EFFECTS OF ORAL SALBUTAMOL AND PIRBUTEROL ON FEV₁, HEART RATE AND BLOOD PRESSURE IN ASTHMATICS

*R.F. WILLEY & I.W.B. GRANT

Respiratory Diseases Unit, Northern General Hospital
and Department of Respiratory Diseases, University of Edinburgh,
Edinburgh EH5 2DQ

S.J. POCKOCK

Medical Computing and Statistics Group,
University of Edinburgh, Edinburgh

- 1 In a double-blind trial the effects on ventilatory function (FEV₁), heart rate and blood pressure of oral pirbuterol and oral salbutamol in various single doses were studied in ten patients with chronic asthma.
- 2 Pirbuterol (15 mg) and salbutamol (4 mg) produced equal peak levels of bronchodilatation.
- 3 There was no significant difference in the mean rise in heart rates caused by the two drugs, and no other significant side-effects were noted.

Introduction

Pirbuterol is 2-hydroxymethyl-3 hydroxy-6 (1-hydroxy - terthutylamino - ethyl) pyridine dihydrochloride. Its chemical structure and those of salbutamol and isoprenaline are shown in Figure 1.

The pharmacology of pirbuterol has been extensively investigated by the manufacturers (Pfizer Limited) who have provided the following information. Preliminary animal studies using the guinea pig histamine aerosol test as described by Van Arman, Miller & O'Malley (1961) showed no difference in potency with respect to bronchodilator capability between salbutamol and pirbuterol. Using isolated right atrial preparations, however, pirbuterol was found to have a much less marked chronotropic effect than salbutamol, indicating that pirbuterol is more selective for β_2 -adrenergic receptors than is salbutamol. Furthermore studies in healthy human volunteers showed no dose-related changes in pulse rate or blood pressure with doses of up to 10 mg pirbuterol twice daily.

This study was designed (1) to establish dose-response curves for the bronchodilator effects of the two drugs in patients with chronic asthma, (2) to determine the lowest single dose of each drug which will produce close to maximum bronchodilatation, (3) to compare their cardiac stimulant effects and (4) to determine the effects of the drugs on haematological, renal and hepatic function.

* Present address: Department of Medicine, Western General Hospital, Edinburgh.

Methods

Patients received on 10 consecutive days capsules containing 5 mg (P₁), 7.5 mg (P₂), 10 mg (P₃), 15 mg (P₄) or 20 mg (P₅) of pirbuterol or 2 mg (S₁), 4 mg (S₂), 6 mg (S₃) or 8 mg (S₄) of salbutamol or a placebo. The sequence of drug administration was determined by a Latin square experimental design. On each day the patient was given four green capsules containing one of the different dosage regimens, so that the identity of the drug and its dosage were unknown to the patient and medical observers. The highest of three recordings of forced expiratory volume in one second (FEV₁) from a Gaensler spirometer was recorded at 10 min, 5 min and 1 min before treatment and at 30, 60, 90, 120, 180, 210, 240, 300 and 360 min after treatment. The heart rate was read from a Hewlett-Packard cardiac monitor at the same times. The blood pressure was recorded with a mercury column sphygmomanometer 5 min before treatment and at hourly intervals after treatment, unless the pulse rate rose by more than 10 beats/min, when recordings were made every half-hour. Samples of venous blood were taken 15 min before treatment on day 1, and 3 h after administration of the capsules on day 10. Analysis of these samples was performed for haemoglobin, white cell count and differential count, urea, electrolytes, bilirubin alkaline phosphatase and SGOT. Urinalysis for specific gravity, pH, glucose, white and red blood cells, protein and casts was also performed on day 1 and day 10.

Figure 1 Chemical structures of (a) pirbuterol, (b) salbutamol and (c) isoprenaline.

Patients were instructed not to take any bronchodilator drugs after 22.00 h on the day prior to each test day, and to avoid any fatty foods on the morning of each test day.

Patient selection

Ten patients (nine men and one woman) were studied. Their ages ranged from 49–71 years (mean 62 years). All had chronic asthma. Four patients were receiving treatment with oral prednisolone and beclomethasone dipropionate by inhalation, two with beclomethasone alone, one with prednisolone alone and three with bronchodilator drugs only. The mean daily dose of prednisolone for the five patients taking this drug was 7 mg (range 2–15 mg). The dose of beclomethasone in every patient receiving this drug was 400 µg daily. The daily doses of prednisolone and beclomethasone were kept constant for at least 5 days before the start of tests and for all of the 10 test days.

All patients on admission to the study had an FEV₁ of at least 25% below the highest figure recorded in the previous 12 months. That they could still attain their maximum figure was confirmed by recording the FEV₁ following salbutamol (0.5% solution) administered by IPPV via a Bennett respirator. The mean pre-treatment FEV₁ was 1.01 litres (range 0.55 to 1.7 litres). If the pre-treatment FEV₁ on any of the 10 days differed by more than 10% from the baseline FEV₁, then that day was not used as a test day to ensure that the pre-treatment FEV₁ values were relatively constant.

Figure 2 Changes in mean FEV₁ in relation to dose of (a) salbutamol (● 2 mg; □ 4 mg; ■ 6 mg; △ 8 mg) and (b) pirbuterol (● 5 mg; □ 7.5 mg; ■ 10 mg; △ 15 mg; ▲ 20 mg). ○ placebo.

Results

FEV₁

Figure 2 shows the trends in mean FEV₁ on each of the ten treatments for a period of 6 h after the capsules were taken. The mean FEV₁ at time zero is based on the three readings for each of the ten patients taken 10, 5 and 1 min prior to administration of the capsules (i.e. a mean of thirty pre-treatment values), whereas the mean FEV₁ at each subsequent time is based on ten values, one from each patient.

The mean FEV₁ increased following all treatments. With most treatments the FEV₁ reached a peak value after 2 h and then steadily

Figure 3 Changes in mean FEV₁ at 2 h for all doses of (a) salbutamol and (b) pirbuterol.

declined. After 6 h, however, the mean FEV₁ for all treatments including placebo remained above the baseline FEV₁. The overall mean rise in FEV₁ after 6 h was 0.15 litre and there were no significant differences between the values for each treatment at this time. Significant differences were

Figure 4 Changes in mean heart rate in relation to dose of (a) salbutamol (● 2 mg; □ 4 mg; ■ 6 mg; △ 8 mg) and (b) pirbuterol (● 5 mg; □ 7.5 mg; ■ 10 mg; △ 15 mg; ▲ 20 mg). ○ placebo.

still detectable up to 5 h after the start of treatment with P₃, P₄, P₅ and S₂, S₃, S₄ all still markedly better than placebo. At 4 h the improvement in FEV₁ was best sustained with treatments P₄, P₅ and S₄.

Figure 3 shows dose-response curves at 2 hours. The placebo produced a mean FEV₁ rise of 0.09 litre which is of marginal significance ($P < 0.1$) so that the true effectiveness of each treatment is best assessed by comparing it with placebo. All treatments except P₁ and P₂ did significantly better than placebo ($P < 0.01$ for S₁ and P₃, $P < 0.001$ for S₂, S₃, S₄, P₄ and P₅).

For both salbutamol and pirbuterol the dose-response curves show a fairly orderly rise from placebo to S₄ and P₅ respectively. In the case of salbutamol, there is a large significant rise from placebo through to S₂ after which the curve appears to plateau with no significant differences between S₂, S₃ and S₄. The difference between S₂ and S₄ was of no significance. This suggests that

Figure 5 Changes in mean heart rate at 2 h for all doses of (a) salbutamol and (b) pirbuterol.

the mean change in FEV_1 following S_2 may be fairly close to the maximum for salbutamol.

In the case of pirbuterol there was a steady rise in FEV_1 up to P_4 followed by a much smaller difference between P_4 and P_5 . Both these higher doses were significantly better than P_1 and P_2 ($P < 0.01$ in all cases) and marginally better than P_3 . Thus, it would appear that P_4 may be the lowest dose of pirbuterol producing near maximal change in FEV_1 .

The mean values plotted in Figures 1 and 2 tend to hide the substantial variation between patients. The mean rise in FEV_1 after 2 h for each patient ranged from 0.14 litre to 0.65 litre, these differences between patients being significant ($P < 0.01$). The order in which treatments were given did not significantly affect the changes in FEV_1 .

Heart rate

Figure 4 shows the mean heart rate on each treatment for the 6 h after capsules were taken.

The higher doses of each drug (i.e. S_2 , S_3 , S_4 , P_4 and P_5) produced an elevation in heart rate

which reached a peak after 2 hours. This mean change in heart rate is plotted in Figure 5. For the five higher doses the mean heart rate was significantly elevated as compared with placebo ($P < 0.1$ for S_3 , $P < 0.05$ for S_2 and P_5 , $P < 0.01$ for S_4 and P_4).

The numbers of patients with any elevation in heart rate after 2 h were:

Placebo	S_1	S_2	S_3	S_4	P_1	P_2	P_3	P_4	P_5
2	3	5	7	8	2	7	5	6	7

The numbers of patients with elevation greater than 10 beats/min were:

Placebo	S_1	S_2	S_3	S_4	P_1	P_2	P_3	P_4	P_5
0	0	3	2	5	1	1	1	2	2

For all five treatments with significantly elevated heart rates at 2 h, there was a subsequent drop to near baseline counts after 3 h, at which time there was no significant difference between treatments. From 4–6 h after treatment there is a secondary rise in heart rates, all five treatments (S_2 – S_4 and P_4 , P_5) showing a significant rise in mean heart rate as compared with placebo at 5 and 6 hours.

As for FEV_1 there were significant differences ($P < 0.05$) between patients in mean changes in heart rate at 2 h, with mean changes ranging from -6.7 to $+7.3$ beats/minute.

Blood pressure

Systolic blood pressure (Figure 6) fell slightly during treatment, the overall mean (based on all 100 treatment runs) falling from 135.6 mmHg initially to 129.2 mmHg after 3 hours. However, there is no evidence of any difference between treatments. A similar pattern of results was obtained for diastolic blood pressure.

Side-effects

Eight patients on a total of twenty occasions complained of symptoms which they attributed to treatment. In every case symptoms were minimal or slight and no patient had to be withdrawn from the study because of side-effects. These subjective observations and the associated treatments are recorded in Table 1.

From laboratory investigations on blood samples taken during the study, no adverse reaction on haematological, renal or hepatic functions was observed following treatment.

The first patient entered into the trial failed to respond on any of the 10 treatment days, and in fact his FEV_1 fell well below the initial baseline value on several occasions. As no other patient had

Figure 6 Changes in mean systolic blood pressure in relation to dose of (a) salbutamol (● 2 mg; □ 4 mg; ■ 6 mg; △ 8 mg) and (b) pirbuterol (● 5 mg; □ 7.5 mg; ■ 10 mg; △ 15 mg; ▲ 20 mg). ○ placebo.

received treatment at this stage and as this was such an unexpected occurrence in a patient who had previously without exception on many occasions improved dramatically following inhalation treatment with salbutamol, there were initial doubts about the activity of the preparations. When the investigations were repeated in the same patient at a later date and under the same double-blind conditions, improvement occurred on

several of the test days. As this represented the more expected result and the trial remained double-blind at that stage, the overall results of the trial are based on the second set of recordings. An analysis was, however, performed using the initial set of recordings for patient 1, and this analysis did not differ significantly from that reported in the text.

Discussion

In this study 15 mg was the lowest dose of pirbuterol which produced near-maximum bronchodilatation after 2 h, 20 mg producing no significantly greater effect. Similarly 4 mg was the smallest dose of salbutamol which produced near-maximum bronchodilatation after the same time interval. However, there is a suggestion that bronchodilatation was sustained for a longer period with the higher doses of both drugs. There was, however, no significant difference between pirbuterol and salbutamol in respect of duration of bronchodilatation produced by these higher doses.

In two uncontrolled studies Steen, Ziment & Thomas (1974a, b) found that pirbuterol was an effective oral bronchodilator producing in a dose of 10 mg (the maximum given) significant increases in specific airway conductance, reaching a peak between 2 and 3 hours.

The rises in heart rate produced by pirbuterol (15 mg) and salbutamol (4 mg) were not significantly different. At 2 h the mean rise in heart rate was 6.6 beats/min for pirbuterol (15 mg) and 5.7 beats/min for salbutamol (4 mg). The reason for the secondary rise in heart rate observed from 4–6 h following treatment remains uncertain. The 4 h recordings were, on most occasions, taken shortly after the patient had finished eating lunch, the only activity that did not occur prior to the preceding recordings, but the secondary rise in

Table 1 Symptoms occurring during period of survey

Symptom	Number of times reported	Dose of drug
Drowsiness	6	S ₁ S ₂ S ₃ S ₄ P ₁ P ₄
Tremor	5	S ₃ S ₄ S ₅ P ₄ P ₅ P ₆
Tremor + agitation	3	S ₂ P ₃ P ₄
Light-headedness	2	P ₁ P ₅
Headache	1	P ₄
Diarrhoea	1	S ₃
Dizziness	1	P ₂
Chest tightness	1	Placebo

heart rate was not observed on days of treatment with placebo or lower doses of active drugs.

The incidence of side-effects was surprisingly low. Previous investigations in this Unit (Parker, Choo-Kang, Cooper, Cameron & Grant, 1971) have shown a high incidence of tremor following administration of oral salbutamol. This side-effect occurred in seven of twelve patients receiving salbutamol (2 mg four times daily) and in eight of twelve patients receiving salbutamol (4 mg four times daily). One patient had to stop treatment because of tremor. Legge, Gaddie & Palmer (1971) also observed tremor in five of twelve patients receiving salbutamol (5 mg). In this survey, however, despite administration of larger single doses of salbutamol than in the two previous studies, only three patients complained of slight tremor, one after salbutamol (6 mg), the second after salbutamol (8 mg) and pirbuterol (20 mg), and the third after salbutamol (4 mg and 6 mg) and pirbuterol (10, 15 and 20 mg). The low incidence of this side-effect may have been due to tolerance since all ten patients had been receiving salbutamol by inhaler for several years, as well as

having had frequent exposure to larger doses of the same drug by IPPV. Since the chemical structures of salbutamol and pirbuterol are very similar, previous use of salbutamol may have also induced tolerance to the side-effects of pirbuterol.

It would appear from this study that pirbuterol is an effective bronchodilator with no significant side-effects when given in single doses of up to 20 mg. The minimum effective dose of pirbuterol is 15 mg and this has bronchodilator activity equivalent to salbutamol (4 mg). Whether effective bronchodilatation can be maintained by pirbuterol for prolonged periods is not known and a further, long-term, study is now in progress. If it can be shown to have a sustained action, then pirbuterol may be acceptable as another effective β_2 -adreno-receptor selective bronchodilator drug.

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