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Effect of xamoterol (ICI 118587), a new beta$_1$ adrenoceptor partial agonist, on resting haemodynamic variables and exercise tolerance in patients with left ventricular dysfunction

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SUMMARY The effect of xamoterol, a beta$_1$ adrenoceptor partial agonist, on resting haemodynamic measurements and exercise tolerance was studied in 10 patients with dyspnoea of effort. All patients had poor left ventricular function due to myocardial infarction with ejection fractions ranging from 15% to 35% (mean 28%). The cardiac index and stroke work index both rose significantly. The mean pulmonary artery pressure fell from 20(2) mm Hg to 16(2) mm Hg and pulmonary artery wedge pressure from 14(2) mm Hg to 10(2) mm Hg within the first four hours. Exercise tolerance, measured on the treadmill, increased significantly in seven patients but was unchanged in the three who had the lowest left ventricular ejection fractions. Exercise heart rate response was attenuated by the drug in all patients.

It is concluded that xamoterol may be beneficial in patients with poor left ventricular function but can be harmful in extremely poor left ventricular function where high sympathetic drive may be important.

Xamoterol {(+/−)-1-(4-hydroxyphenoxy)-3-[2-(4-morpholine carbonamido)ethylamino]-propan-2-ol fumarate)} has been shown in animal experiments to be a beta$_1$ adrenoceptor partial agonist with little effect on arterial impedance.[1] Its partial agonist or intrinsic sympathomimetic activity amounts (at its maximum) to 45% of the maximum activity of the full agonist isoprenaline.[2] Previous studies in volunteers showed that at rest it has positive inotropic properties as indicated by shortening of the systolic time intervals and rise in systolic blood pressure.[3] It attenuates the chronotropic response to exercise.[4 5] The beneficial haemodynamic effect of xamoterol in patients at rest with left ventricular dysfunction has been reported recently.[6] Nevertheless, there is no information about the effect of this drug on exercise tolerance, which is a measurement of practical importance.

We studied the effect of xamoterol on resting haemodynamic variables and exercise tolerance in patients with exertional dyspnoea caused by angiographically confirmed myocardial infarction. The study was single blind; xamoterol was given for two weeks followed by placebo for two weeks and finally xamoterol for four weeks. Effort tolerance was measured before treatment and fortnightly thereafter. Haemodynamic measurements were made before and after the first dose of xamoterol and after eight weeks' treatment with xamoterol.

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Patients and methods

PATIENT POPULATION

Ten patients (nine men and one woman), whose mean (SD) age was 54 (2·4) years, were studied. They all had chronic left ventricular dysfunction and dyspnoea of effort (New York Heart Association (classes II and III). Their mean angiographic left ventricular ejection fraction was 28% (range 15–35%). Two patients (cases 6 and 8) also had moderately severe mitral regurgitation. Table 1 shows the patients' characteristics and treatment at the start of the study. These treatments had failed to improve their symptoms. Vasodilative and antiarrhythmic agents were withdrawn at least two weeks before the start of the study. A prestudy exercise test was performed to determine a suitable exercise protocol for each patient. As a result either

Table 1 *Patient characteristics and treatment at the start of the study*

Case No	*LVEF (%)*	*Coronary angiography*	*Medical treatment (mg daily)*
1	15	LAD blocked, Cx and RCA stenoses	Frusemide 120
2	22	LAD blocked, Cx and RCA stenoses	Frusemide 80; amiloride 10
3	32	LAD and Cx stenoses, RCA blocked	Frusemide 80
4	32	LAD and Cx stenoses, RCA blocked	Frusemide 80; bendrofluazide 5
5	35	LAD and Cx stenosis, RCA blocked	Frusemide 80
6	30	LAD, Cx, and RCA stenoses	Frusemide 120; lanoxin 0·25; amiloride 10
7	26	LAD blocked, RCA and Cx stenoses	Frusemide 80
8	33	LAD, RCA, and Cx stenoses	Frusemide 250; spironolactone 200
9	18	LAD blocked, RCA stenosis	Frusemide 80
10	35	RCA blocked, LAD and Cx stenoses	Frusemide 80

LVEF, left ventricular angiographic ejection fraction; LAD, left anterior descending; RCA, right coronary artery; Cx, circumflex coronary artery.

the standard or modified Bruce protocol[7] was chosen for each patient.

EXERCISE TEST PROCEDURE

Exercise tolerance was assessed approximately 24 hours before the haemodynamic study using the Marquette Case TM Computer Assisted System for Exercise (Marquette Electronics Inc, Milwaukee, USA) using the standard Bruce or a modified Bruce protocol. A maximal symptom limited exercise test was performed. Exercise performance was calculated as the sum of work done during each stage of the Bruce protocol (Fig.1). Work done during each stage of this exercise protocol may be expressed as follows: work done equals Mg (sin θ + cos θ) (S) (T) in Joules, where θ is the angle of inclination of the treadmill; S the speed of the treadmill in m/s; T the time spent on each stage of exercise in seconds; g the gravitational force (9·8 m/s^2); and M the mass of the patient in kg. Modified lead V1, V5, and aVF electrocardiograms were recorded continuously during the test.

RESTING HAEMODYNAMIC MEASUREMENTS

Early—On the first day of the study right heart catheterisation was performed at rest, with the patient supine and without premedication, using a flow directed thermodilution catheter. Baseline measurements of pulmonary artery systolic and diastolic pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, and heart rate were recorded. Cardiac output was measured in triplicate using a Gould Cardiac Index Computer Model SP1435 (Gould Inc., Oxnard, USA). Systemic arterial pressure was measured by a standard sphygmomanometer. Electrocardiographic monitoring was maintained throughout the study. After the baseline haemodynamic variables were measured xamoterol 200 mg was given orally and the measurements repeated 1, 2, 4, 6, and 12 hours later.

Late—During the eighth week of the trial right heart catheterisation was repeated at rest with the patient supine, without premedication, and before the morning dose of xamoterol. After the baseline haemodynamic variables were measured xamoterol 200 mg was given orally and the measurements repeated one and two hours later.

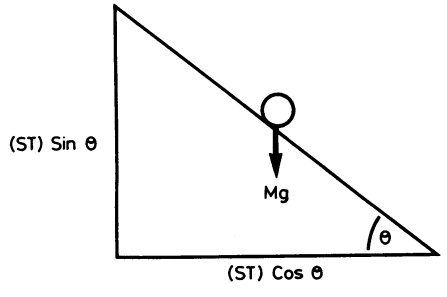


Fig. 1 *Exercise performance calculated as sum of work done (mg) during each stage of protocol: Mg (sin θ + cos θ) (S) (T) (Joules), where θ, angle of inclination (of treadmill); S, speed (of treadmill) m/s); T, time spent on each stage of exercise (s); g, gravitational force (9·8 m/s^2); M, mass of patient (kg).*

OUTPATIENT TREATMENT

Outpatient treatment was continued with xamoterol orally 200 mg twice daily. Clinical examination and exercise tolerance testing were repeated at fortnightly intervals. During the third and fourth weeks patients were changed to treatment with the placebo.

DERIVED HAEMODYNAMIC VARIABLES

Mean systemic arterial blood pressure (MAP) was calculated as: diastolic pressure plus 1/3 (systolic minus diastolic pressures) in mm Hg; body surface area in m^2 was determined from standard tables from their height and weight; cardiac index (CI) was calculated as CO/BSA (l/min per m^2), where CO is cardiac output (l/min); stroke volume index (SVI) as: (CO × 1000)/BSA × HR) (ml/beat/m^2), where HR is heart rate (beats/min); left ventricular stroke work index (LVSWI) as: (MAP-PCWP) × SVI × 0·0136 (g m/m^2), where PCWP is pulmonary capillary wedge pressure; and systemic vascular resistance (SVR) as: MAP

Table 2 *Haemodynamic indices in 10 patients before and after a single oral dose of xamoterol 200 mg. Values are mean (SEM)*

Haemodynamic indices	*Pretreatment value*	*Peak value*	*Time of peak response (h)*	*p value*
Mean systemic arterial pressure (mm Hg)	91(4)	88(4)	4	NS
Heart rate (beats/min)	69(6)	76(5)	4	NS
Pulmonary capillary wedge pressure (mm Hg)	14(2)	10(2)	1	<0·01
Mean pulmonary artery pressure (mm Hg)	20(2)	16(2)	4	<0·001
Cardiac index (l/min per m²)	2·3(0·1)	3·2(0·2)	4	<0·001
Stroke volume index (ml/beat/m²)	40(3)	46(3)	4	<0·0005
Systemic vascular resistance (dyn s cm^{-5})	1693 (59)	1247(124)	4	<0·01
Left ventricular stroke work index (g m/m²)	45(4)	53(5)	4	<0·0025

× 80)/CO (dyn s cm^{-5}. All results are expressed as mean (standard error of mean (SEM)) and analysed using Student's paired *t* test.

Results

RESTING HAEMODYNAMIC VARIABLES

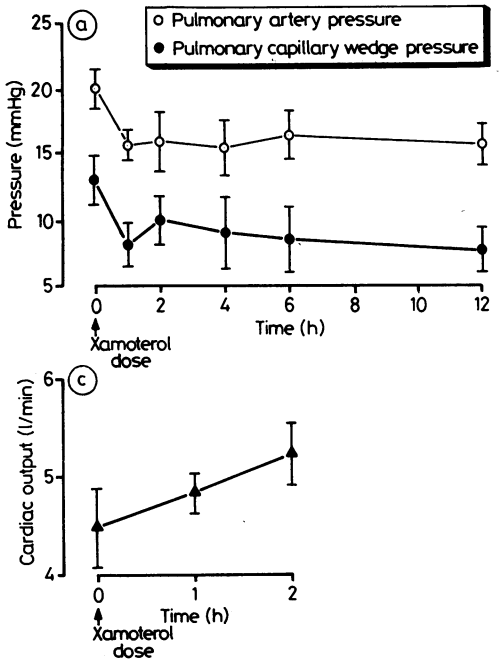
On administration of the drug there was an increase in cardiac index and a fall in pulmonary artery pressure. Maximum change in the haemodynamic variables occurred within four hours of giving xamoterol (Table 2 and Figs. 2–4). The drug increased both cardiac index and stroke volume index from 2·3(0·1) to 3·2(0·2) l/min per m² ($p<0·001$) and from 40(3) to 46(3) ml/beat/m² ($p<0·0005$) respectively (Fig. 4 *a* and *b*). Left ventricular stroke work index (Fig. 4 *d*) was increased from 45(4) to 53(5) g m/m² ($p<0·0025$) while systemic vascular resistance fell from 1693(59) to 1247(124) dyn s cm^{-5} ($p<0·01$) (Fig. 4 *c*).

The maximum change in mean pulmonary artery pressure from 20(2) mm Hg to 16(2) mm Hg occurred at four hours ($p<0·001$) and in pulmonary capillary wedge pressure from 14(2) mm Hg to 10(2) mm Hg at one hour ($p<0·01$) (Table 2, Fig. 2).

Heart rate was not significantly altered in the group as a whole, the control heart rate being 69(6) beats/min and 76(5) at four hours (Table 2). Nevertheless, in the seven patients who subsequently showed an improvement in exercise tolerance the heart rate rose from 69(6) to 80(5) beats/min at four hours ($p<0·05$) (Fig. 3 *a*).

EXERCISE TESTING

All patients had appreciably impaired exercise tolerance before treatment (Fig. 5, Table 3). After two weeks' treatment with xamoterol there was a significant improvement in exercise tolerance in seven patients ($p<0·05$) (Fig. 3). One patient failed to show



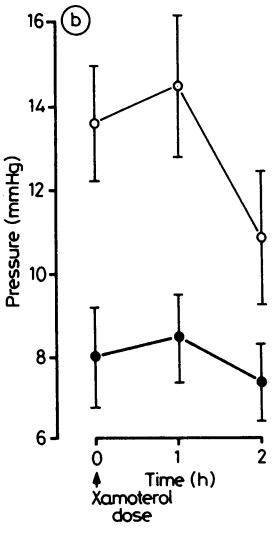


Fig. 2 *Resting haemodynamic variables after a single oral dose of xamoterol on (a) the first day and (b) in the eighth week; (c) resting cardiac index after a single oral dose of xamoterol in the eighth week. Values are mean (SEM).*

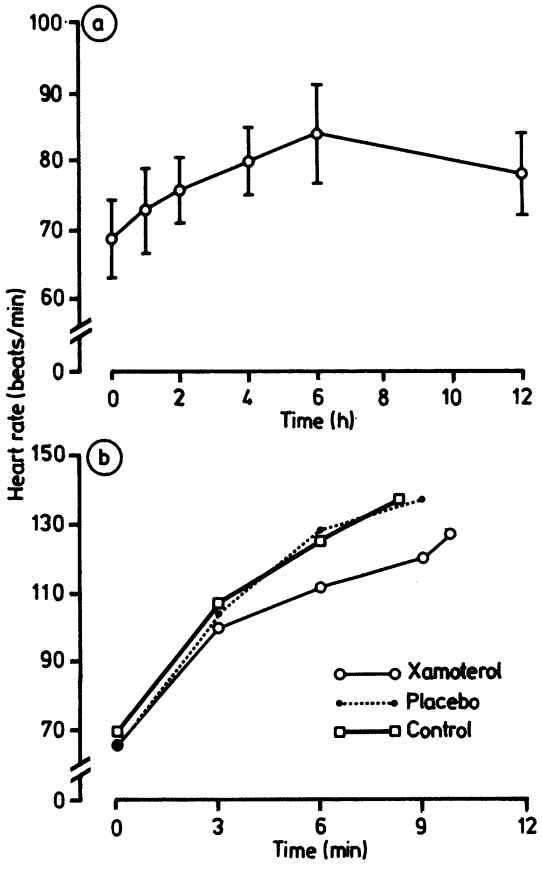


Fig. 3 *Heart rate response to a single oral dose of xamoterol (a) at rest and (b) during exercise. Values are mean (SEM).*

an improvement in exercise tolerance. Two had stopped treatment before two weeks; one because of nausea and the other on his own initiative because of lack of subjective improvement in symptoms. With placebo the exercise tolerance fell to pretreatment levels in six patients whose exercise tolerance had improved on the drug. It was unchanged in two patients. When xamoterol was restarted there was an improvement in exercise tolerance in the six patients who had deteriorated with placebo and in one of the patients who showed no change in exercise tolerance with placebo. The condition of the other patient who showed no change with placebo deteriorated and he was withdrawn from the study after a further two weeks of xamoterol.

The change in exercise tolerance with the drug was significantly greater than that with placebo ($p<0.05$) (Table 3). The increase in heart rate with xamoterol after maximal exercise was significantly lower than that with placebo ($p<0.05$) (Fig. 3 *b*).

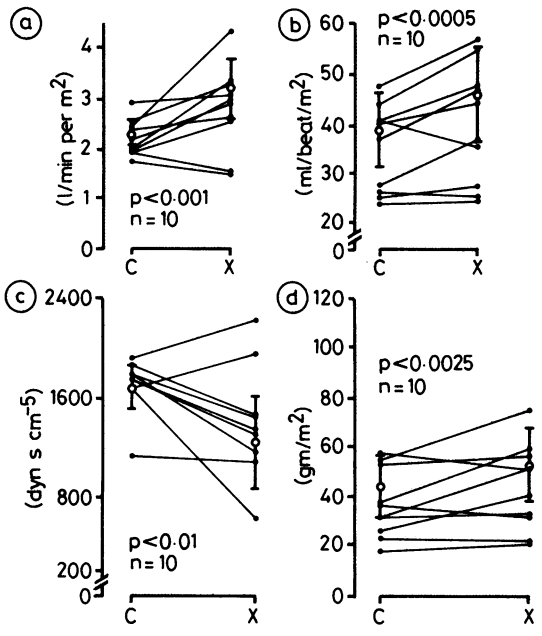


Fig. 4 *Haemodynamic variables before (C) and after (X) peak response to a single oral dose of xamoterol: (a) cardiac index; (b) stroke volume index; (c) systemic vascular resistance; and (d) left ventricular stroke work index.*

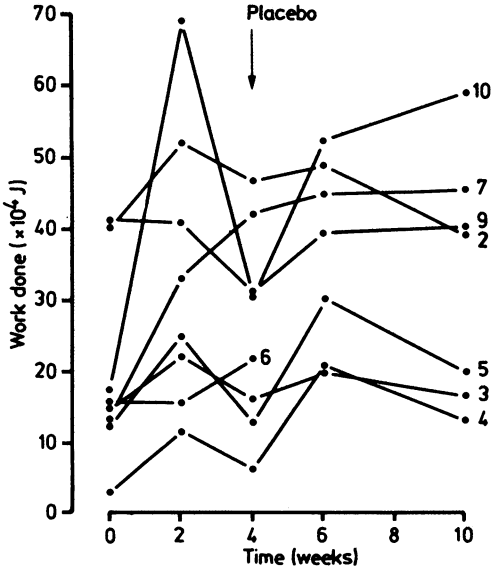


Fig. 5 *Changes in exercise tolerance in the 10 patients during long term administration of xamoterol and placebo. Numbers are case numbers.*

Table 3 *Exercise tolerance in study patients. Values are mean (SEM)*

Time (weeks)	*Treatment given*	*Work done (J×10⁴)*	*p value (n)**
0	Baseline	20·0(4·8)	(10)
0–2	Xamoterol 200 mg twice daily	34·1(6·9)	<0·05(8)
2–4	Placebo	26·7(5·2)	(8)
4–6	Xamoterol 200 mg twice daily	39·7(4·9)	<0·05(7)
6–10	Xamoterol 200 mg twice daily	33·6(6·5)	<0·05(7)

*Significance levels derived from comparison of exercise tolerance with placebo and xamoterol.

Discussion

Previous work suggests that there is increased activity of the sympathetic system as well as changes in the reninangiotensin and vasopressin neurohumoral systems in chronic heart failure.[8] These pathophysiological derangements occur to varying degrees in different patients. Xamoterol has been shown to have 40% of the chronotropic and inotropic effects of the pure agonist isoprenaline.[2] During exercise it reduces the chronotropic response to sympathetic stimulation.[4 9] It therefore shows both beta adrenoceptor agonism and antagonism, depending on the prevailing level of sympathetic activity; it is a $beta_1$ adrenoceptor partial agonist.

This study shows that xamoterol can improve resting haemodynamic variables and exercise tolerance in some patients with pronounced impairment of left ventricular function caused by myocardial infarction. At low levels of sympathetic activity it acts as a $beta_1$ adrenoceptor agonist as shown by the increase in stroke volume, left ventricular stroke work index, and heart rate and the fall in pulmonary capillary wedge pressure that occurred in most patients. The fall in systemic vascular resistance is probably the result of increased cardiac output promoting a reduction in endogenous sympathetic activity rather than a direct vasodilator action. Certainly, work in animals has shown that the drug is not a vasodilator. It is likely that in the two patients in whom the drug did not have a positive inotropic or positive chronotropic effect sympathetic tone was higher and the drug acted as a beta adrenoceptor antagonist. These two patients had the lowest ejection fractions of the group.

The patients in whom the drug caused a positive chronotropic effect at rest experienced an improvement in exercise tolerance, whereas those in whom the drug had a negative chronotropic effect and who presumably had higher levels of sympathetic activity at rest did not benefit in terms of exercise tolerance.

The results from this small study suggest that whereas the drug can be given safely and with benefit to patients with poor left ventricular function (mean ejection fraction 28%) it may be harmful to patients with extremely poor ventricular function who depend on high levels of sympathetic nervous system activity.

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