A Comparison of the Bronchodilating Effects of Oxitropium Bromide and Fenoterol in Patients With Chronic Obstructive Pulmonary Disease*

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Oxitropium bromide is a novel anticholinergic bronchodilator agent. The purpose of this study was to compare the bronchodilating and cardiovascular effects of oxitropium (0.2 mg), fenoterol (0.4 mg), combined oxitropium and fenoterol (0.2 mg and 0.4 mg, respectively) over a 10-h test period. Fourteen patients with chronic obstructive pulmonary disease (COPD) (FEV₁, 0.95 ± 0.38L) were studied in a randomized, double-blind, placebo-controlled trial. Combined oxitropium and fenoterol produced significantly greater improvements in FEV₁ over a time span of 15 min to 10 h and in the area under the time-FEV₁ curve (AUC) than either oxitropium or fenoterol alone. The effects of oxitropium on both FEV₁ and AUC values were similar to those of fenoterol. Oxitropium resulted in a greater increase in FEV₁ than the placebo even after 10 h. In contrast, fenoterol produced a significant improvement in the FEV₁ for only 15 min to 4 h. Oxitropium showed no adverse cardiovascular effects, whereas fenoterol was associated with an increased heart rate at 15 min and 1 h after the administration. We conclude that oxitropium bromide is an effective and safe bronchodilator for even elderly patients with COPD.

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B ronchodilating therapy is an important component of the treatment for chronic obstructive pulmonary disease (COPD). Theophylline, β₂-adrenergic agonists, and anticholinergics have all been used in patients with COPD. The efficacy of inhaled anticholinergics in the treatment of COPD has now been established and their bronchodilating effects are at least equal to and perhaps superior to those of β₂-agonists.1-7 However, physicians do not always prescribe anticholinergics as the first step for COPD. Furthermore, there is still some controversy regarding the benefits of combining anticholinergics and β₂-agonists in treating patients with stable COPD.

Oxitropium bromide is an anticholinergic bronchodilating agent that was developed in 1965 and was recently introduced into clinical use in Japan, the United Kingdom, and some other European countries. The purpose of this study was to compare the effects of typical doses of oxitropium bromide, fenoterol, and combined oxitropium bromide and fenoterol in patients with stable COPD. Since anticholinergic agents may cause prolonged bronchodilation, we evaluated these effects over a 10-h period.

METHODS

Patients

The inclusion criteria for patients in this study were as follows:

1. a maximum ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) of less than 0.7 over several spirometries in an outpatient clinic;
2. a maximal prebronchodilator FEV₁ of less than 80 percent of the predicted value over several spirometries;
3. a smoking history greater than 30 pack-years;
4. no medical history consistent with asthma such as paroxysmal wheezing or dyspnea;
5. chest radiographic findings compatible with pulmonary emphysema;
6. no significant cardiovascular complications; and
7. stable COPD for at least 2 months prior to the study. Patients treated with systemic or inhaled corticosteroids during the preceding 2 weeks were excluded. Informed written consent was obtained from each patient.

Before entering the study, pulmonary function tests, including body plethysmography and serum IgE determination, were performed as part of a routine assessment. The diffusion was measured by the single-breath method (Chestax 6SVH, Chest Co, Tokyo, Japan). Total lung capacity was calculated as the sum of the volume of thoracic gas, determined by body plethysmography (model MBR 2000M, Nihon Kohden Co, Tokyo, Japan), the inspiratory residual volume, and the tidal volume. The residual volume (RV) was calculated as the thoracic gas volume minus the expiratory residual volume. The predicted values for the FEV₁ are from the Japan Society of Chest Diseases (1986).

Study Design

All patients were admitted to the hospital during the study period. Before entering the study, they were trained to use a metered-dose inhaler (MDI) with an accessory device (InspirEase) by the physician in charge. After they had become accustomed to using the MDI, they were randomly assigned two canisters of identical appearance. These canisters contained either (1) oxi-

AUC = area under the time-FEV₁ curve; MDI = metered-dose inhaler

tropium bromide (two puffs, 0.2 mg) and a placebo, (2) fenoterol (two puffs, 0.4 mg) and placebo, (3) oxi-
tropium bromide (0.2 mg) and fenoterol (0.4 mg), or (4) a placebo and another placebo (two inhalations each). The MDI inhalation instructions were as follows: shake the MDI vigorously, pull the bag out fully, and then actuate a single puff into the bag. Inhale slowly for about 5 s from the functional residual capacity (FRC) to the total lung capacity (TLC). At TLC level, hold the breath for as long as possible, up to 10 s.
Table 1—Baseline Characteristics of the 14 Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Predicted</th>
<th>Statistical Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>13/1</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>67.4 ± 7.4</td>
<td></td>
</tr>
<tr>
<td>Smoking index, pack-year</td>
<td>66.0 ± 28.5</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.95 ± 0.38</td>
<td>2.48 ± 0.31</td>
</tr>
<tr>
<td>% pred</td>
<td>38.1 ± 14.0</td>
<td>3.24 ± 0.35</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.26 ± 0.70</td>
<td>4.51 ± 4.5</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>41.0 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Dco/Va, ml/min/mm Hg/L</td>
<td>3.83 ± 1.31</td>
<td>4.45 ± 0.33</td>
</tr>
<tr>
<td>TLC, L (n = 13)</td>
<td>7.29 ± 1.42</td>
<td>5.32 ± 0.53</td>
</tr>
<tr>
<td>RV, L (n = 13)</td>
<td>4.76 ± 1.27</td>
<td>2.30 ± 0.40</td>
</tr>
<tr>
<td>RV/TLC, % (n = 13)</td>
<td>64.8 ± 10.2</td>
<td></td>
</tr>
<tr>
<td>Static compliance, L/cm H₂O (n = 11)</td>
<td>0.55 ± 0.51</td>
<td>0.15-0.30</td>
</tr>
<tr>
<td>Airway resistance, cm H₂O/L/s (n = 13)</td>
<td>4.93 ± 1.40</td>
<td>0.60-2.40</td>
</tr>
<tr>
<td>Blood eosinophil counts /mm³</td>
<td>141 ± 143</td>
<td></td>
</tr>
<tr>
<td>Sputum eosinophilia ±</td>
<td>3/11</td>
<td></td>
</tr>
<tr>
<td>IgE, IU/ml (geometric mean)</td>
<td>147.2</td>
<td></td>
</tr>
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</table>

The interval between the inhalations was about 10 s. Both the patients and the observer were blinded as to the medication, and were not aware of the order of the medications. Each test began at 9 AM. Each patient's baseline blood pressure, heart rate, FEV₁, and FVC were measured after 5 min of rest in a sitting position. Each subject then inhaled two puffs of the aerosol from each canister with the accessory device by himself or herself while under the physician's observation. After inhaling the aerosol, blood pressure, heart rate, FEV₁, and FVC were measured at 15 min, and again at 1, 2, 3, 4, 6, 8, and 10 h. Every measurement was made after at least 5 min of rest. The largest FVC and the largest FEV₁ of at least three acceptable measurements were used to determine the FEV₁ and FVC, in accordance with the American Thoracic Society recommendation.³⁶ Spirometry was performed with a spirometer (Autospiro AS-600, Minato Medical Co, Osaka, Japan) that was calibrated every morning. All individual studies were completed within 2 weeks. None of the patients was treated with theophylline, and treatment with other inhaled bronchodilators was withheld for 12 h before each examination. The patients were asked to refrain from ingesting caffeine-containing beverages such as strong Japanese tea or coffee on the test day.

The data were analyzed by Kruskal-Wallis test and Wilcoxon signed rank test; p<0.05 was considered to be significant. Data are expressed as mean ± SD.

RESULTS

A total of 14 patients with COPD aged 54 to 79 years completed the entire study, with 13 male patients and 1 female patient. The baseline characteristics of the patients are summarized in Table 1. The interval between the two different test days varied from 1 to 6 days and did not influence the results.

The time course for the mean percentage of change in FEV₁ and the mean postinhalation FEV₁ are shown in Figures 1 and 2, respectively. Oxitropium produced a significant improvement in the FEV₁ vs the placebo over the entire test period from 15 min to 10 h, whereas fenoterol produced a significant improvement from 15 min to 4 h. Furthermore, combined oxitropium and fenoterol produced a significantly larger improvement in the FEV₁ over fenoterol alone from 2 to 10 h, and over oxitropium alone at 15 min and from 2 to 6 h. The area under the time-FEV₁ curve represents the net bronchodilation. This area divided by the predicted FEV₁ (AUC/pred FEV₁) for combined

**Figure 1.** Mean percentage of increase in FEV₁ above baseline after inhalation of the indicated treatment for 10 h. † = significantly different from placebo; ‡ = significantly different from fenoterol; § = significantly different from oxitropium; * = p<0.05; ‡‡ p<0.01.
oxitropium and fenoterol was significantly greater than the values of AUC/pred FEV$_1$ for the placebo, fenoterol alone, and oxitropium alone (Table 2). The mean AUC/pred FEV$_1$ of oxitropium was significantly greater than the respective value for the placebo as well as fenoterol (Table 2). The mean durations of at least a 15 percent or greater improvement in the FEV$_1$ were 3.43 h (0 to 8 h) for fenoterol, 3.88 h (0 to 10 h) for oxitropium, and 5.57 h (0 to 10 h) for combined oxitropium and fenoterol (Table 3). Combined oxitropium and fenoterol showed a significantly longer duration than fenoterol alone. There were no significant differences in the durations of bronchodilation between fenoterol and oxitropium and between oxitropium and combined oxitropium and fenoterol.

There were significant increases in the heart rate after the inhalation of fenoterol and combined oxitropium and fenoterol at 15 min and 1 h when compared with oxitropium alone or the placebo (Fig 3). Combined oxitropium and fenoterol was associated with a mildly but significantly lower systolic blood pressure at 1 h vs oxitropium alone, fenoterol alone, or the placebo (mean diastolic pressure, 96.7, 105.3, 104.7, and 108.3 mm Hg, respectively, p<0.05). Three patients complained of palpitations associated with fenoterol. No patient complained of a dry mouth or of difficulty in urination while receiving oxitropium bromide.

**DISCUSSION**

Oxitropium bromide is an anticholinergic agent that has recently been introduced into clinical use in Japan, the United Kingdom, and some other European countries. Although the usefulness of ipratropium bromide in the treatment of patients with COPD has been well established by a large clinical trial, there are few reports comparing the bronchodilating effect of oxitropium with those of $\beta_2$-agonists.

Braun et al$^4$ reported that 36 $\mu$g of ipratropium bromide was at least equal or superior to 0.2 mg of salbutamol in treating patients with COPD. In their study, 0.2 mg of salbutamol showed no cardiac effects. In contrast, the 0.4 mg of fenoterol used in the present study was associated with an increased heart rate. This was probably due to the fact that we used a larger dose of fenoterol as a $\beta$-agonist than did Braun et al, and yet the 0.2 mg of oxitropium bromide showed comparable bronchodilation to fenoterol. Both the magnitude and duration of the oxitropium-induced bronchodilation seen in the present study were similar to the results of previous studies assessing the utility of oxitropium bromide in patients with COPD.$^{11,13}$

When compared with the study of Frith et al,$^{13}$ the bronchodilating response to 0.4 mg of fenoterol observed in the present study was slightly less, although the 0.2 mg of oxitropium showed comparable bronchodilating effects. This may be due to the fact that their patients had shown a 10 percent to 15 percent reversibility of their FEV$_1$ or FVC following inhalation.

![Figure 2. Time course of the mean FEV$_1$ after inhalation of the indicated treatment.](image)

**Table 2—Area Under the FEV$_1$-Curve**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Oxitropium</th>
<th>Fenoterol</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (L)</td>
<td>2.95 ± 13.9</td>
<td>53.3 ± 35.1*†</td>
<td>57.6 ± 35.4*†</td>
<td>89.6 ± 42.0*†‡§</td>
</tr>
</tbody>
</table>

*Significantly different from placebo.
†p<0.01.
‡Significantly different from fenoterol.
§Significantly different from oxitropium.
¶p<0.05.

**Table 3—Postinhalation Duration of a 15 Percent Increase in FEV$_1$**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.02</td>
<td>0-0.25</td>
<td>0</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>3.43</td>
<td>0-8</td>
<td>3.5*†</td>
</tr>
<tr>
<td>Oxitropium</td>
<td>3.88</td>
<td>0-10</td>
<td>3.5*†</td>
</tr>
<tr>
<td>Oxitropium and fenoterol</td>
<td>5.57</td>
<td>0-10</td>
<td>6*†‡§</td>
</tr>
</tbody>
</table>

*Significantly different from placebo.
†p<0.01, Wilcoxon signed rank test.
‡Significantly different from fenoterol.
§p<0.05.
of β-agonists, whereas we did not require reversibility for patient inclusion. This suggests that oxitropium has an equivalent bronchodilating effect even in those patients who have more fixed airflow limitation.

Since anticholinergics can have a longer duration of action than β-agonists, we evaluated the effect for 10 h. We found that oxitropium produced a significant increase in the FEV₁ over the placebo, even 10 h after inhalation, whereas fenoterol showed a significant increase only for 4 h after inhalation. The duration of at least a 15% increase in the FEV₁ also tended to be longer for oxitropium vs fenoterol.

In comparing the bronchodilating effects of anticholinergics with those of β-agonists in patients with chronic airflow limitation, the inclusion of patients with asthmatic components is problematic since asthmatic patients have been found to respond better to β-agonists than to anticholinergics. However, it is sometimes difficult to distinguish COPD from chronic asthma in a normal clinical setting. Furthermore, we could not find any differences in blood eosinophil counts, sputum eosinophilia, serum IgE levels, and pulmonary function parameters between patients who responded better to oxitropium and those who responded better to fenoterol. This suggests that oxitropium bromide is at least as effective as fenoterol in patients with fixed airflow limitation regardless of any asthmatic components, as was stated in a recent review on the pharmacology of oxitropium.

Combined oxitropium and fenoterol was significantly more effective than fenoterol or oxitropium alone for the doses used. It may be misleading to simply compare the effects of combining 0.4 mg of fenoterol and 0.2 mg of oxitropium with the effects of 0.4 mg of fenoterol or 0.2 mg of oxitropium alone. Since 0.4 mg of fenoterol was associated with an increased heart rate, it would not be wise to increase the dosage of fenoterol in order to achieve further bronchodilation in patients with stable COPD. These adverse cardiac effects of higher doses of fenoterol are of great concern in older patients with severe COPD who may be hypoxemic. In addition, oxitropium bromide was administered in a dose of 0.2 mg, which may have been a suboptimal dose. However, conflicting data exist. We may have obtained comparable bronchodilation by increasing the dose of oxitropium to that of the combined oxitropium and fenoterol. However, the maximal response to increased doses of oxitropium was obtained at 1 to 2 h after administration. On the other hand, β₂-agonists may be associated with a more rapid onset of effect and a greater maximal increase of the FEV₁ than oxitropium, leading to more acute relief of airflow limitation. This suggests that the addition of β₂-agonists to anticholinergics in bronchodilating treatment of patients with stable COPD may be indicated only when the patient requires acute symptomatic relief in daily life, and a careful assessment of adverse effects of β₂-agonists must be made.

In conclusion, 0.2 mg of oxitropium is at least as effective as 0.4 mg of fenoterol in achieving bronchodilation in patients with COPD. Both show an additive effect in the range of doses used, and the duration of bronchodilation induced by oxitropium tended to be longer than that induced by fenoterol. Oxitropium bromide may be safer for elderly patients because of its lack of adverse cardiovascular effects.

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