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THE EFFECTS OF INTRAVENOUS PRENALTEROL ON VENTRICULAR PERFORMANCE, AS ASSESSED BY RADIONUCLIDE VENTRICULOGRAPHY, IN PATIENTS WITH ISCHAEMIC HEART DISEASE

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1 We have observed the effects of intravenous prenalterol (1 mg and 2 mg) on ventricular performance, assessed by radionuclide ventriculography, in nine patients with ischaemic heart disease with varying degrees of impairment of ventricular performance. In seven of these patients the effects of prenalterol were compared with those of isoprenaline infused at 1 μg/min.

2 Prenalterol caused no significant increase in heart rate, but systolic blood pressure increased by 26% ($P < 0.002$). In contrast, isoprenaline caused heart rate to increase by 22% ($P < 0.02$) and diastolic blood pressure to fall by 9% ($P < 0.01$).

3 Left ventricular ejection fraction (LVEF) increased with both drugs, but the increase was greater with isoprenaline, as was the fall in the ratio mean ejection time: left ventricular ejection time, which is an index of improved ventricular performance.

4 Because of the increased heart rate and stroke volume produced by isoprenaline, cardiac output increased 45% above control values ($P < 0.001$), but the increase in cardiac output after prenalterol did not reach statistical significance.

5 In three patients with very poor ventricular function (LVEF < 0.30) prenalterol had little effect on ejection fraction, and caused increased regional ventricular dyskinesia.

6 The increase in systolic blood pressure, and therefore cardiac afterload brought about by prenalterol may limit ventricular response. The response might be enhanced by the addition of vasodilator therapy.

Introduction

Prenalterol, (S-(-)-1-(4-hydrophenoxy)-3-isopropyl-amino-propranolol-2 hydrochloride) is a new selective β_1-adrenoceptor agonist, and studies in animals have shown that prenalterol has a more marked effect on myocardial contractility than on heart rate. In doses having the same chronotropic effect, prenalterol has a significantly greater inotropic effect than either isoprenaline or terbutaline (Carlsson *et al.*, 1977).

Pharmacological studies in man have shown that prenalterol, whether given intravenously or orally, shortened left ventricular ejection time, pre-ejection period and total electromechanical systole. Although systolic blood pressure was increased, there was little effect on diastolic blood pressure or heart rate (Johnsson *et al.*, 1978). Using measurements made from changes in thoracic electrical impedance in normal subjects, Scott *et al.* (1979) showed cardiac output increased mainly by an increase in stroke volume.

Substances that increase contractility without changing heart rate, acting through β_1-adrenoceptors, could be of value in the management of cardiac failure, either as an alternative to, or in combination with digoxin. As prenalterol is readily absorbed after oral administration, it might prove a useful adjunct to the management of refractory heart failure. The present study was undertaken to evaluate the cardiovascular effects of prenalterol in patients who had suffered a previous myocardial infarction, resulting in various degrees of impaired ventricular function.

Methods

Patients

Nine patients with ischaemic heart disease were studied: all had sustained a previous myocardial

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infarction and were known from previous radionuclide ventriculography to have a wide range of left ventricular ejection fractions (0.14–0.68). Three patients (numbers 1, 4, and 8) were in chronic left ventricular failure as judged by clinical and radiological examination and had not been improved by large dose diuretic therapy nor by digitalisation. In these three patients, diuretics were continued up to the time of the study, but digoxin administration was stopped 1 week prior to the study. All the patients were informed of the nature of the study and consented to take part. The study had the approval of our Institute's Ethical Committee.

Measurements

In all patients blood pressure was measured by conventional sphygmomanometry. Heart rate was derived from the electrocardiogram which was continuously displayed throughout the study.

Ventricular performance was assessed by radionuclide ventriculography. The patient was positioned under a Nuclear Enterprises Mk V HR gamma camera. The camera head was tilted to give a 30° left anterior oblique view with a 10° caudal tilt as this provides maximum separation of the left ventricle from the right ventricle and left atrium. The patient was injected with 15 mCi of technetium-99m electrolytically labelled human serum albumin (Millar *et al.*, 1979).

Left ventricular ejection fraction (EF) was determined from the gated blood pool method (Muir *et al.*, 1980), where the praecordial counts were stored in the computer in 20 ms frames throughout the cardiac cycle. Counting continued for 500 cardiac cycles. When the acquisition was complete, the accumulated 20 ms frames were displayed in continuous loop fashion on a television display. The left ventricle was identified by direct inspection and by using an edge detection programme. The time-activity curve for this region of interest was corrected for background activity using an automatic correction derived from an area one picture element wide on the lateral and inferior border of the left ventricle. These counts were corrected to an area equal to the left ventricular region. From the background corrected time-activity or volume curve, EF was calculated as (EDC − ESC) /EDC, where EDC and ESC represent the end-diastolic and end-systolic counts respectively.

Relative changes in end-diastolic volume and cardiac output were calculated utilising the measured counts from the left ventricular region. The counts from the left ventricle represent the left ventricular volume and subsequent changes in counts from this region represent changes in volume during the drug infusion periods. Corrections were applied for physical decay of technetium-99m between the control period and the subsequent drug infusion periods. Biological clearance of the labelled albumin was corrected by measuring the activity in 1 ml of blood withdrawn during each study period. The relative cardiac output (CO) for each period was then calculated from the relative end-diastolic volume (EDV), the ejection fraction (EF) and the heart rate (HR): $CO = EF \times EDV \times HR$. Details of the method and its reproducibility have been published (Hannan *et al.*, 1980).

In addition we used the derived ventricular volume curves to examine changes in the weighted mean ejection time. This variable describes changes in the shape of the systolic portion of the curve and is shortened by increased contractility (Muir *et al.*, 1980).

Blood samples, collected into lithium heparin tubes, separated and stored at −18°C, were obtained in the final minute of each ventriculogram. Plasma concentrations of prenalterol were estimated at the research laboratory of Hassle AB, Molndal, Sweden by gas chromatography.

Protocol

In the first two patients a control period was followed by intravenous infusion of 0.5, 1.0 and 2.0 mg of prenalterol, each period lasting 10 min and each infusion being 30 min apart. The variables were assessed 10 min after the infusion of that dose level of prenalterol had been completed.

In all other patients, following a control period, isoprenaline was infused at 1.0 μg/min and the variables measured 5 min after the start of the isoprenaline infusion and while the infusion continued. Twenty minutes after the isoprenaline infusion was completed, 1.0 mg prenalterol was intravenously infused over a 10 min period and the variables assessed 10 min after the injection had been completed. The patient then received a further injection of 2.0 mg of prenalterol and all variables were again re-measured 10 min after this injection had been completed. As the first two patients did not follow the same protocol, they were excluded from statistical analysis. Statistical analysis was carried out by analysis of variance using patient data as blocks. The difference between paired data was calculated by Student's *t*-test.

Results

No patient complained of adverse effects on either drug, but in one patient (number 8) ventricular premature beats occurred whilst being treated with the second dose level of prenalterol. Figure 1 shows changes in heart rate, blood pressure and ejection fraction in the first two patients treated with three increments of prenalterol. In the patient with poor ventricular function ($EF < 0.30$), there was no change

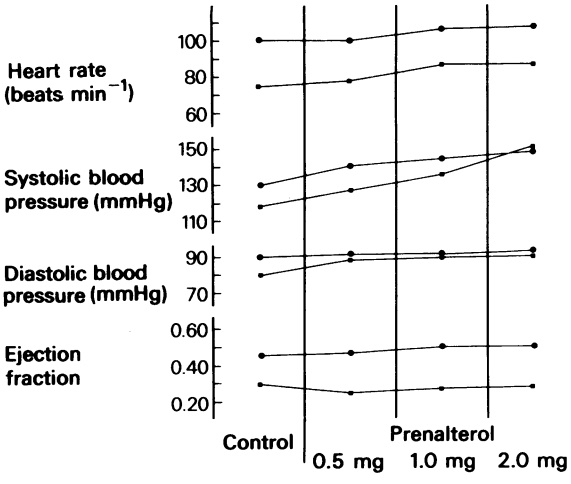

Figure 1 The effects of incremental doses of intravenous prenalterol (0.5 mg, 1.0 mg and 2.0 mg) on heart rate, blood pressure and left ventricular ejection fraction in two patients with ischaemic heart disease. Note that despite an increase in heart rate and systolic blood pressure in patient 2 (■), left ventricular ejection fraction failed to increase.

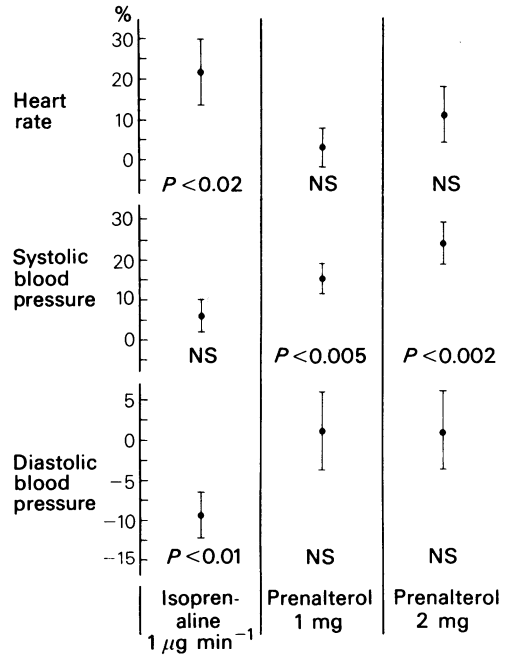

Figure 2 Percentage change after isoprenaline and prenalterol from control values for heart rate, systolic and diastolic blood pressure in seven patients with ischaemic heart disease (mean ± s.e. mean).

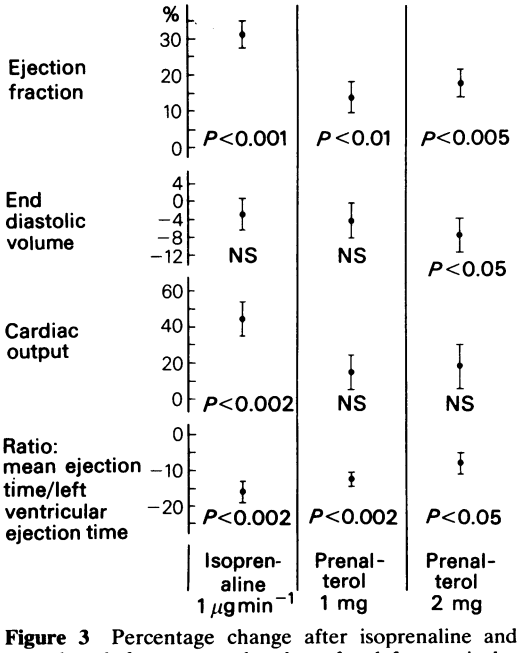

Figure 3 Percentage change after isoprenaline and prenalterol from control values for left ventricular ejection fraction, relative end diastolic volume, relative cardiac output and the ratio mean ejection time/left ventricular ejection time in seven patients with ischaemic heart disease (mean ± s.e. mean).

in EF, despite an increase in blood pressure and heart rate. The changes in the EF in the other patient with relatively good ventricular function was also small (EF 0.46 at rest and 0.51 after prenalterol 2 mg).

Because of these small changes the protocol for all other patients was modified, dropping the first infusion level of prenalterol and including an isoprenaline infusion as a comparison. For these seven patients the mean resting heart rate was 79.9 ± 6.8 beats/min (s.e. mean) and the ejection fraction 0.41 ± 0.07 (Figures 2 and 3). Individual ejection fractions ranged from 0.14 to 0.68 (Table 1). The two patients with the lowest EF showed marked regional dyskinesia. Mean systolic blood pressure was 112.0 ± 5.6 mm Hg and diastolic blood pressure was 71.7 ± 4.3 mm Hg. The mean ejection time (ts), normalized by left ventricular time (LVET) was 0.59 ± 0.01.

During the infusion of isoprenaline heart rate was 94.6 ± 4.6 beats/min and the EF 0.52 ± 0.0-8. The systolic blood pressure was higher than in the control period at 118.0 ± 7.1 mm Hg, but the diastolic was lower at 64.9 ± 4.3 mm Hg. The normalized mean ejection time was 0.50 ± 0.02 and the relative cardiac output 1.44 ± 0.10 of the control values. The relative end-diastolic volume was 0.97 ± 0.04.

After 1 mg of prenalterol the heart rate was 81.3 ± 5.3 beats/min, not significantly different from the control period, but the EF was 0.47 ± 0.09, a mean increase of 0.06 over control values. Mean systolic blood pressure was 128.0 ± 65.4 mm Hg and the mean

Table 1 The effect of prenalterol on ventricular performance in nine subjects

Patient	*State*	*Plasma prenalterol* ($nmol\ l^{-1}$)	*Heart rate* (*beats/min*)	*Systolic blood pressure* (*mm Hg*)	*Diastolic blood pressure* (*mm Hg*)	*Ejection fraction*	*Relative EDV*	*ts* (*ms*)	*ts/LVET*	*Relative CO*
1	Control		75	120	80	0.30	100	107	0.55	100
	Pren 0.5 mg	29	79	128	88	0.24	76	125	0.52	66
	Pren 1.0 mg	72	88	136	90	0.28	68	132	0.57	75
	Pren 2.0 mg	79	88	154	90	0.28	68	125	0.63	71
2	Control		100	130	90	0.46	100	136	0.57	100
	Pren 0.5 mg	24	100	144	92	0.47	94	110	0.55	96
	Pren 1.0 mg	55	107	146	92	0.51	72	112	0.56	84
	Pren 2.0 mg	117	107	150	94	0.51	70	99	0.41	82
3	Control		83	135	85	0.68	100	140	0.58	100
	Isopren 1.0 μg		94	150	78	0.78	101	109	0.46	150
	Pren 1.0 mg	28	88	156	88	0.79	112	124	0.52	138
	Pren 2.0 mg	61	88	166	92	0.77	106	120	0.60	128
4	Control		75	100	62	0.14	100	222	0.55	100
	Isopren 1.0 μg		83	100	52	0.18	95	167	0.49	136
	Pren 1.0 mg	38	83	120	74	0.13	82	195	0.49	85
	Pren 2.0 mg	69	88	134	74	0.14	88	179	0.50	81
5	Control		65	130	80	0.52	100	167	0.59	100
	Isopren 1.0 μg		79	130	64	0.67	113	122	0.51	177
	Pren 1.0 mg	68	68	142	70	0.65	98	132	0.55	128
	Pren 2.0 mg	128	75	152	76	0.67	106	112	0.56	157
6	Control		71	105	75	0.52	100	152	0.63	100
	Isopren 1.0 μg		112	130	78	0.68	99	118	0.48	129
	Pren 1.0 mg	28	65	136	70	0.55	88	131	0.54	85
	Pren 2.0 mg	80	71	154	74	0.58	84	124	0.62	84
7	Control		88	100	56	0.37	100	144	0.60	100
	Isopren 1.0 μg		100	100	52	0.50	87	110	0.46	117
	Pren 1.0 mg	98	79	122	66	0.46	88	122	0.51	93
	Pren 2.0 mg	216	79	124	64	0.47	85	124	0.52	96
8	Control		115	114	82	0.18	100	—	—	100
	Isopren 1.0 μg		106	106	72	0.27	84	—	—	115
	Pren 1.0 mg		107	108	76	0.22	106	—	—	120
	Pren 2.0 mg		111	114	74	0.22	92	—	—	109
9	Control		62	100	62	0.45	100	167	0.60	100
	Isopren 1.0 μg		88	116	58	0.57	100	124	0.57	182
	Pren 1.0 mg	75	79	114	58	0.50	96	134	0.48	151
	Pren 2.0 mg	224	94	116	52	0.54	84	114	0.49	169

Pren = Prenalterol, isopren = isoprenaline

diastolic blood pressure was 71.7 ± 3.5. The normalized mean ejection time was 0.52 ± 0.01, and the relative cardiac output was 1.14 ± 0.10 of control. End diastolic volume was little changed, being 0.96 ± 0.04 of control.

At the second dose level of prenalterol (2 mg) the heart rate increased to 86.6 ± 5.1 beats/min and the EF increased to 0.48 ± 0.09. The systolic blood pressure increased to 137.1 ± 7.7 mm Hg and the diastolic blood pressure was 72.3 ± 4.6 mm Hg. The relative cardiac output was 1.18 ± 0.13 and the normalized mean ejection time was 0.55 ± 0.02 with a relative EDV of 0.92 ± 0.04.

Discussion

Radionuclide ventriculography offers a useful non-invasive means of assessing changes in ventricular performance following drug intervention. Isoprenaline causes an increase in left ventricular ejection fraction and a change in shape in the systolic portion of the left ventricular volume curve (Muir *et al.*, 1980). Theoretically, this change in shape should be reflected by an increase in the maximum rate of change of volume in systole, but statistical noise in the generated curve makes differentiation difficult and therefore we derived an index of a weighted mean time of systolic emptying (ts). When this was related to the left ventricular ejection time (LVET) isoprenaline caused a shortening in the ratio ts/LVET. This was not a heart rate effect as atropine caused a similar change in rate, but no change in ts/LVET. In this study on patients who had suffered a previous myocardial infarction and had a wide range of ventricular performance, we again document similar changes with isoprenaline. The drug caused an increase in heart rate and a decrease in diastolic blood pressure. The ejection fraction increased in all patients (+ 0.11 mean) and the ratio ts/LVET was shortened in all patients. From changes in the end-diastolic counts in the left ventricular outline, relative changes in end-diastolic volume and cardiac output indicated that isoprenaline caused little change in end-diastolic volume, but an increase in cardiac output, half of this increase being due to the increased heart rate.

Prenalterol, too, produced an increase in ejection fraction and a decrease in the ratio ts/LVET, but the magnitude of these changes is less than with isoprenaline. This is particularly marked in the two patients with chronic heart failure. Moreover, in patient 1, who also had heart failure, but had not received isoprenaline, ejection fraction was not increased by prenalterol, although heart rate and systolic blood pressure was increased. Prenalterol caused a greater increase in systolic blood pressure and in mean systemic pressure, and as an increase in afterload adversely affects ventricular performance (Noble, 1978), this may account for some of the difference in measured effects between isoprenaline and prenalterol. Although an increased afterload might be expected to cause an increase in end diastolic volumes, the calculated end diastolic volumes fell more with prenalterol than with isoprenaline, so that stroke volume was less for a given ejection fraction. As heart rate changes were less for prenalterol than isoprenaline, this suggests an additional effect on venous tone, so that venous filling was reduced.

In this analysis ejection fraction and the ratio ts/LVET are used to assess ventricular performance and not to describe changes in contractile state. These ejection phases indices, whilst relatively insensitive to changes in preload, are sensitive to changes in afterload, and so are poor guides to contractility in a changing state. Recent attention has focused on the left ventricular pressure-volume ratio at end systole as a measure of the contractile state that is insensitive to loading states (Sagawa *et al.*, 1977). Although in the present study intraventricular pressure was not measured, end systolic pressure could be approximated by the systolic blood pressure as no patient had aortic valve disease. Using the pressure-volume relation at end systole (P/V_{es}), we found that in the control state P/V_{es} was 1.12 (± 0.06 SEM) after isoprenaline 1.61 (± 0.14) and after prenalterol 1.78 (± 0.13). Although these results must be interpreted with caution because of the approximations, they indicate an increased contractile state with both isoprenaline and prenalterol. Moreover, prenalterol has at least as great an effect on the contractile state as isoprenaline.

In studies in healthy man (Scott *et al.*, 1979) prenalterol (1 mg) produced a significant increase in cardiac output, with a 17% increase in stroke volume, but studies in patients have given more conflicting results. Ariniego *et al.* (1979) studied the effects of prenalterol in patients with acute myocardial infarction and showed that in contrast to those without failure, patients who had had an episode of heart failure were unable to shorten their pre-ejection period. The similar and poor response to prenalterol in the three patients with chronic heart failure in this study may indicate that in ischaemic heart disease inotropic agents alone may produce little beneficial effect at rest. Direct inspection of the ventriculograms in these patients showed that in two patients the dyskinesia increased after prenalterol. Increased dyskinesia has been reported with inotropic agents, but it is of note that in this study isoprenaline did not increase dyskinesia. It is interesting to speculate that this too may be related to afterload reduction. Reduction in afterload by vasodilators combined with enhanced inotropic action on the myocardium, without the adverse tachycardias produced by isoprenaline, might provide a more satisfactory means of dealing with the problem of refractory heart failure.

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