Oxitropium Bromide Improves Exercise Performance in Patients With COPD*

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Inhaled anticholinergics may be the first-line therapy for stable COPD. However, the effect of inhaled anticholinergic agents on exercise capacity is still controversial. Fourteen patients with stable COPD (age, 64.6 ± 5.9 years) completed a randomized, double-blind placebo-controlled crossover trial. All the patients were studied by symptom-limited progressive exercise test before and 90 min after the inhalation of either oxtropium bromide, 800 μg, or an identical placebo. Spirometry was assessed before and after each exercise test. While FEV1 averaged 0.85 ± 0.34 L at 90 min after the inhalation of placebo, FEV1 was 1.01 ± 0.41 L at 90 min after the inhalation of oxtropium, 800 μg (significant from placebo, p<0.001). The maximal workload of 94.0 ± 25.8 W after oxtropium administration was significantly greater than the 87.6 ± 24.7 W measured after placebo (p<0.01). The maximal minute ventilation was 40.2 ± 12.3 L/min after oxtropium inhalation and 38.5 ± 10.5 L/min after placebo inhalation (p<0.05). The differences in maximal oxygen consumption, maximal carbon dioxide production, and maximal heart rate between oxtropium and placebo inhalation also were statistically significant (p<0.05, p<0.05, and p <0.01, respectively). There was a significant correlation between the change in maximal workload and the change in FEV1 before and after inhalation (r=0.625, p<0.01). The inhalation of oxtropium bromide, 800 μg, can improve the exercise capacity of patients with stable COPD. It is suggested that the effect is due to the bronchodilation induced by this drug.

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Key words: anticholinergics; bronchodilator; chronic obstructive pulmonary disease; exercise capacity; oxtropium bromide; progressive cycle ergometry

Patients with COPD complain of dyspnea and exertional intolerance. In these patients, functional exercise capacity is generally thought to be curtailed by limited breathing capacity and impaired gas exchange. Therapy with bronchodilators frequently is used in an attempt to relieve symptoms and airflow obstruction. Three types of bronchodilators—inhaled β2-agonists, anticholinergic agents, and orally administered theophylline—are widely used for the management of the stable phase of COPD. Recently, many investigators have expressed the opinion that either an inhaled anticholinergic agent or β2-agonist is superior to theophylline.1,2 Furthermore, there is evidence to suggest that ipratropium bromide may be more effective than β2-agonists in patients with COPD.3-5

The goal of treatment with bronchodilators is to relieve the airway obstruction, to improve exercise tolerance, and to minimize impairment. While the bronchodilating effect of inhaled bronchodilators in

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exacerbation. Entry criteria included age greater than 55 years, history of smoking, chest radiograph showing hyperinflation with or without a vascular deficiency pattern suggestive of pulmonary emphysema, a ratio of FEV1 to forced vital capacity (FVC) of less than 70%, FEV1 less than 60% of the predicted value, and the absence of other disorders likely to affect exercise. Those with an exacerbation of their pulmonary disease within the last 3 months, a history of asthma, moderate to severe hypoxemia (PaO2 less than 60 mm Hg at rest) were excluded. None of the patients was taking oral or inhaled corticosteroids in the preceding 2 weeks. In order to familiarize patients with the testing technique and to confirm that their exercise tolerance was limited by mechanical ventilatory capacity, each subject had undergone progressive exercise studies on at least two occasions before entering the trial. Written informed consent was obtained prior to initiation of the study.

Upon admission into the study the subjects underwent an evaluation including complete blood cell count, automated blood chemical analysis, serum immunoglobulin E assay, sputum examination, and an ECG. All patients underwent baseline pulmonary function testing after the withdrawal of bronchodilators. In accordance with the method described in the American Thoracic Society 1987 update,10 spirometric testing for determining the FEV1, FVC, and FEV1/FVC ratio was performed using a spirometer (AUTOSPIRO AS-600, Minato Medical Science Co. Ltd, Osaka, Japan) which was calibrated with a 3.0-L syringe before every measurement. The largest FEV1 and the largest FVC among three maneuvers were analyzed. The predicted values of FEV1 and FVC were those of the Japan Society of Chest Diseases.12 Functional residual capacity (FRC) was determined by plethysmography (MBR-600, Nihon Kohden Co, Tokyo, Japan), and residual volume was calculated as FRC minus expiratory reserve volume measured by spirometric testing. Total lung capacity (TLC) was determined as the sum of vital capacity (VC) and residual volume. Static compliance and airway resistance were also measured by plethysmography. The single-breath diffusing capacity for carbon monoxide (Dsb) was measured (Chestac-65, Chest, Tokyo).

Progressive Exercise Test

The progressive exercise test to a symptom-limited maximum was performed on a calibrated electrically braked cycle ergometer (Corival WLP-400, Lode, Groningen, the Netherlands). Subjects breathed through a high-velocity, low-resistance unidirectional valve (Rudolph face mask exercise testing, Hans Rudolph, Inc, Kansas City, MO) with simultaneous breath-by-breath measurement using an exercise testing system (Deskop Diagnostics/CPX, Medical Graphic Corporation, St. Paul, Minn). Minute ventilation (Ve) and oxygen and carbon dioxide tension in the expired air were determined every eight breaths by a rapidly responding analyzer and the mean Ve, oxygen consumption (VO2), and carbon dioxide production (VCO2) were then calculated. The analyzer was calibrated just before the study with known gas mixtures: (1) the oxygen analyzer with air (20.93% oxygen) and a 15% oxygen mixture and (2) the carbon dioxide analyzer with air and a 5% carbon dioxide mixture. Patients began unloaded cycling for 5 min, after which the power output was increased progressively at the rate of 20 W/min until the patient could no longer continue the required cadence of 40 revolutions per minute due to severe dyspnea or exhaustion. Arterial oxygen saturation (SaO2) was measured continuously by pulse oximetry (N-200 pulse oximeter, Nellcor Inc, Hayward, Calif) and heart rate (HR) by electrocardiography (Life Scope 8, Nihon Koden Co, Tokyo, Japan). At the end of each exercise, symptoms of leg effort and breathlessness were scored with the Borg scale (0 to 10), which was presented within easy view of the subject. None of the tests was terminated by the attending physician because of untoward clinical signs or electrocardiographic changes suggestive of significant myocardial ischemia during the study. Analysis of the expired gas and monitoring of SaO2 and HR continued for 3 min after stopping exercise. Maximal work rate was defined as the highest work level that was reached. Similarly, maximal HR, maximal VO2, maximal Ve, and oxygen pulse (VO2/HR) were the endpoint levels reached during the exercise. All the exercise tests were performed by the same physician (H.K.) who was blinded to all the results of spirometry.

Study Design

The present study, conducted between January and September 1992, was performed in a randomized, double-blind, placebo-controlled crossover fashion at approximately the same time on two separate days within the same week. The patients were requested to stop taking theophylline preparation for 48 h and inhaled bronchodilators for at least 12 h before each test day. Patients underwent symptom-limited progressive cycle ergometry before (first exercise) and 90 min after (second exercise) the inhalation of oxtropium bromide, 800 μg, or an identical placebo. Spirometry was assessed before the first exercise prior to the inhalation, after the first exercise, 90 min after the inhalation prior to the second exercise, and 120 min after the inhalation after the second exercise (Fig 1). Prior to each spirometric measurement, pulse rate and blood pressure were measured at least 5 min of rest.

All of the patients inhaled oxtropium bromide, 800 μg (8 puffs) or matching placebo (Nippon Boehringer Ingelheim Co, Ltd, Kawanishi, Japan) using a metered-dose inhaler with a spacer device (InspirEase, Schering-Plough K.K., Osaka, Japan).13 Patients received detailed instructions on the use of the metered-dose inhaler. The spacer attached to the metered-dose inhaler was held in the mouth, and after the patient exhaled to FRC, the canister was activated. Patients inhaled very slowly until total lung capacity was reached, and then the breath was held for at least 10 s. To ensure that the drugs were administered correctly, the inhalation technique was carefully observed by the same physician (A.I.). This physician (A.I.) also carefully observed all of the spirometric measurements.

Statistical Analysis

All data are expressed as the mean ± SD. The significance of the differences between values observed with oxtropium and placebo was determined by repeated measured analysis of variance. When appropriate, means were compared using the paired t test (two-tailed). The relationship between two sets of data was analyzed

![Figure 1. Study design and results of FEV1. Open circles indicate placebo inhalation. Solid circles indicate oxtropium bromide, 800 μg, inhalation. Bars indicate SEM. Asterisks indicate probability of less than 0.001.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/cheet/21704/ on 06/21/2017)
Table 1—Baseline Clinical Data for 14 Patients (Values are Mean ± Standard Deviation)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67.6 ± 6.4</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>59.3 ± 22.8</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>85.5 ± 0.34</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>33.3 ± 15.3</td>
</tr>
<tr>
<td>FEV1/FVC ratio, %</td>
<td>39.5 ± 11.2</td>
</tr>
<tr>
<td>V/L</td>
<td>79.3 ± 19.1</td>
</tr>
<tr>
<td>Dsh, ml/min/mm Hg</td>
<td>20.3 ± 5.2</td>
</tr>
<tr>
<td>Dsh, % predicted</td>
<td>84.7 ± 20.6</td>
</tr>
<tr>
<td>TLC, L</td>
<td>8.55 ± 1.42</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>155.2 ± 23.6</td>
</tr>
<tr>
<td>Static compliance, L/cm H2O⁻¹</td>
<td>0.35 ± 0.37</td>
</tr>
<tr>
<td>Airway resistance, cm H2O⁻¹ L⁻¹ s⁻¹</td>
<td>77.0 ± 8.6</td>
</tr>
<tr>
<td>Resting PaO₂, mm Hg</td>
<td>77.0 ± 8.6</td>
</tr>
<tr>
<td>Resting PaCO₂, mm Hg</td>
<td>44.0 ± 2.6</td>
</tr>
<tr>
<td>Blood eosinophils, mm⁻³</td>
<td>140 ± 75</td>
</tr>
<tr>
<td>IgE, IU/L</td>
<td>geometric mean 93.6 (24-282)</td>
</tr>
</tbody>
</table>

*Alveolar ventilation per minute, Vₜ.*
†Not measured in one patient because of severe airflow limitation.
‡Not measured in three patients because of severe airflow limitation.

by the Spearman rank correlation test. A probability value of less than 0.05 was considered to be statistically significant for all tests.

RESULTS

Fourteen male patients completed the entire study. The clinical background and the results of baseline tests of pulmonary function in these patients are summarized in Table 1. Their mean age was 67.6 ± 6.4 years (range, 56 to 78 years). All had spirometric evidence of severe airflow obstruction with a mean FEV1 of 0.85 ± 0.34 L (33.3 ± 13.1% of predicted). The patients were mildly hypoxemic when breathing room air, with a mean PaO₂ of 77.0 ± 8.6 mm Hg. The TLC averaged 155% of predicted because FRC was determined using body plethysmography.

The resting pulse rates measured before spirometry were similar before inhalation but increased significantly more after inhalation of oxitropium than after placebo inhalation (Table 2). Blood pressure was not different after administration of oxitropium or placebo in four measurements for the individual. No patient complained of adverse symptoms.

The results of the spirometric measurements in the study are shown in Figure 1 and Table 2. The FEV₁ and FVC were identical prior to inhalation for both placebo and oxitropium. After all four progressive cycle ergometries (two on each test day), there were no significant changes in spirometric variables compared with values before exercise. Inhalation of oxitropium, 800 μg, resulted in significant changes in airflow limitation. At 90 min after inhalation of oxitropium, 800 μg (before exercise values, second exercise), FEV₁ and FVC were significantly improved from levels after administration of placebo (p<0.001 and p<0.01, respectively). This significant improvement, owing to inhalation of oxitropium, was similarly shown at 120 min after inhalation (after exercise values, second exercise).

The results of progressive cycle ergometry before inhalation were similar on the two separate test days (Table 3). Furthermore, the maximal work rate, maximal VE, V̇O₂, V̇CO₂, HR, oxygen pulse, and Borg scale at maximal exercise after inhalation of the placebo were also similar to values recorded prior to the inhalation.

Maximal exercise capacity was 86.1 ± 26.2 W before and 94.0 ± 25.8 W after inhalation of oxitropium (p<0.01). Maximal V̇E was 33.5 ± 9.7 before and 40.2 ± 12.3 L/min after oxitropium inhalation (p<0.01). The V̇O₂, V̇CO₂, and HR at maximum exercise were also significantly improved by oxitropium administration. However, SaO₂ and oxygen pulse at maximum exercise and the Borg scale ratings of perceived effort were not significantly changed.

Comparing oxitropium, 800 μg, inhalation with the placebo inhalation, maximal workload was 94.0 ± 25.8 W after oxitropium administration and 87.6 ± 24.7 W after placebo (p<0.01). The maximal V̇O₂ was 40.2 ± 12.3 L/min after oxitropium inhalation and 36.8 ± 10.5 after placebo inhalation (p<0.05). The differences in maximal V̇O₂, maximal V̇CO₂, and maximal HR between oxitropium inhalation and placebo inhalation also were statistically significant (p<0.05, p<0.05, and p<0.01, respectively). The SaO₂, and oxygen pulse at maximum exercise and dyspnea as measured on the Borg scale at the end of the test were not different between the two groups.

To determine whether the observed improvement in exercise capacity was related to individual improvements in airflow limitation, we examined the relationship between FEV₁ and maximal workload for all 28 tests, i.e., 1 test with oxitropium and 1 with placebo for each patient. A significant correlation was found between the change in maximal workload and the change in FEV₁ (r=0.625, p<0.01 [Fig 2]).

DISCUSSION

The present study is the first comprehensive report to establish that an inhaled anticholinergic agent can improve exercise capacity in patients with COPD. While FEV₁ and FVC increased significantly after the inhalation of oxitropium bromide, 800 μg, compared with placebo inhalation, many parameters obtained during symptom-limited progressive cycle ergometry (maximum values of the following: workload, VE, V̇O₂, V̇CO₂, and HR) also were improved. There was a good correlation between the change in maximal workload and the change in FEV₁, suggest-
ing that the improvement in exercise capacity was related to the improvement in airflow limitation in individual patients.

Previous oxitropium dose-response data for COPD patients indicate that the dose we used (800 μg) produced either maximal or very near maximal response. The 25% improvement in the baseline FEV$_1$ that we observed seems to be relatively small when compared with the results of previous studies on oxitropium bromide dose-response relationships. Since the COPD patients included in the present study may have had irreversible chronic airflow limitation, we believe that near maximum bronchodilation was achieved. There is a strong possibility that the improvement in exercise tolerance depends on the reduction in airflow limitation induced by a relatively large dose of an inhaled anticholinergic agent. If smaller doses of inhaled oxitropium bromide were used, the effect on exercise capacity might not be apparent. The present study did not address the question of whether the commercially recommended dose (100 μg) would also improve effort tolerance.

The bronchodilating effect of inhaled bronchodilators in patients with COPD has been established. In fact, therapy with bronchodilators frequently is used in an attempt to relieve symptoms and airway obstruction. However, the effect on exercise capacity of inhaled bronchodilators still is under debate.

### Table 2—Results of Spirometric Measurement (Values are Mean ± Standard Deviation)

<table>
<thead>
<tr>
<th>Spirometric Values</th>
<th>Medication</th>
<th>First Exercise</th>
<th>Second Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>Placebo</td>
<td>0.85 ± 0.50</td>
<td>0.83 ± 0.50</td>
</tr>
<tr>
<td></td>
<td>Oxitropium</td>
<td>0.81 ± 0.54</td>
<td>0.84 ± 0.54</td>
</tr>
<tr>
<td>FVC, L</td>
<td>Placebo</td>
<td>1.82 ± 0.49</td>
<td>1.81 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>Oxitropium</td>
<td>1.80 ± 0.67</td>
<td>1.85 ± 0.64</td>
</tr>
<tr>
<td>Pulse rate, beats per minute</td>
<td>Placebo</td>
<td>74 ± 8</td>
<td>77 ± 8</td>
</tr>
<tr>
<td></td>
<td>Oxitropium</td>
<td>75 ± 11</td>
<td>78 ± 11</td>
</tr>
</tbody>
</table>

*Significantly different from placebo (p<0.001).
†Significantly different from placebo (p<0.01).
‡Significantly different from placebo (p<0.002).

### Figure 2. Correlation between the change in maximal workload and the change in FEV$_1$ before exercise. Open circles indicate placebo inhalation. Solid circles indicate oxitropium bromide, 800 μg, inhalation. The correlation was significant (r=0.625, p<0.01).

### Table 3—Results of Progressive Cycle Ergometry (Values are Mean ± Standard Deviation)

<table>
<thead>
<tr>
<th>Values</th>
<th>Placebo</th>
<th>After</th>
<th>Oxitropium</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal work rate, W</td>
<td>88.1±24.7</td>
<td>87.6±24.7</td>
<td>86.1±26.2</td>
<td>94.0±25.8*</td>
</tr>
<tr>
<td>Maximal V_E, L/min</td>
<td>34.0±7.1</td>
<td>36.8±10.5</td>
<td>35.5±9.7</td>
<td>40.2±12.3†</td>
</tr>
<tr>
<td>Maximal VO$_2$, mL/min</td>
<td>707±367</td>
<td>761±363</td>
<td>755±400</td>
<td>841±419†</td>
</tr>
<tr>
<td>Maximal VO$_2$ CO$_2$, mL/min</td>
<td>689±374</td>
<td>750±378</td>
<td>718±398</td>
<td>843±423†</td>
</tr>
<tr>
<td>Maximal HR, beats per minute</td>
<td>120±11</td>
<td>116±15</td>
<td>119±15</td>
<td>126±15*</td>
</tr>
<tr>
<td>O$_2$ pulse at maximal work, milliliters per beat</td>
<td>6.7±3.4</td>
<td>6.9±3.2</td>
<td>6.7±3.5</td>
<td>6.9±3.3</td>
</tr>
<tr>
<td>SaO$_2$ at maximal work, %</td>
<td>91±4</td>
<td>95±4</td>
<td>93±4</td>
<td>93±4</td>
</tr>
<tr>
<td>Borg scale at maximal work (0-10)</td>
<td>7.4±1.1</td>
<td>7.4±1.5</td>
<td>7.3±1.1</td>
<td>7.1±1.1</td>
</tr>
</tbody>
</table>

*Significantly different from values recorded before oxitropium inhalation (p<0.01). Significantly different from values recorded after placebo inhalation (p<0.01).
†Significantly different from values recorded before oxitropium inhalation (p<0.01). Significantly different from values recorded after placebo inhalation (p<0.05).
‡Significantly different from values recorded before oxitropium inhalation (p<0.001). Significantly different from values recorded after placebo inhalation (p<0.05).
Dullinger et al\textsuperscript{19} reported that inhaled metaproterenol has no effect on the 12-min walk and progressive cycle ergometry when compared with placebo. On the contrary, Guyatt et al\textsuperscript{20} showed that inhaled salbutamol improved airflow obstruction and the 6-min walk distance. Berger and Smith\textsuperscript{21} reported that the 12-min walk distance was improved by inhaled metaproterenol even in patients with fixed airflow limitation.

Furthermore, several studies have suggested that inhaled anticholinergic agents are superior to inhaled $\beta_2$-agonists in stable COPD.\textsuperscript{3-5} While Leitch et al\textsuperscript{8} indicated that ipratropium bromide did not influence the 12-min walk distance, Tobin et al\textsuperscript{7} reported that laboratory exercise capacity was improved by inhaled ipratropium bromide. Hay et al\textsuperscript{9} showed that oxitropium bromide increased the 6-min walking distance and symptoms unrelated to bronchodilation. Teramoto et al\textsuperscript{10} demonstrated that inhaled oxitropium bromide produced a small improvement both in dyspnea during exercise and in exercise performance but not in $V_E$.\textsuperscript{10} In addition, several preliminary studies with inhaled anticholinergic agents described conflicting effects on exercise capacity despite improvement in airflow limitation.\textsuperscript{22-28}

Since only small doses of inhaled anticholinergic agents were evaluated in most of these studies, maximal bronchodilation was not achieved.

Orally administered theophylline has been employed for several decades\textsuperscript{2} as a bronchodilator. In addition, theophylline may improve exercise tolerance, prevent the development of the sensation of dyspnea during exercise, and reduce the incidence of dyspnea. These effects of theophylline are most likely related to improvements in respiratory muscle performance rather than bronchodilation.\textsuperscript{29,30} It was reported that both theophylline and inhaled metaproterenol can ameliorate exercise intolerance without remarkable bronchodilation.\textsuperscript{19,20} Some investigators pointed out that it is necessary to reevaluate the role of oral administration of theophylline combined with inhaled bronchodilators for stable COPD.\textsuperscript{2} Thus, the effect of combined bronchodilator therapy on exercise capacity should be evaluated further.

In conclusion, the inhalation of oxitropium bromide, 800 $\mu$g, can improve the exercise capacity in patients with stable COPD. This effect most likely depends on significant bronchodilation, and inhaled anticholinergic agents can be the first-line therapy for stable COPD.

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