Bronchiodilator and Cardiac Effects of Isoprenaline, Orciprenaline, and Salbutamol Aerosols in Asthma

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Milner, A. D., and Ingram, D. (1971). Archives of Disease in Childhood, 46, 502. Bronchodilator and cardiac effects of isoprenaline, orciprenaline, and salbutamol aerosols in asthma. The bronchodilator and cardiac effects of 0.5% isoprenaline, 2.5% orciprenaline, and 0.5% salbutamol, and a placebo solution inhaled as a nebulized mist from a Wright nebulizer were compared with the help of 12 asthmatic children. All three active drugs produced similar relief of bronchoconstriction, but salbutamol was followed by only a 13% increase in heart rate compared with 26% after orciprenaline and 29% after isoprenaline, and only a 9% increase in systolic blood pressure compared to 13% after orciprenaline and 15% after isoprenaline.

For many years nebulized isoprenaline solutions have proved useful in the treatment of asthmatic children admitted with severe bronchoconstriction. Their use gives the child some relief from his symptoms but almost always is accompanied by tachycardia, and may actually cause a fall in arterial Po2 by augmenting ventilation/perfusion mismatch (Palmer and Diament, 1967).

Three bronchodilators—isoprenaline, orciprenaline, and salbutamol—were investigated to see which produced most relief of bronchospasm with least cardiac disturbance.

Subjects

The 12 children (6 boys and 6 girls) all attended the asthma clinic of The Hospital for Sick Children. Their ages ranged from 10 years 6 months to 14 years 4 months, with a mean of 11 years 9.5 months. All the children had had symptoms of asthma for over 7 years, and 10 had been on steroids for at least 6 months at some time. At the time of the trial 3 were on steroids and 11 were on disodium cromoglycate, with or without isoprenaline (Intal co. and Intal). Six of the children were below the 3rd centile for height.

Procedure

Each child attended on four occasions. The visits tended to be at irregular intervals but each child was kept to a morning or afternoon session to reduce errors from fluctuations in airways resistance during the day (Lewinsohn, Capel, and Smart, 1960). The parent was asked not to give the child any bronchodilator or isoprenaline on the day of the test but steroids were not discontinued.

On arrival, lung function was assessed from measurements of the forced vital capacity (FVC) and the forced expiratory volume over 0.75 sec (FEV0.75) using a reverse plethysmograph. The FEV0.75 was measured rather than the FEV1.0 because some young healthy children are able to breathe out their FVC in 1 second (Lunn, 1965). The reverse plethysmograph consists of a rigid container, volume 1,500 litre (Fig. 1). The

REVERSE PLETHYSMOGRAPH SYSTEM

Pressure transducer

FIG. 1.—The reverse plethysmograph.
Bronchodilator and Cardiac Effects of Isoprenaline, Orciprenaline, and Salbutamol Aerosols 503

Fig. 2.— Mean values for vital capacity before and after inhalation of isoprenaline, orciprenaline, salbutamol, and placebo.

The child blows into the container which causes pressure changes in it of the order of 0·7 cmH₂O per litre of air expired. The changes are relayed to a fast hot wire Devices recorder by an Ether strain gauge transducer situated in the base of the tank. The system was calibrated against a 500 ml syringe on each occasion. The advantage of this system over wet and dry spirometers is that it has no moving parts and is, therefore, not liable to errors from inertial drag and overswing. The system will detect 10 ml volume changes and the standard error on repeated measurements of 500 ml volumes delivered by a glass syringe was 1·68 ml. The best of three attempts was selected on each occasion and these results are expressed at ambient temperature and pressure. The pulse rate was measured using a Devices ECG preamplifier and recorder. The systolic and diastolic blood pressures were measured using a sphygmomanometer.

The child then breathed from a face mask connected to a Wright nebulizer containing 1·5 ml active drug or placebo (distilled water). A compressed air cylinder provided a flow of 8 l/min to the nebulizer. The child continued to breathe from this system until the nebulizer ceased to produce a mist, usually after 2 to 3 minutes. Initial experiments had shown that at this stage approximately 1 ml solution had been nebulized, 0·5 ml remaining on the walls of the nebulizer. Lung function tests, pulse and blood pressure measurements were repeated at 5, 10, 15, 30, 45, 60, 90, 120, and 150 minutes after administration of the mist.

Statistical Analysis

The measurements of lung and heart function that were made after each treatment were used to assess four characteristics of the response. These are as follows:

I Peak effect, i.e. maximum effect minus basal value.
II Time to peak, i.e. number of minutes after dosing at which peak occurred.
III Total effect, i.e. area under the response-time curve above basal value.
IV Duration, i.e. duration of average effect.

Each of these aspects was examined by analysis of covariance to make allowance for the difference in basal value that were observed (Quenouille, 1953).

Drugs

The three bronchodilator drugs, 0·5% isoprenaline, 2·5% orciprenaline, and 0·5% salbutamol, and the placebo (distilled water) were prepared in individual vials and coded by random selection by Allen and Hanburys Ltd. Benzalkanion chloride, 0·01%, was added to all samples as a preservative. Each sample was identified by a number relating to the patient and a letter identifying the solution within. Thus, each child received each of the four solutions under double-blind control conditions.

Results

Bronchodilator effect of drugs. The mean results of the improvement in FVC and the FEV₀.₇₅ after inhalation of the three active drugs and placebo are shown in Figs. 2 and 3. There was response to all solutions including the placebo. The peak effects of the three active solutions were very similar and only the difference in peak vital capacity between salbutamol and the placebo was statistically significant (Tables I and II). In 10 of the 12 children, the FEV₀.₇₅ rose by more than 25% from control levels after inhalation of the placebo. There was no significant difference in the rate of rise or the duration of effect over the
period of the investigation as judged by the FVC, but the total effect of salbutamol, as measured by integration of the area under the curve, was significantly larger than the placebo.

2. Cardiac effects of drugs. All four solutions were followed by an increase in the pulse rate (Fig. 4). This was very small after the placebo (+3%) and relatively small after salbutamol (+13%) but was significantly larger after isoprenaline (+29%) than after salbutamol and placebo, and significantly larger after orciprenaline (+26%) than after the placebo (Table III). The tachycardia after salbutamol lasted significantly

TABLE I
Mean Changes in Forced Vital Capacity after Inhalation of Placebo, Isoprenaline, Orciprenaline, and Salbutamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basal Value (ml)</th>
<th>Peak (ml)*</th>
<th>Time to Peak (min)</th>
<th>Area (l. min)*</th>
<th>Duration (min)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1683</td>
<td>305</td>
<td>44</td>
<td>26</td>
<td>79</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>1881</td>
<td>433</td>
<td>32</td>
<td>45</td>
<td>73</td>
</tr>
<tr>
<td>Orciprenaline</td>
<td>1771</td>
<td>453</td>
<td>54</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>1837</td>
<td>464</td>
<td>57</td>
<td>50</td>
<td>73</td>
</tr>
<tr>
<td>Difference required for significance (P = 0.05)</td>
<td>149</td>
<td>38</td>
<td>22</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

*Significantly related to basal values, and adjusted accordingly.

TABLE II
Mean Changes in FEV_{0.75} after Inhalation of Placebo, Isoprenaline, Orciprenaline, and Salbutamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basal Value (ml)</th>
<th>Peak (ml)*</th>
<th>Time of Peak (min)</th>
<th>Area (l. min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>773</td>
<td>349</td>
<td>53</td>
<td>31</td>
<td>84</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>997</td>
<td>463</td>
<td>59</td>
<td>41</td>
<td>76</td>
</tr>
<tr>
<td>Orciprenaline</td>
<td>822</td>
<td>536</td>
<td>63</td>
<td>53</td>
<td>96</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>968</td>
<td>446</td>
<td>68</td>
<td>48</td>
<td>84</td>
</tr>
<tr>
<td>Difference required for significance (P = 0.05)</td>
<td>186</td>
<td>36</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

*Significantly related to basal values, and adjusted to allow for variation among the four mean basal values.
Bronchodilator and Cardiac Effects of Isoprenaline, Orciprenaline, and Salbutamol Aerosols

TABLE III
Mean Changes in Pulse after Inhalation of Placebo, Isoprenaline, Orciprenaline, and Salbutamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basal Value (beats/min)</th>
<th>Peak (beats/min)</th>
<th>Time to Peak (min)</th>
<th>Area (beats/min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>104</td>
<td>10</td>
<td>36</td>
<td>520</td>
<td>22</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>100</td>
<td>32</td>
<td>11</td>
<td>743</td>
<td>25</td>
</tr>
<tr>
<td>Orciprenaline</td>
<td>107</td>
<td>28</td>
<td>20</td>
<td>1427</td>
<td>42</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>101</td>
<td>17</td>
<td>20</td>
<td>908</td>
<td>45</td>
</tr>
</tbody>
</table>

Difference required for significance (P = 0.05) 11 27 784 19

longer than after isoprenaline. Orciprenaline had the largest effect on the heart rate as judged by the 'area under the curve', but this only reached significance when compared to placebo (Table III).

Only the placebo solution produced no rise in systolic blood pressure (Fig. 5) but the effect of salbutamol was slight. Isoprenaline and orciprenaline were both followed by significant increases compared to the placebo solution (Table IV and V). Orciprenaline again had the largest total effect.

As regards diastolic pressure, only isoprenaline had an appreciable effect, causing a 13% increase.

**Order of drug administration.** The results were also examined to see whether there was any difference in the cardiovascular and bronchodilator response between the first and subsequent sessions, as it was felt that on the initial visit the

TABLE IV
Mean Changes in Systolic Blood Pressure after Inhalation of Placebo, Isoprenaline, Orciprenaline, and Salbutamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basal Value (mmHg)</th>
<th>Peak (mmHg)</th>
<th>Time to Peak (min)</th>
<th>Area (mm.min)*</th>
<th>Duration (min)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>99</td>
<td>4</td>
<td>28</td>
<td>168</td>
<td>19</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>101</td>
<td>15</td>
<td>5</td>
<td>500</td>
<td>25</td>
</tr>
<tr>
<td>Orciprenaline</td>
<td>98</td>
<td>13</td>
<td>10</td>
<td>555</td>
<td>37</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>97</td>
<td>9</td>
<td>29</td>
<td>409</td>
<td>41</td>
</tr>
</tbody>
</table>

Difference required for significance (P = 0.05) 6 30 327 19

*Significantly related to basal value, and adjusted accordingly.

TABLE V
Mean Changes in Diastolic Blood Pressure after Inhalation of Placebo, Isoprenaline, Orciprenaline, and Salbutamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basal Value (mmHg)*</th>
<th>Peak (mmHg)</th>
<th>Time to Peak (min)</th>
<th>Area (mm.min)*</th>
<th>Duration (min)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>61</td>
<td>3</td>
<td>2</td>
<td>88</td>
<td>11</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>60</td>
<td>7</td>
<td>18</td>
<td>257</td>
<td>27</td>
</tr>
<tr>
<td>Orciprenaline</td>
<td>63</td>
<td>3</td>
<td>26</td>
<td>94</td>
<td>22</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>60</td>
<td>3</td>
<td>10</td>
<td>214</td>
<td>28</td>
</tr>
</tbody>
</table>

Difference required for significance (P = 0.05) 3 24 157 19

*Significantly related to basal value, and adjusted accordingly.

*Significantly related to basal value, and adjusted accordingly.

Fig. 5.—Mean values for systolic and diastolic blood pressure before and after inhalation of isoprenaline, orciprenaline, salbutamol, and placebo.
children might be more anxious and less able to achieve their best results. Analysis showed that the improvement in forced vital capacity as judged by its total effect was significantly less on the first than on subsequent occasions. No significant differences could be detected from examination of the pulse record.

Four children received salbutamol, 4 isoprenaline 3 placebo, and 1 orciprenaline on their first visit.

**Side effects.** Two children felt dizzy after isoprenaline and one felt dizzy after orciprenaline.

**Discussion**

One of the main problems in any trial designed to compare bronchodilator drugs is the dose selection. In this trial we selected doses which we hoped would be equipotent as regards relief of bronchoconstriction, so that we could then compare the cardiac effects. However, the information available on dose relation is contradictory. Some workers, e.g. Cullum et al. (1969) using cats and dogs, and Grant (1969), Choo-Kang, Simpson, and Grant (1969), Kamburoff and Prime (1970), and Riding, Dinda, and Chatterjee (1970), with normal and asthmatic adults, found that dose for dose salbutamol was several times more potent than isoprenaline. However, Warrell et al. (1970), using more sophisticated techniques, obtained very similar response curves for the two drugs, and Riding, Chatterjee, and Dinda (1969) found very similar relief of bronchoconstriction in asthmatic adults after the inhalation of 0.5 % salbutamol and 0.5 % isoprenaline delivered by an ultrasonic nebulizer. Hambleton and Shinebourne (1970) reported that 100 μg doses of isoprenaline and salbutamol delivered as an aerosol produced very similar relief of airways obstruction in 10 children with asthma, but that the effect of salbutamol was more prolonged. When compared to salbutamol, orciprenaline was less effective in relieving bronchospasm even with six times the dose (Kennedy and Simpson, 1969), but it was not felt justified to exceed the relatively high concentration of 2.5 % in these children. Our results showed very similar improvements in FEV$_{0.75}$ and FVC after all three active drugs. However, they were less striking than in the other series, partly because these children have had severe asthma for many years and now have some permanent underlying lung damage. The response to placebo was striking, with 10 of the children showing an obvious improvement in FEV$_{0.75}$ again illustrating the need for good controls when assessing any treatment in asthma.

The cardiac effects of the drugs showed greater variation. As was expected, isoprenaline caused an increase in heart rate of up to 70%; in only two children was the increase less than 20%. The effect on the cardiovascular system was also reflected in the increase in systolic and diastolic pressure. Rather more surprising was the tachycardia and increase in systolic blood pressure associated with the orciprenaline. These changes persisted for longer than the changes after isoprenaline. Salbutamol did produce an increase in the heart rate which persisted for significantly longer than after isoprenaline, but the increase was much less marked than after the other two drugs. Riding et al. (1969) found a similar rise in the pulse rate after the inhalation of a nebulized solution of 0.5 % in adults. However, Kennedy and Simpson (1969) found no change in pulse and blood pressure after the inhalation of 400 μg salbutamol from an aerosol, and Riding et al. (1970) actually observed a fall after 200 μg.

It is possible that a similar degree of bronchodilation could have been achieved with a considerably lower dose, but we were anxious to reproduce the doses likely to be given to a child admitted to the ward in severe bronchospasm. In conclusion, a 0.5 % salbutamol solution delivered by a Wright nebulizer is as effective a bronchodilator agent as 0.5 % isoprenaline or 2.5 % orciprenaline, but had considerably less effect on the cardiovascular system and thus should be used in place of isoprenaline for children with severe bronchoconstriction.

We wish to thank Dr. A. P. Norman and Dr. D. Hull for their advice and encouragement, and Allen and Hanburys Ltd. who supplied the samples and carried out the statistical analysis. Financial support was provided by the Asthma Research Council.

**REFERENCES**


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