The Bronchodilator Effect of Salbutamol Administered by IPPB to Patients with Asthma

A Controlled Comparison with Isoproterenol and Placebo

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Salbutamol, a new beta adrenergic receptor stimulant, is widely used in Western Europe in the form of pressurized inhalant and orally administered tablets in the management of chronic asthma.

Salbutamol, which combines a selective and potent action on the bronchial beta receptors with minimal cardiovascular stimulation, would appear suitable for aerosolization in nebulizers powered by compressed air, oxygen, handblows, electrical compressors and IPPB machines.

This study compares the bronchodilator and cardiovascular activity of Salbutamol, isoproterenol (Isuprel) and a placebo (saline) in solution form administrated by IPPB.

PLAN OF TRIAL

The study was designed in three parts. In the first part, Salbutamol 5 mg and isoproterenol 5 mg were administered by inhalation on two consecutive days respectively to ten asthmatic patients. In the second part, 2.5 mg of Salbutamol only was administered by inhalation to ten asthmatic patients and in the third part, 1 ml of saline was similarly administered to ten asthmatic patients.

Basal measurements of forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were made after a resting period of 15 to 20 minutes at least. Heart rate and blood pressure were recorded with the patient in the relaxed seated position. Heart rate, blood pressure, FEV₁, and FVC were measured 5, 10, 30, 60, 120, 180 and 360 minutes after aerosol inhalation. In the placebo group, these were measured up to 60 minutes only. Any side-effects noted were recorded.

DRUGS AND MODE OF ADMINISTRATION

Salbutamol and isoproterenol were freshly prepared as a 0.5 percent solution and kept in dark bottles. The order of administration was randomized and neither the technician nor the patients knew the order of administration. Group I received 1 ml of each solution. Group II received 0.5 ml of the Salbutamol solution diluted with 0.5 ml of normal saline while group III received 1 ml of normal saline. The drugs were totally nebulized and delivered during a period of five minutes in 40 percent oxygen by IPPB from a Bennett ventilator. The drugs were nebulized during each inspiratory cycle and delivered directly to the patient's mouthpiece. Since all solutions were administered in equal quantities, the amount of aerosol wasted was identical in all patients. The above mentioned doses of drug administered represent, therefore, the upper limit of the dose. The purpose of the study was explained to the patients of group I who were requested to express their preference for one of the two drugs.

MATERIAL (Table 1)

Thirty consecutive patients from the pulmonary outpatient clinic suffering from chronic asthma, with proved reversible airway obstruction were selected. They were divided into three groups.

Group I consisted of ten patients, seven men and three

273
women, aged 25 to 59 years (mean 40.1 years). Six patients were receiving long-term daily corticosteroid therapy while four were on bronchodilator drugs only. Group II consisted of ten patients: six men and four women, aged 23 to 59 years (mean 43 years). Four patients were on long-term daily corticosteroid therapy and six on bronchodilator drugs only. Group III consisted of ten patients: seven men and three women, aged 24 to 62 years (mean 53.7 years). Five patients were receiving long-term daily corticosteroid therapy and five bronchodilator drugs only. The initial FEV 1, percent, FVC percent, heart rate and blood pressure values of all three groups are illustrated in Table 1.

MEASUREMENTS AND ANALYSIS OF RESULTS
Forced expiratory spiograms were recorded on a Vitalograph (Vitalograph Limited, Buckingham, England). The spirometry was performed on each occasion in triplicate and the best of the three was chosen for analysis. These were analyzed for forced expiratory volume in 1 second as percent of predicted FEV 1, (FVC; percent) and forced vital capacity in percent of predicted FVC (FVC percent). Heart rate and blood pressure were recorded on each occasion.

The difference between the pretreatment and after-treatment values of FEV 1, percent and FVC percent as well as in heart rate and blood pressure were plotted against time. The mean and standard deviation of the absolute values and the percent change were calculated and the Student's t test used to ascertain their significance.

RESULTS
Group I
a) Salbutamol, 5 mg
The mean initial FEV 1, percent and FVC percent values were 34.0 percent and 57.0 percent respectively. These increased significantly (P < 0.001) within five minutes of administration and reached a peak value of 64 percent and 100 percent respectively at 30 minutes. There was a net peak mean increase in FEV 1, percent and FVC percent of 30 percent and 43 percent respectively. The mean increase at 240 minutes was still 11 percent and 21

Table 1—Details of the Three Groups: Age, Sex, Steroid Therapy and Initial Mean FEV 1, Percent, FVC Percent, Heart Rate and Blood Pressure.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age Range</th>
<th>Sex</th>
<th>Steroids</th>
<th>Initial FEV 1, Percent Mean &amp; SD</th>
<th>Initial FVC Percent Mean &amp; SD</th>
<th>Initial Heart Rate Mean &amp; SD</th>
<th>Initial Systolic Blood Pressure &amp; SD</th>
<th>Initial Diastolic Blood Pressure &amp; SD</th>
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<tbody>
<tr>
<td>Group I</td>
<td>10</td>
<td>25-59</td>
<td>m=7</td>
<td></td>
<td>34.0 ± 15.3</td>
<td>57 ± 20.3</td>
<td>89.6 ± 11.2</td>
<td>111.5 ± 12</td>
<td>70.5 ± 9.3</td>
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<td></td>
<td></td>
<td>(40.1)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Group II</td>
<td>10</td>
<td>24-59</td>
<td>m=6</td>
<td></td>
<td>32.0 ± 15.9</td>
<td>61 ± 22.5</td>
<td>91.2 ± 14.2</td>
<td>117.5 ± 8.2</td>
<td>73.5 ± 9.1</td>
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<tr>
<td></td>
<td></td>
<td>(43)</td>
<td></td>
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</tr>
<tr>
<td>Group III</td>
<td>10</td>
<td>24-62</td>
<td>m=7</td>
<td></td>
<td>43 ± 19.5</td>
<td>68 ± 23.3</td>
<td>93.2 ± 17</td>
<td>121 ± 14.5</td>
<td>78.5 ± 9.7</td>
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<tr>
<td></td>
<td></td>
<td>(33.7)</td>
<td></td>
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<tr>
<td>Placebo</td>
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<td></td>
<td>37.1 ± 17.5</td>
<td>78.7 ± 14.3</td>
<td>90.6 ± 11.4</td>
<td>118.5 ± 8.8</td>
<td>83.5 ± 4.1</td>
</tr>
</tbody>
</table>

FIGURE 1. Mean changes in FEV 1, percent after inhalation of Salbutamol 5.0 and 2.5 mg, isoproterenol 5.0 mg and placebo. For explanation, see text.

FIGURE 2. Mean changes in FVC percent after inhalation of Salbutamol 5.0 and 2.5 mg, isoproterenol 5.0 mg and placebo. For explanation, see text.

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percent respectively higher (P<0.01) than the initial values (Fig 3).
Following administration of the aerosol the mean heart rate diminished gradually through the first hour and remained significantly lower throughout the four hour period (Fig 3). No change was noted in systolic, diastolic or pulse pressure (Fig 4). Four patients manifested side-effects in the form of mild tremor (2) and headache (2).

b) Isopropenol, 5 mg
The mean initial FEV₁ percent and FVC percent were 33 percent and 61 percent respectively. These increased significantly (P<0.001) within five minutes and reached a peak value of 63 percent and 98 percent respectively within the first ten minutes of administration. There was a net peak mean increase in FEV₁ percent and FVC percent of 30 percent and 37 percent respectively. These measurements declined rapidly and reached approximately the initial value by 180 minutes (Fig 1 and 2). However, in two patients the FEV₁ percent and in six patients the FVC percent values were significantly below the initial values at 240 minutes. The mean heart rate increased significantly during the first ten minutes and then diminished gradually to below initial values at 60 minutes (Fig 3). No significant change in systolic and diastolic pressures was observed; however, a slight increase in pulse pressure was noted in this group (Fig 4). Six patients manifested one or more side-effects consisting of palpitations (four), headaches (two), tremor (two) and dizziness (one).

Group II
Salbutamol, 2.5 mg
The mean FEV₁ percent and FVC percent were 43 percent and 68 percent respectively. These increased significantly (P<0.01) within five minutes and reached a peak value of 63 percent and 98 percent at 60 minutes respectively. There was a net peak mean increase in FEV₁ percent and FVC percent of 30 percent and 30 percent respectively (Fig 1 and 2). The mean increase at 240 minutes was still 12 percent and 16 percent higher respectively than the initial value (p<0.01) (Fig 1, 2).
The mean heart rate, systolic, diastolic and pulse pressure behaved similarly to those in the 5 mg Salbutamol group (Fig 3 and 4).

Group III
Placebo group
No significant change in FEV₁ percent, FVC percent, heart rate, systolic, diastolic and pulse
pressure were observed through the 60 minutes following the administration of saline by IPPB.

Comparison of Groups

1. Salbutamol 5.0 mg vs isoproterenol 5.0 mg.

The mean percent increase in FEV₁ percent and FVC percent was initially similar in both groups. The decline in both parameters in the isoproterenol group occurred rapidly after ten minutes, while in the Salbutamol group the increase in these parameters was maintained up to 120 minutes. This difference was significant (P<0.05) from 60 minutes after the mediation was given (Fig 1 and 2). The heart rate in the isoproterenol group was significantly higher than in the Salbutamol group for the first ten minutes (P<0.05) (Fig 3). There were no significant differences in blood pressure (Fig 4).

2. Salbutamol 2.5 mg vs isoproterenol 5.0 mg.

The mean percent increase in FEV₁ percent was initially greater in the isoproterenol group. However the increase was more prolonged in the Salbutamol group and from 180 minutes, the difference was significant (P<0.05) (Fig 1). The mean percent increase in FVC percent was greater in the isoproterenol group up to 60 minutes. From then, a significant difference (P<0.05) in the two groups, in favor of Salbutamol, was noted (Fig 2). The differences in heart rate were similar to those described previously.

3. Salbutamol 5.0 mg vs Salbutamol 2.5 mg.

The mean percent increase in FEV₁ percent and FVC percent was significantly greater up to the 60 minutes point in the 5.0 mg Salbutamol group. From then on the decline in the 5 mg group was steeper and the difference between the two became insignificant (Fig 1 and 2). No difference in heart rate and blood pressure was noted between the two groups.

Patients' Preference

Nine out of ten patients in group I preferred Salbutamol over isoproterenol. The reasons given by the patients for this preference were: lack of palpitations and longer lasting relief. One patient did not prefer either drug.

Discussion

It has been shown that the responses of patients receiving 5 mg isoproterenol and 5 mg Salbutamol are equal in respect to peak bronchodilating effect but the peak effect was reached much earlier with isoproterenol. Salbutamol has, however, the distinct advantage over isoproterenol in its longer and more persistent bronchodilator activity, without having the rebound bronchoconstriction seen following the subsidence of the isoproterenol effect.

Isoproterenol had a significant initial effect on heart rate which lasted approximately 30 minutes while Salbutamol at this dose did not cause an increase in heart rate. Rather a decrease in heart rate followed the point when peak bronchodilating effect was observed. No significant effect on blood pressure of either was noted.

The side-effects following inhalation of each of the drugs were similar except for the prominence of palpitation after isoproterenol.

From the comparison of the two Salbutamol doses it was concluded that the 5 mg dose was more effective in respect to peak bronchodilating effect and total effect during the first one to two hours. Thereafter, no advantage in the higher dose was noted. The side-effects noted with the 5 mg Salbutamol dose (tremor and headache) were not observed with the 2.5 mg dose. No cardiovascular activity was noted with the doses administered in this trial.

It can be concluded that Salbutamol, administered in the form of an aerosol, is an effective beta-adrenergic stimulant with potent and long persistent bronchodilating activity. The response to isoproterenol was more rapid. The response to Salbutamol, though less rapid in action, demonstrated more persistent effects. Salbutamol can be used with great advantage in the form of an aerosol administered by a powered nebulizer or IPPB in patients with asthma, at a dose of 2.5 to 5.0 mgm. It can be used freely in most patients where isoproterenol must be used with caution (heart disease, hypertension, etc.).

In testing the bronchodilator responsiveness of patients in the pulmonary function laboratory, it has to be remembered that the peak bronchodilating effect of Salbutamol is reached at 30 minutes.

References


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