Acute haemodynamic effects of oral prenalterol in severe heart failure

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SUMMARY The acute haemodynamic effects of oral prenalterol were studied in 14 patients with severe heart failure (NYHA class III) due to ischaemic heart disease. All had received treatment with digoxin, diuretics, and in most cases vasodilators. Prenalterol was administered at two hourly intervals to give cumulative doses of 20, 50, and 100 mg and mean plasma concentrations of 53, 97, and 175 nmol/l. Haemodynamic measurements were made two hours after each dose with Swan-Ganz catheterisation; cardiac output was measured by thermodilution. There were no significant changes in heart rate, mean arterial pressure, or pulmonary artery diastolic pressure after the drug. Cardiac index rose significantly after 50 mg and 100 mg prenalterol.

Oral prenalterol has a beneficial short term haemodynamic effect in patients with severe heart failure. If this effect is sustained prenalterol may be of value in the long term management of patients with this disabling condition.

Prenalterol (1-(4-hydroxyphenoxy)-3-isopropyl-amino-2-propanol) (Figure) is a new β_1 selective adrenoceptor agonist which is active in both the parenteral and oral forms.¹ When given intravenously to patients with severe left ventricular failure it exerts a beneficial effect on cardiac performance.²⁻⁵ The purpose of this study was to assess the acute haemodynamic effects of a long acting oral preparation of prenalterol in patients with heart failure refractory to other forms of treatment.

Patients and methods

Fourteen patients with severe left ventricular failure due to ischaemic heart disease were studied (Table 1). In all activity was severely limited by fatigue and dyspnoea (NYHA class III) and had received treatment with digoxin, diuretics, and in most cases vasodilators (Table 1). All patients had previously had at least one myocardial infarction, and two had undergone surgery for the resection of a left ventricular aneurysm. Left ventricular function was examined before the study by either conventional contrast

angiography or multiple gated blood pool scintigraphy; in no patient was a discrete aneurysm found. All patients were in sinus rhythm apart from one who was paced, and her heart rate values have been omitted from the calculations.

Patients were studied during the course of one day. A Swan-Ganz catheter was inserted percutaneously for measuring cardiac output by thermodilution and left ventricular filling pressure (pulmonary artery diastolic pressure). All cardiac outputs were measured in triplicate. Systemic arterial pressure was measured by sphygmomanometry. Two hours were allowed to elapse after the insertion of the catheter, and providing that the patient's condition was stable prenalterol was given in three oral doses (20 mg, 30 mg, and 50 mg) at two hourly intervals. Haemodynamic data were recorded before prenalterol treatment and two hours after each dose; at the same time blood was taken for the estimation of plasma prenalterol concentrations in 11 patients. Systemic vascular resistance was calculated using the formula: $80 \times (\text{mean arterial pressure minus mean right atrial pressure}) (\text{dyn s cm}^{-5})$ divided by cardiac output, assuming a mean right atrial pressure of zero.

Each patient gave informed consent and the study was approved by the ethical committee of the Cambridgeshire Area Health Authority. Statistical analysis was performed using the Wilcoxon signed rank test.

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Figure Structure of prenalterol and other beta agonists.

Results

Prenalterol was well absorbed. After cumulative doses of 20, 50, and 100 mg mean (range) plasma concentrations of 53 (23–93), 97 (56–166), and 175 (125–240) nmol/l were obtained. The drug was well tolerated. No side effects were encountered and no arrhythmias observed.

The haemodynamic results are presented in Table 2. No change occurred two hours after 20 mg prenalterol. After a total dose of 50 mg cardiac index increased from a pretreatment mean (SD) value of 2.05 (0.51) l/min/m² to 2.36 (0.60) l/min/m² ($p < 0.01$). Two hours after a total dose of 100 mg prenalterol cardiac index increased further to 2.68 (0.84) l/min/m² ($p < 0.05$ vs control) and stroke volume index increased from a control value of 24.7 (6.6) ml to 30.8 (8.1) ml ($p < 0.05$). There were no significant changes

Table 1 Details of left ventricular function and drug treatment in the 14 patients studied

Case No	Age (yr) and sex	LVEF	Treatment (mg/day unless stated)											
			D	F	P	T	B	BK†	S	A	H	I	W	M†
1	54 M	0.21	0.50	160	1.0									
2	54 M	0.15	0.25	120	1.5	100								
3	58 M	0.15	0.25	160			5.0		100		150		2.5	
4	55 F	*	0.125	160					300			30	7.5	
5	63 M	0.20	0.25	80					300			30	7.5	
6	59 M	0.16	0.25	120						20		30	3.0	
7	60 M	0.27	0.50	40	0.5				50				4.0	
8	47 M	0.27	0.25	80					100					
9	50 M	0.46	0.25					1						1
10	41 F	0.38		80										
11	66 M	0.16	0.25	120					100					
12	58 M		0.25	120										
13	59 M	0.29	0.25		6.0			1	100					
14	57 M	0.17	0.125	120	6.0				200					
Mean	56													
Range	41–56													

*Too low for accurate measurement.

†No of tablets.

LVEF, left ventricular ejection fraction; M, moduretic; D, digoxin; F, frusemide; T, triamterene; B, bendrofluazide; BK, bumetamide; S, spironolactone; A, amiloride; P, prazosin; H, hydralazine; I, isosorbide dinitrate; W, warfarin.

Table 2 Haemodynamic measurements before and after treatment with prenalterol. Values are means (SD)

Haemodynamic indices	Before	After		
		20 mg	50 mg	100 mg
Heart rate (beats/min)	84 (10.8)	87.3 (7.9)	85.1 (11.8)	86.4 (12.5)
Systemic arterial pressure (mm Hg)	106/70 (15/10)	107/73 (20/10)	109/72 (21/12)	109/70 (22/11)
LV filling pressure (mm Hg)	21.6 (8.3)	20.2 (8.0)	20.2 (9.9)	19.3 (8.1)
Cardiac index (l/min/m ²)	2.05 (0.51)	2.23 (0.49)	2.36 (0.60)**	2.68 (0.84)*
Stroke volume index (ml/m ²)	24.7 (6.6)	25.6 (5.5)	27.9 (7.5)	30.8 (8.1)*
Systemic vascular resistance (dyn s cm ⁻⁵)	1919 (519)	1771 (364)	1706 (491)*	1588 (596)

* $p < 0.05$; ** $p < 0.01$.

in heart rate, blood pressure, or pulmonary diastolic pressure during the study. There was no relation between pretreatment left ventricular ejection fraction and the increase in cardiac index or stroke volume index, nor between plasma prenalterol concentrations and the increase in cardiac index or stroke volume index. In three patients a fall in cardiac index was observed at the highest dose of prenalterol.

Discussion

The pharmacological management of patients with myocardial failure is a subject of considerable interest. The symptoms of fluid retention, especially dyspnoea, can be readily alleviated by diuretics. Improvement in cardiac function is more difficult to achieve. There are two options, which may be tried singly or in combination. Firstly, vasodilator drugs may be used to manipulate ventricular preload and afterload to bring about a maximal increase in cardiac output at an appropriate filling pressure. Secondly, positive inotropic agents can be used to increase myocardial contractility.

Both catecholamines and digitalis glycosides increase the force of ventricular contraction. The former have an established role in the treatment of low output states associated with acute cardiac damage, for example after open heart surgery. They have to be given intravenously and are thus of limited value in chronic heart failure. Most physicians accustomed to managing patients with severe heart failure do not doubt the efficacy of digitalis glycosides⁶; support for their sustained beneficial effects continues to accrue.⁷⁻¹⁰ Unfortunately, their effect is weak and they are toxic, especially in the elderly. A need exists therefore for an alternative orally active positive inotropic agent.

Prenalterol is a beta₁ adrenoceptor agonist with a relatively strong positive inotropic and a weakly positive chronotropic effect.¹ When given intravenously to patients with heart failure left ventricular function is improved with an increase in cardiac output and fall in left ventricular filling pressure.²⁻⁵ In our study a beneficial haemodynamic effect was observed after oral prenalterol in doses of 50 and 100 mg. These doses gave blood concentrations comparable with those at which a response had been observed after intravenous prenalterol (100–200 nmol/l). The increase in cardiac index was due to the increase in stroke volume. This implies that oral prenalterol is capable of exerting a positive inotropic effect even in patients with severe cardiac damage. Moreover, this effect is apparent despite the concomitant use of digoxin, diuretics, and vasodilators. The reduction in systemic vascular resistance in our study was unexpected since prenalterol has little or no beta₂

effect.^{11,12} Although we cannot completely rule out some direct vasodilating effect, the evidence from experimental animals¹² coupled with the lack of reflex tachycardia suggests that the decline in systemic vascular resistance towards normal in our patients may have been secondary to improved cardiac function rather than vice versa.

In three of our patients a small decline in cardiac index occurred after the 100 mg dose without a change in other variables such as heart rate. This was probably due to chance. These three patients had, however, the lowest cardiac indices, and it is possible that since prenalterol is only a partial beta agonist¹³ it may exert a modest beta blocking effect at high doses in some patients, especially those with high concentrations of circulating catecholamines.

All our patients had proved ischaemic heart disease with portions of their left ventricular muscle replaced by fibrous scar tissue. This being so it might be expected that any response to positive inotropic stimulation would be governed by the amount of remaining healthy myocardium. The increase in cardiac index in our patients was not related to their resting left ventricular function, as judged by the ejection fraction. Only one study has hitherto suggested such a relation in man; Erbel *et al* found a smaller increase in peak rate of change in left ventricular end diastolic pressure (dP/dt) after intravenous prenalterol in patients with congestive cardiomyopathy who had lower initial dP/dt values compared with patients with ischaemic heart disease.⁵ This concept is plausible but will be difficult to confirm or refute in man because of the inaccuracy of assessing left ventricular performance in severely compromised hearts.

We cannot extrapolate our results to the long term use of oral prenalterol in the treatment of heart failure. Tolerance to chronic beta adrenergic stimulation is well recognised and may occur in man. Another beta agonist, pirbuterol, has been shown to cause a reduction in lymphocyte beta adrenoceptor density after one month's treatment.¹⁴ If this "down regulation" of adrenoceptors occurs in the heart then the value of chronic treatment with beta agonists may be limited.

Another potential drawback to the use of prenalterol in patients with failure due to ischaemic heart disease is the possibility of provoking cardiac pain. Our patients were deliberately selected to exclude those with angina pectoris, and none experienced chest pain during the study. The increase in heart rate, which is major determinant of myocardial oxygen consumption, was, however, insignificant in this and all previous studies. Moreover, any increase in left ventricular contractility should be offset by the lower filling pressure, decreased wall tension, and improved relaxation. In practice decreased myocar-

dial oxygen consumption and unchanged lactate extraction have both been reported after intravenous prenalterol in man.^{2,15} Thus the propensity of prenalterol to cause cardiac pain may be slight.

Prenalterol is a drug of great theoretical importance and some therapeutic value. It has a short term positive inotropic effect when given intravenously or orally and is useful in a number of clinical situations associated with acute heart failure, for example reversing beta blockade. Further work is indicated, particularly longer term and exercise studies.

References

- 1 Kendall MJ, Goodfellow RM, Westering S. Prenalterol—a new cardioselective inotropic agent. *J Clin Hosp Pharm* 1982; 7: 107–18.
- 2 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.
- 3 Kirlin PC, Pitt B. Hemodynamic effects of intravenous prenalterol in severe heart failure. *Am J Cardiol* 1982; 47: 670–5.
- 4 Awan AA, 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 Erbel R, Meyer J, Lambertz H, *et al.* Hemodynamic effects of prenalterol in patients with ischemic heart disease and congestive cardiomyopathy. *Circulation* 1982; 66: 361–9.
- 6 Petch MC. Digoxin for heart failure in sinus rhythm. *Thorax* 1979; 34: 147–9.
- 7 Arnold SB, Byrd RC, Meister W, *et al.* Long-term digitalis therapy improves left ventricular function in heart failure. *N Engl J Med* 1980; 303: 1443–8.
- 8 Lee D C-S, Johnson RA, Bingham JB, *et al.* Heart failure in out-patients: a randomised trial of digoxin versus placebo. *N Engl J Med* 1982; 306: 699–705.
- 9 Murray RG, Tweddel AC, Martin W, Pearson D, Hutton I, Lawrie TDV. Evaluation of digitalis in cardiac failure. *Br Med J* 1982; 284: 1526–8.
- 10 Griffiths BE, Penny WJ, Lewis MJ, Henderson AH. Maintenance of the inotropic effect of digoxin on long term treatment. *Br Med J* 1982; 284: 1819–22.
- 11 Carlsson E, Dahlöf C-G, Hedberg A, Persson H, Tängstrand B. Differentiation of cardiac chronotropic and inotropic effects of β -adrenoceptor agonists. *Naunyn Schmiedeberg Arch Pharmacol* 1977; 300: 101–5.
- 12 Manders WT, Vatner SF, Braunwald E. Cardio-selective beta adrenergic stimulation with prenalterol in the conscious dog. *J Pharmacol Exp Ther* 1980; 215: 266–70.
- 13 Mattsson H, Hedberg A, Carlsson E. Basic pharmacological properties of prenalterol. *Acta Med Scand* 1982; suppl 659: 9–37.
- 14 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.
- 15 Kupper W, Schütt M, Bleifeld W. Effect of intravenous prenalterol on haemodynamics and myocardial lactate extraction in patients with left ventricular failure. *Acta Med Scand* 1982; suppl 659: 287–98.