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# The effect of oral dosing of xamoterol on systolic time intervals in man and xamoterol plasma concentrations in heart failure patients

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**1** Six healthy male human volunteers of mean age 30.8 years (range 23–37) were given single oral doses of xamoterol (20, 50, 100 or 250 mg) and placebo with a 1 week interval between each dose. Xamoterol produced a significant decrease in systolic time intervals ($QS_2I$, LVETI and PEPI) and a significant increase in systolic blood pressure indicating a positive inotropic effect on the heart at rest. The changes in $QS_2I$ were dose-related. Maximum decreases in $QS_2I$ were noted 1 to 2 h after dosing and were achieved with a dose of 100 mg.

**2** In a second study, oral administration of xamoterol at 3 doses (100, 200 or 300 mg) and placebo were studied in 12 patients of mean age 60.4 years (range 52–73) with mild to moderate heart failure. Each dose was given twice daily for 7 days in a random order. Each dose of xamoterol produced a significant decrease in systolic time intervals indicating a positive inotropic effect on the heart at rest in patients with heart failure. It was not possible to distinguish between the effects of the three doses of xamoterol.

**3** In heart failure patients, peak plasma concentrations of xamoterol occurred 1 to 2 h after dosing at all dosage levels and there was a linear relationship between dose and plasma concentration.

**4** In both studies xamoterol was well tolerated and only minor adverse experiences were reported.

**5** We conclude that, at rest, xamoterol has a positive inotropic effect on the heart when given orally to healthy volunteers or patients with mild to moderate heart failure.

**Keywords** xamoterol heart failure systolic time intervals

## Introduction

Xamoterol (Corwin, Xamtol, ICI 118587) has been shown to significantly improve exercise capacity and symptoms in patients with chronic heart failure (The German Austrian Xamoterol Study Group, 1988; Waller *et al.*, 1989). It is a partial agonist acting directly on the heart via the $\beta_1$-adrenoceptor, the maximum stimulant effect being equivalent to about 43% of the agonist effect of isoprenaline (Nuttall & Snow, 1982). In both healthy volunteers (Marlow *et al.*, 1980) and animals (Snow *et al.*, 1983) xamoterol showed positive inotropic effects when given intravenously at rest. The purpose of this study was to assess the effect of oral dosing on systolic time intervals in healthy volunteers and patients with heart failure as well as measuring the plasma concentrations of xamoterol following oral dosing in patients.

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## Methods

### *Design*

The investigation was performed in two phases. Study 1 was a randomised, double-blind, within-subject comparison of the effects of single oral doses of xamoterol and placebo on haemodynamics, haematology and biochemical parameters in healthy volunteers. Study 2 was a randomised, double-blind, crossover comparison of three doses of xamoterol and placebo in patients with mild to moderate heart failure.

### *Subjects*

Study 1 included six healthy male volunteers of mean age 30.8 years (range 23–37) with no abnormality on clinical examination, haematology, biochemistry or the electrocardiogram (ECG). The volunteers had not received chronic drug therapy for 3 months preceding the study or regular drug therapy for 1 week prior to or during the study.

Study 2 included 12 patients (eight males and four females) with a mean age of 60.4 years (range 52–73). All patients had cardiac disease and eight had suffered a previous myocardial infarction. The majority of patients (9/12) had mild heart failure NYHA Class II but one patient was classified as NYHA Class I and two patients were NYHA Class III. Patients were not on any cardiovascular therapy except maintenance diuretics.

Both studies were conducted in accordance with the Declaration of Helsinki (Tokyo revision) and subjects gave their written informed consent prior to participation. The protocols were approved by the ICI ethics committee (Study 1) or the local hospital ethics committee (Study 2).

### *Dosage*

Xamoterol and placebo tablets were provided by ICI Pharmaceuticals.

*Study 1* Xamoterol at doses of 20, 50, 100 and 250 mg (in ascending order for safety reasons, as this was the first oral administration of xamoterol to human subjects) and placebo were given as single doses with an interval of 1 week between doses. Two placebo doses were randomly allocated between the active doses.

*Study 2* Each patient took 100, 200 or 300 mg of xamoterol or placebo twice daily for 7 days in a randomly determined order.

### *Assessments*

Heart rate (HR) was measured by palpation of the radial pulse and blood pressure (BP) was measured using a standard sphygmomanometer and with the subject in a supine position; Korotkoff phase IV (study 1) or phase V (study 2) sounds were used to determine diastolic blood pressure.

Systolic time intervals (STI) were measured from simultaneously recorded electrocardiogram (ECG), phonocardiogram and arterial pulse tracings at a paper speed of 100 mm $s^{-1}$ (Weissler *et al.*, 1968). For each patient the best position of the microphone for good phonocardiogram recordings was established and the best ECG lead for clear Q waves was used. The carotid pulse recordings were obtained at the end of quiet expiration avoiding a Valsalva manoeuvre. The following STI were measured: total electromechanical systole i.e. Q wave of ECG to second heart sound ($QS_2$), left ventricular ejection time (LVET) i.e. the upstroke of the carotid impulse to the second heart sound, and the pre-ejection period (PEP) calculated by subtracting LVET from $QS_2$. The values were corrected for heart rate and expressed as indices (I) using the standard formula $QS_2I = QS_2 + (2.1 \times HR)$; $LVETI = LVET + (1.7 \times HR)$; $PEPI = PEP + (0.4 \times HR)$.

Safety was assessed by clinical examination and in study 1 standard haematological and biochemical tests were also performed.

In study 2 venous blood samples were taken immediately after haemodynamic measurements. Plasma was stored at −20° C and xamoterol plasma concentrations were measured by radioimmunoassay at ICI Pharmaceuticals (Bastain *et al.*, 1988). Area under the plasma concentration curves in the dosage interval (AUC(0,12)) on day 7 of each treatment was calculated by trapezoidal rule.

### *Procedures*

*Study 1* Heart rate, blood pressure and STI were assessed prior to dosing and at 1, 2, 4 and 6 h after dosing. Biochemical and haematological data were obtained at 24 and 72 h after dosing. For safety reasons the effects of each dose were assessed before the next higher dose was administered. This also enabled the maximum response to be determined after which no higher doses would be given.

*Study 2* All measurements each week were made at similar times of the day. Baseline measurements were made on day 1 of the study. STI, heart rate and blood pressure were measured

at 1, 2, 3, 6 and 12 h post-dose. Tablets for the first treatment period were given and patients attended the clinic on day 7 without taking the morning dose. Assessments on each of days 7, 14, 21 and 28 were in the following order: STI, HR, BP, blood sample. Sample times were predose (i.e. 12 h since last dose) and 1, 2, 3, 6 and 12 h post dose starting at about 09.00 h. After the 12 h post-dose sample the evening dose was taken. At each clinic visit the patient was asked about his well-being.

In both studies smoking, caffeine containing drinks and alcohol were prohibited on study days and 12 h (smoking and caffeine containing drinks) and 24 h (alcohol) prior to the first measurement on these days.

*Statistical analysis*

*Study 1* An analysis of covariance model was used for results at each post-dose time point. The statistical significance of the difference of the adjusted mean for each dose and for placebo was calculated using a *t*-test.

*Study 2* A repeated measures model was fitted to the heart rate, blood pressure and STI data to see if treatments behaved in a similar way over time. When there was a significant interaction between time and treatment (assessed by an *F* test) pairs of treatments were compared by a *t*-test. Where the time and treatment interaction was not significant, the results were meaned over time.

## Results

*Study 1*

Five subjects completed the study. One was withdrawn because a number of premature ventricular contractions were noted on his ECG tracing during a pre-dose assessment; data from this subject were not included in the analysis.

Significant reductions were found in $QS_2I$ after all doses of xamoterol (Table 1) with maximum effects noted 1 to 2 h after dosing. Effects persisted for up to 4 h after doses of 50 mg or more. There

**Table 1** Study 1: Adjusted means (± s.e. mean) for $QS_2I$ (ms) following single oral doses of xamoterol and placebo

| | | *Time after dosing (h)* | | | |
|---|---|---|---|---|---|
| *Treatment* | n | *1* | *2* | *4* | *6* |
| Placebo | 10 | 541.9 (1.5) | 535.0 (1.7) | 527.5 (2.2) | 528.2 (2.4) |
| 20 mg | 5 | 526.5 (2.1) *** | 525.7 (2.4) ** | 524.8 (3.0) | 526.0 (3.2) |
| 50 mg | 5 | 523.6 (2.2) *** | 519.1 (2.5) *** | 514.3 (3.2) ** | 520.3 (3.4) |
| 100 mg | 5 | 515.1 (2.1) *** | 513.5 (2.4) *** | 514.8 (3.1) ** | 516.2 (3.3) ** |
| 250 mg | 5 | 514.1 (2.1) *** | 514.7 (2.4) *** | 504.6 (3.1) *** | 510.8 (3.3) *** |

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

**Table 2** Study 1: Adjusted means (± s.e. mean) for LVETI (ms) following single oral doses of xamoterol and placebo

| | | *Time after dosing (h)* | | | |
|---|---|---|---|---|---|
| *Treatment* | n | *1* | *2* | *4* | *6* |
| Placebo | 10 | 413.3 (2.0) | 409.6 (2.0) | 412.0 (2.0) | 414.0 (2.0) |
| 20 mg | 5 | 406.9 (3.1) | 401.2 (3.2) * | 407.8 (3.1) | 408.5 (3.1) |
| 50 mg | 5 | 413.5 (2.9) | 404.4 (3.0) | 409.1 (2.9) | 408.2 (2.9) |
| 100 mg | 5 | 404.3 (2.8) * | 404.4 (2.9) | 404.4 (2.9) * | 404.9 (2.8) * |
| 250 mg | 5 | 408.1 (3.1) | 403.0 (3.2) | 403.0 (3.3) * | 404.4 (3.2) * |

Significance levels compared with placebo control: * $P < 0.05$.

**Table 3** Study 1: Adjusted means (± s.e. mean) for PEPI (ms) following single oral doses of xamoterol and placebo

| | | *Time after dosing (h)* | | | |
|---|---|---|---|---|---|
| *Treatment* | n | *1* | *2* | *4* | *6* |
| Placebo | 10 | 127.8 (2.1) | 123.9 (2.2) | 114.6 (2.4) | 113.1 (2.2) |
| 20 mg | 5 | 121.2 (3.1) | 127.0 (3.2) | 118.1 (3.5) | 120.0 (3.3) |
| 50 mg | 5 | 112.2 (3.2) ** | 117.1 (3.3) | 107.3 (3.6) | 114.3 (3.3) |
| 100 mg | 5 | 109.7 (2.9) *** | 107.9 (3.0) *** | 109.2 (3.3) | 110.3 (3.0) |
| 250 mg | 5 | 105.3 (2.8) *** | 107.2 (3.0) *** | 101.7 (3.2) ** | 105.7 (3.0) |

Significance levels compared with placebo control: * $P < 0.01$, ** $P < 0.001$.

**Table 4** Study 1: Adjusted means (± s.e. mean) for heart rates (beats $min^{-1}$) following single oral doses of xamoterol and placebo

| | | *Time after dosing (h)* | | | |
|---|---|---|---|---|---|
| *Treatment* | $n^+$ | *1* | *2* | *4* | *6* |
| Placebo | 10 | 62.3 (1.2) | 59.6 (1.5) | 66.4 (1.0) | 72.7 (1.8) |
| 20 mg | 5 | 64.6 (1.9) | 66.5 (2.4) * | 73.3 (1.7) ** | 71.2 (2.9) |
| 50 mg | 5 | 62.4 (1.8) | 66.3 (2.3) * | 70.7 (1.6) * | 69.4 (2.7) |
| 100 mg | 5 | 68.3 (1.7) ** | 67.6 (2.1) ** | 71.0 (1.5) * | 73.1 (2.5) |
| 250 mg | 5 | 62.9 (1.7) | 66.0 (2.1) * | 69.4 (1.5) | 72.5 (2.5) |

Significance levels compared with placebo control: * $P < 0.05$, ** $P < 0.01$, $^+ n = 4$.

were reductions in LVETI at several doses but only consistently at doses of 100 mg or more (Table 2) when reductions were sustained at 6 h. Reductions after other doses were variable. Reductions in PEPI were significant at 1 h for doses of 50 mg or more and persisted for 2 h at 100 mg and 4 h after the 250 mg dose (Table 3).

Small but significant increases in heart rate were found at varying times and were present for all doses at 2 h (Table 4); increases never exceeded 10 beats $min^{-1}$.

Significant increases in systolic blood pressure were found 1 h after doses of 100 and 250 mg (adjusted mean ± s.e. mean: 132.6 ± 5.0 and 130.6 ± 5.0 mm Hg respectively compared with 112.6 ± 3.5 mm Hg for placebo; $P < 0.01$) and persisted for 4 h (143.4 ± 4.3 and 135.4 ± 4.3 mm Hg compared with 123.9 ± 3.9 mm Hg for placebo; $P < 0.01$ and $P < 0.05$ respectively). A significant increase was found for the 50 mg dose at 2 h (134.0 ± 5.2 *vs* placebo 119.2 ± 3.7; $P < 0.05$).

There were occasional small increases in diastolic blood pressure after xamoterol but these did not exceed 8 mm Hg and were only significant at 1 h after the 100 mg dose (xamoterol 77.9 ± 1.4, placebo 71.6 ± 1.0 mm Hg; $P < 0.01$) and 2 h after 20 mg and 100 mg of xamoterol (20 mg 79.8 ± 1.9, 100 mg 76.9 ± 1.8 mm Hg compared with placebo 72.1 ± 1.3 mm Hg; $P < 0.01$ and $< 0.05$ respectively).

The only adverse experiences reported were headaches in two subjects, one of whom subsequently developed symptoms of a cold. Haematological and biochemical data were within the normal range.

*Study 2*

All the patients completed the study. However technical problems with the STI recordings in two patients precluded the use of their data and they were assessed for safety only.

Throughout the 12 h period of assessment, STI followed a similar pattern after dosing with placebo and the three doses of xamoterol (Table 5). The $QS_2$ increased during the morning, decreased after midday and increased slightly in the evening. Mean values for $QS_2$ after all three doses of xamoterol were always less than measurements made at baseline and after placebo, the largest effects being seen at 1, 2 and 3 h after dosing. When the results were meaned over time, $QS_2$ was reduced significantly from the placebo values at the lower doses and the reduction almost achieved statistical significance for the higher dose ($P = 0.052$). The magnitude of response was not significantly different at each dose. There were no significant changes in any of the other STI variables.

Heart rate showed a small but significant increase at all dosage levels and this was maximal at 2 to 3 h after dosing. The mean increase was only 4.6 beats $min^{-1}$ and the greatest increase did not exceed 8 beats $min^{-1}$ (Table 6). There were no significant changes in blood pressure at any dose.

Peak plasma concentrations of xamoterol were achieved 1 to 2 h after dosing at all dosage levels (Figure 1) and there was a linear relationship between dose and plasma concentrations as judged by area under the curve analysis (Figure 2). The mean peak plasma concentrations of xamoterol after the 100, 200 and 300 mg doses were 95, 175 and 269 ng $ml^{-1}$, respectively, while the respective mean plasma concentrations 12 h after dosing were 25, 56 and 85 ng $ml^{-1}$.

Adverse experiences reported were of a minor nature not requiring withdrawal from the study

**Table 5** Study 2: Adjusted means (± s.e. mean) for $QS_2$ (ms)

| | *Baseline* | *Xamoterol 100 mg* | *Xamoterol 200 mg* | *Xamoterol 300 mg* | *Placebo* |
|---|---|---|---|---|---|
| Predose | | 405.2 (10) | 405.1 (9.4) | 407.7 (9.9) | 419.8 (6.7) |
| 1 h | 424.9 (8.1) | 412.2 (8.3) | 419.4 (10.4) | 419.1 (8.9) | 431.2 (7.0) |
| 2 h | 432.1 (9.8) | 415.7 (8.9) | 414.7 (7.9) | 420.0 (8.2) | 433.9 (6.6) |
| 3 h | 435.0 (9.1) | 416.3 (10.6) | 424.7 (8.4) | 420.4 (8.1) | 436.5 (7.7) |
| 6 h | 408.9 (9.0) | 393.3 (11.7) | 399.5 (10.4) | 405.1 (10.1) | 407.3 (7.9) |
| 12 h | 420.1 (11.6) | 410.0 (13.1) | 405.8 (11.4) | 408.3 (10.8) | 412.5 (8.7) |
| *$QS_2$ meaned over time* | | | | | |
| Adjusted mean (s.e. mean) | | 408.2 (3.6) | 411.3 (3.6) | 413.8 (3.6) | 424.1 (3.6) |
| Significance | | $P < 0.01$ | $P < 0.05$ | $P = 0.0523$ | |

**Table 6** Study 2: Adjusted means (± s.e. mean) for heart rate (beats $min^{-1}$)

| | *Baseline* | *Xamoterol 100 mg* | *Xamoterol 200 mg* | *Xamoterol 300 mg* | *Placebo* |
|---|---|---|---|---|---|
| Predose | | 72.5 (3.1) | 73.1 (3.6) | 72.1 (3.6) | 68.5 (3.5) |
| 1 h | 66.4 (4.4) | 67.0 (3.3) | 68.0 (3.3) | 69.3 (3.2) | 63.9 (3.4) |
| 2 h | 62.4 (4.6) | 67.1 (3.4) | 67.4 (2.8) | 69.1 (3.2) | 61.7 (3.2) |
| 3 h | 60.8 (4.4) | 68.3 (4.1) | 67.1 (3.3) | 68.4 (2.9) | 60.8 (3.6) |
| 6 h | 70.0 (5.6) | 72.9 (4.1) | 73.1 (3.4) | 70.4 (3.1) | 69.4 (5.1) |
| 12 h | 68.8 (5.1) | 72.0 (3.8) | 73.6 (4.5) | 73.3 (4.4) | 70.9 (4.3) |
| *HR meaned over time* | | | | | |
| Adjusted mean (s.e. mean) | | 70.1 (1.2) | 70.4 (1.2) | 71.1 (1.2) | 65.8 (1.2) |
| Significance | | $P < 0.05$ | $P < 0.05$ | $P < 0.01$ | |

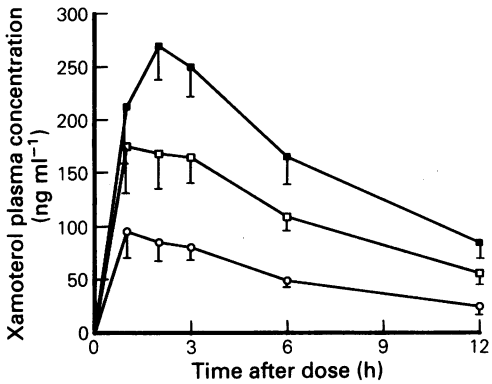


**Figure 1** Relationship between plasma concentrations of xamoterol (mean ± s.e. mean, ○ 100 mg, □ 200 mg, ■ 300 mg) and time after dose

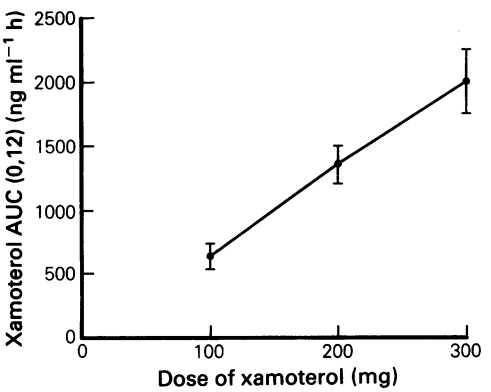


**Figure 2** Relationship between dose of xamoterol and plasma area under the curve (AUC) values

and were usually associated with the underlying disease, e.g. dyspnoea, chest pain. Headache was reported by three patients, two of whom also experienced headache during placebo treatment. The adverse experiences did not appear to be related to treatment with xamoterol.

## Discussion

In healthy volunteers oral administration of xamoterol produced a decrease in STI (all components) and an increase in systolic blood pressure, indicating a positive inotropic effect on the heart at rest. The minor increases in heart rate with xamoterol indicated a relative lack of chronotropic effect which has been confirmed in a larger study using chronic oral dosing (Waller *et al.*, 1989). The relatively minor changes in diastolic blood pressure are consistent with the animal data which showed that xamoterol lacks $\beta_2$-vasodilator activity (Nuttall & Snow, 1982). Xamoterol produced maximum decreases in total electromechanical systole ($QS_2I$) 1 to 2 h after dosing indicating that it is rapidly absorbed. Doses of 20, 50 and 100 mg produced progressively larger effects but increasing the dose to 250 mg resulted in no further decrease in $QS_2I$. This suggests that a dose of 100 mg produced a response which was at the top of the dose-response curve. Xamoterol was well tolerated and did not adversely affect haematological or biochemical parameters.

Xamoterol was also well tolerated in patients with mild to moderate heart failure dosed with 100, 200 and 300 mg twice daily. At these doses the pharmacokinetics of xamoterol were linear with respect to the AUC(0,12). Throughout the 12 h dosing period and at each dose, $QS_2$ was shorter than at baseline and after placebo. These results indicate positive inotropic effects of xamoterol in heart failure patients at rest. It was not possible to distinguish between the effects of the three doses with regard to magnitude or duration. This may have been due to the relatively large diurnal variation in STI or the fact that the lowest and highest mean blood levels of 25 and 269 ng $ml^{-1}$ result in 60% and 95% of the maximum response, respectively (Marlow *et al.*, 1990). It is, therefore, likely that these plasma concentrations maintained a relatively high response (between 60% and 95% of maximum) throughout the 12 h dosing period.

In conclusion, our observations are consistent with xamoterol having a positive inotropic effect when given orally at rest. Xamoterol was well tolerated by healthy volunteers and heart failure patients. The positive inotropic action of xamoterol may be useful in the management of patients with mild to moderate heart failure.

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