Effects of xamoterol, a β_1 adrenoceptor partial agonist, in patients with ischaemic dysfunction of the left ventricle

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SUMMARY The effects of xamoterol (200 mg twice a day) in 21 patients with left ventricular dysfunction were studied in a double blind, randomised, crossover, placebo controlled trial with treatment periods of four weeks. Most patients had moderate heart failure (New York Heart Association class II), all had ischaemic heart disease, a history of a myocardial infarction, and symptoms of dyspnoea on exertion. Patients were assessed in terms of exercise duration (bicycle ergometer), clinical signs of heart failure, symptoms and activities, and ejection fraction. Xamoterol increased exercise duration (mean (SD)) (from 445 (8) seconds to 484 (8) seconds) and ejection fraction (from 41.9 (1.3)% to 46.6 (1.3)%) and reduced the signs and symptoms of heart failure.

The results of this study show that xamoterol is a safe and effective treatment for left ventricular dysfunction resulting from ischaemic heart disease.

Treatment of patients with heart failure associated with ischaemic heart disease has conflicting goals. The use of stimulant drugs can exacerbate ischaemia particularly during exercise but the use of drugs that depress cardiac function or lower blood pressure can exacerbate the symptoms of heart failure.

Xamoterol is a β_1 adrenoceptor partial agonist with no agonist activity at the β_2 adrenoceptor.¹ The overall action of xamoterol is to stabilise the response of the heart to sympathetic stimulation such that at rest and during low levels of activity the heart receives inotropic support and during more severe exercise heart rate is reduced.² For these reasons xamoterol has been classified as a "cardiostabiliser".³

The aim of the present study was to examine the effects of xamoterol (200 mg twice a day) in a group of patients with moderate heart failure (New York Heart Association II) because of ischaemic left ventricular dysfunction.

A preliminary report of this study was made to the American Heart Association.⁴

Patients and methods

PATIENTS

Table 1 lists the characteristics of the patients. Twenty one patients (14 men and seven women; mean age 62.2 (range 44-73)) with mild to moderate heart failure entered the study. Twenty patients were in New York Heart Association class II and one was in class III. All patients had ischaemic heart disease and a history of a myocardial infarction. The main presenting symptoms were dyspnoea in 21 patients for a mean period of 24.8 months, angina pectoris in 15 patients for a mean period of 31.5 months, and fatigue in 11 patients for a mean period of 16.3 months. Six patients had had peripheral oedema for a mean period of 26.2 months. All patients had previous episodes of heart failure with pulmonary congestion. The heart was enlarged (cardiothoracic ratio > 0.5) in 16 patients.

Patients were excluded from the study if they had severe cardiac failure (New York Heart Association class IV); myocardial infarction less than two months previously; pulmonary disease causing breathlessness on exercise; sinus tachycardia exceeding 90 beats/minute; any arrhythmias requiring treatment; aortic stenosis; hypertrophic obstructive cardiomyopathy; serious renal, haemopoietic, endocrine

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Table 1 Data on study group

Patient No	Age (yr)	Sex	Cardiovascular diagnosis/history (NYHA class)	Drug treatment at entry (mg/day)
1	69	F	Cardiac failure (NYHA II), previous myocardial infarction, hypercholesterolaemia	Glyceryl trinitrate, potassium chloride (1146), bendrofluazide (5)
2	52	M	Cardiac failure (NYHA III), previous myocardial infarction	Sorbide dinitrate (80)
3	72	M	Cardiac failure (NYHA II), previous myocardial infarction, ventricular aneurysm	Hydrochlorothiazide (50), amiloride (5)
4	56	F	Cardiac failure (NYHA II), previous myocardial infarction	Bendrofluazide (5), potassium chloride (1146)
5	54	M	Cardiac failure (NYHA II), previous myocardial infarction, hyperlipaemia	Bendrofluazide (5), potassium chloride (1146)
6	68	M	Cardiac failure (NYHA II), previous myocardial infarction	None
7	70	F	Cardiac failure (NYHA II), previous myocardial infarction	Bendrofluazide (2.5), potassium chloride (573)
8	61	F	Cardiac failure (NYHA II), previous myocardial infarction	Furosemide (40), potassium chloride (2250)
9	57	M	Cardiac failure (NYHA II), previous myocardial infarction	Furosemide (80), potassium chloride (2250)
10	70	M	Cardiac failure (NYHA II), previous myocardial infarction	Bendrofluazide (5), potassium chloride (1146)
11	44	M	Cardiac failure (NYHA II), previous myocardial infarction	Glyceryl trinitrate (19.5), furosemide (40), potassium chloride (2250)
12	49	M	Cardiac failure (NYHA II), previous myocardial infarction, angina pectoris	Glyceryl trinitrate (19.5), bendrofluazide (5), potassium chloride (1146)
13	46	M	Cardiac failure (NYHA II), previous myocardial infarction, hypercholesterolaemia	Glyceryl trinitrate, furosemide (40), potassium chloride (1500)
14	71	F	Cardiac failure (NYHA II), previous myocardial infarction	Hydroflumethiazide (25), potassium chloride (1146)
15	69	F	Cardiac failure (NYHA II), previous myocardial infarction, hypertension	Glyceryl trinitrate (5.2), bendrofluazide (5), potassium chloride (3396)
16	73	M	Cardiac failure (NYHA II), previous myocardial infarction	Glyceryl trinitrate (6.5), furosemide (40), potassium chloride (750)
17	62	M	Cardiac failure (NYHA II), previous myocardial infarction	Furosemide (80), potassium chloride (2250)
18	72	M	Cardiac failure (NYHA II), previous myocardial infarction	Furosemide (80), potassium chloride (2250)
19	64	F	Cardiac failure (NYHA II), previous myocardial infarction	Furosemide (40), potassium chloride (2250)
20	64	M	Cardiac failure (NYHA II), previous myocardial infarction	Furosemide (40), potassium chloride (1500)
21	64	M	Cardiac failure (NYHA II), previous myocardial infarction	Bumetanide (2), potassium chloride (2250)

NYHA, New York Heart Association.

Fig 1 Design of study.

disorders; or mental problems and inability to complete the first three minutes of the exercise protocol; or concurrent treatment with digitalis, β blockers, vasodilators (except long acting nitrates), antiarrhythmic agents; or furosemide exceeding 80 mg daily, bumetanide exceeding 2 mg daily, or spironolactone exceeding 100 mg daily.

STUDY DESIGN

The study had two phases (fig 1). After selection at visit 1, patients entered phase 1, a single blind placebo period of seven to 14 days. Baseline assessments were carried out at visit 2. This was followed by phase II, which consisted of two double blind randomised treatment periods (placebo and

Please ask the patient the following questions and tick (✓) the appropriate box.

Do you find that you suffer from:	Never ☐ 1	A little of the time ☐ 2	Some of the time ☐ 3	A good part of the time ☐ 4	All or most of the time ☐ 5
Tiredness	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Breathlessness	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Chest Pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Palpitations	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Do you find that you can walk with:	No difficulty ☐ 1	A little difficulty ☐ 2	Noticeable difficulty ☐ 3	A great deal of difficulty ☐ 4	
Do you find that you can walk:	Very quickly ☐ 1	Quickly ☐ 2	At a medium pace ☐ 3	Slowly ☐ 4	Very slowly ☐ 5
Do you find that you can do your daily tasks with:	No difficulty ☐ 1	A little difficulty ☐ 2	Noticeable difficulty ☐ 3	A great deal of difficulty ☐ 4	
Do you find that you can do your daily tasks:	Very quickly ☐ 1	Quickly ☐ 2	At a medium pace ☐ 3	Slowly ☐ 4	Very slowly ☐ 5
Do you feel weepy/miserable/low:	Never ☐ 1	A little of the time ☐ 2	Some of the time ☐ 3	A good part of the time ☐ 4	All or most of the time ☐ 5
Do you find that your confidence is:	Very good ☐ 1	Good ☐ 2	Adequate ☐ 3	Poor ☐ 4	Very poor ☐ 5
Do you find that your sleeping is:	Very good ☐ 1	Good ☐ 2	Adequate ☐ 3	Poor ☐ 4	Very poor ☐ 5

Fig 2 Symptoms/activity questionnaire administered by the physician at the end of each treatment period.

xamoterol) of four weeks in a crossover design, with assessments at the end of each period (visits 3 and 4). The dose of xamoterol was 200 mg twice a day. Concurrent treatment was maintained throughout the study (table 1). On entry to the study seven patients were taking nitrates for relief of angina pectoris and 20 patients were taking diuretics. One patient (case 6) was not taking any concurrent treatment.

The protocol was approved by the ethics committee of the Amtssygehus Århus and the study was conducted in accordance with the Declaration of Helsinki (1964). Each patient gave verbal consent to be included in the study.

ASSESSMENTS

Assessment of the patients at visit 2, 3, and 4 included the following:

Clinical examination.—Patients were examined by auscultation of the heart and lungs and for the presence of peripheral oedema, raised jugular venous pressure, and hepatomegaly.

Symptoms and activities.—The patient's "quality of

life" was assessed by a series of questions about symptoms and activities. The questions were asked by the physician at the end of each treatment period and the answers were classified as one of either four or five grades (fig 2).

Echocardiography.—Patients were examined with an Aloka 710 Sector Scanner while supine or in the left reclining position. An M mode scan of the left ventricle was made at the level of the chordae tendineae. The left ventricular end diastolic diameter was measured at the time of the peak of the R wave and the end systolic diameter at the time of the peak anterior movement of the posterior wall of the left ventricle. Systolic and diastolic volumes were calculated.⁷ The mitral-septal distance was also measured. The positions of the patients and the transducer were maintained as consistently as possible at each subsequent investigation.

Exercise capacity.—A symptom limited exercise test was performed on a Siemens ergometer cycle. The initial workload was 50 W; this was increased by 25 W every three minutes. During the exercise test a nine lead electrocardiogram was recorded and

Fig 3 Exercise duration at the end of each treatment period in 21 patients. At baseline the mean duration of exercise was 440 (37.2) seconds (not shown), after treatment with placebo it was 445 (8) seconds, and after treatment with xamoterol it was 484 (8) seconds. Exercise duration was increased in 15 patients, decreased in four patients, and remained the same in two patients.

evidence of myocardial ischaemia was assessed at the end of each load. Heart rate and systolic blood pressure were measured at the end of each three minute period and at maximum exercise. The duration of exercise was recorded and the total work done was calculated.

Statistical analysis.—An analysis of variance, allowing for the effects of sequence, treatment, and treatment order was used to analyse duration of exercise, work done during exercise, heart rate at maximum exercise, and ejection fraction. The Likert scores, for assessing symptoms and activities, were analysed by a non-parametric technique.

Results

EXERCISE

At baseline all 21 patients were able to achieve a work rate of 100 W; 13 patients achieved 125 W and six patients 150 W. The mean (SE) duration of exercise at baseline was 440 (37) seconds. After treatment with placebo the adjusted mean for duration was 445 (8) seconds and after treatment with xamoterol it was 484 (8) seconds. The mean difference in exercise

Fig 4 Work done at the end of each treatment period in 21 patients. The adjusted mean for work done after placebo was 32.6 (0.9) kJ and after xamoterol it was 36.7 (0.9) kJ.

duration between the two treatment periods (39 (12) s) was significant ($p < 0.01$). Compared with the placebo treatment, 15 patients exercised for a longer time on xamoterol treatment, two exercised for the same time, and four patients exercised for a shorter time (fig 3). The adjusted mean (SE) for work done during placebo treatment was 32.6 (0.9) kJ and that during xamoterol treatment was 36.7 (0.9) kJ—a difference of 4.1 (1.3) kJ, which was significant ($p < 0.01$) (fig 4).

Figure 5 shows the effects of xamoterol on the mean resting and exercise heart rates at each exercise load. Heart rate was reduced by xamoterol at each exercise load. The adjusted mean (SE) for heart rate at maximum exercise was reduced from 129.4 (2.1) beats/minutes (placebo) to 111.1 (2.1) beats/minutes (xamoterol) ($p < 0.001$). Figure 6 shows the effects of xamoterol on the mean systolic blood pressure at rest and at each exercise load. There was a tendency for systolic blood pressure during xamoterol treatment to be increased at rest and reduced at the higher levels of exercise. ST depression was not seen in any exercise electrocardiogram.

ASSESSMENT OF SYMPTOMS AND ACTIVITIES

Table 2 shows the results with the Likert scales. A

Fig 5 Heart rates after treatment with xamoterol and placebo at rest (R) and after three, six, nine, and 12 minutes' exercise.

non-parametric analysis was carried out and differences in the assessment by the physician in response to each question at the end of the two treatment periods were recorded as "better", "same", or "worse". Those patients who were not troubled by a particular symptom throughout the study were not included in the analysis. Table 2 shows the total number of patients who had each symptom and the difference between their answers at the end of each treatment period. The score for the two questions on walking, the two questions on daily tasks, and the two questions on mood were aggregated. Apart from mood, the answers to every question showed a trend in favour of xamoterol, which achieved statistical significance for breathlessness ($p < 0.02$) and chest pain ($p < 0.05$).

CLINICAL SIGNS OF HEART FAILURE

Each patient was examined clinically at baseline and at the end of each treatment period for the following signs of heart failure: crepitations on auscultation of the lungs, abnormal heart sounds, peripheral oedema, hepatomegaly, jugular venous distension, and irregular arterial pulse. Overall, 19 of the 21 patients had one or more signs of heart failure at baseline. The most frequent sign of heart failure was crepitations, which were found at baseline in 12 out of 21 patients, after placebo in nine, and after xamoterol in six. In two patients crepitations developed during xamoterol treatment. An irregular pulse (ventricular extrasystoles) was present in three patients at baseline, in six patients during placebo

Fig 6 Mean systolic blood pressure after treatment with xamoterol and placebo at rest (R) and after three, six, nine, and 12 minutes' exercise.

treatment, and in three patients during xamoterol treatment. The pulse became regular on treatment with xamoterol in four of the six patients who had an irregular pulse on placebo treatment. The only other sign of heart failure was jugular venous distension in two patients; this was not present after xamoterol in one patient and not present after placebo in either patient. In general, the most frequent signs of heart failure were crepitations and an irregular pulse both of which tended to be reduced during treatment with xamoterol.

ECHOCARDIOGRAPHY

Echocardiography was carried out in 17 patients at baseline and 18 patients after treatment with placebo and xamoterol. At baseline the mean (SE) ejection fraction, calculated from the end systolic and end

Table 2 Total number of patients with each symptom or impairment of activities and the difference between treatments expressed as the number of patients feeling "better", "worse", or the "same" when treated with xamoterol

	Total	Better	Worse	Same
Tiredness	20	8	2	10
Chest pain*	18	9	1	8
Breathlessness†	17	9	0	8
Palpitation	13	8	1	4
Walking	21	10	4	7
Difficulty with tasks	20	7	2	11
Mood/confidence	13	5	4	4
Sleep	9	5	2	2

* $p < 0.05$; † $p < 0.02$

Fig 7 Ejection fraction after treatment with xamoterol and placebo. The mean ejection fraction at baseline was 42.4 (3.4)%, after treatment with placebo it was 41.9 (1.3)%, and after treatment with xamoterol it was 46.6 (1.3)% (an increase of 4.7% ($p < 0.05$)).

diastolic diameters of the heart, was 42.4 (3.4)%. After treatment with placebo the ejection fraction was 41.9 (1.3%) and after treatment with xamoterol it was 46.6 (1.3)%—an increase of 4.7 (1.9)% ($p < 0.05$) corresponding to a relative increase of about 12%. When patients were treated with xamoterol the ejection fraction increased in 12 patients, remained the same in one patient, and decreased in five patients (fig 7).

The improvement was independent of the initial ejection fraction; and hearts with an ejection fraction $< 40\%$ (10 patients) improved from 35.2 (2.1)% after placebo treatment to 41.3 (2.1)% after xamoterol treatment (an increase of 6.1 (3.0)% ($p = 0.076$), corresponding to a relative increase of about 17%).

Discussion

The patients entered into this study had mild to moderate heart failure (New York Heart Association class II and III) as a result of ischaemic heart disease. There was evidence of heart failure in all patients, despite treatment with diuretics. The mean work rates achieved (mean 120 W) were below normal for a population of similar age and sex,⁶ as were the mean ejection fractions (42%). Not all patients had signs of congestive heart failure. Crepitations, which were

found in 12/21 patients at baseline, were the most common sign. This low incidence of signs of congestive heart failure, despite evidence of left ventricular dysfunction, probably reflects the adequacy of treatment with diuretics.

The increase in exercise tolerance was associated with both a reduction in maximum exercise heart rate and a tendency for systolic blood pressure to be reduced. The resulting reduction in the pressure-rate product can account only in part for the prolongation of exercise in these patients with ischaemic heart disease, because there was no difference between the treatment groups in the frequency of chest pain as a reason for stopping exercise (three placebo, two xamoterol). In contrast, breathlessness was a reason for stopping exercise in most patients (20 placebo, 17 xamoterol). In patients with ischaemic heart disease symptoms of chest pain and breathlessness during a maximal exercise test may be confused. The signs and symptoms of patients in this study however, suggest that angina was not the predominant symptom and that the patients had considerable dysfunction of the left ventricle. The mechanisms by which heart failure causes breathlessness are disputed. During maximum exercise both pulmonary wedge pressure and end diastolic pressure in the left ventricle are known to increase dramatically in patients with ischaemic heart disease and this increase has been associated with symptoms of breathlessness. Lipkin and Poole-Wilson, in an exercise protocol similar to ours, recently reported that the sensation of breathlessness was related to plasma concentrations of lactate rather than pulmonary capillary wedge pressure.⁷ Sato *et al* showed that a single dose of xamoterol reduced pulmonary wedge pressure at rest and during exercise, even when heart rates were reduced.² These results with xamoterol are consistent with the earlier findings of Detry *et al*.⁸ In both studies, during maximum exercise heart rate was reduced, cardiac output unchanged, and pulmonary wedge pressure reduced. Therefore, it is possible that prolongation of exercise tolerance in the present study is related to a delay in the acute rise in pulmonary wedge pressure. The assessment of symptoms also showed a trend for a significant reduction in breathlessness and a trend for an increase in physical activities.

The significant reduction in resting ejection fraction and the tendency for a reduction in the signs of congestion, in particular crepitations, are probably related to the modest stimulant action of xamoterol at rest and during moderate activity. In those patients who had difficulties in sleeping, xamoterol improved the quality of sleep, again an effect probably related to modest stimulation of the heart and the resulting fall in pulmonary wedge pressure.^{9,10} Xamoterol is hydrophilic, does not cross the blood-brain barrier to any appreciable extent, and has no known action on the central nervous system.

In a previous study carried out in our laboratory in a selected group of patients with moderate heart failure (New York Heart Association class II and III on treatment with digoxin and diuretics), who deteriorated clinically on withdrawal of digoxin, exercise duration was on average 27% higher on digoxin and 17% higher on xamoterol.¹¹ In these patients there was no significant difference between the effects of digoxin and xamoterol on functional assessment score and exercise duration. More recently results in 349 patients randomised to placebo, xamoterol, or digoxin and treated for three months showed that xamoterol significantly improved exercise tolerance compared with both placebo and digitalis.¹² Patients selected for this study were similar to those in the present study. So patients with mild to moderate heart failure will benefit more from xamoterol, whereas some patients with more severe heart failure may respond better to digoxin.

The effects of xamoterol described in this study are consistent with the known pharmacology of xamoterol as a selective β_1 adrenoceptor partial agonist that modulates the sympathetic control of the heart and stabilises the response of the heart to sympathetic stimulation at about a level equal to its own intrinsic sympathomimetic activity.¹² Consequently, at rest or during moderate activity the heart receives additional inotropic support from xamoterol without any appreciable increase in heart rate; whereas during more severe exercise, heart rate is reduced.^{8,13-15}

Evidence for this cardiostabilising activity of xamoterol in the present study comes from the increase in ejection fraction at rest with no significant change in resting heart rate and the reduction in maximum exercise heart rate. The acute effect of xamoterol in patients with left ventricular dysfunction has been described elsewhere.^{8,16,17} An increase in cardiac output and a decrease in pulmonary capillary wedge pressure was reported. In three previous studies in which haemodynamic measurements were made at rest in patients with heart failure the inotropic effects of xamoterol were maintained for up to nine months.^{16,18,19} These results indicate that tachyphylaxis does not occur. So both modest inotropism and the reduction of exercise heart rate are likely to be important in explaining the long term clinical benefits of xamoterol.

We found that xamoterol increased exercise duration and improved the signs and symptoms of heart failure. These changes were associated with an increase in resting ejection fraction.

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