Cardiac and Pulmonary Effects of Therapy with Albuterol and Isoproterenol*

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This study evaluated the cardiac and pulmonary effects of administering multiple inhaled doses of albuterol, isoproterenol sulfate, and placebo in ten patients with reversible obstructive disease of the airways. The pulmonary effects of therapy with albuterol were similar in magnitude to those of isoproterenol but lasted longer. The inotropic and chronotropic effects of therapy with isoproterenol were greater than those of albuterol. It appears that albuterol has β2-adrenergic selectivity over a wide range of dosages and is an effective bronchodilator drug.

Inhalation of isoproterenol and other bronchodilator drugs, using a Freon propellant, is common among patients with reversible obstructive disease of the airways. This method of treatment usually produces a rapid but transient relief of bronchospasm and has been associated with cardiac stimulation.

Because of the limited duration of action of isoproterenol and its potential for cardiac toxic effects, alternative drugs have been sought. One such drug, albuterol (marketed in other countries as salbutamol), may offer the advantages of a longer duration of action and a decreased cardiac effect compared to isoproterenol;1-13 however, assessment of the cardiac effects in these studies was limited to determinations of blood pressure and heart rate, determinations which may be misleading, since it is clear that the absence of chronotropic effects of a drug does not preclude the possibility of positively inotropic activity. Only one study in humans has evaluated the inotropic effects of oral therapy with albuterol, and although the results suggested the effects were "clinically insignificant,"14 some increase in inotropic activity was observed. The structural formulas for isoproterenol and albuterol are shown in Figure 1.

The purposes of this study were to correlate the cardiac and pulmonary effects of administering a broad range of dosages of albuterol and to compare them to administration of isoproterenol sulfate and a placebo in patients with reversible obstructive disease of the airways.

Materials and Methods

Subjects

Ten male patients with reversible obstructive disease of the airways (range of ages, 18 to 61 years) were entered into a randomized double-blind crossover study of three treatments. Reversible obstruction of the airways was defined by at least a 20 percent increase in the one-second forced expiratory volume (FEV1) measured 15 minutes after administration of 0.15 mg (two inhalations) of aerosol isopro-

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Figure 1. Structural formulas of albuterol and isoproterenol.
terenol sulfate from a metered-dose dispenser (Medihaler-Iso). Patients were excluded from the study if they had diabetes mellitus, hypertension, or cardiovascular, hepatic, hematologic, renal, or neurologic disease. Patients entered the study after meeting the criteria for acceptance and signing a form giving informed consent.

**Design of the Study**

This double-blind crossover study evaluated each of five sequentially administered doses of albuterol, isoproterenol, and placebo. On separate days, each dose was given by inhalation from identical looking containers designed to deliver either albuterol (88µg as the base), isoproterenol sulfate (79µg as the base), or placebo (propellant only). Completion of each treatment involved receiving one, two, four, six, and eight inhalations of albuterol, isoproterenol, and placebo. Patients were instructed to hold their breath at full inspiration following each dose. No attempt was made to regulate the rapidity of inhalation. The time between inhalations was not controlled but was approximately 20 seconds. The order of administration was randomized at each level.

Intolerance to a dose was defined as either a heart rate of 120 beats per minute or an increase of 40 percent in the heart rate. When either occurred, a higher dose of that treatment was not administered.

On each morning of study, patients reported to the laboratory in a fasting state and were allowed only water until completion of that day’s evaluation. They received no bronchodilator drugs for at least 12 hours prior to each day of study or during the controlled observations. In order to qualify for each dose of a drug under study, each patient underwent spirometric studies, and the FEV₁ had to be less than 81 percent of the value obtained following the original screening challenge with isoproterenol.

**Measurements**

Before (zero time) and at 1, 5, 10, 15, 30, 60, 90, and 120 minutes after completion of the last inhalation, the following measurements were obtained: (1) blood pressure; (2) heart rate; (3) preejection period; (4) electrocardiogram; (5) forced vital capacity (FVC); (6) FEV₁; and (7) mean forced expiratory flow during the middle half of the FVC (FEF25-75%). The preejection period was measured with a multichannel recorder (Elema-Schönander Mingograph) by simultaneously recording the ECG, phonocardiogram, and contour of the carotid pulse at 100 mm/sec. Derived calculations of the preejection period and heart rate were the average values taken from ten consecutive beats, as previously described. Blood pressure was measured by an automatic blood pressure recorder (Arteriosonde-Rocom).

Measurements of pulmonary function were taken from records of the best of two consecutive forced expiratory maneuvers recorded on a Stead-Wells spirometer (Collins). The FEF25-75% at zero time was used to measure end-points for the forced expiratory flow after administration of the drug, so that all measurements of forced expiratory flow were at isovolume.

**Analysis of Data**

Values for observations at one and five minutes and for those at 10 and 15 minutes were averaged to reduce the amount of data. A three-way analysis of variance was performed, with testing for effects due to times and treatments and subjects. Although the percentage of change has been used for graphic presentation of the results, statistical analysis was performed on the raw data. A compilation of the mean and standard error of both raw data and the percentage of change for each dose, along with the results of the corresponding statistical tests for the data on pulmonary function (FEV₁, FVC, and FEF25-75%) and the cardiovascular data (preejection period, blood pressure, and heart rate) may be obtained from the National Auxiliary Publication Service.

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Table 1—Data on Patients before and 15 Minutes after Inhalation of 0.15 mg of Isoproterenol Sulfate

<table>
<thead>
<tr>
<th>Patient, Age (yr)</th>
<th>Before FEV₁* (Percent)</th>
<th>After FEV₁* (Percent)</th>
<th>Before FVC* (Percent)</th>
<th>After FVC* (Percent)</th>
<th>FEF25-75%*, L/sec Before</th>
<th>After FEF25-75%* (Percent)</th>
<th>Preejection Period, msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 35</td>
<td>2.52 (57)</td>
<td>3.18 (26)</td>
<td>4.87 (89)</td>
<td>5.41 (11)</td>
<td>1.07</td>
<td>1.92 (86)</td>
<td>97</td>
</tr>
<tr>
<td>2, 49</td>
<td>0.95 (27)</td>
<td>1.20 (26)</td>
<td>2.31 (52)</td>
<td>3.10 (34)</td>
<td>0.33</td>
<td>0.62 (88)</td>
<td>110</td>
</tr>
<tr>
<td>3, 54</td>
<td>1.57 (47)</td>
<td>2.10 (34)</td>
<td>2.56 (58)</td>
<td>3.22 (26)</td>
<td>0.74</td>
<td>2.06 (178)</td>
<td>101</td>
</tr>
<tr>
<td>4, 57</td>
<td>0.87 (27)</td>
<td>1.24 (42)</td>
<td>1.24 (29)</td>
<td>1.65 (33)</td>
<td>0.70</td>
<td>1.24 (77)</td>
<td>115</td>
</tr>
<tr>
<td>5, 24</td>
<td>2.48 (56)</td>
<td>3.10 (25)</td>
<td>4.21 (79)</td>
<td>4.13 (−2)</td>
<td>1.53</td>
<td>2.31 (51)</td>
<td>126</td>
</tr>
<tr>
<td>6, 61</td>
<td>0.87 (29)</td>
<td>1.24 (42)</td>
<td>1.40 (35)</td>
<td>1.98 (41)</td>
<td>0.58</td>
<td>1.11 (91)</td>
<td>99</td>
</tr>
<tr>
<td>7, 24</td>
<td>1.86 (46)</td>
<td>2.43 (31)</td>
<td>2.97 (62)</td>
<td>3.63 (22)</td>
<td>0.91</td>
<td>2.06 (126)</td>
<td>128</td>
</tr>
<tr>
<td>8, 55</td>
<td>2.06 (59)</td>
<td>2.97 (44)</td>
<td>2.97 (64)</td>
<td>4.75 (60)</td>
<td>1.65</td>
<td>2.97 (180)</td>
<td>140</td>
</tr>
<tr>
<td>9, 47</td>
<td>3.51 (93)</td>
<td>4.21 (20)</td>
<td>2.10 (44)</td>
<td>5.49 (5)</td>
<td>2.10</td>
<td>3.84 (83)</td>
<td>124</td>
</tr>
<tr>
<td>10, 18</td>
<td>2.23 (47)</td>
<td>3.22 (44)</td>
<td>4.99 (87)</td>
<td>5.32 (7)</td>
<td>0.91</td>
<td>2.23 (145)</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean: 1.89 (49) 2.49 (33) 2.96 (60) 3.87 (24) 1.05 0.24 (110) 114

SE: 0.27 (6) 0.33 (3) 0.42 (7) 0.44 (6) 0.17 0.29 (14) 5

*Percentage of predicted value.

**Percentage of increase after inhalation.
RESULTS

Ten subjects began this study, and eight completed all 15 sessions. Subject 1 did not receive six and eight inhalations of isoproterenol because his heart rate rose to 165 beats per minute after four inhalations. Subject 7 failed to receive eight inhalations of isoproterenol because six inhalations caused a heart rate of 135 beats per minute.

Baseline Data

The clinical data from each patient are found in Table 1. There was an average increase in FEV₁ of 33 percent (range, 20 to 44 percent) following inhalation of isoproterenol. Analysis of variance confirmed the consistency of each individual’s FEV₁ at zero time. Thus, we concluded that pulmonary function was comparable at the beginning of each session.

Pulmonary Effects

The effects of each dose of placebo, isoproterenol, and albuterol on FEV₁ are shown in Figure 2. No statistically significant changes in FEV₁ were seen after administration of placebo. Dose-related increases in FEV₁ were seen after inhalation of isoproterenol and albuterol. No differences were seen in the onset of the effect, but the duration of action was longer after inhalation of albuterol. Although the peak effects occurred at five minutes and at 60 minutes for isoproterenol and for albuterol, respectively, there were no significant differences in the absolute response. The observations at all periods of time following inhalation of each dose of albuterol were significantly (P < 0.05) different from the corresponding baseline measurement. The increases in FEF25-75% and FVC were similar to those observed for FEV₁.

Cardiovascular Effects

Following inhalation of isoproterenol, there was a transient dose-related increase in heart rate, followed by a progressive slowing (Fig 3). Inhalation of the placebo appeared to produce a dose-related slowing in heart rate, but this was not confirmed by analysis of variance. The slight increase in heart rate observed after six and eight inhalations of albuterol was not statistically significant. The peak effect on the heart rate after inhalation of the highest dose of albuterol was comparable to the lowest dose of isoproterenol. Administration of six and eight inhalations of isoproterenol produced a decrease in diastolic pressure (8 to 10 mm Hg) that lasted 30 minutes or less. There were no changes in blood pressure related to the administration of albuterol or placebo.

Variations in the preejection period occurring after inhalation of placebo were generally within the range of ±7 percent (Fig 4). The shortening of the preejection period seen after inhalation of isoproterenol was related to the dose. The peak effect occurred at five minutes after inhalation and represented a decrease in the preejection period of 5 to 15 percent. The effect was dissipated by 30 minutes after administration. Inhalation of albuterol also shortened the preejection period by 5 to 8 percent, produced a peak effect at 15 minutes after inhalation, and had a duration of effect of 30 minutes. The effects of inhalation of albuterol were not related to the dose.

DISCUSSION

This study has demonstrated that in patients with reversible obstructive disease of the airways, the
cardiovascular and pulmonary effects of inhaled albuterol were different from those of inhaled isoproterenol. The maximal cardiopulmonary effects of inhalation of isoproterenol occurred by five minutes and immediately began to decrease. The peak pulmonary effect of inhalation of albuterol did not occur until one hour after inhalation and had a rapid onset (80 percent in five minutes) with sustained action (80 percent in two hours). Thus, there was a stable response from five minutes to two hours after inhalation. This was contrasted to the relatively abbreviated effects of inhalation of isoproterenol.

Most studies correlating cardiovascular and pulmonary effects in humans have only measured blood pressure and heart rate.\(^1,3,7,8,10-13\) Such studies are insufficient, since \(\beta\)-adrenergic stimulation of the heart may cause disproportionate effects on chronotropic and inotropic activity. In a previous report from this laboratory,\(^14\) the inotropic effect of oral therapy with albuterol was evaluated in patients with reversible obstructive disease of the airways. In that study, oral therapy with albuterol had a brief, clinically insignificant, positively inotropic effect at dosages of 4 and 6 mg. The current study has demonstrated a small positively inotropic effect with large dosages of albuterol that was clinically inconsequential compared to therapy with isoproterenol. It was surprising that the peak inotropic effect seen at 10 to 15 minutes after administration, in the dosage of four to eight inhalations, did not coincide with the peak pulmonary effect. The duration of the positive-

Figure 3. Effects of inhalation of placebo, isoproterenol, and albuterol on percentage of change in heart rate (HR). Values are means of data from eight patients. Values for two individuals who developed tachycardia after inhalation of isoproterenol and did not receive higher doses were excluded from this illustration. Asterisks indicate \(P < 0.05\), comparing each observation to baseline value.

Figure 4. Effects of inhalation of placebo, isoproterenol, and albuterol on percentage of change in pre-ejection period (PEP). Values are means of data from ten patients. Asterisks indicate \(P < 0.05\), comparing each observation to baseline value.
ly inotropic response was considerably less than the duration of the pulmonary effect. Both of these observations for albuterol demonstrate widely disparate dose-response curves separating the cardiac and pulmonary responsiveness.

The effect of four to eight inhalations of isoproterenol was a decrease of 17 msec in the preejection period. This response was approximately 50 percent less than the effect of an intravenous infusion of 2.5μg of isoproterenol per minute and was equivalent to an infusion of dopamine at 4μg/kg/min or to 1.2 mg of deslanoside (Cedilanid-D). Inhilation of the higher doses of isoproterenol had an equivalent inotropic and chronotropic effect.

The effects of therapy with albuterol on blood pressure and heart rate were similar to those in previous reports and appear to be clinically desirable. Although the effects of inhalation of isoproterenol on blood pressure and heart rate were small, these effects could be detrimental to certain patients.

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