Acute intravenous and sustained oral treatment with the beta₁ agonist prenalterol in patients with chronic severe cardiac failure

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SUMMARY Prenalterol, a beta₁ agonist, was given in a single blind acute intravenous study to seven patients with cardiac failure (New York Heart Association class II and III). It was then given in a double blind crossover study of sustained oral prenalterol to six of them. As a result of dose titration studies the oral dose of prenalterol given was 100 mg twice a day in all patients. Erect bicycle sprint tests were performed to exercise tolerance before and after treatment had been started. Cardiac function was assessed at rest and during graded supine bicycle exercise by determining haemodynamic indices using a Swan-Ganz catheter and radionuclide left ventricular ejection fractions. In the intravenous study cardiac function was assessed at rest and during exercise after a control infusion of dextrose and after an infusion of 5 mg prenalterol. In the oral crossover study a placebo or prenalterol were given for two periods of two weeks; at the end of each period exercise tolerance was measured and cardiac function assessed at rest and during exercise.

Throughout the study period there was no change in symptoms, medication, or exercise tolerance. Intravenous prenalterol significantly improved cardiac function; left ventricular ejection fraction and cardiac index increased and left ventricular filling pressure fell both at rest and during exercise. Sustained oral treatment with prenalterol, however, did not improve resting left ventricular filling pressure or left ventricular ejection fraction at rest or during exercise but did increase heart rate at rest, and mean blood pressure and peripheral vascular resistance at rest and during exercise; in fact, during exercise left ventricular filling pressure was significantly increased while cardiac index and stroke volume index were decreased by prenalterol.

Sustained oral treatment with prenalterol did not have the beneficial effects on cardiac function produced by intravenous treatment and in fact had a deleterious effect on the measured indices of cardiac function during exercise.

Prenalterol is a selective beta₁ adrenergic agonist which in both normal subjects^{1,2} and in patients with coronary artery disease³ has appreciable positive inotropic properties with only a modest positive chronotropic action. In contrast with most other sympathomimetic inotropic agents, it is pharmacologically active both orally and parenterally. Recent studies have shown that intravenous prenalterol is an effective inotropic agent both at rest⁴⁻⁶ and during

exercise^{7,8} in patients with cardiac failure. There have been only preliminary reports regarding the efficacy of oral prenalterol treatment in the management of patients with chronic cardiac failure.^{7,9,10}

We report a single blind acute study with intravenous prenalterol, followed by a double blind crossover study of oral prenalterol given for two weeks in patients with chronic severe cardiac failure. Symptoms, exercise tolerance, rest and exercise haemodynamic indices, and left ventricular ejection fraction were assessed at rest and during graded supine exercise. The effects on cardiac function of prenalterol given intravenously and orally were compared to determine whether the beneficial acute

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Table 1 Details of study patients

Case No	Sex	Age (yr)	Aetiology of LV failure	NYHA class	Duration of symptoms	LVEF at rest (%)	Outcome of study	Other medications
1	M	58	Idiopathic	II	1 yr	34	Completed	Frusemide, prazosin, nitrates
2	M	64	Idiopathic	II	3-8 yr	30	Completed	Digoxin, chlorthalidone, prazosin, nitrates
3	M	54	Idiopathic	III	8 months	35	Completed	Digoxin, frusemide, prazosin, nitrates
4	M	51	Idiopathic	III	5 yr	10	Withdrawn	Digoxin, frusemide, prazosin, nitrates, spironolactone
5	M	50	CAD/no MI	III	3 yr	15	Withdrawn	Digoxin, frusemide, prazosin, nitrates, spironolactone
6	M	53	Idiopathic	III	2-9 yr	16	Completed	Digoxin, frusemide, prazosin, nitrates, spironolactone
7	M	57	CAD/MI	III	3-2 yr	18	Completed	Digoxin, frusemide, prazosin
8	M	50	CAD/MI	II	3-3 yr	25	Completed	Digoxin, frusemide, nitrates

CAD, coronary artery disease; LVEF, radionuclide left ventricular ejection fraction at study entry; NYHA, New York Heart Association; MI, myocardial infarction; LV, left ventricular.

effects could be maintained during sustained oral administration.

Patients and methods

STUDY POPULATION

Patients were entered into the study if they had (a) chronic left ventricular failure due to idiopathic dilated cardiomyopathy or a previous myocardial infarction, (b) symptoms of New York Heart Association (NYHA) class II or III severity for at least three months and were in a stable condition; and (c) were not taking concomitant beta adrenergic blocking drugs or positive inotropic agents other than digoxin.

The study population consisted of eight men (mean age 55 (range 50-64) years). The mean duration of symptoms was 2.8 (range 0.8-5) years. All patients had had at least one previous episode of overt cardiac failure requiring hospital admission. The aetiology of their cardiac failure was clinically idiopathic cardiomyopathy in six patients and multiple myocardial infarctions without recent chest pain in two. All patients with clinically idiopathic cardiomyopathy underwent diagnostic coronary angiography, and in one unsuspected two vessel coronary disease was

detected. The study was approved by the hospital ethics committee and informed consent was obtained from all patients. No further patient entered the study after reports indicated an increased carcinogenicity in mice treated with prenalterol (personal communication, G Moore 1983).

PROTOCOL

The trial consisted of (a) an open dose titration study followed by a two week washout period, (b) an intravenous single blind study, and (c) a sustained oral double blind crossover study (Fig. 1).

DOSE TITRATION

The patients were first admitted to hospital for the dose titration study. Baseline measurements of electrolyte concentrations, liver function tests, and 12 hour Holter ambulatory monitoring were performed. Exercise tolerance was assessed by a symptom limited erect bicycle sprint test with increments in workload of 100 kpm/min each minute until the maximum tolerated workload was achieved.¹¹ Oral prenalterol was given at a starting dose of 20 mg twice a day. The dose was increased in a stepwise manner by 40 mg/day to a maximum dose of 100 mg twice a day or the max-

Fig. 1 Schematic representation of the protocol of the study: (A) the dose titration study, (B) the single blind acute intravenous (IV) study, and (C) the double blind crossover oral study. Four erect bicycle sprint tests (thin arrows) were performed to assess maximal exercise tolerance and four other studies (thick arrows) to assess left ventricular function at rest and during graded supine bicycle exercise.

imum dose tolerated, determined by predefined endpoints. These endpoints were a rise from baseline values of heart rate to 100 beats/min or an increase of >15 beats/min or a rise in systolic blood pressure to 180 mm Hg or an increase of >40 mm Hg. All baseline investigations were repeated for patients receiving the 100 mg maximum dose. Blood was taken for estimation of prenalterol concentrations each day immediately before and two hours after the morning dose of prenalterol. After completion of the dose titration studies prenalterol was stopped and the patients were discharged from hospital for a washout period of two weeks before the intravenous study.

ACUTE INTRAVENOUS STUDY

The intravenous study was performed in a fasting state two to three hours after the administration of the patient's routine treatment for cardiac failure. Haemodynamic measurements and radionuclide left ventricular ejection fraction were recorded in the supine position at rest and for 10 minutes after a five minute control infusion of dextrose, then during graded supine bicycle exercise tests, and finally for 60

minutes after the exercise. At the end of this 60 minute period, these observations were repeated after a five minute infusion of 5 mg prenalterol. Blood was collected for acute pharmacokinetic studies before and during the 12 hours following the infusion of prenalterol.

Exercise testing

The graded supine exercise test was performed on the same electronically braked bicycle ergometer used for the erect sprint tests at two workload levels which were 30% and 60% of the maximum tolerated in the erect sprint test of the baseline study before the oral dose titration. These levels were chosen because the maximum workloads achieved with an erect 1 minute/stage bicycle sprint test are substantially higher than patients can sustain for the longer workload durations needed for steady state haemodynamic measurements and equilibrium radionuclide ventriculography.^{11 12} For each patient the two workloads used for graded supine exercise were identical throughout the study, both in the intravenous and the

Table 2 Indices of cardiac function at rest and during exercise in the acute intravenous study after the control infusion (A) and prenalterol infusion (B) (5 mg over 5 minutes) (n=7) and at rest in the oral study after two weeks' treatment with either the placebo (A) or prenalterol (B) (n=6). Values are means $\pm$ SEM.

	Heart rate (beats/min)		Mean blood pressure (mm Hg)		LVEF (%)		Cardiac index (l/min/m ²)		LVFP (mm Hg)		SVI (ml/m ²)		SVR (dyn s cm ⁻⁵)	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
<i>Intravenous study</i>														
Before treatment*	76 $\pm$ 7	79 $\pm$ 7	95 $\pm$ 4	95 $\pm$ 3	25 $\pm$ 4	24 $\pm$ 3	2.3 $\pm$ 0.2	2.4 $\pm$ 0.2	21 $\pm$ 5	21 $\pm$ 5	32 $\pm$ 3	32 $\pm$ 3	1597 $\pm$ 127	1564 $\pm$ 147
At rest (minutes after infusion)*:														
0	75 $\pm$ 7	83 $\pm$ 6	96 $\pm$ 5	98 $\pm$ 3	28 $\pm$ 4	31 $\pm$ 6	2.4 $\pm$ 0.2	2.9 $\pm$ 0.4	22 $\pm$ 4	17 $\pm$ 5	33 $\pm$ 4	36 $\pm$ 5	1620 $\pm$ 162	1440 $\pm$ 199
5	74 $\pm$ 7	81 $\pm$ 7	96 $\pm$ 4	96 $\pm$ 3	26 $\pm$ 4	31 $\pm$ 5	2.3 $\pm$ 0.2	2.9 $\pm$ 0.3	21 $\pm$ 4	17 $\pm$ 6	33 $\pm$ 4	38 $\pm$ 6	1643 $\pm$ 150	1299 $\pm$ 136
10	73 $\pm$ 6	80 $\pm$ 7	96 $\pm$ 4	94 $\pm$ 3	24 $\pm$ 3	29 $\pm$ 6	2.1 $\pm$ 0.2	2.9 $\pm$ 0.3	21 $\pm$ 5	16 $\pm$ 5	31 $\pm$ 4	38 $\pm$ 5	1820 $\pm$ 171	1342 $\pm$ 136
After exercise (minutes after infusion)†:														
30	85 $\pm$ 7	89 $\pm$ 6	99 $\pm$ 3	93 $\pm$ 3	23 $\pm$ 4	30 $\pm$ 5	2.7 $\pm$ 0.3	3.0 $\pm$ 0.4	19 $\pm$ 4	14 $\pm$ 5	32 $\pm$ 4	35 $\pm$ 4	1536 $\pm$ 184	1323 $\pm$ 162
45	84 $\pm$ 6	88 $\pm$ 6	90 $\pm$ 3	93 $\pm$ 3	25 $\pm$ 4	30 $\pm$ 5	2.8 $\pm$ 0.3	2.9 $\pm$ 0.3	20 $\pm$ 4	15 $\pm$ 5	34 $\pm$ 4	33 $\pm$ 3	1379 $\pm$ 187	1342 $\pm$ 111
60	79 $\pm$ 6	84 $\pm$ 5	93 $\pm$ 3	94 $\pm$ 3	25 $\pm$ 4	27 $\pm$ 5	2.5 $\pm$ 0.2	2.6 $\pm$ 0.2	16 $\pm$ 4	13 $\pm$ 5	32 $\pm$ 3	32 $\pm$ 3	1519 $\pm$ 187	1472 $\pm$ 138
90	—	80 $\pm$ 8	—	94 $\pm$ 3	—	26 $\pm$ 4	—	2.6 $\pm$ 0.2	—	13 $\pm$ 5	—	34 $\pm$ 4	—	1488 $\pm$ 132
120	—	84 $\pm$ 9	—	95 $\pm$ 3	—	22 $\pm$ 3	—	2.4 $\pm$ 0.4	—	19 $\pm$ 4	—	29 $\pm$ 4	—	1674 $\pm$ 234
<i>Oral study</i>														
Before last dose (baseline values)‡:	68 $\pm$ 3	73 $\pm$ 3	86 $\pm$ 4	96 $\pm$ 3	28 $\pm$ 3	26 $\pm$ 3	2.4 $\pm$ 0.2	2.6 $\pm$ 0.3	14 $\pm$ 4	13 $\pm$ 3	35 $\pm$ 3	36 $\pm$ 4	1460 $\pm$ 124	1584 $\pm$ 210
After oral dose (minutes)‡:														
30	64 $\pm$ 3	71 $\pm$ 3	89 $\pm$ 3	96 $\pm$ 3	27 $\pm$ 4	28 $\pm$ 4	2.2 $\pm$ 0.1	2.6 $\pm$ 0.3	16 $\pm$ 3	13 $\pm$ 3	34 $\pm$ 3	36 $\pm$ 4	1630 $\pm$ 142	1602 $\pm$ 218
45	66 $\pm$ 3	73 $\pm$ 4	89 $\pm$ 4	100 $\pm$ 4	27 $\pm$ 4	28 $\pm$ 4	2.1 $\pm$ 0.1	2.7 $\pm$ 0.3	17 $\pm$ 3	13 $\pm$ 3	33 $\pm$ 3	37 $\pm$ 3	1651 $\pm$ 124	1558 $\pm$ 178
60	66 $\pm$ 3	74 $\pm$ 4	88 $\pm$ 3	99 $\pm$ 3	28 $\pm$ 4	28 $\pm$ 4	2.2 $\pm$ 0.1	2.5 $\pm$ 0.2	15 $\pm$ 4	13 $\pm$ 3	34 $\pm$ 3	34 $\pm$ 4	1578 $\pm$ 120	1591 $\pm$ 142
90	66 $\pm$ 3	73 $\pm$ 4	90 $\pm$ 3	99 $\pm$ 3	26 $\pm$ 3	26 $\pm$ 4	2.2 $\pm$ 0.1	2.3 $\pm$ 0.2	14 $\pm$ 4	16 $\pm$ 3	33 $\pm$ 3	32 $\pm$ 4	1662 $\pm$ 130	1809 $\pm$ 261
120	69 $\pm$ 3	73 $\pm$ 3	92 $\pm$ 3	102 $\pm$ 3	26 $\pm$ 3	26 $\pm$ 4	2.3 $\pm$ 0.2	2.4 $\pm$ 0.2	15 $\pm$ 4	16 $\pm$ 3	34 $\pm$ 3	33 $\pm$ 4	1581 $\pm$ 169	1768 $\pm$ 252
150	67 $\pm$ 3	72 $\pm$ 4	91 $\pm$ 3	103 $\pm$ 4	25 $\pm$ 6	25 $\pm$ 4	2.3 $\pm$ 0.2	2.3 $\pm$ 0.3	16 $\pm$ 4	17 $\pm$ 3	34 $\pm$ 2	32 $\pm$ 4	1618 $\pm$ 147	1833 $\pm$ 203
180	69 $\pm$ 3	73 $\pm$ 4	92 $\pm$ 3	105 $\pm$ 3	26 $\pm$ 3	25 $\pm$ 3	2.2 $\pm$ 0.2	2.3 $\pm$ 0.2	17 $\pm$ 3	22 $\pm$ 3	33 $\pm$ 3	33 $\pm$ 3	1688 $\pm$ 226	1795 $\pm$ 204
Legs raised*	69 $\pm$ 3	73 $\pm$ 4	92 $\pm$ 3	105 $\pm$ 3	26 $\pm$ 3	25 $\pm$ 3	2.2 $\pm$ 0.2	2.3 $\pm$ 0.2	17 $\pm$ 3	22 $\pm$ 3	33 $\pm$ 3	33 $\pm$ 3	1688 $\pm$ 226	1795 $\pm$ 204

BP, blood pressure; LVEF, left ventricular ejection fraction; LVFP, left ventricular filling pressure; SVI, stroke volume index; SVR, systemic vascular resistance.

*With legs raised on ergometer pedals ready for exercise.

†With legs dependent.

‡With legs dependent for 180 minutes of monitoring at rest.

two oral studies. Each workload was of four minutes' duration.

Haemodynamic measurements

Right heart catheterisation was performed under fluoroscopy with a thermodilution Swan-Ganz catheter. Pulmonary artery pressure, left ventricular filling pressure, right atrial pressure, and cardiac output were measured at rest and in the last two minutes of each four minute workload level of graded exercise. Left ventricular filling pressure was defined as either mean pulmonary artery wedge pressure or pulmonary artery end diastolic pressure if the former was unobtainable. Thermodilution cardiac output estimations were performed in triplicate using ice cold dextrose. Continuous recording of pulmonary pressures, electrocardiogram, and thermodilution curves was performed with a multichannel Elema Mingograph fitted with an ink jet recorder.

Equilibrium radionuclide ventriculography was performed in the left anterior oblique projection with the best septal separation at 15° caudal tilt, and left ventricular ejection fraction was calculated using a standard variable region of interest technique.¹² Studies in this laboratory have shown that the results of this technique correlate well with, and are not systematically higher or lower than, those obtained at cardiac catheterisation ($r=0.94$).¹³ The lower limit of normal for the laboratory is 55% (mean value in normal subjects 67%, standard deviation $\pm 7\%$).^{12, 13} Each acquisition was for two minutes at rest and for the last two minutes of each four minute workload level. Exercise was terminated by either the completion of the two workload levels or because of dyspnoea or fatigue.

Heart rate and blood pressure were recorded at rest and during the last two minutes of each four minute workload level using a calibrated sphygmomanometer; the validity of heart rate measurements was verified by continuous electrocardiographic recording.

CALCULATED VARIABLES

Mean blood pressure (mBP) was calculated from the formula: $mBP = 2/3 \times \text{diastolic BP} + 1/3 \times \text{systolic BP}$ (mm Hg); rate pressure product (RPP) from the formula: $RPP = \text{systolic blood pressure} \times \text{heart rate}/100$ (mm Hg/min/100); systemic vascular resistance (SVR) from the formula: $SVR = 80 \times (mBP - RA)/CO$ (dyn s cm^{-5}) where CO=cardiac output (l/min) and RA=right atrial pressure (mm Hg); and stroke work index (SWI) from the formula: $SWI = 0.0136 \times SVI \times (mBP - LVFP)$ (g m m^{-2}) where SVI=stroke volume index (ml/ m^2) and LVFP=left ventricular filling pressure (mm Hg).

SUSTAINED ORAL STUDY:

In the oral double blind crossover study the patients received either 100 mg prenalterol or placebo twice daily for two weeks with a two week washout period between the two treatments. At the end of each treatment exercise capacity was assessed two to three hours after the morning dose of prenalterol with an erect bicycle sprint test. On the following morning haemodynamic indices and left ventricular ejection fraction were measured at rest immediately before and after the final oral dose of the placebo or 100 mg prenalterol and repeated at half hourly intervals for three hours in the supine position; after three hours these measurements were recorded during graded supine exercise. Blood samples for estimating prenalterol concentrations were collected before the 100 mg prenalterol dose and during the subsequent 30 hours after the second oral study.

PRENALTEROL PLASMA CONCENTRATIONS

Prenalterol concentrations were measured by a high pressure liquid chromatography method described by E J Sainsbury and J J Ashley (unpublished data).

STATISTICAL ANALYSIS

All data are expressed as means $\pm$ SEM. Stepwise regression analysis was used to analyse the data, with the patient main effects being the first variable to be entered into the equations. For the intravenous study the data obtained ≥ 60 minutes after the intravenous infusion were excluded from the final analysis because they were not paired.

Results

DOSE TITRATION STUDY

Clinical details

All eight patients reached the maximum dose of 100 mg twice daily without clinically significant side effects apart from a feeling of mild mental stimulation at the higher doses. There was an associated emotional "let down" feeling for the first few days after withdrawal of the drug. No patient had clinical deterioration during the dose titration period.

Two patients were withdrawn from the trial because their underlying cardiac condition deteriorated. One patient developed acute pulmonary oedema on the day before the intravenous study and the other was withdrawn because his underlying cardiac condition deteriorated the day after completing the intravenous study.

Exercise tolerance

The maximum workload achieved with the baseline erect exercise sprint test (835 ± 80 kpm/min) was not significantly different from that with the erect sprint

Fig. 2 Cardiac function at rest and during graded supine exercise with prenalterol and the placebo (a) after intravenous infusion of prenalterol and (b) after two weeks' treatment with either prenalterol or the placebo. Heart rate, cardiac index, left ventricular filling pressure (LVFP), and left ventricular ejection fraction (LVEF) were measured (a) before the administration of the intravenous infusion at rest (baseline), 10 minutes after completion of the intravenous infusion at rest, and on the first (1) and second (2) levels of graded supine bicycle exercise, and (b) before the administration of the last 100 mg oral dose of prenalterol or placebo at rest (baseline), 180 minutes after the dose at rest, and on the first (1) and second (2) levels of graded supine bicycle exercise.

test in patients taking the maximum dose of 100 mg prenalterol twice daily (850 ± 98 kpm/min).

Erect exercise haemodynamic measurements

Prenalterol caused no significant change in the resting heart rate (day 1, 83 ± 5 beats/min; day 8, 88 ± 4 beats/min) or the resting rate pressure product (day 1, 98 ± 7 mm Hg/min/100; day 8, 96 ± 6 mm Hg/min/100). There was, however, a significant fall with prenalterol in the maximum exercise heart rate (day 1, 155 ± 7 beats/min; day 8, 133 ± 6 beats/min; $p < 0.001$) and rate pressure product (day 1, 260 ± 24 mm Hg/min/100; day 8, 195 ± 22 mm Hg/min/100; $p < 0.001$).

Prenalterol plasma concentrations

The mean plasma prenalterol concentrations on day 8 were 35 ± 5 ng/ml (range 14–59) before the dose and 71 ± 7 ng/ml (range 42–104) two hours after the 100 mg dose.

ACUTE INTRAVENOUS STUDY

Haemodynamic measurements

The effects of the control and prenalterol infusions on measurements of cardiac function at rest are shown in Table 2 and on exercise measurements in Fig. 2. Prenalterol produced a slight but significant rise in the resting heart rate ($p < 0.001$). During exercise, however, prenalterol significantly diminished the exercise induced tachycardia ($p < 0.001$) (exercise level 2 control infusion 132 ± 8 beats/min; prenalterol 119 ± 6 beats/min). There was no significant effect of prenalterol on the mean blood pressure at rest or during exercise. The rate pressure product was higher with prenalterol at rest but was significantly lower during exercise than with the control infusion ($p < 0.001$).

Cardiac index rose significantly with increasing exercise ($p < 0.001$). Both cardiac index and stroke volume index were significantly higher at rest and during exercise with prenalterol ($p < 0.001$). The baseline left ventricular filling pressures were abnormally raised (21 ± 5 mm Hg) and did not change with the control infusion. With prenalterol the left ventricular filling pressures at rest decreased (Table 2) ($p < 0.001$), and, although these pressures increased during exercise with both the control infusion and prenalterol, values with prenalterol were significantly lower than with the control ($p < 0.001$) (exercise level 2 control infusion 35 ± 5 mm Hg; prenalterol 29 ± 5 mm Hg).

Systemic vascular resistance fell significantly with exercise ($p < 0.001$). Prenalterol produced a significantly lower value both at rest and during exercise than the control infusion ($p < 0.001$). Stroke work index was higher with prenalterol than with the control infusion ($p < 0.001$) both at rest (control infusion 32 ± 5 ; prenalterol 42 ± 7) and during exercise (exercise

Table 3 Prenalterol plasma concentrations after intravenous (5 mg over 5 minutes) and oral (100 mg) administration. Values are means $\pm$ SEM

Intravenous infusion (n=7):							
Time (mins post infusion)	0	5	10	20	30	60	120
Prenalterol (ng/ml)	135 $\pm$ 30	37 $\pm$ 3	29 $\pm$ 3	21 $\pm$ 2	17 $\pm$ 1	11 $\pm$ 1	8 $\pm$ 1
Oral administration (n=3):							
Time (hours)	0	1	2	3	4	8	12
Prenalterol (ng/ml)	40 $\pm$ 5	114 $\pm$ 9	106 $\pm$ 12	76 $\pm$ 6	85 $\pm$ 16	55 $\pm$ 9	48 $\pm$ 11

level 2 control infusion 41 $\pm$ 8; prenalterol 53 $\pm$ 8).

Left ventricular ejection fraction

The baseline left ventricular ejection fraction was considerably depressed (25 $\pm$ 4%) and was not changed by either exercise or the control infusion. Prenalterol increased left ventricular ejection fraction both at rest (31 $\pm$ 4%) and during exercise (exercise level 2 31 $\pm$ 4%) (p <0.001).

SUSTAINED ORAL STUDY

Clinical details

The degree of disablement of the six patients who completed the entire study remained in the same baseline NYHA class throughout. Three patients felt slightly better with prenalterol than with the placebo, two slightly worse, and one noticed no change.

Throughout the study, medications for cardiac failure—including digoxin, diuretics, and vasodilators—remained unchanged. There was no significant change in the patients' weight, chest x ray appearance, serum electrolyte estimations, or renal function.

Exercise tolerance

There was no significant difference between the maximum workloads achieved by the six patients in the erect bicycle sprint test at baseline levels (916 $\pm$ 79 kpm/min), at the end of the dose titration study (967 $\pm$ 80 kpm/min), or after the oral study with the placebo (967 $\pm$ 95 kpm/min) or prenalterol (917 $\pm$ 101 kpm/min).

All six patients were able to complete the two levels of graded supine bicycle exercise both with prenalterol and with the placebo. The workloads achieved during the supine graded exercise were 300 $\pm$ 55 kpm/min for the first level of exercise and 600 $\pm$ 45 for the second.

Haemodynamic indices

Erect bicycle sprint test—Prenalterol did not significantly change the resting heart rate (prenalterol 87 $\pm$ 4 beats/min; placebo 83 $\pm$ 7 beats/min) or the rate pressure product (prenalterol 107 $\pm$ 9 mm Hg/min/100; placebo 95 $\pm$ 8 mm Hg/min/100). Prenalterol, however, produced a significant fall in the maximum exercise heart rate (126 $\pm$ 7 beats/min) compared with

the placebo (159 $\pm$ 9 beats/min, p <0.001). There was also a significant fall in the maximum exercise rate pressure product with prenalterol (189 $\pm$ 28 mm Hg/min/100) compared with the placebo (237 $\pm$ 22 mm Hg/min/100, p <0.001).

Supine graded exercise test—The effect of two weeks' treatment with the placebo and oral prenalterol on resting measurements of cardiac function are shown in Table 2 and on exercise measurements in Fig. 2b. The heart rate was higher at rest with prenalterol than with the placebo (p <0.001), but prenalterol reduced the exercise induced tachycardia (p <0.001). The mean blood pressure was significantly higher with prenalterol (p <0.001) both at rest (Table 2) and during exercise (level 2: placebo 111 $\pm$ 4 mm Hg; prenalterol 119 $\pm$ 3 mm Hg). The rate pressure product was significantly higher with prenalterol at rest before and after the last oral dose (p <0.001). During exercise prenalterol produced a progressively lower rate pressure product compared with the placebo during increased exercise (p <0.01).

Prenalterol did not significantly affect the resting left ventricular filling pressures, but it did produce significantly higher left ventricular filling pressures with exercise (p <0.001) (level 2: placebo 26 $\pm$ 5 mm Hg; prenalterol 34 $\pm$ 5 mm Hg). The cardiac index was significantly increased at rest with prenalterol (p <0.001) but was lower with prenalterol during exercise (p <0.001). During exercise the stroke volume index was significantly lower with prenalterol (p <0.05).

There was a significant rise in the systemic vascular resistance with prenalterol compared with the placebo (p <0.05) both at rest and during exercise (level 2: placebo 928 $\pm$ 128; prenalterol 1175 $\pm$ 150 dyn s cm⁻⁵). The stroke work index was higher with prenalterol at rest (p <0.001) both before the oral dose (placebo 35 $\pm$ 4; prenalterol 40 $\pm$ 5) and one hour after (placebo 34 $\pm$ 5; prenalterol 45 $\pm$ 6), but during exercise the stroke work index was not significantly different with either prenalterol or placebo (level 2: placebo 44 $\pm$ 6; prenalterol 42 $\pm$ 7).

Left ventricular ejection fraction

Neither exercise nor prenalterol produced any significant change in left ventricular ejection fraction (Fig. 2b).

Prenalterol plasma concentrations

The prenalterol plasma concentrations obtained during both the acute intravenous and oral studies are shown in Table 3. The peak concentrations were similar for both the acute intravenous and sustained oral study, but as expected the values fell more rapidly after the intravenous infusion (12 hours after dose: intravenous 2.5 ± 0.8 ng/ml; oral 48.4 ± 11 ng/ml).

Discussion

Our results with intravenous prenalterol are in accord with those of recent studies which have found that intravenous prenalterol acutely improved cardiac function at rest⁴⁻⁶ and during exercise^{7,8} in patients with cardiac failure. This improvement is shown by a significant decrease in left ventricular filling pressure and by the increase in cardiac index, stroke volume index, left ventricular ejection fraction, and stroke work index at rest and during exercise after an intravenous infusion of prenalterol. The blunting of the heart rate response to exercise by prenalterol suggests a partial beta blocking action which was apparent only during exercise and which did not block the improvement in haemodynamic indices and ejection fraction during exercise.

In contrast with the results of acute intravenous treatment the only effects on cardiac function after two weeks of sustained oral treatment were deleterious and were associated with increased blood pressure and peripheral vascular resistance at rest and during exercise. Exercise capacity, left ventricular ejection at rest and exercise, stroke volume indices, and left ventricular filling pressures at rest were all unchanged with prenalterol compared with the placebo. Prenalterol increased stroke work indices at rest but not during exercise. During exercise prenalterol increased left ventricular filling pressures and decreased both cardiac and stroke volume indices.

The differing responses between the acute intravenous and sustained oral studies are not attributable to a change in the underlying cardiac status with time. Some haemodynamic measurements at rest, particularly the left ventricular filling pressures, differed according to whether the feet were raised on the ergometer pedals ready for exercise or dependent ready for prolonged observation at rest (Table 2). The control measurements obtained with feet dependent were, however, all comparable during both the acute intravenous and sustained oral studies (Table 2).

Few studies have assessed the efficacy of oral prenalterol treatment and most of these studies have assessed only single dose effects using small oral doses. Waagstein *et al* reported a crossover study in eight patients taking oral prenalterol at various doses

between 30–200 mg/day for six days and reported no significant improvement in echocardiographic ejection fraction, systolic time intervals, or exercise tolerance with prenalterol.⁷ Lambertz *et al* in a preliminary report found that prenalterol produced a significant improvement in resting cardiac function after one week's treatment which was no longer significant after three and six months of continuous treatment.⁹ These two studies are in agreement with our findings that sustained oral treatment with prenalterol does not improve these indices of cardiac function at rest. Sharpe and Coxon showed a significant improvement in exercise tolerance and radionuclide ejection fraction and improved resting haemodynamic indices with both acute intravenous and acute oral treatment.¹⁰ None of these previous studies assessed the effect of sustained oral treatment on exercise haemodynamic indices or exercise left ventricular function.

Several possible mechanisms may contribute to the reversal of beneficial acute effects during sustained oral prenalterol treatment, inadequate oral dosing, classical tachyphylaxis, a cardiodepressant effect due to a partial beta antagonist action of prenalterol, and increased peripheral vascular resistance, due either to activation of the renin angiotensin system or to the direct action of prenalterol on peripheral adrenoreceptors.

The discordance of results in our study between the effects of acute intravenous and chronic oral prenalterol on cardiac function both at rest and during exercise is not explained by inadequate oral dosing. All patients reached the maximum dose of 100 mg twice a day on dose titration studies. The peak plasma concentrations obtained during the oral study were comparable with those obtained during the intravenous study. Plasma concentrations of prenalterol at the time of exercise following the infusion (10–20 minutes) were, however, approximately one third of those obtained at the time of exercise following the oral dose (three hours), because of the rapid decrease in plasma concentrations following the intravenous infusion (Table 3). The possibility that some of the unfavourable effects with sustained oral treatment may be attributable to the direct cardiotoxicity of sustained high blood concentrations of prenalterol cannot be excluded. Sustained excessive catecholamine concentrations have been reported directly to cause a cardiomyopathy.^{14,15}

Tachyphylaxis has been shown to be an important factor operating against sustained effectiveness of a number of sympathomimetic agents.¹⁶⁻¹⁸ Colucci *et al* reported that tachyphylaxis, which developed with the oral beta₂ agonist pirbuterol over a one month period, was associated with a depletion of lymphocyte beta adrenoreceptors.¹⁹ Weiss *et al* did not find that

tachyphylaxis developed after 10 days of oral prenalterol treatment in normal volunteers.¹ If the loss of acute benefit in our study was due only to tachyphylaxis the persistent increase in resting heart rate and blood pressure during sustained oral administration and actual deterioration in cardiac function during exercise would both remain unexplained.

In our study prenalterol increased resting heart rate but significantly reduced the heart rate response to exercise, a phenomenon also noted by Tweddel *et al.*⁸ One likely mechanism for this reduction of heart rate is that a partial antagonist effect may become prominent at cardiac beta receptors under conditions of high endogenous sympathetic tone. Such a mechanism, however, would not alone account for the deleterious effect of sustained oral treatment with prenalterol during exercise. A double blind crossover study of one month's treatment with the beta₁ adrenergic blocking drug, metoprolol, in a similar group of patients and using the same techniques for assessing cardiac function at rest and during exercise showed that sustained oral beta blockade produced a fall in heart rate but neither beneficial nor deleterious effect on cardiac function.²⁰

The significantly increased peripheral vascular resistance and blood pressure after two weeks of prenalterol treatment occurred despite concomitant vasodilator treatment and could contribute to a deterioration in the measured indices of cardiac function during exercise. Our results do not exclude a continuing direct positive inotropic effect of oral prenalterol on the myocardium that is masked by unfavourable loading conditions resulting from increased blood pressure and peripheral vascular resistance.

Possibly, the observed changes in peripheral vascular tone could arise from prenalterol activating peripheral adrenoreceptors and hence producing peripheral vasoconstriction and a rise in systemic vascular resistance. Against this possibility is the claim that prenalterol has no peripheral action at all,¹ but no data on this point are available on such high sustained blood concentrations in humans. Another possible explanation is prenalterol's reported antagonist properties at peripheral beta₂ receptors,²¹ which may promote a pressor action. An alternative mechanism for these peripheral changes is activation of the renin angiotensin system by prenalterol; this possibility is supported by the report of an increase in renin activity by prenalterol.²² In view of this last possibility, a study of the merits of combined treatment with angiotensin converting enzyme inhibitors and oral sympathomimetic agents may be worthwhile.

We did not consider it to be ethical to withhold conventional treatment for cardiac failure from the patients in this study, as they all had severe left ven-

tricular dysfunction by both clinical and objective criteria. While the data validly indicate the effects of prenalterol in patients already receiving treatment for cardiac failure different results could possibly be obtained in those receiving no other treatment.

While the results could also be affected by the presence of ischaemic heart disease, in our study they did not differ significantly between those with or without coronary disease. This is likely to reflect the fact that all patients with coronary disease were selected because their clinical symptoms were of cardiac failure without recent angina. Different results could be obtained in patients with coronary disease and angina.

The reported carcinogenicity of prenalterol and its consequent withdrawal limits the clinical relevance of the specific characteristics of prenalterol. Nevertheless, the results of this study re-emphasise the need to assess cardiac function both at rest and during exercise and after both acute intravenous and sustained oral treatment in order to assess adequately the benefit from cardiac positive inotropic agents. The mechanisms by which loss, or even reversal, of beneficial acute effects may occur during sustained oral treatment need to be understood and counteracted before such agents can be used to produce sustained improvement in cardiac function.

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References

- 1 Weiss A, Pfister B, Imhof P, Degen PH, Burckhardt D, Dubach UC. Haemodynamic effects, plasma concentrations and tolerance of orally administered prenalterol in man. *Eur J Clin Pharmacol* 1980; 18: 383-90.
- 2 Johnsson G, Jordö L, Lundborg P, Rönn O, Welin-Fogelberg I, Wikstrand J. Haemodynamic and tolerance studies in man of a new, orally active, selective B-1 adrenoreceptor agonist H 80/62. *Eur J Clin Pharmacol* 1978; 13: 163-70.
- 3 Hutton I, Murray RG, Boyes RN, Rae AP, Hillis WS. Haemodynamic effects of prenalterol in patients with coronary heart disease. *Br Heart J* 1980; 43: 134-7.
- 4 Awan NA, Needham KE, Evenson MK, Win A, Mason DT. Hemodynamic actions of prenalterol in severe congestive heart failure due to chronic coronary disease. *Am Heart J* 1981; 101: 158-61.
- 5 Kirlin PC, Pitt B. Hemodynamic effects of intravenous prenalterol in severe heart failure. *Am J Cardiol* 1981; 47: 670-5.
- 6 Erbel R, Meyer J, Lambertz H, *et al.* Hemodynamic effects of prenalterol in patients with ischemic heart dis-

- ease and congestive cardiomyopathy. *Circulation* 1982; 66: 361-9.
- 7 Waagstein F, Reiz S, Ariniego R, Hjalmarson A. Clinical results with prenalterol in patients with heart failure. *Am Heart J* 1981; 102: 548-54.
 - 8 Tweddel AC, Murray RG, Pearson D, Martin W, Hutton I. Cardiovascular effects of prenalterol on rest and exercise haemodynamics in patients with chronic congestive cardiac failure. *Br Heart J* 1982; 47: 375-80.
 - 9 Lambert H, Meyer J, Erbel R, Effert S. Long term treatment of severe congestive heart failure with the B-agonist prenalterol [Abstract]. *Circulation* 1982; 66 (suppl II):11-20.
 - 10 Sharpe N, Coxon R. Oral prenalterol in chronic heart failure [Abstract]. *Circulation* 1982; 66 (suppl II):11-20.
 - 11 Bailey IK, Anderson SD, Rozea PJ, Bernstein L, Nyberg G, Korner PI. Effect of beta-adrenergic blockade with alprenolol on ST-segment depression and circulatory dynamics during exercise in patients with effort angina. *Am Heart J* 1976; 92: 416-26.
 - 12 Kalff V, Kelly MJ, Jennings GL, *et al.* The radionuclide assessment of left ventricular function using graded exercise in normal subjects. *Aust NZ J Med* 1980; 10: 533-9.
 - 13 Kelly M, Kalff V, Rose D, Harper R, Anderson, S, Pitt A. A comparative evaluation of two ECG-gated radionuclide methods for measuring ventricular ejection fraction [Abstract]. *Aust NZ J Med* 1979; 9: 761.
 - 14 Garcia R, Jennings JM. Pheochromocytoma masquerading as a cardiomyopathy. *Am J Cardiol* 1972; 29: 568-71.
 - 15 Schaffer MS, Zuberbuhler P, Wilson G, Rose V, Duncan WJ, Rowe RD. Catecholamine cardiomyopathy: an unusual presentation of pheochromocytoma in children. *J Pediatr* 1981; 99: 276-9.
 - 16 Plummer AL. Drug tolerance to beta-2 adrenergic agents. *Chest* 1978; 73: 994-1004.
 - 17 Lefkowitz RJ. Direct binding studies of adrenergic receptors: biochemical, physiologic, and clinical implications. *Ann Intern Med* 1979; 91: 450-8.
 - 18 Unverferth DV, Blanford M, Kates RE, Leier CV. Tolerance to dobutamine after a 72 hour continuous infusion. *Am J Med* 1980; 69: 262-6.
 - 19 Colucci WS, Alexander RW, Williams GH, *et al.* Decreased lymphocyte beta-adrenergic-receptor density in patients with heart failure and tolerance to the beta-adrenergic agonist pirbuterol. *N Engl J Med* 1981; 305: 185-90.
 - 20 Currie PJ, Kelly MJ, McKenzie A, *et al.* Oral beta adrenergic blockade in chronic severe dilated cardiomyopathy. *J Am Coll Cardiol* 1984; 3: 203-9.
 - 21 Williams RS. Selectivity of prenalterol for adrenergic receptor subtypes: a potential mechanism of inotropic selectivity. *J Cardiovasc Pharmacol* 1983; 5: 266-71.
 - 22 Fitzpatrick D, Ikram H, Nicholls MG, Espiner EA. Hemodynamic, hormonal and electrolyte responses to prenalterol infusion in heart failure. *Circulation* 1983; 67: 613-9.