac episodes that are not clearly associated with symptoms is less clear. A 24 hour ambulatory electrocardiographic study by Bjerregaard of 260 healthy people found that ventricular pauses > 1.5 s were common.¹¹ It has been suggested that while bradycardia is common in young people, especially at night, sinus pauses are a cause for concern in older people and should never exceed 2.5 s at any age.¹² Ventricular pauses in atrial fibrillation reflect extensive degeneration of pacemaker and conduction tissue.¹³ Atrial fibrillation per se is known to reduce cerebral blood flow¹⁴ and recurrent ventricular standstill would be likely to exacerbate this. Rebello and Brownlee showed that ventricular demand pacing may relieve dizziness as well as syncope in such

patients.² Most of our patients continued to have symptoms even after treatment with digoxin was stopped or reduced.

Though the maximum exercise heart rate on placebo was not as high as in other studies,¹⁵⁻¹⁷ it may have limited exercise duration. The maximum exercise heart rate was significantly reduced by xamoterol but not by low dose digoxin. Treatment with digoxin clearly increased the maximum ventricular pause beyond 2.04 s (93% CI: 2.2 to 2.8 s)—the longest pause in Bjerregaard's study—whereas xamoterol tended to reduce it to less than 2.1 s (95% CI: 1.5 to 2.1 s). Rebello and Brownlee thought that dizziness, which occurred in eight of our patients while they were being treated with digoxin, might suggest the need for pacemaker insertion.² Xamoterol, however, relieved dizziness in three and improved the symptom in four others, leaving only one unaltered. Elderly patients who are more liable to have atrial fibrillation are more likely to develop a slow ventricular response because of concomitant atrioventricular nodal disease.¹⁸⁻²⁰ This accords with the age of our patients (55 to 84) and the high incidence of conduction abnormalities on the electrocardiogram. The underlying heart disease too might have contributed to the conduction defects in our patients.

Digitalis is regarded as the best drug to control the ventricular response to atrial fibrillation.²¹ At rest, vagal tone predominates and this may be enhanced by digoxin.³ Increases in sympathetic tone during stress override the vagal effects of digoxin and limit its effect on the heart rate during exercise.²² Increasing the dose of digoxin may well improve control of heart rate during exercise but it will exacerbate resting bradycardia.²³ β blockers and calcium antagonists tend to act preferentially on the exercise heart rate,^{24,25} but both can exacerbate bradycardia,^{16,26} and their negative inotropic effect detracts from their beneficial effect on the control of heart rate.^{27,28} Interestingly, digoxin further depressed nocturnal bradycardia and this was consistent with an increase in vagal tone. Xamoterol increased nocturnal heart rate; this effect is consistent with an increased expression of the agonist activity of xamoterol at a time of low endogenous sympathetic activity.

Xamoterol decreased the number and duration of ventricular pauses in patients with sick sinus syndrome,²⁹ and gave better control of exercise heart rate.³⁰ On the other hand, xamoterol combined with digoxin gave better control of exercise heart rate than digoxin

Table 4 Comparative data from 24 hour ambulatory electrocardiography (mean (SEM))

	Placebo (Pl)	p (Pl v X)	Xamoterol (X)	p (X v D)	Digoxin (D)	p (D v Pl)
HHR max (beats/min)	139 (8)	NS	132 (8)	NS	131 (8)	NS
HHR min (beats/min)	50 (4)	< 0.05	59 (5)	< 0.001	45 (3)	NS
No of VP in 24 h	3322 (1443)	NS	2732 (1451)	< 0.05	5238 (1707)	NS
Max VP in 24 h (s)	2.3 (0.1)	< 0.005	1.8 (0.1)	< 0.001	2.5 (0.1)	NS

HHR max, highest maximum hourly heart rate in 24 h; HHR min, lowest minimum hourly heart rate in 24 h; VP, ventricular pause.

alone.³⁰ These apparent actions of xamoterol are consistent with its selective β_1 partial adrenoceptor activity and are used to advantage in our patients. Xamoterol also seems to be of more benefit than digoxin in patients with mild to moderate heart failure who remain in sinus rhythm³¹; this may be relevant because heart failure often accompanies atrial fibrillation.³²

Xamoterol is the best drug in patients with chronic atrial fibrillation who have episodes of bradycardia with ventricular pauses. Xamoterol reduces the duration and frequency of the pauses while improving the control of heart rate during exercise, and this is associated with an improvement in symptoms. Xamoterol may be especially useful in patients with mild heart failure; it must not be used in patients with severe heart failure.

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