Are the clinical benefits of oral prenalterol in ischaemic heart failure due to beta blockade?
A six month randomised double blind comparison with placebo

DAVID R GLOVER,* CHRISTOPHER G WATHEN,† R GORDON MURRAY,* MICHAEL C PETCH,‡ ALEXANDER L MUIR,† WILLIAM A LITTLER*

From the Departments of Cardiovascular Medicine, *East Birmingham Hospital, Birmingham, †Royal Infirmary, Edinburgh; and ‡Papworth Hospital, Cambridge.

SUMMARY The clinical effects of the oral beta1 partial agonist, prenalterol, were investigated in 37 patients (29 male, eight female; mean age 57 years) with chronic ischaemic left ventricular failure using a placebo controlled randomised double blind protocol over six months. All patients were limited by dyspnoea (New York Heart Association class III) despite treatment with digoxin and diuretics. Twenty eight patients completed the protocol. Moderate clinical improvement was seen in the prenalterol group, whereas there was little change in the placebo group. Bicycle exercise capacity increased over six months in the prenalterol and placebo groups but only achieved statistical significance for prenalterol when compared with baseline values. Maximum exercise heart rate was significantly reduced in the prenalterol group compared with placebo. Radionuclide left ventricular ejection fraction at rest and during exercise and cardiothoracic ratio showed no significant improvement in either group over six months. Prenalterol was well tolerated and produced no increase in frequency of angina or ventricular arrhythmias.

Prenalterol produced clinical benefits and improved exercise tolerance while reducing exercise heart rate. A moderate placebo response was noted. The apparent beta blocking effect of prenalterol may be as important as the beta1 agonist effect in producing these benefits. Prenalterol has, however, been withdrawn because of side effects in animals.

The management of patients with chronic ischaemic left ventricular failure is often difficult and unsatisfactory and usually requires multiple drug treatment.1 The prognosis is poor despite treatment.2 The conventional management is with diuretics and cardiac glycosides,1 and, although the role of cardiac glycosides remains controversial,3–4 recent studies have confirmed that some inotropic support is maintained in patients in sinus rhythm,5–7 especially those with an audible third heart sound.8 In the past decade there has been increasing interest in both vasodilator treatment9,10 and inotropic drugs, particularly amrinone11 and beta agonists.

The role of beta agonists in the management of heart failure has recently been reviewed.12–13 The beta2 agonists salbutamol and pirbuterol produce beneficial effects mainly by vasodilatation.14 At present, there are apparently only two orally active selective beta1 partial agonists: prenalterol and xamoterol [Corwin] (maximum agonist activity is 80%15 and 43%16 of that of isoprenaline respectively). Both drugs exert a positive inotropic effect acutely16,17 and during short term maintenance treatment.18,19 There is, however, a need for long term placebo controlled studies of these drugs in the management of left ventricular failure.13 The occurrence of side effects in animals has led to the withdrawal of prenalterol, but our studies may be of more general interest.
Are the clinical benefits of oral prenalterol due to beta blockade?

Table 1  Patient characteristics. Figures are numbers of patients unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Prenalterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/6</td>
<td>16/2</td>
</tr>
<tr>
<td>Mean (SD) (yr)</td>
<td>57 (6-8)</td>
<td>57 (7-3)</td>
</tr>
<tr>
<td>Mean (SD) weight (kg)</td>
<td>66 (10-0)</td>
<td>71 (11-5)</td>
</tr>
<tr>
<td>Mean (SD) ejection fraction</td>
<td>0.27 (0.119)</td>
<td>0.26 (0.076)</td>
</tr>
<tr>
<td>Mean (SD) duration of left ventricular failure (yr)</td>
<td>2 (2-2)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Angina present</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Mean (SD) dose (mg): Digoxin</td>
<td>0.25 (0.079)</td>
<td>0.23 (0.050)</td>
</tr>
<tr>
<td>Frusemide</td>
<td>107 (65-9)</td>
<td>120 (54-8)</td>
</tr>
<tr>
<td>Antianginal treatment</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

No statistically significant differences prenalterol vs placebo.

In this study the clinical effects of the beta partial agonist prenalterol were assessed using a placebo controlled double blind protocol of six months' duration in patients with stable chronic ischaemic left ventricular failure.

Patients and methods

STUDY POPULATION

Patients were recruited during routine outpatient practice at three centres (Birmingham, Edinburgh, and Cambridge). A total of 37 patients entered the study (29 men, eight women), aged from 41 to 70 years (mean (SD) 57(7) years). All the patients were selected on the basis of having chronic left ventricular failure (duration >3 months) secondary to ischaemic heart disease and exercise tolerance limited by dyspnoea (New York Heart Association functional class III) despite treatment with digoxin and diuretics. Patients were excluded from the study if they had sustained a myocardial infarction within the previous three months, had valvar heart disease, or obstructive airways disease.

Table 1 summarises the patient characteristics. The presence of coronary artery disease was confirmed in all patients: in 23 by coronary angiography (18 of whom had a previous myocardial infarction) and in the remaining 14 by documented transmural myocardial infarction. Seven patients in each group were receiving antianginal treatment in the form of isosorbide dinitrate (20–90 mg/day) or nifedipine (30–

---

**Fig. 1  Study protocol.**

- **PP** = Placebo period
- **D** = Dose titration with prenalterol
- **E** = Exercise test
- **OSD** = Off study drug
- **P** = Physical examination
- **R** = Radionuclide angiography
- **T** = Ambulatory electrocardiographic monitoring
- **X** = Chest radiography
60 mg/day) or both, which was maintained throughout the study.

**STUDY DESIGN**

Figure 1 shows the study design. It consisted of a two week single blind placebo period followed by a single blind dose titration period. Oral prenalterol (prenalterol hydrochloride controlled release tablets: AB Hassle) was given in incremental doses of 20 mg, 30 mg, and 50 mg at two-hourly intervals. The optimal dose was judged to be that which resulted in a moderate increase in resting heart rate of not more than 10 beats/min, with or without a rise in systolic blood pressure of not more than 20 mm Hg, and which could be tolerated without unwanted effects. Patients were then randomised to receive the optimal dose of prenalterol or matching placebo for six months. At the end of this period the treatment was withdrawn in a double blind fashion and a final assessment made one month later. The assessments were performed at the same time of day and at the same time after tablet administration in each patient. The doses of digoxin, diuretics, and other medication were kept constant throughout the study except where clinical deterioration necessitated alteration.

The protocol for this study was accepted by the United Kingdom Committee on Safety of Medicines under the Clinical Trial Certificate (CTC) scheme. The local ethical committees approved the study, which was performed according to the principles of the World Health Association’s Declaration of Helsinki. Written consent was obtained from each patient.

**Methods**

**TRIAL PROCEDURE**

**Clinical assessments**—At each visit the patient and examining physician independently were asked to assess progress from the previous visit on a scale 1 to 7: 1, markedly worse; 2, moderately worse; 3, slightly worse; 4, about the same; 5, slightly improved; 6, moderately improved; 7, markedly improved. The patient’s subjective score (based on symptoms) and the physician’s objective score (based on physical signs) were then combined to give an overall clinical score. The baseline clinical score was taken to be 8 (4+4) in every case and at each visit the score increased or decreased in a cumulative fashion depending on the degree of changes from the previous visit. The patient’s NYHA functional classification was also estimated by the physician.

**Exercise tests**—Maximal symptom limited exercise tests were performed on an electrically braked upright bicycle ergometer using a protocol which commenced at 20 W for two minutes and subsequently increased by 10 W per minute. The patient’s heart rate and rhythm were continuously monitored and the heart rate and systolic blood pressure recorded at the end of each workload. Blood pressure was measured using a standard mercury sphygmomanometer.

**Radionuclide angiography**—Radionuclide angiography was performed following in vivo red cell labelling with 740 MBq technetium 99 m. Image data were acquired using a mobile gammacamera in the anterior and left anterior oblique projections at rest and the left anterior oblique projection during supine dynamic exercise. Count dependent global left ventricular ejection fraction was calculated from the background corrected time-activity curves from resting and exercise left anterior oblique images. Exercise was performed supine using an electrically braked bicycle ergometer. A single step protocol was used with a work level approximately 50% of the erect maximal level previously determined. A total of four minutes supine exercise was performed with image data acquisition during the last three minutes.

**Chest radiography**—A standard posteroanterior chest x-ray film was taken at six feet for determination of the cardiothoracic ratio.

**Ambulatory electrocardiographic monitoring**—Standard 24 hour single channel recordings were made using an Oxford Medical Series 4.24 portable cassette recorder (Oxford Electronic Instruments, Oxford). Analysis of the recordings was carried out using a Pathfinder Mark II (Reynolds Medical Instruments) by a single operator. The results were reported using the Lown grading system. 20

**Haematological and biochemical analyses**—Blood samples for routine haematological and biochemical tests and samples for subsequent plasma prenalterol 21 and digoxin assay were taken at the time of each clinical assessment.

**Unwanted effects**—Any unwanted effects were recorded at the time of each clinical assessment.

**STATISTICAL ANALYSIS**

All results are expressed as mean (standard deviation). Baseline values for resting and exercise heart rate and blood pressure were calculated as the mean of the two pretreatment measurements, whereas for radionuclide angiography and chest radiography the single pretreatment value was used. Student’s t test for unpaired data was used to compare the differences in the baseline values and changes from baseline between the two groups, while a Student’s paired t test was used to test the significance of the change from baseline within each treatment group. A Wilcoxon sum of ranks test was used to compare the cumulative clinical score between the two treatment groups.
Are the clinical benefits of oral prenalterol due to beta blockade?

Results

Nineteen patients were randomised to receive prenalterol and 18 to receive placebo. The patients were well matched at entry with no significant differences between the treatment groups (Table 1).

The optimal doses of prenalterol determined by dose titration were as follows: 100 mg twice daily, 17 patients (16 male, one female); 50 mg twice daily, 15 patients (nine male, six female); and 20 mg twice daily, 5 patients (four male, one female).

DEATHS, WITHDRAWALS, AND PROTOCOL VIOLATIONS

Two patients in each group died during the study, and two patients taking prenalterol and three placebo were withdrawn from the study (Table 2). During the study period the dose of diuretic (frusemide) had to be increased in two patients, from 80 mg to 160 mg/day in one case and from 80 mg to 240 mg/day in the other, because of deteriorating heart failure. Both patients were in the placebo group.

Table 2  Number of deaths and withdrawals

<table>
<thead>
<tr>
<th>Reason for death:</th>
<th>Prenalterol (n=19)</th>
<th>Placebo (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Progressive severe heart failure with Mobitz type II heart block</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Events leading to withdrawal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive cardiac failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased angina pectoris</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Acute onset diabetes mellitus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

No statistically significant differences prenalterol vs placebo.

Table 3  Results of assessments made throughout the trial. Values are mean (SD) (figures in square parentheses are numbers of patients)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>At entry</th>
<th>During treatment</th>
<th>With no treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 month</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>83 (11-4)</td>
<td>82 (12-1)</td>
<td>82 (10-3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>87 (14-3)</td>
<td>83 (12-4)</td>
<td>87 (10-5)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>126 (19-5)</td>
<td>124 (22-1)</td>
<td>124 (19-9)</td>
</tr>
<tr>
<td>Placebo</td>
<td>117 (13-0)</td>
<td>118 (14-4)</td>
<td>115 (15-4)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>80 (10-7)</td>
<td>78 (12-0)</td>
<td>75 (12-3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>75 (6-9)</td>
<td>78 (10-5)</td>
<td>76 (13-7)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>66-5 (9-4)</td>
<td>67-2 (10-20)</td>
<td>68-4 (11-63)</td>
</tr>
<tr>
<td>Placebo</td>
<td>68-7 (11-06)</td>
<td>69-4 (11-75)</td>
<td>67-8 (12-50)</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>2-9 (0-27)</td>
<td>2-7 (0-67)</td>
<td>2-6 (0-74)</td>
</tr>
<tr>
<td>Placebo</td>
<td>3-0 (0-13)</td>
<td>2-9 (0-52)</td>
<td>2-8 (0-44)</td>
</tr>
<tr>
<td>Radionuclide ejection fraction at rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>0-27 (0-119)</td>
<td>0-30 (0-150)</td>
<td>0-27 (0-135)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0-26 (0-076)</td>
<td>0-21 (0-092)</td>
<td>0-24 (0-093)</td>
</tr>
<tr>
<td>Heart rate at rest (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>82 (14-5)</td>
<td>83 (14-0)</td>
<td>84 (9-8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>85 (10-3)</td>
<td>86 (13-0)</td>
<td>83 (12-3)</td>
</tr>
<tr>
<td>Radionuclide ejection fraction during exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>0-23 (0-120)</td>
<td>0-25 (0-161)</td>
<td>0-22 (0-110)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0-24 (0-077)</td>
<td>0-20 (0-092)</td>
<td>0-22 (0-095)</td>
</tr>
<tr>
<td>Heart rate during exercise (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>122 (18-5)</td>
<td>112 (12-8)</td>
<td>107 (12-5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>120 (10-0)</td>
<td>117 (19-9)</td>
<td>117 (22-1)</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>0-55 (0-069)</td>
<td>0-54 (0-069)</td>
<td>0-54 (0-066)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0-52 (0-056)</td>
<td>0-52 (0-055)</td>
<td>0-53 (0-051)</td>
</tr>
<tr>
<td>Holter Lown score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>2-4 (1-64)</td>
<td>2-2 (1-63)</td>
<td>2-2 (1-39)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2-9 (1-57)</td>
<td>2-5 (1-37)</td>
<td>2-2 (1-05)</td>
</tr>
<tr>
<td>Plasma prenalterol concentrations (nmol/l of plasma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>—</td>
<td>193 (132-5)</td>
<td>190 (152-4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Plasma digoxin concentrations (nmol/l of plasma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenalterol</td>
<td>1-9 (0-80)</td>
<td>2-1 (1-65)</td>
<td>2-3 (1-44)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1-9 (0-91)</td>
<td>2-1 (1-20)</td>
<td>2-1 (1-18)</td>
</tr>
</tbody>
</table>

*p<0.05 between the treatment groups.
RESTING OBSERVATIONS
Table 3 shows resting heart rate and blood pressures. There were no significant differences between the groups before or during the study.

CLINICAL SCORES AND NYHA CLASSIFICATION
Figure 2 summarises the clinical scores. In the prenalterol group the increase in clinical scores corresponds to moderate improvement at three and six months. Fourteen of the 19 patients showed a positive clinical response with an increased score. In the placebo group the increase in clinical score corresponds to slight improvement, with 10 of the 18 patients having a small increase in score. The standard deviations (SD) for this group were large in contrast to the prenalterol group, which is a reflection of the variability in clinical response in the placebo group. Statistical significance (Wilcoxon test) was not reached for the differences in cumulative clinical score between the prenalterol and placebo groups.

The NYHA classification (Table 3) showed a trend in favour of the prenalterol group which was not statistically significant.

Fig. 2 Mean clinical scores for patients treated with prenalterol or placebo. Bars denote SD.

Fig. 3 Maximal exercise test results for patients treated with prenalterol or placebo: (a) maximum heart rate; (b) systolic blood pressure at end of exercise; (c) maximum workload; and (d) total work. Values are mean (SD). *p<0.05; **p<0.01; ***p<0.001 (between groups).
Are the clinical benefits of oral prenalterol due to beta blockade?

EXERCISE TESTS
The exercise tests were performed without incident. The limiting symptom was breathlessness or fatigue or both in all cases throughout the study. Figure 3 shows the results.

Maximum heart rate was significantly reduced in the prenalterol group at one month (p<0.001), three months (p<0.05), and six months (p<0.01) compared with placebo. On drug withdrawal there was a return to control values.

During the control period systolic blood pressure at the end of exercise was significantly higher in the prenalterol group than in the placebo group (p<0.05). There was a tendency for the systolic blood pressure to be reduced in the prenalterol group during the treatment period, and this change reached statistical significance compared with placebo after one month (p<0.05). There was little change in the placebo values.

Rate pressure products were calculated from the above data and were found to be significantly reduced in the prenalterol group at one month (p<0.001), three months (p<0.05), and six months (p<0.01) compared with placebo.

The maximum workload (watts) achieved by the prenalterol group was significantly increased at one month (p<0.05) and six months (p<0.01) compared with control values. There was a significant increase in the placebo group at one month (p<0.05), but there were no significant differences between the treatment groups. On drug withdrawal there was no significant change in maximum workload achieved in either group.

The total work performed (watts mins) by the prenalterol group was significantly increased at one month (p<0.05) and at six months (p<0.01) compared with control values. In the placebo group there was a significant improvement at one month (p<0.05) compared with control values, but this was not maintained. There were, however, no significant differences between the groups.

RADIONUCLIDE ANGIOGRAPHY AND CHEST RADIOGRAPHY
Seven of the patients were in atrial fibrillation and were not studied. Table 3 shows the radionuclide left ventricular ejection fractions at rest and during exercise. There were no significant changes in the resting or exercise ejection fractions within the treatment groups during the study. Nevertheless, the differences between the groups for resting values alone at one month achieved statistical significance (p<0.05). The heart rate during supine exercise was significantly reduced in the prenalterol group compared with placebo at one and three months (p<0.05) (Table 3).

There was little change (NS) in the cardiothoracic ratio in both groups during the study (Table 3).

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING
Cardiac arrhythmias were often recorded in the absence of symptoms in both groups at entry and during the trial period. Nevertheless, there was no significant difference in the occurrence of ventricular arrhythmias (Lown score) during the trial between the treatment groups (Table 3).

HAEMATOLOGICAL AND BIOCHEMICAL ANALYSES
No significant changes were observed in any of the standard haematological or biochemical analyses during the study period. In particular, there were no changes in serum glucose, potassium, or creatinine concentrations. Plasma digoxin and prenalterol concentrations confirmed drug compliance in all patients (Table 3).

UNWANTED EFFECTS
Table 4 shows the unwanted effects reported by patients. There was little difference in the incidence of unwanted effects between the groups. Four patients in each treatment group had the dose of study drug reduced because of unwanted effects. Digoxin was reduced in one patient in the placebo group and isosorbide dinitrate in one patient on prenalterol with good effect.

<table>
<thead>
<tr>
<th>Effects</th>
<th>Prenalterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased angina pectoris</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Palpitations</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Central nervous system:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reactions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bizarre dreams</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

No statistically significant differences prenalterol vs placebo.

Discussion
In this study long term oral prenalterol treatment has been shown to be clinically beneficial, tending to improve symptoms and exercise tolerance in patients with chronic ischaemic left ventricular failure. These
benefits appear to have occurred in the absence of any
detectable improvement in left ventricular perfor-
mance and were associated with a heart rate sparing
effect during exercise. We also noted pronounced
placebo response.

The selective beta, agonist, prenalterol, has been
shown to have a significant positive inotropic effect
when given intravenously,22-25 and recently the ino-
tropic effect has been confirmed during an acute oral
dose-response study,17 and during a short term oral
double blind crossover study against placebo.18 These
changes have occurred in the absence of alterations in
left ventricular preload and afterload. The improve-
ment in exercise capacity which we found provides
some indirect evidence of a positive inotropic effect,
which was not detected by radionuclide angiography.
Small changes in left ventricular ejection fraction are
difficult to detect in patients with dilated poorly con-
tracting hearts but could be of clinical importance.
The lack of correlation between exercise capacity and
left ventricular ejection fraction has been well
documented in patients with left ventricular fail-
ure,26 27 and compensatory mechanisms have been
suggested to explain this.28

Chronic treatment with beta agonists could possibly
produce tachyphylaxis owing to activation of the
renin-angiotensin system29 and “down regulation” of
beta receptors.30 It is interesting that we did not
observe such tachyphylaxis. There was a small but
insignificant weight gain in the prenalterol group.
Nevertheless, none of these patients developed
oedema or other symptoms of fluid retention, and we
have attributed this increase in weight gain to the
improved appetite and general well being observed
during prenalterol treatment. Another possible disad-
antage of beta stimulation is induction of cardiac
arrhythmias and angina. We found no evidence that
ventricular arrhythmias increased in the prenalterol
group, and only two patients were withdrawn from
the study because of increasing angina; both were tak-
ing placebo.

The attenuation in heart rate on maximal and sub-
maximal exercise could have been the main way in
which benefit was produced.31 This attenuation was
similar to that observed with conventional beta
blocker treatment, even in patients with cardiac fail-
ure.32 This leads us to propose that prenalterol
reduces exercise heart rate by partial beta blockade.
Consequently, the theoretical disadvantage of a full
beta agonist—namely, increased myocardial oxygen
demand—would be prevented. Indeed analysis of the
rate-pressure product which approximates to myocar-
dial oxygen consumption33 is in keeping with this
view. It may also explain our observation that the
incidence of angina was not increased and that few
arrhythmias were encountered. The finding that pre-

Glover, Wathen, Murray, Petch, Muir, Littler
nalterol did not depress left ventricular performance
supports the fact that it is not a full beta blocker.32

The observed clinical improvement in 10 patients
in the placebo group warrants further comment. This
was perhaps due to the extra interest shown in the
patients. They were severely limited by symptoms
despite maximal conventional treatment and conse-
quently were grateful for any hope offered by trial
treatment. Compliance in such patients is usually
excellent and was confirmed in this study.

Our study was designed to determine whether pre-
alterol produced improvement in exercise tolerance
in patients with severe resistant heart failure. This
assessment was used as an objective way of determin-
ning quality of life. The results show a definite trend
wards improvement. The fact that evidence of
improvement in left ventricular performance was
lacking does not detract from the results.

Two placebo controlled studies have recently
reported that prenalterol was of little benefit.34 35
Why are our findings different? In both of these
studies several of the patients had cardiomyopathy
with normal coronary arteries or left ventricular fail-
ure of unknown origin, and some of the patients were
in NYHA class IV. In contrast, all our patients had
left ventricular failure of ischaemic origin and class IV
patients were specifically excluded so that we studied
a more homogenous group of patients. Additionally,
the greater number of patients in our study may have
enabled us to observe changes not apparent in the
small groups of Lambertz (n=16)34 and Currie
(n=6).35 The dose of prenalterol used in the Lamb-
ertz study34 was lower than that which we used with
resulting serum concentrations approximately half of
those we obtained. In Currie’s study35 the treatment
period was short so that it would have missed the
clinical benefits which became apparent in our study
after three months’ treatment.

In conclusion, we found that prenalterol was well
tolerated and no serious unwanted effects were
observed. It appeared to be tolerated well in patients
with angina as well as dyspnoea. The chronic effect of
this partial beta, agonist on the myocardial beta,
receptors and on the circulating endogenous
catecholamines should be investigated to further
elucidate its mode of action. Partial beta, agonist
treatment appears to be of benefit in patients with
ischaemic failure who are symptomatic despite maxi-
mal conventional treatment.

We thank Dr R A Elton, Edinburgh University, for
kindly providing the statistical advice, and Dr B Tip-
lady, Astra Clinical Research Unit, for performing the
data analysis, Astra Clinical Research Unit, Edin-
burgh, for generous financial support, and AB Hassle,
Molndal, Sweden, for providing the prenalterol tab-
Are the clinical benefits of oral prenalterol due to beta blockade?  

lets and for performing plasma analysis for prenalterol and digoxin.

References
Are the clinical benefits of oral prenalterol in ischaemic heart failure due to beta blockade? A six month randomised double blind comparison with placebo.

D R Glover, C G Wathen, R G Murray, M C Petch, A L Muir and W A Littler

Br Heart J 1985 53: 208-215
doi: 10.1136/hrt.53.2.208

Updated information and services can be found at:
http://heart.bmj.com/content/53/2/208

These include:

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/