The Effects of Oxitropium Bromide on Exercise Performance in Patients with Stable Chronic Obstructive Pulmonary Disease
A Comparison of Three Different Exercise Tests

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The purpose of the present study was to compare the characteristics of three different exercise tests in evaluating the effects of oxtropium bromide on exercise performance. Thirty-eight males with stable chronic obstructive pulmonary disease (COPD) (FEV₁ = 40.8 ± 16.5% predicted; mean ± SD) completed randomized, double-blind, placebo-controlled, crossover studies for each exercise test. The exercise tests were performed 60 min after the inhalation of either oxtropium bromide 400 μg or placebo. The patients performed 6-min walking tests (6MWTs) on Days 1 and 2, progressive cycle ergometry (PCE) on Days 3 and 4, and cycle endurance tests at 80% of the maximal workload of PCE on Days 5 and 6. Spirometry was conducted before and at 45 and 90 min after the inhalation. Oxitropium bromide significantly increased FEV₁ as compared with placebo. Oxitropium bromide increased the endurance time significantly, by 19% (p < 0.001), and caused a small but significant increase in the 6-min walking distance by 1% (p < 0.05), but induced no significant increase in maximal oxygen consumption (VO₂max) in PCE. The responses in these three exercise tests were different, and we conclude that the endurance test was the most sensitive in detecting the effects of inhaled anticholinergic agents on exercise performance in patients with stable COPD. An endurance procedure may be performed to detect clinical changes in evaluating the effects of oxtropium bromide on exercise performance.

Patients with chronic obstructive pulmonary disease (COPD) complain of exertional breathlessness and exercise intolerance, mainly due to reduced ventilatory capacity and impaired gas exchange. Inhaled anticholinergic agents are recommended as the first-line drugs to relieve these patients’ symptoms and to improve their airflow limitation (1, 2). Although the bronchodilating effects of these drugs in COPD have been established (3, 4), there is sometimes controversy about whether anticholinergic agents affect exercise performance (5-10).

The effects of anticholinergic bronchodilators may depend on the type of exercise test performed. In investigating the effects of bronchodilators on exercise performance in patients with COPD, a walking test and progressive cycle ergometry (PCE) are often used (5-10). However, in assessing the effects of pulmonary rehabilitation, endurance tests are sometimes used because measures of endurance may be responsive to training. An effective pulmonary rehabilitation program usually results in an improvement in exercise endurance, but little or no change in maximal exercise capacity (11). Recently, O’Donnell and coworkers reported that after bronchodilator therapy, exercise time was a reliable measure of exercise endurance, being reproducible and responsive to changes in severe COPD (12).

There is no consensus about which measurement should be used in the clinical evaluation of exercise performance in patients with COPD. In the present study we applied an endurance test in addition to a walking test and PCE to patients with stable COPD. We hypothesized that the endurance test would be the most sensitive test for detecting the effects of oxtropium bromide on exercise performance, as previously reported in the field of pulmonary rehabilitation (11). The purpose of the present study was to compare the characteristics of three different exercise tests in evaluating the effects of oxtropium bromide on exercise performance in patients with COPD.

METHODS

Patients
Forty-two consecutive male patients with clinically stable COPD as defined by the American Thoracic Society (ATS) were recruited between November 1995 and September 1998 (1). The entry criteria for the study were: (1) age over 45 yr; (2) a history of cigarette smoking of more than 20 pack-years; (3) chest radiographs showing hyperinflation; (4) an FEV₁ of less than 80% of the predicted value; and (5) a best postbronchodilator FEV₁-to-vital capacity (VC) ratio of less than 0.7. Reasons for exclusion included: (1) an exacerbation of airflow limitation within the preceding 3 mo; (2) a history of asthma; (3) other diseases likely to affect exercise; and (4) hypoxemia, defined as a PaO₂ of less than 60 mm Hg at rest. None of the patients had taken oral or inhaled corticosteroids during the 4 wk preceding the study. Before the study, each subject had practiced how to use a metered dose inhaler (MDI) with a spacer device. Written informed consent was obtained from all patients prior to initiation of the study.

All patients underwent baseline pulmonary function testing and had an electrocardiogram (ECG) at least 12 h after administration of the bronchodilator used in the study. In accordance with the method recommended by the ATS, the spirometric testing for determining FEV₁ and FVC was done with a spirometer (Autospiro A S-600; Minato Medical Science Co. Ltd., Osaka, Japan) that was calibrated with a 3.0-L syringe before every measurement (13). The largest FEV₁ and largest FVC from three maneuvers were analyzed. The residual volume (RV) was measured with the closed-circuit helium method, and the diffusing capacity of carbon monoxide (D LCO) was measured with the single-breath technique (CHESTAC-65V; Chest, Tokyo, Japan). The predicted values for the pulmonary function indices were those proposed by the Japan Society of Chest Diseases (14).

Exercise Tests
During the initial screening, the patients had undergone 6-min walking tests (6MWTs) and PCE on at least two occasions. Before entering the trial, patients were familiarized with the Borg scale (0 to 10) for evaluating their symptoms of breathlessness at rest and at the end of exercise (15). The 6MWTs were performed in a hospital corridor 50 m long (16). No encouragement was given during the walk. In advance of the practice walks, we emphasized to the patients that the aim of the test was to walk as far as they could in 6 min, and that they would not be encouraged during the walk. A tritium oxygen saturation (5A₂O) and heart
rate (HR) were monitored through pulse oximetry (N-200 pulse oximeter; Nellcor Inc, Hayward, CA). The Borg scores were recorded at rest and immediately after walking cessation. The distance the patients covered was measured as the 6-min walking distance (6MW D). The minimal $S_{A\text{O}_2}$ ($S_{A\text{O}_2}\text{min}$) and the maximal HR (HR max) reached during the 6MW WT were also recorded.

The symptom-limited progressive exercise tests were performed on a calibrated, electrically-braked cycle ergometer (Corival WLP-400; Lode, Groningen, The Netherlands). A face mask connected to a low-resistance unidirectional valve (Rudolph Face Mask for Exercise Testing: H ans R rudolph Inc, Kansas City, Mo) was placed on the patient’s face without leakage. A fter unloaded pedaling for 3 min, the workload was increased automatically by increments of 1 W every 3 s until the patient could no longer continue the required cadence of 40 cycles per minute because of severe dyspnea or exhaustion. The exercise data were recorded with an automated exercise testing system (Desktop Diagnostics/CPX; Medical Graphics Corporation, St. Paul, Mn) that converts breath-by-breath analog input to digital form in an on-line fashion. Minute ventilation ($V_e$) and oxygen and carbon dioxide tension in the expired air were determined every eight breaths, and the mean $V_e$, oxygen consumption ($V\text{O}_2$) and carbon dioxide production ($V\text{CO}_2$) were then calculated rapidly. The gas analyzer was calibrated just before the study with air and with a standard reference gas mixture (15% oxygen, 5% carbon dioxide). $S_{A\text{O}_2}$ was measured through pulse oximetry (N-200 pulse oximeter), and HR was recorded electrocardiographically (Life Scope 8; Nihon Koden Co., Tokyo, Japan) through pulse oximetry (N-200 pulse oximeter), and HR was recorded.

The Borg score ($B_5$) was defined as the highest work level that was loaded pedaling, the power output increased to the work-rate level. The minimal work rate ($W_{max}$) was considered statistically significant for all analyses.

**RESULTS**

**Subjects**

Of the 42 patients enrolled, 38 completed the study. Their clinical backgrounds and the results of their baseline pulmonary function tests are presented in Table 1. The patients had moderate to severe airflow limitation, moderate hyperinflation, and reduced diffusing capacity. Four patients dropped out of the study during cycle tests. Respiratory exacerbations were the reason for the withdrawal of two of the patients. One patient had left knee pain, and one patient had uncontrolled atrial fibrillation.

**Resting Physiologic Variables**

The resting spirometric measurements, dyspnea, and $S_{A\text{O}_2}$ did not differ among the three exercise tests. $F_{\text{VE}1}$ and $F_{\text{VCO}2}$ at 45 min after placebo were 1.12 ± 0.42 L (mean ± SD) and 2.34 ± 0.63 L, respectively, for the walking test, 1.12 ± 0.46 L and 2.35 ± 0.68 L, respectively, in the endurance test. The resting $B_5$ score and $S_{A\text{O}_2}$ for each of the three types of tests were 0.8 ± 0.8 and 96 ± 1%, 0.6 ± 0.4 and 96 ± 2%, and 0.6 ± 0.5 and 96 ± 2%, respectively.

Oxitropium bromide produced significant increases in $F_{\text{VE}1}$ and $F_{\text{VCO}2}$ at 45 min. The differences in $F_{\text{VE}1}$ and $F_{\text{VCO}2}$ at 45 min were 0.15 ± 0.16 L and 0.24 ± 0.30 L, respectively, with oxitropium bromide and placebo ($p < 0.001$ and $p < 0.001$, respectively).

**Statistical Analysis**

The results of the study were expressed as mean ± SD unless otherwise stated. Comparisons of the values observed with oxitropium bromide and placebo were made with a two-tailed paired $t$ test. The significance of the differences in the values observed for three exercise tests was determined with a repeated measures analysis of variance. When a significant difference was noted, post hoc analysis was done with Fisher’s protected least squares difference method to identify where the differences were significant. Comparisons between PCE and endurance test results were made with a two-tailed paired $t$ test. The dyspnea ratios were arbitrarily expressed as the ratio of the change in the Borg score ($\Delta B_5$) to: (1) the walking distance ($\Delta B_5$-D-distance); (2) maximal work rate ($\Delta B_5$-W-max); (3) change in $V_{\text{CO}2}$ ($\Delta B_5$-$\Delta V_{\text{CO}2}$); (4) change in $V_{\text{CO}2}$ ($\Delta B_5$-$\Delta V_{\text{CO}2}$); (5) change in $V_{\text{E}}$ ($\Delta B_5$-$\Delta V_{\text{E}}$); and (6) endurance time ($\Delta B_5$-Time) (12, 18). Wilcoxon’s signed ranks tests were used to compare the dyspnea ratios observed with oxitropium bromide and placebo. Spearman’s rank correlation tests were performed for analyzing the correlations between the dyspnea ratios and between their changes after oxitropium bromide. A value of $p < 0.05$ was considered statistically significant for all analyses.

**Table 1**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CHARACTERISTICS OF THE 38 MALE PATIENTS WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE WHO COMPLETED THIS STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>69.0 ± 6.6</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
<td>55.4 ± 26.0</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>1.09 ± 0.45</td>
</tr>
<tr>
<td>FEV$_1$/FVC, % predicted</td>
<td>0.69 ± 0.45</td>
</tr>
<tr>
<td>RV/TLC, % predicted</td>
<td>40.8 ± 16.5</td>
</tr>
<tr>
<td>TCO$_2$, % predicted</td>
<td>2.72 ± 0.69</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>79.2 ± 17.9</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>39.3 ± 10.7</td>
</tr>
<tr>
<td>DLCO, ml/min/mm Hg</td>
<td>5.99 ± 1.05</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>110.5 ± 17.1</td>
</tr>
<tr>
<td>DLCO/VA, ml/min/L/mm Hg</td>
<td>51.1 ± 10.3</td>
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<tr>
<td>Resting Pa$_{O_2}$, mm Hg</td>
<td>15.19 ± 4.99</td>
</tr>
<tr>
<td>Resting Pa$_{CO_2}$, mm Hg</td>
<td>62.7 ± 21.3</td>
</tr>
<tr>
<td>Definition of abbreviations: DLCO = diffusing capacity of carbon monoxide; VA = alveolar volume.</td>
<td></td>
</tr>
</tbody>
</table>
The changes in the peak physiologic variables after oxitropium bromide are shown in Table 2. The peak Borg dyspnea significantly reduced by 19%, among the exercise performance indices. The 6MWD improved a little, but significantly, by 1%, V̇O₂max increased by 3% in both PCE and in the endurance test, but the increase was not significant.

### DISCUSSION

This study showed that oxitropium bromide in a dose of 400 µg administered via an MDI brought about a large increase in cycle endurance time and a small but significant increase in 6MWD, but no significant changes in V̇O₂max in PCE. We showed that the effects of oxitropium bromide on exercise performance in patients with stable COPD could be determined differentially by the type of exercise test.

The endurance time showed the largest increase among the three exercise tests after oxitropium bromide. Endurance tests

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**TABLE 2**

**PEAK PHYSIOLOGIC VARIABLES AFTER PLACEBO IN THREE EXERCISE TESTS IN 38 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

<table>
<thead>
<tr>
<th></th>
<th>GMWT</th>
<th>PCE</th>
<th>Endurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak dyspnea, Borg</td>
<td>3.3 ± 1.8</td>
<td>5.5 ± 1.3</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>SaO₂ min, %</td>
<td>88 ± 7</td>
<td>90 ± 5</td>
<td>90 ± 4</td>
</tr>
<tr>
<td>HRmax, beats/min</td>
<td>112 ± 20</td>
<td>119 ± 19</td>
<td>125 ± 17</td>
</tr>
<tr>
<td>6-min walking distance, m</td>
<td>490 ± 67</td>
<td>— —</td>
<td>189 ± 92</td>
</tr>
</tbody>
</table>

**TABLE 3**

**CHANGES IN PEAK PHYSIOLOGIC VARIABLES AFTER OXITROPIUM BROMIDE IN THREE EXERCISE TESTS IN 38 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

<table>
<thead>
<tr>
<th></th>
<th>GMWT</th>
<th>PCE</th>
<th>Endurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak dyspnea, Borg</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>SaO₂ min, %</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>HRmax, beats/min</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>6-min walking distance, m</td>
<td>— —</td>
<td>— —</td>
<td>— —</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** HRmax = maximum heart rate; 6MWT = 6-min walking test; PCE = progressive cycle ergometry; SaO₂ min = minimal arterial oxygen saturation; V̇O₂max = maximal oxygen consumption; Wmax = maximal minute ventilation; V̇CO₂max = maximal carbon dioxide production; Ve max = maximal minute ventilation; Wmax = maximal minute ventilation; V̇CO₂ max = maximal carbon dioxide production; V̇O₂ max = maximal oxygen consumption; Wmax = maximal work rate.

* All values are expressed as mean ± SD.
† p < 0.001, significantly different from GMWT.
‡ p < 0.01, significantly different from GMWT.
§ p < 0.01, significantly different from PCE.
‡ p < 0.01, significantly different from GMWT.

**Dyspnea Ratios**

Oxitropium bromide significantly reduced ΔBS Time in the endurance test, from 0.335 ± 0.015 BS/s to 0.033 ± 0.013 (p = 0.003), and ΔBS Distance in the walking test, from 0.0053 ± 0.0033 BS/m to 0.0047 ± 0.0036 (p = 0.037). Oxitropium bromide also changed ΔBS ΔV̇O₂ in PCE from 0.018 ± 0.021 BS/ml/ min to 0.017 ± 0.018 BS/ml/min, but this was not a significant change. ΔBS Wmax, ΔBS ΔCO₂, and ΔBS ΔVe during PCE were also not significantly changed after oxitropium bromide.

There were significant correlations between ΔBS ΔTime and ΔBS ΔVO₂ in PCE (r = 0.62, p < 0.001, as well as between ΔBS ΔVO₂ and ΔBS ΔTime (r = 0.55, p < 0.001) and between ΔBS ΔTime and ΔBS ΔDistance (r = 0.54, p = 0.001) in PCE after placebo. The change in ΔBS ΔTime after oxitropium bromide was not correlated with the change in ΔBS ΔDistance (r = -0.02, p = 0.92), although these two dyspnea ratios were both significantly reduced by oxitropium bromide.
measured the ability to sustain a submaximal exercise capacity, which could characteristically improve when there was no significant increase in maximal exercise capacity. O'Donnell and coworkers also reported the reliability of exercise endurance as being both reproducible and responsive to change (12). In the present study, \( V_{O2\max} \) was an insensitive measure of improvement in a symptom-limited exercise test. In addition, Ikeda and coworkers reported that a dose of at least four times the standard dose of ipratropium bromide was necessary to improve the maximal cycle exercise capacity (19). Moreover, in the present study, the patients were more affected by reduced ventilatory capacity in PCE than in the endurance test. Therefore, it might be insufficient to measure the maximal exercise capacity in the incremental test in patients with COPD. In the 6MWT, patients sustained their steady state just below the maximum exercise capacity that they could reach within 6 min (20). Thus, the 6MWT would assess a mixture of endurance and maximal exercise capacity, although no physiologic data were obtained in the present study. Therefore, it is consistent that there was a small but significant improvement in the 6MWD when there was a large improvement in the endurance time and no significant increase in the maximal exercise capacity. The percent increase in the walking distance was small, partly because the patients' habitual walking speed prevented them from showing the maximal beneficial effect (20).

Endurance exercise tests had some other advantages besides being sensitive to changes in exercise performance after oxtitropium bromide. In the present study, the endurance test imposed a greater load on the patients with respect to ventilation and circulation, which had been preserved by the exercise limitation of breathlessness in exercise performance tests in patients with COPD in a previous study (21). Our patients got closest to their true maximal exercise level in the endurance test. Furthermore, considering that the activities of daily living of patients with COPD are submaximal, measuring the submaximal exercise capacity might be more meaningful than measuring the maximal exercise capacity. This will be one of the reasons why endurance procedures are used more often in pulmonary rehabilitation.

Breathlessness is the symptom that most commonly limits exercise in patients with COPD, and this symptom should therefore be regarded as an important outcome measure when evaluating the effects of interventions. We compared dyspnea ratios with placebo and oxtitropium bromide, because peak Borg scores were often similar before and after the intervention, and were not appropriate in evaluating dyspneic symptom responses to therapy (12). Oxtitropium bromide significantly reduced \( \Delta BS-Distance \) and \( \Delta BS-Time \), although it did not change any dyspnea ratios significantly in PCE. These reductions in exertional dyspnea may have been related to the improvements observed in exercise capacity. The baseline dyspnea ratios were significantly correlated with each other in three exercise tests. There was no significant relationship between the changes in \( \Delta BS-Distance \) and \( \Delta BS-Time \), which were both significantly reduced by oxtitropium bromide. Changes in breathlessness after oxtitropium bromide were quite different according to the type of exercise test. Oxtitropium bromide caused greater ventilation in both PCE and the endurance test, but the patients experienced higher peak dyspnea than with placebo only in PCE. The patients might also have been more susceptible to changes in ventilation in terms of breathlessness during the incremental test.

Some limitations in the present study should be mentioned. First, the order of the three exercise tests was not randomized. However, PCE was designed to be performed before the endurance test, in order to find the appropriate intensity of exercise. Second, the incremental work rate of 1 W every 3 s in the present study might have been higher than in other trials. The progressive work rate has not been standardized for exercise performance tests for patients with pulmonary diseases. In our previous studies (9, 18, 19), this incremental rate was useful in detecting the effects of bronchodilators on exercise performance. \( V_{O2\max} \) could be obtained from a ramp cycle exercise test of short duration (22), and a shorter exercise time will clear the reasons for stopping the exercise. We adopted a higher incremental rate for comparison with the endurance test, and to make the best use of the merits of PCE. However, further study will be required for determining an appropriate incremental rate in patients with COPD. Third, with respect to the higher intensity for the endurance test, an appropriate intensity, reported in the literature, has not been established. An ideal exercise performance test would place a greater load on patients during exercise, and a shorter exercise time would prevent a test from being stopped for psychological reasons in patients with COPD. This high intensity was effectively used in other studies (23, 24). Fourth, we evaluated symptoms mainly affected by dyspneic sensation and possible lower-extremity fatigue. However, separate evaluation for leg fatigue might have given us further useful information, since reduced peripheral muscle mass could limit exercise in patients with COPD.

In conclusion, our study showed that the three exercise tests examined had different capabilities in detecting changes produced by inhaled bronchodilators in exercise performance in patients with stable COPD. The endurance test showed the largest increase after oxtitropium bromide, and the endurance test was considered to be the most appropriate indicator of effect on exercise performance. When cycle ergometry is performed to examine the effects of some interventions on exercise performance, an endurance procedure should be considered to detect those changes that may not be observed with an incremental test.

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References


