Relationship between positive inotropic responses and plasma concentrations of xamoterol in middle-aged and elderly patients

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1 We examined the relationship between the contractile state of the left ventricle and the plasma concentration of xamoterol in patients with ischaemic heart failure.

2 Identical studies were conducted in 14 middle-aged (all male; mean age 51.3 years, range 42–61) and 10 elderly patients (six male, four female; mean age 67.7 years, range 64–72).

3 Patients received seven cumulative doses (0.0005–0.2 mg kg⁻¹) of xamoterol. After each dose the rate of change of pressure in the left ventricle at a developed pressure of 40 mm Hg and normalised for this pressure, (dP/dt)/DP₄₀, and plasma concentrations of xamoterol were measured.

4 There were dose-related increases in (dP/dt)/DP₄₀. Curves relating changes in (dP/dt)/DP₄₀, expressed as a percent of the maximum observed response, to changes in xamoterol plasma concentrations were constructed for the middle-aged and elderly patients. From these curves the mean effective concentration (EC) value to produce a particular response could be calculated. In the sample sizes studied, the differences between the EC values over a range of responses for the middle-aged and elderly patients did not reach statistical significance, indicating that cardiac responsiveness to xamoterol was similar in the two groups of patients.

5 Plasma concentrations of xamoterol over the range of 39 to 150 ng ml⁻¹ produced positive inotropic responses which varied between 70% and 90% of the maximum observed effect of xamoterol.

Keywords xamoterol heart failure inotrope

Introduction

Xamoterol (Corwin, Xamtol, ICI 118,587) is a partial agonist which acts on the β_1 -adrenoceptor and thereby stabilises the cardiac response to variations in sympathetic drive (Nuttall & Snow, 1982; Ohyagi *et al.*, 1984). In this way it offers a novel approach to treating heart failure by directly affecting the impaired myocardial contractility and relaxation at rest (Rousseau *et al.*, 1983) and during exercise (Virk *et al.*, 1989).

In order to select the most appropriate dosing regime for a new drug it is necessary to establish the relationship between the therapeutic response to the drug and its plasma concentration. The problems of defining the relationship between the dose (or plasma concentration) of a drug and its therapeutic response in heart failure are formidable. The clinical efficacy of drugs in heart failure have usually been assessed by measuring changes in effort tolerance, symp-

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tomatology and haemodynamics produced by the drug. All present difficulties, both because of inherent methodological problems and because of interpretation of results, e.g. changes in haemodynamic parameters may not correlate with changes in effort tolerance (Franciosa *et al.*, 1984). Effort tolerance has a large subjective element and is dependent not only on cardiac performance but also on lung function and musculo-skeletal factors. Symptoms are variable, difficult to quantify and may be subject to a variety of factors unrelated to cardiac status, e.g. social conditions.

The haemodynamic changes produced by a drug are therefore an attractive alternative as they are objective and can be more accurately measured. Haemodynamic measurements are, however, not without their problems. Some drugs, such as the phosphodiesterase inhibitors, have multiple sites of action and exert both positive inotropic and vasodilator effects (Benotti *et al.*, 1978; Weishaar *et al.*, 1987; Wilmschurst *et al.*, 1983); this raises the question of which haemodynamic change should be used as a measure of clinical efficacy. Other drugs, such as hydralazine, produce haemodynamic improvements which do not result in clinical benefit (Franciosa *et al.*, 1982). Yet others, such as prazosin, produce acute haemodynamic improvements which disappear on chronic administration because of tachyphylaxis (Elkayam *et al.*, 1979; Markham *et al.*, 1983).

In the case of xamoterol, however, these problems do not appear to be relevant. Xamoterol acts directly on the cardiac β_1 -adrenoceptor and is devoid of peripheral β_2 -vasodilator effects (Nuttall & Snow, 1982). Improvements in resting haemodynamic variables were accompanied by improved effort tolerance in patients with heart failure (Molajo & Bennett, 1985). Xamoterol has been shown to improve effort tolerance and symptoms in patients with heart failure and these clinical benefits have been maintained during chronic administration (The German and Austrian Xamoterol Study Group, 1988; Waller *et al.*, 1989). Consequently it was decided to use haemodynamic measurements to explore the relationship between the cardiac response and plasma concentrations of xamoterol. The haemodynamic changes would therefore permit an appropriate therapeutic dose of xamoterol to be selected on the basis of pharmacodynamic and pharmacokinetic parameters which could be defined with the necessary degree of sensitivity and precision.

The aim of this investigation was to determine the relationship between the contractile state of the left ventricle, as measured by changes in the

rate of change of pressure in the left ventricle, and the increases in plasma concentration produced by cumulative intravenous doses of xamoterol. In order to establish whether this relationship was influenced by age, identical studies were conducted in middle-aged (study 1) and elderly patients (study 2).

Methods

Patient population

Patients with ischaemic heart disease were selected for both studies. They had been referred to the university clinic for diagnostic investigation, using routine cardiac catheterisation procedures, because of symptoms of left ventricular dysfunction or because they were suffering symptoms from a previous myocardial infarction. All patients complained of one or more of dyspnoea, fatigue and chest pain in spite of treatment which included β -adrenoceptor blockers, nitrates, calcium antagonists or diuretics. Patients aged less than 65 years were selected for study 1 whereas patients in study 2 were between 65 and 80 years old.

Exclusion criteria were: premenopausal females; symptoms or a history of asthma; supraventricular tachycardia; arrhythmias requiring therapy; aortic stenosis; hypertrophic obstructive cardiomyopathy; serious renal, haemopoietic, hepatic or endocrine disorders. All cardiac drugs were stopped 3 days before the study, except nitrates on demand for angina pectoris.

The investigation was conducted as part of the clinical investigation of the patients, immediately following the diagnostic catheterisation procedure, in accordance with the Declaration of Helsinki 1964, and was approved by the hospital ethics committee. All patients gave informed consent to participate.

Drug administration

Xamoterol was supplied in the form of a sterile solution of the fumarate salt at a concentration of 2 mg ml⁻¹ xamoterol free base. Patients received seven doses with intervals of 5 min between doses. The doses were 0.0005, 0.0005, 0.0001, 0.003, 0.005, 0.01 and 0.18 mg kg⁻¹ which corresponded to cumulative doses of 0.0005, 0.001, 0.002, 0.005, 0.01, 0.02 and 0.2 mg kg⁻¹, respectively. A previous study had shown that maximum increases in contractility were achieved with a dose of 0.05 mg kg⁻¹ (Simonsen, 1984).

Assessments

Changes in cardiac contractility in response to increasing doses of xamoterol were measured using a Millar micromanometer-tip catheter. The first derivative of left ventricular pressure at a developed pressure of 40 mm Hg and normalised for this pressure, $(dP/dt)/DP_{40}$ (Braunwald *et al.*, 1976), was recorded.

Blood samples (2.5 ml), withdrawn for the measurement of plasma concentration of xamoterol, were collected into lithium/heparin tubes, centrifuged and the plasma stored at -20°C . The analyses were performed at ICI Pharmaceuticals using a radioimmunoassay (Bastain *et al.*, 1988).

Procedures

The micromanometer-tip catheter was introduced percutaneously under local anaesthesia via the femoral artery into the left ventricle. In order to administer xamoterol, another catheter was introduced into the inferior vena cava via the femoral vein. Baseline haemodynamic measurements were made and the average values over a 65s period were recorded. The first dose of xamoterol was administered over a 30s period. Average haemodynamic values were recorded over a 65s period beginning 3 min 30s after the start of drug infusion (a pilot study in two patients had indicated that haemodynamic changes were stable by 3 min). An arterial blood sample was withdrawn at the end of the 65s period for measurement of plasma concentrations of xamoterol. Five min after the start of administration of the first dose, the second dose was infused over a 30s period and the measurements performed as before. This procedure was repeated for the subsequent doses.

Data analysis

Ninety-five per cent confidence limits and *t*-tests were calculated for the differences between $(dP/dt)/DP_{40}$ measured at baseline (zero dose) and after each dose of xamoterol. The difference between the baseline value and the value after the maximum dose was calculated for each patient. This was defined as the maximum observed response (100%) and the value after each intermediate dose was expressed as a percentage of this maximum observed response. Curves describing the relationship between the dose or the plasma concentrations of xamoterol and the percentage response were prepared from the data for individual patients. Data from those patients who did not show an adequate response

were excluded. From the plasma concentration-response curves, the individual and mean EC (effective concentration) values were calculated where, for example, EC_{70} is the effective concentration required to produce 70% of the maximum observed response and EC_{90} is the effective concentration required to produce 90% of the maximum observed response. It was considered more appropriate to discuss the relationship between response and concentration at the top of the curve in terms of the EC_{90} , a 'near-maximum' response, rather than the EC_{100} as the plasma concentrations required to produce 100% response would, theoretically, approach infinity. The respective mean EC values were compared between the two studies and 95% confidence limits calculated to ascertain if the differences were statistically significant.

Results

Demographic details

Study 1 included 14 patients (patients 1 to 14, Table 1) with a mean age of 51.3 years (range 42–61). Thirteen patients had suffered a previous myocardial infarction and all had ventricular dysfunction with evidence of abnormal systolic and/or diastolic function related to angiographically-proven ischaemic heart disease. Presenting symptoms included angina pectoris (12 patients), dyspnoea (9) and fatigue (8). All patients had a reduced ejection fraction (normal value was defined as 66%) and in nine patients this was below 50%.

Study 2 included 10 patients (patients 15 to 24, Table 1) with a mean age of 67.7 years (range 65–72). Four patients had suffered a myocardial infarction and all patients had ventricular dysfunction with evidence of abnormal systolic and/or diastolic function related to angiographically-proven ischaemic heart disease. Presenting symptoms included angina pectoris (10 patients), dyspnoea (5) and fatigue (4). Eight patients had a reduced ejection fraction and in one patient this was below 50%.

Withdrawals and adverse experiences

There were no withdrawals from either study and no adverse experiences were reported.

Haemodynamic and pharmacokinetic data

After each dose of xamoterol the mean value for $(dP/dt)/DP_{40}$ was always higher than at baseline. In the middle-aged patients (study 1) the mean

Table 1 Demographic details

<i>Patient number</i>	<i>Sex</i>	<i>Age (years)</i>	<i>Presenting symptoms</i>	<i>Symptom duration (months)</i>	<i>Symptom severity (*)</i>	<i>Cardiovascular medical history</i>	<i>Ejection fraction (%)</i>
1	M	42	Angina pectoris	1	2	Inferior infarct	49
			Dyspnoea	1	2	2 vessel disease	
			Fatigue	1	2		
2	M	60	Angina pectoris	6	3	Anterior infarct	60
						2 vessel disease	
3	M	56	Angina pectoris	7	3	3 vessel disease	61
4	M	55	Angina pectoris	1	2	Anterior infarct	51
			Dyspnoea	1	2	2 vessel disease	
5	M	52	Angina pectoris	3	2	Inferior infarct	54
			Dyspnoea	3	1	2 vessel disease	
			Fatigue	3	2		
6	M	52	Angina pectoris	1	3	Anterior infarct	64
						1 vessel disease	
7	M	51	Angina pectoris	2	2	Inferior infarct	32
			Dyspnoea	2	2	2 vessel disease	
			Fatigue	2	1		
8	M	53	Dyspnoea	5	2	Anterior infarct	48
						1 vessel disease	
9	M	43	Dyspnoea	4	2	Inferior infarct	47
			Fatigue	4	2	Mitral incompetence	
						1 vessel disease	
10	M	49	Angina pectoris	12	3	Anterior infarct	43
			Dyspnoea	12	1	3 vessel disease	
11	M	61	Angina pectoris	5	3	Anterior infarct	42
			Fatigue	5	2	Ventricular aneurysm	
						2 vessel disease	
12	M	53	Angina pectoris	14	3	Inferior infarct	39
			Dyspnoea	36	2	2 vessel disease	
			Fatigue	36	1		
13	M	47	Angina pectoris	6	3	Anterior infarct	28
			Dyspnoea	13	3	Ventricular aneurysm	
			Fatigue	13	1	1 vessel disease	
14	M	44	Angina pectoris	3	3	Anterior infarct	40
			Fatigue	3	1	3 vessel disease	
15	F	68	Angina pectoris	54	3	3 vessel disease	65
16	M	71	Angina pectoris	2	2	Inferior infarct	54
						2 vessel disease	
17	F	66	Angina pectoris	5	2	2 vessel disease	54
						Diabetes mellitus	
18	F	65	Angina pectoris	24	3	1 vessel disease	65
			Dyspnoea	24	2		
			Fatigue	24	3		
19	F	66	Angina pectoris	3	3	1 vessel disease	69
20	M	65	Angina pectoris	6	1	3 vessel disease	
			Dyspnoea	6	1	Hypertension	
			Fatigue	6	1		
21	M	72	Angina pectoris	1	3	Anterior/inferior infarct	28
			Dyspnoea	1	3	3 vessel disease	
			Fatigue	1	2	Mitral incompetence	
22	M	67	Angina pectoris	2	3	1 vessel disease	68
23	M	69	Angina pectoris	72	3	Inferior infarct	59
			Dyspnoea	72	3	3 vessel disease	
24	M	69	Angina pectoris	24	1	Inferior infarct	59
			Dyspnoea	24	2	2 vessel disease	

* Symptom Severity: 1 = mild, 2 = moderate, 3 = severe

Figure 1 Relationship between response in $(dP/dt)/DP_{40}$ and xamoterol plasma concentration.

value at baseline was $27.3 \pm 1.3 \text{ l s}^{-1}$ compared with $37.5 \pm 2.3 \text{ l s}^{-1}$ after the maximum dose (0.2 mg kg^{-1}). In the elderly patients (study 2) the mean value at baseline was $33.0 \pm 1.7 \text{ l s}^{-1}$ compared with $44.9 \pm 2.1 \text{ l s}^{-1}$ after the maximum dose.

The results of the *t*-tests showed that there were significant treatment effects for differences in $(dP/dt)/DP_{40}$ from baseline for all doses in both studies ($P < 0.05$).

Construction of dose-response curves indicated a dose-related increase in $(dP/dt)/DP_{40}$. Due to minimal responses it was not possible to construct meaningful response curves for $(dP/dt)/DP_{40}$ in two middle-aged patients.

Figure 1 shows the results of study 1 expressed as percent increases in $(dP/dt)/DP_{40}$ vs plasma concentration of xamoterol. Results from study 2 were similar with the curve being shifted slightly to the left. The EC values, derived from these curves, are given in Table 2 together with differences between the values obtained in the two studies and the 95% confidence limits. Although there was a trend toward lower EC values in elderly patients compared with middle-aged patients, the differences were not statistically significant in the sample sizes studied, as shown by the fact that the 95% confidence limits encompassed zero for each value between EC_{10} and EC_{90} .

Discussion

The main objective of this study was to define the relationship between the plasma concentration of xamoterol and response in $(dP/dt)/DP_{40}$, a sensitive measurement of the left ventricular contractile state. Xamoterol is a β_1 -adrenoceptor partial agonist which has a modest

Table 2 Effective concentration (EC) values (ng ml^{-1} ; mean $\pm$ s.e. mean) derived from $(dP/dt)/DP_{40}$ response-plasma concentration curves in middle-aged and elderly patients with differences and 95% confidence limits

	EC_{10}	EC_{20}	EC_{30}	EC_{40}	EC_{50}	EC_{60}	EC_{70}	EC_{80}	EC_{90}
Middle-aged patients	1.8 ± 0.4	4.2 ± 0.9	7.1 ± 1.5	11.1 ± 2.4	16.6 ± 3.6	24.9 ± 5.3	38.8 ± 8.3	66.5 ± 14.2	149.5 ± 32.0
Elderly patients	0.9 ± 0.2	2.1 ± 0.4	3.6 ± 0.7	5.7 ± 1.0	8.5 ± 1.6	12.8 ± 2.4	19.9 ± 3.7	34.0 ± 6.3	76.6 ± 14.2
Difference	0.9	2.0	3.5	5.4	8.1	12.2	18.9	32.4	73.0
Lower limit	-0.1	-0.1	-0.2	-0.4	-0.6	-0.9	-1.4	-2.3	-5.2
Upper limit	1.9	4.2	7.2	11.2	16.8	25.2	39.2	67.2	151.2

positive inotropic action resulting in improved myocardial contractility and relaxation. It is highly cardioselective and, as it is devoid of β_2 -adrenoceptor stimulant activity, does not produce arterial vasodilation (Nuttall & Snow, 1982). Only one metabolite of xamoterol, the sulphate conjugate, has been identified in humans and is pharmacologically inactive (Marten *et al.*, 1984). The measured plasma concentrations of xamoterol should therefore reflect the concentration of the active substance.

To base a decision about the appropriate dose of a drug to be used in the clinical management of patients with heart failure, on haemodynamic responses to the drug, can be criticised. The difficulties of deciding which measurement should be used to judge the clinical efficacy of drug therapy in heart failure have recently been reviewed (Packer, 1987). For some drugs, such as vasodilators, haemodynamic changes correlate poorly with changes in exercise capacity (Franciosa *et al.*, 1984) although, as Packer (1987) points out, it is only those drugs which reduce left ventricular filling pressure at rest and during exercise that have produced consistent clinical benefit. In this respect, it should be noted that xamoterol reduces left ventricular filling pressure as well as improving contractility at rest (Rousseau *et al.*, 1983) and during exercise (Sato *et al.*, 1987). A number of studies have demonstrated the clinical efficacy of chronic dosing with xamoterol in patients with mild to moderate heart failure; increases in exercise capacity were observed and these were accompanied by improvements in the symptoms and signs of heart failure (The German and Austrian Xamoterol Study Group, 1988; Vigholt-Sørensen *et al.*, 1989; Waller *et al.*, 1989).

Because xamoterol acts solely on the heart its therapeutic efficacy should be related to the improved function of the heart. On the assumption, therefore, that changes in $(dP/dt)/DP_{40}$ produced by xamoterol are related to its therapeutic efficacy, EC values may be used to define effective therapeutic plasma concentrations of xamoterol during long-term dosing provided that there is no β -adrenoceptor down-regulation and tachyphylaxis. A study in the rat demonstrated that xamoterol did not produce down-regulation of ventricular β_1 -adrenoceptors (Barnett & Maguire, 1986). Several studies in patients have shown that the haemodynamic changes and clinical efficacy of xamoterol are maintained after long-term dosing (Pouleur *et al.*, 1990; Kayanakis & Snow, 1988). In the study by Pouleur *et al.* (1990) of 14 patients treated with xamoterol, decreases in left ventricular filling pressure and increases in $(dP/dt)/$

DP_{40} were still observed after a mean treatment period of 51 months (range 16 to 71).

It may therefore be predicted from the data obtained in this study that a dosing regime which achieves concentrations ranging between 39 and 150 ng ml⁻¹ will produce cardiac responses ranging between 70% and 90% of the maximum observed response, respectively. Pharmacokinetic data from a study in 12 patients of mean age 60.4 years (range 52–73) with heart failure (James *et al.*, 1985) showed that mean plasma concentrations of xamoterol achieved with a dose of 200 mg twice daily ranged from 175 ng ml⁻¹, 1 h after dosing (peak concentration), to 56 ng ml⁻¹, 12 h after dosing (trough concentration). It is therefore predicted that these plasma concentrations of xamoterol will produce responses ranging between approximately 90% (peak effect 1 h post-dose) and 75% (trough effect 12 h post-dose) of the maximum observed effect of xamoterol over the 12 h dosing interval.

The responsiveness of the heart to β -adrenoceptor stimulation is determined by the affinity of the agonist (in this case xamoterol) for the β -adrenoceptor and the magnitude of response which is evoked by the agonist. Although the respective EC values were lower for elderly patients compared with middle-aged patients (i.e. the concentration-response curve was shifted slightly to the left, suggesting a trend towards increased responsiveness in the elderly patients), the differences between the EC values in the two groups were not statistically significant. In view of the relatively small sample sizes, the differences may have achieved statistical significance if the numbers of patients had been larger. Since doses of xamoterol used in clinical practice (200 mg twice daily) are designed to maintain the cardiac response near the top of the dose-response curve, the differences in the respective EC values between the elderly and middle-aged patients are not of clinical importance. Nevertheless, it is important to note that the responsiveness of the myocardium to the agonist effect of xamoterol was not diminished in the ageing heart in the age-range studied where the oldest patient was 72 years old. This contrasts with findings in the rat showing a reduced positive inotropic response to isoprenaline in aged rat heart *in vitro* (Guarnieri *et al.*, 1980; Lakatta *et al.*, 1975) and studies in humans showing reduced chronotropic responses to isoprenaline *in vivo* (Lakatta, 1979) and *in vitro* (Yin *et al.*, 1976), and terbutaline *in vivo* (Kendall *et al.*, 1982).

In conclusion, we have established a relationship between the positive inotropic response to xamoterol and its plasma concentrations. Extra-

polation of the data should allow predictions to be made of the expected cardiac response to xamoterol from plasma concentration data obtained during chronic oral dosing. Data available from chronic dosing studies predict that a 200 mg twice daily oral dosing schedule gives

responses varying between 75% and 90% of the maximum observed response to xamoterol over the 12 h dosing interval. The study also demonstrates that the cardiac responsiveness to xamoterol is similar in middle-aged and elderly patients.

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(Received 21 December 1989,
accepted 5 January 1990)