The cardiovascular effects of xamoterol, a β_1 -adrenoceptor partial agonist, in healthy volunteers at rest

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1 The cardiovascular effects of three single intravenous doses of a β_1 -adrenoceptor partial agonist, xamoterol (0.025, 0.05 and 0.1 mg kg⁻¹) and placebo were studied in six healthy volunteers at rest using a single-blind design.

2 In addition to heart rate and blood pressure measurements, cardiac contractility was measured by means of M-mode echocardiography and systolic time intervals. Ambulatory 24 h Holter-monitoring of the electrocardiogram was performed. Plasma concentrations of xamoterol were measured.

3 Compared to baseline, xamoterol (0.025 mg kg⁻¹) increased heart rate (61 ± 3 – 68 ± 3 beats min⁻¹, means and SEM) and systolic blood pressure (119 ± 3 – 138 ± 5 mm Hg) but decreased pre-ejection period (100 ± 4 – 76 ± 5 msec). Stroke volume (88 ± 6 – 104 ± 10 ml), cardiac output (4.8 ± 0.4 – 6.6 ± 0.6 l min⁻¹), velocity of circumferential fibre shortening (1.15 ± 0.06 – 1.50 ± 0.06 circ s⁻¹) were increased by xamoterol. No significant changes were produced by placebo.

4 No dose-dependent effects were seen and maximum effects were produced by 0.025 mg kg⁻¹ xamoterol. Significant effects were observed for 2 h. The areas under the plasma concentration curves (AUC_{0–12}) showed a linear dose response.

5 No adverse effects attributable to xamoterol were seen in haematological, biochemical, urinalysis or electrocardiographic tests. Four volunteers were aware of a more forceful heart beat after xamoterol, but this was mild and transient.

6 It is concluded that xamoterol has a positive inotropic action.

Keywords xamoterol cardiovascular effects β_1 -adrenoceptor partial agonist non-invasive techniques pharmacokinetics

Introduction

Xamoterol (ICI 118, 587, Corwin) is a new β_1 -adrenoceptor partial agonist which is undergoing clinical evaluation for the treatment of mild to moderate heart failure. In anaesthetised areflexic dogs it has been shown to have 43% of the intrinsic sympathomimetic activity of isoprenaline on the β_1 -adrenoceptor without any accompanying stimulation of the β_2 -adrenoceptor (Nuttall & Snow, 1982). A study performed in six healthy volunteers at rest by Marlow *et al.* (1980) showed that intravenous doses of

xamoterol had positive inotropic properties as indicated by changes in systolic time intervals. Similar results were obtained by Marlow *et al.* (1981) in resting healthy volunteers after oral dosing with xamoterol. These findings demonstrated that, at rest when the sympathetic tone was low, the agonist properties of xamoterol were manifest. In order to demonstrate the antagonist properties of xamoterol a multistage exercise test was performed in six healthy volunteers by Harry *et al.* (1981). At the heaviest

workload which produced a mean heart rate of 150 beats min^{-1} on placebo, the mean heart rate was reduced by xamoterol to 136 beats min^{-1} indicating that the antagonist effect was manifest when the sympathetic tone was high.

Thus it was of interest, in a single-blind placebo controlled study, to examine the effect of intravenously administered xamoterol in a group of six healthy Japanese volunteers using non-invasive haemodynamic monitoring to determine its effect on cardiac function at rest.

Methods

Subjects

Six healthy Japanese male volunteers (aged 20–25 years) were entered into the study. No abnormalities were present after an extensive clinical examination which included haematology and blood biochemistry analyses, urine analysis, renal function test, chest X-ray and ECG tests. It was confirmed, prior to entering any volunteer into the study, that it was possible to obtain reproducible and measurable echocardiograms. Informed written consent was obtained from each subject only after the volunteer had received a full explanation about the study.

Administration schedule

Single bolus injections of placebo, 0.025, 0.05 and 0.1 mg kg^{-1} xamoterol were administered to each volunteer. In three subjects the administration of xamoterol was preceded by an injection of placebo whereas in the other three subjects placebo was administered after the final dose of xamoterol. The subjects were arbitrarily divided into these two groups. The study was single-blind and the doses of xamoterol were not randomized. There was a 14 day interval between each treatment.

Each phase of the study began after an overnight fast. The volunteers were not permitted to smoke or consume caffeine-containing beverages for 12 h before and 24 h after dosing. Alcoholic drinks were prohibited for 14 h before and after dosing. Breakfast was only taken after the 4 h measurement and after the 24 h measurement on the following day.

The volunteers rested quietly throughout the observation period.

Measurements

Heart rate (HR) and blood pressure (consecutive automatic sphygmomanometer, Nippon Colin

BP 203Y), electrocardiographic, systolic time intervals and echocardiographic (Irex System II) measurements were made pre-dose and at 5, 15, 30 min, 1, 2, 4, 8 and 24 h post-dose with the volunteers resting quietly in the supine position.

Systolic time intervals (STI) were measured, from simultaneous high speed recordings (100 mm s^{-1}) of the ECG lead II, carotid pulse tracing and phonocardiogram (Johnson *et al.*, 1981). The total electromechanical systole (QS_2) was measured from the beginning of the QRS-complex to the beginning of the aortic component of the second heart sound. Left ventricular ejection time (LVET) was measured from the initial systolic upstroke to the incisura of the carotid pulse tracing. Pre-ejection period (PEP) was calculated by subtracting LVET from QS_2 . The results quoted for STI are the mean values obtained from five consecutive cardiac cycles.

Echocardiograms were recorded at a paper speed of 50 mm s^{-1} and the M-mode echocardiography results quoted are for the mean of five consecutive beats. The echocardiography was supervised by two examiners each having more than 5 years' experience and measurements were made according to the method of Felner *et al.* (1980). In the presence of enlarged cardiac size or dyskinesia, calculations of the cardiac volume based on M-mode echocardiography are unreliable (Popp *et al.*, 1973; Teicholz *et al.*, 1976). However, in this study subjects were healthy and they were selected after echocardiographic screening. Left ventricular internal dimensions were measured at the level of the posterior mitral valve chordae between the endocardial surfaces of the posterior wall and septum. End-diastolic dimension (LVDd) was measured at a point coincident with the peak of the R-wave of the ECG. The end-systolic dimension (LVDs) was calculated as the smallest distance separating the left ventricular endocardial surfaces. The end-systolic volumes (ESV) and end-diastolic volumes (EDV) were calculated from the equation of Pombo *et al.* (1971). Other indices of cardiac function were derived from standard equations *viz*: stroke volume (SV) = EDV – ESV (ml), cardiac output (CO) = SV $\times$ HR (l min^{-1}), mean velocity of circumferential fibre shortening (mean Vcf) = (LVDd – LVDs)/ (LVDd $\times$ LVET) (circ s^{-1}).

The electrocardiogram (ECG) was monitored for 1 h post-drug administration using lead II from a standard 12 lead ECG. In addition, the ECG was continuously monitored over a 24 h period following dosing using standard ambulatory Holter monitoring equipment.

Venous blood samples were taken for estimation of the plasma concentration of xamoterol

when haemodynamic measurements were made as well as at 6 h and 12 h after dosing. The analysis was carried out by ICI Pharmaceuticals Division using a radioimmunoassay technique. Xamoterol was made immunogenic by using a succinyl bridge to link an amino group in the side chain to bovine serum albumin. This immunogen was then administered to sheep to induce antibody production. The resulting antisera and ^3H -labelled xamoterol of high specific activity ($18.7 \text{ Ci mmol}^{-1}$) form the basis of the radioimmunoassay procedure. This method allows direct assay of xamoterol in human plasma using 20 or 50 μl aliquots and gives an assay sensitivity of $1\text{--}2 \text{ ng ml}^{-1}$.

The relationship between the decrease in mean PEP (ΔPEP) and mean plasma concentration $[X]$ of xamoterol was plotted using the equation, $\Delta\text{PEP} = [X]/A + B[X]$ where A and B are constants. A computerised curve fitting procedure which minimised the residual sum of squares was used to produce a 'best fit' of 80%.

Statistical analysis of the results was made by analysis of variance and all values identified as significant have a minimum P value of $P < 0.05$ when compared to placebo.

Results

All subjects received placebo and 0.025 and 0.05 mg kg^{-1} xamoterol but only five received 0.1 mg kg^{-1} . The mean values for heart rate, systolic and diastolic blood pressure, and plasma concentration of xamoterol at each time point after placebo and the three doses of xamoterol are given in Table 1. There were no significant changes in heart rate and blood pressure after placebo. Heart rate was significantly increased by all three doses of xamoterol at times between 15 min and 1 h. After the dose of 0.025 mg kg^{-1} , mean heart rate increased from a baseline value of 61 ± 3 to $68 \pm 3 \text{ beats min}^{-1}$ at the 15 min time point. Systolic blood pressure was significantly increased by all three doses at times from 5 min to 1 h. Mean systolic blood pressure increased from $119 \pm 3 \text{ mm Hg}$ at baseline to $138 \pm 5 \text{ mm Hg}$ 15 min after the dose of 0.025 mg kg^{-1} . Mean diastolic blood pressure was not significantly altered by xamoterol.

The peak plasma concentration of xamoterol was present at 5 min after all three doses. The drug was detected at 24 h only after the largest dose. The areas under the plasma concentration curves (AUC_{0-12}) were 78 ± 4 , 154 ± 9 and $318 \pm 15 \text{ ng ml}^{-1} \text{ h}$ for doses of 0.025, 0.05 and 0.1 mg kg^{-1} , respectively. The peak plasma concentration and AUC for the three doses corre-

lated with the dose given. The terminal elimination half-life was not defined.

The mean values for the haemodynamic measurements are given in Table 2. There were no significant changes in any parameter after placebo.

The PEP was significantly decreased by all three doses of xamoterol compared to baseline at all time points between 5 min and 1 h. The doses of 0.05 and 0.1 mg kg^{-1} also produced changes at 2 h. There were no significant differences between the effects of the three doses and the smallest dose (0.025 mg kg^{-1}) decreased the mean PEP from $100 \pm 4 \text{ ms}$ at baseline to $76 \pm 5 \text{ ms}$ at 15 min post-dose.

The LVDD was unaltered by xamoterol but the LVDs were significantly reduced by all three doses at all time points between 5 min and 1 h. The smallest dose decreased the mean LVDs from $32.2 \pm 0.5 \text{ mm}$ to $29.0 \pm 1.0 \text{ mm}$ at 15 min post-dose. The mean Vcf was significantly increased by all three doses of xamoterol. A mean increase from 1.15 ± 0.06 to $1.50 \pm 0.06 \text{ circ s}^{-1}$ was observed 15 min after a dose of 0.025 mg kg^{-1} .

The above improvements in left ventricular contractility were reflected in increases in stroke volume and cardiac output following all three doses of xamoterol. The mean stroke volume increased from a baseline value of $88 \pm 6 \text{ ml}$ to $104 \pm 10 \text{ ml}$ 15 min after 0.025 mg kg^{-1} xamoterol. Significant increases in stroke volume after the two higher doses were seen for up to 30 min after dosing. The mean cardiac output increased from 4.8 ± 0.4 to $6.6 \pm 0.6 \text{ l min}^{-1}$ 15 min after the dose of 0.025 mg kg^{-1} and significant increases were still present at 30 min and 1 h. The higher two doses also produced increases 2 h after dosing.

The relationship between the decrease in mean PEP (ΔPEP) and the plasma concentration of xamoterol was described by a typical sigmoid-shape curve (Figure 1). The calculated maximum response was 34.8 ms and the EC_{50} was 30 ng ml^{-1} .

Analysis of the measurements recorded by 12-lead ECG and 24 h ECG Holter monitoring revealed that in one volunteer, following all doses of xamoterol there was flattening of the T-wave in the II, III and aVF leads which lasted for up to 4 h after 0.1 mg kg^{-1} . The volunteer did not have any adverse subjective symptoms. In another volunteer complete right bundle branch block (CRBBB) was observed and further investigation on completion of the study showed that this was associated with an increase in heart rate independent of the nature of the increase. This volunteer was withdrawn from the study because his 24 h Holter-monitored ECG

Table 1 Changes in heart rate, blood pressure and plasma concentrations after intravenous administration of xamoterol (mean $\pm$ s.e. mean, $n = 6$)

	Dose (mg kg ⁻¹)	Pre-dose	5 min	15 min	30 min	1 h	2 h	4 h	6 h	8 h	12 h	24 h
Heart rate (beats min ⁻¹)	0	58 $\pm$ 3	58 $\pm$ 4	56 $\pm$ 3	57 $\pm$ 3	56 $\pm$ 3	58 $\pm$ 4	55 $\pm$ 3	64 $\pm$ 2	58 $\pm$ 2	61 $\pm$ 2	55 $\pm$ 2
	0.025	61 $\pm$ 3	66 $\pm$ 3	68 $\pm$ 3**	67 $\pm$ 2*	67 $\pm$ 2	63 $\pm$ 2	61 $\pm$ 2	68 $\pm$ 3	61 $\pm$ 2	59 $\pm$ 2	58 $\pm$ 2
	0.05	56 $\pm$ 2	62 $\pm$ 2	64 $\pm$ 2**	66 $\pm$ 2**	67 $\pm$ 2**	65 $\pm$ 2	60 $\pm$ 2	66 $\pm$ 3	62 $\pm$ 3	62 $\pm$ 1	54 $\pm$ 2
	0.1†	58 $\pm$ 3	66 $\pm$ 5	66 $\pm$ 4	67 $\pm$ 4**	68 $\pm$ 5	67 $\pm$ 4	59 $\pm$ 2	68 $\pm$ 3	67 $\pm$ 5	62 $\pm$ 1	59 $\pm$ 3
Systolic blood pressure (mm Hg)	0	116 $\pm$ 3	115 $\pm$ 3	118 $\pm$ 2	114 $\pm$ 3	110 $\pm$ 3	117 $\pm$ 4	118 $\pm$ 5	120 $\pm$ 4	116 $\pm$ 3	118 $\pm$ 3	119 $\pm$ 3
	0.025	119 $\pm$ 3	135 $\pm$ 4**	138 $\pm$ 5**	136 $\pm$ 4**	131 $\pm$ 5**	126 $\pm$ 4	127 $\pm$ 4	120 $\pm$ 2	119 $\pm$ 3	121 $\pm$ 2	117 $\pm$ 2
	0.05	116 $\pm$ 2	128 $\pm$ 4*	133 $\pm$ 5*	133 $\pm$ 4**	131 $\pm$ 3**	128 $\pm$ 5	122 $\pm$ 3	122 $\pm$ 2	118 $\pm$ 3	120 $\pm$ 3	114 $\pm$ 2
	0.1†	116 $\pm$ 3	126 $\pm$ 5	128 $\pm$ 4	127 $\pm$ 4*	134 $\pm$ 5**	127 $\pm$ 5	122 $\pm$ 4	123 $\pm$ 3	121 $\pm$ 2	119 $\pm$ 3	121 $\pm$ 3
Diastolic blood pressure (mm Hg)	0	67 $\pm$ 4	70 $\pm$ 4	71 $\pm$ 6	70 $\pm$ 4	72 $\pm$ 5	70 $\pm$ 7	65 $\pm$ 4	57 $\pm$ 4	63 $\pm$ 6	62 $\pm$ 4	71 $\pm$ 5
	0.025	72 $\pm$ 5	73 $\pm$ 4	72 $\pm$ 6	71 $\pm$ 4	68 $\pm$ 6	71 $\pm$ 6	68 $\pm$ 6	62 $\pm$ 4	61 $\pm$ 4	61 $\pm$ 4	69 $\pm$ 4
	0.05	68 $\pm$ 4	71 $\pm$ 4	70 $\pm$ 4	71 $\pm$ 4	74 $\pm$ 5	70 $\pm$ 4	68 $\pm$ 4	61 $\pm$ 6	60 $\pm$ 3	62 $\pm$ 3	68 $\pm$ 4
	0.1†	63 $\pm$ 3	68 $\pm$ 7	65 $\pm$ 6	68 $\pm$ 6	69 $\pm$ 5	68 $\pm$ 7	70 $\pm$ 6	60 $\pm$ 4	65 $\pm$ 5	61 $\pm$ 3	69 $\pm$ 3
Plasma concentration (ng ml ⁻¹)	0.025	N.D.	69 $\pm$ 3	56 $\pm$ 5	36 $\pm$ 1	21 $\pm$ 1	10 $\pm$ 1	3.6 $\pm$ 0.3	1.5 $\pm$ 0.2	0.8 $\pm$ 0.1	N.C.	N.D.
	0.05	N.D.	132 $\pm$ 9	103 $\pm$ 6	69 $\pm$ 4	41 $\pm$ 3	21 $\pm$ 1	7.1 $\pm$ 0.5	4.1 $\pm$ 0.5	2.1 $\pm$ 0.3	0.6 $\pm$ 0.1	N.D.
	0.1†	N.D.	325 $\pm$ 31	214 $\pm$ 10	147 $\pm$ 7	78 $\pm$ 6	38 $\pm$ 2	14 $\pm$ 1	7.5 $\pm$ 0.8	4.9 $\pm$ 0.4	1.7 $\pm$ 0.2	0.4 $\pm$ 0.1

N.D. not detected, N.C. not calculated,

* $P < 0.05$, ** $P < 0.01$ when compared with placebo. † $n = 5$.

Table 2 Changes in haemodynamic parameters after intravenous administration of xamoterol (mean $\pm$ s.e. mean, $n = 6$)

	Dose (mg kg ⁻¹)	Pre-dose	5 min	15 min	30 min	1 h	2 h	4 h	8 h	24 h
PEP (ms)	0	96 $\pm$ 5	101 $\pm$ 6	98 $\pm$ 6	103 $\pm$ 4	99 $\pm$ 4	100 $\pm$ 6	95 $\pm$ 6	95 $\pm$ 7	99 $\pm$ 6
	0.025	100 $\pm$ 4	79 $\pm$ 5**	76 $\pm$ 5**	78 $\pm$ 5**	81 $\pm$ 6**	91 $\pm$ 4	95 $\pm$ 7	95 $\pm$ 4	101 $\pm$ 5
	0.05	101 $\pm$ 5	80 $\pm$ 7**	79 $\pm$ 9**	77 $\pm$ 9**	83 $\pm$ 5**	88 $\pm$ 8*	91 $\pm$ 5	91 $\pm$ 6*	101 $\pm$ 4
	0.1†	95 $\pm$ 2	72 $\pm$ 7**	66 $\pm$ 7**	61 $\pm$ 5**	72 $\pm$ 6**	77 $\pm$ 7**	87 $\pm$ 4	84 $\pm$ 3	90 $\pm$ 1
LVDd (mm)	0	49.0 $\pm$ 0.8	49.2 $\pm$ 0.8	49.3 $\pm$ 0.9	49.7 $\pm$ 1.2	49.2 $\pm$ 0.9	48.8 $\pm$ 0.7	48.8 $\pm$ 0.9	48.3 $\pm$ 0.7	49.3 $\pm$ 0.8
	0.025	49.5 $\pm$ 0.7	49.3 $\pm$ 0.8	50.3 $\pm$ 1.4	50.3 $\pm$ 1.2	48.5 $\pm$ 1.1	48.3 $\pm$ 0.6	48.5 $\pm$ 1.1	47.8 $\pm$ 1.0	48.7 $\pm$ 0.8
	0.05	47.3 $\pm$ 1.0	48.5 $\pm$ 1.0	48.8 $\pm$ 0.8	48.5 $\pm$ 1.1	47.2 $\pm$ 1.0	47.5 $\pm$ 0.7	47.7 $\pm$ 0.6	46.3 $\pm$ 0.6	48.0 $\pm$ 0.6
	0.1†	47.6 $\pm$ 0.7	48.4 $\pm$ 0.7	48.8 $\pm$ 0.4	49.0 $\pm$ 0.6	47.4 $\pm$ 0.8	46.8 $\pm$ 0.4	47.2 $\pm$ 0.4	46.6 $\pm$ 0.5	48.6 $\pm$ 0.7
LVDs (mm)	0	33.3 $\pm$ 1.1	33.2 $\pm$ 1.0	33.7 $\pm$ 1.2	33.5 $\pm$ 1.4	33.5 $\pm$ 1.3	32.5 $\pm$ 1.2	32.5 $\pm$ 1.6	31.7 $\pm$ 1.3	33.0 $\pm$ 1.0
	0.025	32.2 $\pm$ 0.5	29.3 $\pm$ 0.7*	29.0 $\pm$ 1.0**	29.3 $\pm$ 0.8**	29.0 $\pm$ 0.7*	30.0 $\pm$ 0.3	30.2 $\pm$ 1.0	30.0 $\pm$ 0.8	31.5 $\pm$ 0.4
	0.05	32.0 $\pm$ 0.9	28.0 $\pm$ 1.2**	26.7 $\pm$ 0.7**	28.0 $\pm$ 0.7**	29.0 $\pm$ 0.8*	29.5 $\pm$ 0.6	30.8 $\pm$ 0.7	28.7 $\pm$ 0.4	31.3 $\pm$ 0.6
	0.1†	30.8 $\pm$ 0.6	26.4 $\pm$ 1.0**	27.8 $\pm$ 0.6**	26.6 $\pm$ 0.8**	26.8 $\pm$ 0.9*	28.0 $\pm$ 0.6	29.8 $\pm$ 0.9	28.0 $\pm$ 0.9	32.6 $\pm$ 0.4*
SV (ml)	0	81 $\pm$ 4	82 $\pm$ 3	82 $\pm$ 3	85 $\pm$ 5	81 $\pm$ 3	82 $\pm$ 2	82 $\pm$ 2	81 $\pm$ 5	84 $\pm$ 4
	0.025	88 $\pm$ 6	95 $\pm$ 5	104 $\pm$ 10*	103 $\pm$ 8	90 $\pm$ 6	86 $\pm$ 4	87 $\pm$ 6	83 $\pm$ 6	85 $\pm$ 6
	0.05	74 $\pm$ 5	92 $\pm$ 5**	98 $\pm$ 5**	93 $\pm$ 6*	81 $\pm$ 5	82 $\pm$ 4	79 $\pm$ 3	76 $\pm$ 4	80 $\pm$ 3
	0.1†	79 $\pm$ 5	95 $\pm$ 4*	95 $\pm$ 4	99 $\pm$ 6*	87 $\pm$ 6	81 $\pm$ 3	79 $\pm$ 3	79 $\pm$ 4	80 $\pm$ 4
CO (l min ⁻¹)	0	4.7 $\pm$ 0.4	4.7 $\pm$ 0.4	4.7 $\pm$ 0.4	4.8 $\pm$ 0.5	4.6 $\pm$ 0.4	4.7 $\pm$ 0.3	4.6 $\pm$ 0.4	4.7 $\pm$ 0.5	4.6 $\pm$ 0.3
	0.025	4.8 $\pm$ 0.4	6.0 $\pm$ 0.4**	6.6 $\pm$ 0.6**	6.6 $\pm$ 0.7**	5.7 $\pm$ 0.5**	5.3 $\pm$ 0.4	5.1 $\pm$ 0.4	5.0 $\pm$ 0.5	4.6 $\pm$ 0.4
	0.05	4.0 $\pm$ 0.4	5.7 $\pm$ 0.4**	6.1 $\pm$ 0.3**	5.8 $\pm$ 0.4**	5.2 $\pm$ 0.3**	5.1 $\pm$ 0.3**	4.7 $\pm$ 0.2*	4.6 $\pm$ 0.3	4.1 $\pm$ 0.4
	0.1†	4.4 $\pm$ 0.4	6.1 $\pm$ 0.4**	6.1 $\pm$ 0.3**	6.3 $\pm$ 0.4**	5.8 $\pm$ 0.4**	5.3 $\pm$ 0.3**	4.8 $\pm$ 0.3	4.7 $\pm$ 0.3	4.5 $\pm$ 0.4
Mean Vcf (circ/s)	0	1.03 $\pm$ 0.06	1.06 $\pm$ 0.05	1.03 $\pm$ 0.06	1.06 $\pm$ 0.06	1.04 $\pm$ 0.06	1.10 $\pm$ 0.06	1.08 $\pm$ 0.07	1.15 $\pm$ 0.07	1.04 $\pm$ 0.04
	0.025	1.15 $\pm$ 0.06	1.47 $\pm$ 0.06**	1.50 $\pm$ 0.06**	1.46 $\pm$ 0.05**	1.39 $\pm$ 0.02**	1.31 $\pm$ 0.04	1.25 $\pm$ 0.06	1.28 $\pm$ 0.06	1.13 $\pm$ 0.05
	0.05	1.00 $\pm$ 0.04	1.44 $\pm$ 0.08**	1.58 $\pm$ 0.04**	1.46 $\pm$ 0.04**	1.34 $\pm$ 0.04**	1.30 $\pm$ 0.03**	1.19 $\pm$ 0.03	1.30 $\pm$ 0.05	1.08 $\pm$ 0.04
	0.1†	1.12 $\pm$ 0.06	1.57 $\pm$ 0.10**	1.46 $\pm$ 0.06**	1.56 $\pm$ 0.09**	1.49 $\pm$ 0.11**	1.37 $\pm$ 0.10	1.26 $\pm$ 0.06	1.34 $\pm$ 0.08	1.05 $\pm$ 0.04

PEP: Pre-ejection period, LVDd: Left ventricular end-diastolic dimension,

LVDs: Left ventricular end-systolic dimension, SV: Stroke volume CO: Cardiac output, Vcf: Velocity of circumferential fibre shortening.

* $P < 0.05$, ** $P < 0.01$ when compared with placebo. † $n = 5$.

Figure 1 The relationship between the decrease in mean PEP (Δ PEP) and the plasma concentration of xamoterol.

revealed a few extrasystoles (less than 50) after xamoterol. The volunteer was not given 0.1 mg kg^{-1} xamoterol but placebo instead and the 24 h Holter monitoring after placebo revealed a similar number of extrasystoles. Ventricular extrasystoles were also noticed in another volunteer but the number observed were negligible and were observed after placebo as well as after each dose of drug.

Xamoterol was well tolerated by all volunteers, the only subjective symptom reported being palpitation, a term used to describe an awareness of a more forceful heart beat. Two of the six volunteers noted this after 0.05 mg kg^{-1} and two of the five after 0.1 mg kg^{-1} . However, the sensation was mild and disappeared within 30 min of the injection.

Discussion

In the present study in six healthy volunteers xamoterol produced significant increases in heart rate and systolic blood pressure while there was no effect on diastolic blood pressure. The effects on heart rate and systolic pressure can be attributed to stimulation of cardiac β_1 -adrenoceptors and the absence of an effect on diastolic pressure suggests that xamoterol does not significantly affect β_2 -adrenoceptors at the dosage levels administered. These observations are consistent with the results of animal experiments (Nuttall & Snow, 1982).

The M-mode echocardiography and STI results showed that xamoterol significantly increased stroke volume, cardiac output and Vcf while it produced a significant decrease in the

PEP. These changes demonstrate that xamoterol had a positive inotropic action. No significant dose-related differences were seen between each of the three doses of xamoterol on PEP, cardiac output and Vcf. It may therefore be assumed that all three doses produced maximum responses, i.e. the top of the dose-response curve had been reached with the dose of 0.025 mg kg^{-1} xamoterol. Cardiac output increased by 38–52% after all three doses, heart rate by 11–20% and stroke volume by 18–25%, which suggests that cardiac output is augmented mainly by the increase in stroke volume which is related to the positive inotropic action of the drug. The increased cardiac contractility was reflected in an increase in systolic blood pressure.

It is evident from the animal experiments in dogs (Nuttall & Snow, 1982) and the studies in volunteers (Marlow *et al.*, 1980, 1982; Harry *et al.*, 1981) that the response to xamoterol, which is a partial agonist, varies according to the individual's degree of sympathetic activity. When sympathetic activity is low, the drug acts as an agonist; when it is high the drug acts as an antagonist. In this study performed in resting volunteers, who consequently had a low sympathetic tone, xamoterol produced the expected agonist action by increasing cardiac contractility and heart rate.

One volunteer showed flattening of the T-wave in leads II, III and aVF but the significance of this was uncertain. CRBBB was observed in another volunteer after the injection of xamoterol but this was apparently related to the increase of heart rate because it was also observed in a subsequent exercise tolerance test and atropine tolerance test. This phenomenon is defined as tachycardia dependent RBBB (Cohen *et al.*, 1977). A small number of ventricular extrasystoles was observed in the 24 h Holter ECG in two volunteers but were not considered to be attributable to xamoterol in either case.

Two volunteers were aware of a more forceful heart beat at higher dosage levels, but the symptom was mild and disappeared spontaneously within 30 min after dosing. No abnormal findings were observed in the haematology, biochemistry and urine analyses.

Positive inotropic drugs are used for the treatment of cardiac failure. These include digitalis and catecholamines such as dopamine and dobutamine. It is well known that digitalis has a small safety margin, particularly in the elderly where special care is needed to avoid possible intoxication. Catecholamines cannot be orally administered and are rapidly inactivated after parenteral administration. When given intravenously, xamoterol has a long duration of effect

with significant changes being observed at least 2 h after dosing as shown in our study. It is also active when given orally (Marlow *et al.*, 1982) and has a relatively long half-life of 13 h (Bastain *et al.*, 1983).

On the basis of the results in this study it is concluded that xamoterol has a positive inotropic action. It might therefore be expected to

be clinically useful in the management of patients with mild to moderate grades of cardiac failure but requires further investigation to define its therapeutic role.

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