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Effects of pirbuterol and sodium nitroprusside on pulmonary haemodynamics in hypoxic cor pulmonale

W MacNee, C G Wathen, W J Hannon, D C Flenley, A L Muir

Abstract

The acute haemodynamic effects of oral pirbuterol (a beta-agonist) were contrasted with those of sodium nitroprusside, a vasodilator, in six patients with hypoxic chronic bronchitis and emphysema. Sodium nitroprusside (1-5 mg/kg intravenously) reduced mean pulmonary arterial pressure and total pulmonary vascular resistance significantly (p < 0.01) without change in cardiac output or right ventricular ejection fraction, measured by radionuclide ventriculography. Oral pirbuterol (22.5 mg) produced a greater reduction in total pulmonary vascular resistance than sodium nitroprusside, largely as a result of increasing cardiac output. Right ventricular ejection fraction also increased significantly after pirbuterol (p < 0.01). Pirbuterol in a lower dosage (15 mg by mouth) in six further patients with hypoxic chronic bronchitis and emphysema produced similar changes in total pulmonary vascular resistance and right ventricular ejection fraction. Nine of the patients who were studied acutely thereafter received pirbuterol 15 mg thrice daily for six weeks, which produced a significant fall in systolic pulmonary arterial pressure and a rise in right ventricular ejection fraction (p < 0.01), without a significant fall in arterial oxygen tension. Pirbuterol acts as a vasodilator on the pulmonary circulation in these patients and may in addition improve right ventricular performance by an inotropic action.

Introduction

The association between the arterial hypoxaemia of chronic lung diseases and the development of pulmonary hypertension is well known,1-4 the hypoxaemia producing pulmonary vasoconstriction by a mechanism as yet unknown. Although the pro-

References


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pulmonary artery pressure. The relation to measurements after assessed shown with those. The chronic effects of oral pirbuterol were assessed after six weeks' treatment with the drug. We combined radionuclide ventriculography with pulmonary haemodynamic measurements to obtain a detailed assessment of the effects of pirbuterol on right ventricular performance.

Patients and methods

We studied 12 patients (six men, six women) aged 42-72 with severe irreversible airflow obstruction as a result of chronic bronchitis and emphysema (forced expiratory volume in one second 0.65-2 (SD 0.2), forced vital capacity 1.75 (0.59)). All had hypoxaemia (arterial oxygen tension 7-28 (0.28) kPa (55 (2) mm Hg), and most had hypercapnia (arterial carbon dioxide tension 6-65 (0.80) kPa (50 (6) mm Hg)) with a compensated respiratory acidosis (hydrogen ion concentration 42 (4) mmol/l). All had peripheral oedema, indicating that they had had cor pulmonale at some time in the past, but all were in a stable state at the time of study as defined by a stable body weight, stable forced expiratory volume in one second, and the absence of acute respiratory infection or peripheral oedema for three weeks before study. Arterial blood gas tensions were also stable for this period.

ACUTE STUDIES

All patients were receiving inhaled beta2 sympathomimetics and ipratropium and also diuretics. One patient was receiving digoxin. To ensure a stable physical and haemodynamic state during the study no drugs were given on the morning of study, each patient's normal drug treatment being given on the preceding evening. The patients were studied while semisupine in bed in the afternoon after a light lunch; no premedication was given.

Haemodynamic measurements were made with the patient at rest; during infusion of sodium nitroprusside; and at intervals of 30 minutes for two hours after oral pirbuterol was given. Ten of the 12 patients received intravenous sodium nitroprusside in a dose of 1-5 mg/kg body weight, which reduced systemic arterial blood pressure by at least 10 mm Hg and mean pulmonary artery pressure by at least 5 mm Hg. When all of the haemodynamic variables had returned to control values pirbuterol was given by mouth in a dose of 22-5 mg (six patients) or 15 mg (six patients).

CHRONIC STUDIES

Nine of the 12 patients who were studied acutely also then received oral pirbuterol 15 mg three times a day in addition to their usual drugs for six weeks, at which time pulmonary artery pressure and right and left ventricular ejection fractions were measured. Three patients did not complete this study: two developed an arrhythmia possibly associated with pirbuterol, and one had an intercurrent infective exacerbation of bronchitis at the time at which the six week study was planned.

MEASUREMENTS

Arterial blood gas tensions when the patients breathed air were measured during the control period, 90 minutes after pirbuterol was given, and after six weeks' treatment. Ear oxygen saturation was measured continuously during the acute study with a Hewlett-Packard (47201A) ear oximeter. Heart rate was measured from the electrocardiograph, and systemic arterial blood pressure with a sphygmomanometer. Right atrial, right ventricular, and pulmonary artery pressures were measured with a Swan-Ganz flow directed triple lumen catheter. Measurements were averaged over five respiratory cycles. All intracardiac pressures were referenced to a point 5 cm below the sternal angle. Cardiac output was measured in triplicate by thermodilution. As left atrial pressure is not always easy to assess from pulmonary artery wedge pressure in these patients total pulmonary vascular resistance was calculated by the formula:

\[
\text{Total pulmonary vascular resistance (kPa s/cm}^2\text{)=} \frac{\text{pulmonary artery pressure (mm Hg)}}{\text{cardiac output (l)}} \times 8
\]

Right and left ventricular ejection fractions were measured by a modified gated equilibrium blood pool radionuclide technique. Briefly, after intravenous injection and equilibration in the blood pool of human serum albumin labelled with 750 MBq technetium-99m imaging is carried out in a 20° left anterior oblique position with a 10° caudal tilt. Left ventricular ejection fraction is calculated in the normal manner, but for the right ventricle separate regions of interest at end systole and end diastole must be identified. This is accomplished by a combination of inspection of the ventriculogram, an edge detection programme, and a Fourier based phase analysis. The method gives values close to those obtained with the "single pass" technique, with lower interobserver and intraobserver variation, and, moreover, allows multiple ventriculograms to be obtained under different physiological and pharmacological conditions.

End diastolic volumes were calculated from the following equations:

\[
\text{Stroke volume} = \frac{\text{cardiac output}}{\text{heart rate}}
\]

Ejection fraction = \frac{\text{end diastolic volume} - \text{end systolic volume}}{\text{end diastolic volume}}

Twelve minute walking distance was measured in seven patients before and after six weeks of treatment with oral pirbuterol. In 10 patients pirbuterol concentrations were assayed in venous plasma one and two hours after the drug was given. Values are expressed as means (SEM). Differences between means were compared with a paired t test or with analysis of variance when repeated measurements were made.

Results

ACUTE STUDY

The maximum effects of pirbuterol occurred 90 minutes after the drug was given, and therefore we quote only these results. In the six patients who received 22-5 mg pirbuterol neither sodium nitroprusside nor pirbuterol significantly changed ear oxygen saturation or arterial oxygen and carbon dioxide tensions (table 1). Systemic arterial blood pressure fell with sodium nitroprusside but was unaltered by pirbuterol. Both drugs produced a small increase in heart rate of an average of five beats/min. Sodium nitroprusside also reduced pulmonary arterial pressure, by 23%, but had no significant effect on cardiac output, whereas pirbuterol reduced pulmonary artery pressure by 13% and increased cardiac output by 21%, and stroke volume by 9%. Sodium nitroprusside and pirbuterol both reduced pulmonary vascular resistance, but this was more noticeable with pirbuterol (table 1). Both drugs reduced systemic vascular resistance by a similar amount. Left ventricular ejection fraction rose with both sodium nitroprusside and pirbuterol, but this increase was not significant after pirbuterol. The greater increase in left ventricular ejection fraction with sodium nitroprusside was associated with a reduction in left ventricular end diastolic volume. In contrast, sodium nitroprusside did not significantly change right ventricular ejection fraction, whereas this rose with pirbuterol.

In the six patients given 15 mg pirbuterol the effects on arterial blood gas tensions and haemodynamics were similar to those produced
by the higher dose of the drug, although the changes in pulmonary artery pressure were no longer significant (table II). Two patients were not given intravenous sodium nitroprusside during the acute study; this did not alter the effects of oral pirbuterol given subsequently.

Pulmonary arterial pressure was given in 10 patients with pulmonary hypertension as a result of severe hypoxic chronic bronchitis and emphysema. This effect was sustained after six weeks of oral treatment with pirbuterol. Moreover, cardiac output and right ventricular ejection fraction increased in all patients, with both 15 and 22.5 mg pirbuterol. Cardiac output rose principally as stroke volume increased. Pulmonary vascular resistance fell, this reduction being greater than with the vasodilator sodium nitroprusside. Pulmonary vasodilatation was induced by pirbuterol with no change in systemic blood pressure.

Pirbuterol increases cardiac output in patients with severe congestive cardiac failure, but these effects, as in our study, are not well correlated with plasma concentration. In our study the maximum effects of pirbuterol occurred at 90 minutes.

Debate continues over whether the mechanism of these haemodynamic effects of pirbuterol is inotropic or simply secondary to the vasodilator properties. In this study vasodilatation by sodium nitroprusside produced a fall in pulmonary artery pressure but no change in cardiac output, whereas pirbuterol produced a fall in pulmonary artery pressure and an increase in cardiac output. Arguably, sodium nitroprusside is not the ideal vasodilator to be contrasted with pirbuterol because of its combined arterial and venous effects. The comparison may, however, be valid as pirbuterol is also thought to have venodilator properties. Assessment of contractility in man is difficult. Ventricular ejection fractions and other variables of the ejection phase are influenced by alterations in the loading conditions of the ventricles, and in particular by changes in the afterload. Sagawa et al suggested that the relation of the end systolic pressure to the end systolic volume is not influenced by the loading conditions of the ventricle but is

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sensitive to inotropic interventions.\textsuperscript{25} We drew idealised loops of right ventricular pressure and volume when the pressure changes were greatest for the six patients given 22.5 mg pirbuterol (figure). The pressure and volumes at end systole and end diastole were measured; others were not. Sodium nitroprusside displaces the end systolic pressure volume point downward. If pirbuterol was acting only as a vasodilator the relation between the two variables would fall on the same line, but after pirbuterol this point is displaced leftwards, implying that pirbuterol has an additional inotropic action.

The beta agonist terbutaline usually has effects on pulmonary artery pressure, cardiac output, and pulmonary vascular resist-

ance similar to those of pirbuterol,\textsuperscript{22} at least when given either intravenously\textsuperscript{26} or subcutaneously,\textsuperscript{27} but the effects of oral dosing are unknown.

As pirbuterol produced only modest reductions in pulmonary artery pressure, the fall in pulmonary vascular resistance was largely due to an increase in cardiac output, which occurred in all patients. However, no significant further fall in arterial oxygen saturation occurred in these patients as a result of the haemodynamic effects of pirbuterol. This is in contrast to results of previous studies in patients with acute bronchial asthma, in which both aminophylline\textsuperscript{28} and non-selective adrenergic agents\textsuperscript{29} reduced arterial oxygen saturation despite improving airway resistance. A recent study, however, showed that the beta\textsubscript{2} agonist terbutaline when given intravenously did not change venous admixture or arterial oxygen tension in patients with chronic bronchitis and emphysema.

The reductions in pulmonary artery pressure produced by acute administration of pirbuterol were sustained after six weeks' oral treatment. Side effects of pirbuterol were few, but multiple ventricular ectopic beats occurred in one patient during the acute study after 22.5 mg pirbuterol, and atrial fibrillation occurred in another patient during the chronic study. Both had had frequent ventricular and supraventricular ectopic beats before starting the drug. Five further patients showed no increase in the number of ectopic beats during 24 hour ambulatory cardiac monitoring during the chronic study. We suggest, however, that pirbuterol is contraindicated in patients with frequent ectopic beats, as has been recommended by others.\textsuperscript{19}

These initial results in a group of severely disabled patients suggest that pirbuterol may be valuable in patients with the "blue and bloated" syndrome of chronic bronchitis and emphysema because it vasodilates the pulmonary circulation, so improving right ventricular performance and thus systemic oxygen delivery, and does not aggravate hypoxaemia. Whether these haemodynamic benefits, if produced by pirbuterol over the long term, will improve the grave outlook for such patients remains to be determined, as also does the role of pirbuterol given in addition to long term continuous oxygen treatment in such patients.\textsuperscript{21}

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\textbf{References}


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