Three doses of fenoterol were administered by metered-dose inhaler to 20 adult subjects with asthma in order to determine the optimal dose for routine administration. Inhaled doses of 100μg, 200μg, and 400μg of fenoterol with isoproterenol and placebo controls were administered in a randomized double-blind crossover regimen. We found that 200μg of fenoterol by metered-dose inhaler produced a longer duration of action, greater peak response, and greater overall time-weighted responses in the forced expiratory volume in one second, in the mean forced expiratory flow during the middle half of the forced vital capacity, and in airway resistance than did the other drug regimens. The 400μg dose of fenoterol produced no increase in response over that seen after the 200μg dose. Side effects were minimal and no greater than with isoproterenol.

Optimal Dose of Fenoterol by Metered-Dose Inhaler in Asthmatic Adults*

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Inhaled sympathomimetic agents are a mainstay in the short-term and long-term management of patients with asthma. Fenoterol is a derivative of metaproterenol with relatively selective β2 sympathomimetic activity and sustained duration of action.14 The efficacy of fenoterol has been demonstrated in several previous trials with different methods of administration, but recommended dosages have varied. The purpose of this study was to evaluate the effect on pulmonary function of increasing doses of aerosol fenoterol in comparison with isoproterenol and placebo in asthmatic adults and to determine the effective dose range in adults. We studied spirometric data, airway resistance (Raw), and cardiovascular side effects of fenoterol administered by metered-dose inhaler.

MATERIALS AND METHODS

In asthmatic adults, a double-blind, randomized crossover study was conducted in which placebo, isoproterenol, and three doses of fenoterol were administered.

Selection of Subjects

Twenty-two adults with mild to moderate asthma that was relatively stable were voluntarily enrolled in the study. Subjects with significant cardiac, renal, hepatic, or metabolic disease were excluded, as were pregnant subjects and those receiving corticosteroids. Concomitant medication with steroids was permitted if the subject's condition was stabilized on the equivalent of 10 mg of prednisone per day or less.

The studied group consisted of eight male and 14 female subjects between the ages of 21 and 64 years (mean, 41 years). All patients demonstrated reversible bronchospasm by a 20 percent increase in the forced expiratory volume in one second (FEV1) in response to a test dose of 150μg of isoproterenol from a metered-dose inhaler on a screening evaluation. All subjects met the criteria of the American Thoracic Society for the diagnosis of asthma. The mean duration of disease was 20.0 years, and the mean FEV1 was 1.31 L/sec on the initial screening examination. One subject was classified as having mild disease, 13 as having moderate disease, and eight subjects as having severe disease. One subject with severe disease had both chronic bronchitis and asthma.

Two subjects did not complete the study; results from the remaining 20 subjects formed the basis for this report.

Administration of Medication

All short-acting bronchodilator drugs and sympathomimetic drugs were withheld for at least eight hours before each session of the study. Sustained-release bronchodilators were withheld for 12 hours. Each subject received a total of five treatments in a double-blind crossover design. Fenoterol (100μg, 200μg, and 400μg), isoproterenol (150μg), and placebo were administered on separate days as two puffs from a coded but unlabelled metered-dose inhaler. The order of administration of the drugs was randomized, but fenoterol was always administered in consecutively increasing doses. Each of the five regimens was administered in the morning at the same time of day. Sessions of study in the same subject were separated by an interval of at least 24 hours.

Observations

The response to each drug was measured by pulmonary function tests and determination of heart rate and blood pressure. The FEV1 and the mean forced expiratory flow during the middle half of the forced vital capacity (FEF25-75%) were measured just prior to administration of the drug (baseline); at 1, 15, and 30 minutes; and at one, two, three, four, six, and eight hours after administration. The Raw and specific airway conductance (Gaw/VL) were measured at the same intervals except for one minute after administration of the drug. Patients were rescheduled if the baseline FEV1 at the start of each session exceeded 80 percent of the patient's maximum FEV1, obtained in the screening challenge.

Spirometric measurements were made with an electronic dry rolling-seal spirometer (Cardio-Pulmonary Instruments). The Raw and thoracic gas volume were measured with a 600-L constant-volume body plethysmograph (Cardio-Pulmonary Instruments). Three to five spiromgrams were recorded, and the best of at least three.

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Optimal Dose of Fenoterol (Conrad, Light, George)
consistent tracings was used. Three determinations of Raw were made and the average value used for the result.

Pulse and blood pressure were measured on all testing days at the same intervals as pulmonary function tests. The physician's clinical impression of efficacy and the patient's own evaluation of his response to therapy were recorded after each tested dose. The development of any adverse reaction was recorded.

**Analysis of Data**

Observed values were expressed as percent change from the baseline values obtained at the start of each session just prior to administration of the drug. Peak response was the maximal change from baseline without regard to time. Onset of action was defined as the time that a 15 percent or greater change occurred. Duration of action was defined as the length of time between onset of action and a return to within 15 percent of the baseline. For each testing session a time-weighted average value was calculated over the first six hours after administration of the drug. As another indicator of overall relative response, the areas under the time curves generated by changes from baseline values for FEV, at each interval through six hours was determined for each subject. The means of the square roots of these areas were determined for each subject.

Onset of action, duration of action, peak response, and average values for each measured variable as well as the square root of the area of the time curve for FEV, were subjected to analysis of variance. Means were compared for differences using Duncan's multiple range test.

A dose-response relationship for fenoterol was evaluated by testing for regression of the square root of the area under the FEV, time curve during the first four hours after administration against the administered dose. Stepwise regression using a cubic equation as the dose-response model was employed.

**RESULTS**

**Onset of Action**

Improvements in FEV₁ of at least 15 percent above baseline were observed in all 20 subjects following administration of 200μg of fenoterol and 150μg of isoproterenol and in 19 of 20 subjects with 100μg and 400μg of fenoterol (Fig 1). The median time of onset of action as determined by all pulmonary function tests was one minute. Eighty-two percent (49/60) of the subjects who received fenoterol responded within 15 minutes, as did 85 percent (17/20) of those given isoproterenol. The difference was not significant. One subject receiving 100μg of fenoterol and another subject receiving 400μg of fenoterol did not reach a 15 percent improvement in FEV₁.

**Duration of Action**

The duration of action as determined by FEV₁ and FEF25-75% was similar for isoproterenol and 100μg of fenoterol. Longer durations of action were noted for 200μg and 400μg of fenoterol (Table 1), but the difference between the 200μg and 400μg doses did not reach statistical significance.

**Peak Response**

Mean peak response in FEV₁ after isoproterenol was

**Table 1—Mean Duration* in Hours following Administration of Drugs**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Isoproterenol</th>
<th>Fenoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(150 μg)</td>
<td>100 μg</td>
<td>200 μg</td>
</tr>
<tr>
<td>FEV₁</td>
<td>...</td>
<td>3.36</td>
<td>3.26</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>...</td>
<td>4.23</td>
<td>3.82</td>
</tr>
</tbody>
</table>

*Defined as duration above threshold of 15 percent.
†Did not reach 15 percent threshold.

**Table 2—Mean Peak Percent Changes from Baseline following Administration of Drugs**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Isoproterenol</th>
<th>Fenoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(150 μg)</td>
<td>100 μg</td>
<td>200 μg</td>
</tr>
<tr>
<td>FEV₁</td>
<td>...</td>
<td>+40</td>
<td>+38</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>...</td>
<td>+46</td>
<td>+48</td>
</tr>
<tr>
<td>Raw</td>
<td>...</td>
<td>-38</td>
<td>-35</td>
</tr>
</tbody>
</table>

*Did not reach 15 percent increase.
Table 3—Time-Weighted Average Percent Changes from Baseline over Six Hours following Administration of Drugs

<table>
<thead>
<tr>
<th>Data</th>
<th>Placebo</th>
<th>Isoproterenol (150 µg)</th>
<th>100 µg</th>
<th>200 µg</th>
<th>400 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>-2.5</td>
<td>17.5</td>
<td>23.4b</td>
<td>36.5c</td>
<td>42.9c</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>7.8</td>
<td>38.10</td>
<td>44.10b</td>
<td>48.9b</td>
<td>73.20b</td>
</tr>
<tr>
<td>Raw</td>
<td>27.4</td>
<td>38.11</td>
<td>-9.6</td>
<td>-28.5c</td>
<td>-31.4c</td>
</tr>
<tr>
<td>Gaw/Vl</td>
<td>11.13</td>
<td>38.13</td>
<td>68.23c</td>
<td>122.41c</td>
<td>183.56c</td>
</tr>
</tbody>
</table>

*Expressed as mean + SE. Means with common superscript horizontally (a; b; c) are not significantly different.

40 percent, and the responses after fenoterol were 38 percent, 55 percent, and 54 percent for the 100 µg, 200 µg, and 400 µg doses, respectively (Table 2). All were significantly different from placebo (14 percent), but only the 200 µg dose of fenoterol was significantly greater than isoproterenol. There was no difference in mean peak response between the 100 µg and 400 µg doses of fenoterol and 150 µg of isoproterenol.

**Overall Response**

Time-weighted average changes from baseline for the FEV₁, FEF25-75%, and Gaw/Vl are summarized in Table 3. For all three measured variables the 200 µg and 400 µg doses of fenoterol were significantly greater than isoproterenol. No difference was noted between the 200 µg and 400 µg doses of fenoterol.

Mean values for the square roots of the areas under the FEV₁ time curves are given in Table 4. All regimens of drugs produced responses which were significantly greater than placebo. The 200 µg dose of fenoterol produced a significantly greater response than 100 µg of fenoterol or 150 µg of isoproterenol, but no difference was detected between the two highest doses of 200 µg and 400 µg. A significant dose-response relationship was established between the square root of the area under the FEV₁ time curve and the dose of fenoterol administered (p<0.001).

**Global Evaluation**

Global evaluations by physicians of response to treatments were greater for all four regimens of drugs than for placebo. The scores for 200 µg and 400 µg doses of fenoterol were greater than the scores for 100 µg of fenoterol and 150 µg of isoproterenol. The highest evaluation was achieved by the regimen of 200 µg of fenoterol. Global evaluations by the subjects of their own response to treatment for all four regimens of drugs were greater than for placebo. The highest rating was for 200 µg of fenoterol, but no statistical difference among the four regimens of drugs was found.

**Cardiovascular Responses**

No clinically significant changes in mean pulse or blood pressure occurred. Mean changes in pulse from baseline after fenoterol ranged from a decrease of 6.8 percent (two hours after a 400 µg dose) to an increase of 2.9 percent (four hours after a 200 µg dose). Isoproterenol produced responses ranging from -6 percent to +1.1 percent. Changes in pulse after placebo ranged from -4.6 percent to +0.9 percent. Even smaller percentage changes from baseline were noted in blood pressure, with no difference between regimens of drugs and placebo.

**Adverse Reactions**

Adverse experiences following fenoterol were minimal and of the type generally associated with the administration of sympathomimetic agents (nervousness and tremor). One and two subjects experienced these effects following 200 µg and 400 µg of fenoterol, respectively, as did two different subjects following isoproterenol.

**Discussion**

The effects of three different single doses of fenoterol inhaled from a metered-dose inhaler were evaluated in 20 adults with bronchial asthma and were compared with those of isoproterenol and placebo. The 150 µg dose of isoproterenol was chosen to approximate the dosage form commercially available in our institution. Williams and Kane have demonstrated no significant difference in bronchodilator effect between 20 µg and 160 µg of isoproterenol in asthmatic subjects. A higher dose would likely increase the incidence or severity of adverse effects without improving bronchodilation.

In comparison with placebo, significant improvement in pulmonary function was found after inhalation of all three doses of fenoterol and the one dose of isoproterenol. The onset of action after each dose of fenoterol (100 µg, 200 µg, and 400 µg) and isoproterenol (150 µg) by metered-dose inhaler occurred within one minute in the majority of patients.

Table 4—Means of Square Root of Area under FEV₁, Time Curve

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Isoproterenol (150 µg)</th>
<th>100 µg</th>
<th>200 µg</th>
<th>400 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.3</td>
<td>26.5c</td>
<td>34.2b</td>
<td>43.6c</td>
<td>40.3c</td>
</tr>
</tbody>
</table>

*Means with common superscript (a; b; c) are not significantly different.
Comparisons among the four regimens of drugs revealed that significantly greater improvement in pulmonary function occurred following the administration of 200μg and 400μg of fenoterol as compared with 100μg of fenoterol and 150μg of isoproterenol. We could not demonstrate a significant difference in onset of action, peak response, duration of action, or weighted average effect between the 200μg and 400μg doses of fenoterol. Although a significant difference was not demonstrated, the peak and average responses and the duration of action of 400μg of fenoterol as measured by FEF25-75% was greater than that for 200μg. This difference may reflect a greater sensitivity of FEF25-75% to small airway function than the FEV1. Selected patients may respond better to 400μg, but our data do not support this.

Our study confirms previous investigations that fenoterol is an effective, relatively long-acting bronchodilator. Using administration by nebulized aerosol, Tweel1 in 1971 reported maximal effect at a dose of 200μg using doses of 200μg through 800μg. His studied group was small (ten patients) and consisted of eight with asthma and two with chronic bronchitis. Watanabe et al8 found that 500μg by nebulizer (of a range of 500μg through 2,500μg) was equally effective as 400μg from a metered-dose inhaler, but smaller doses were not tested.

Various recommendations have appeared concerning the optimal dose of fenoterol by metered-dose inhaler. De Troyer et al10 compared 400μg and 1,200μg and found no difference in change in Raw. A dose smaller than 400μg was not administered. In a study of exercise-induced asthma in 12 young adults, 800μg of fenoterol by metered-dose inhaler was no more effective than 400μg in the prevention of exercise-induced asthma.8

Pennock et al15 studied lower doses of fenoterol by metered-dose inhaler in asthmatic adults with moderately severe asthma. Doses administered were 100μg, 200μg, and 400μg. It was found that 100μg was as effective as the two higher doses. In contrast, we found that 200μg was required to produce a maximal response. It is possible that our optimal dose is greater because of a slightly different study group. Our patients were older (mean of 41 vs 31 years) and may have had more severe disease.

Albuterol and terbutaline are two other β2-selective inhaled bronchodilator drugs which are presently available. The bronchodilator responses and adverse effects obtained with fenoterol are similar to those reported for these other two agents.10,11

REFERENCES
5 Williams MH Jr, Kane C. Dose response of patients with asthma to inhaled isoproterenol. Am Rev Respir Dis 1975; 111:321-24