Original Articles

Effects of high-dose ipratropium bromide and oral aminophylline on spirometry and exercise tolerance in COPD

U. SHIVARAM*, M. E. CASH*, F. MATEO† AND C. SHIM‡

*Pulmonary Section, Department of Medicine, Brooklyn, VA Medical Center, SUNY, Health Science Center at Brooklyn, Brooklyn, NY, U.S.A. 
†Greenville Regional Hospital, Division of Horizon Hospital, Greenville, PA, U.S.A. 
‡Pulmonary Division, Van Etten Hospital, Bronx, NY, U.S.A.

Exercise tolerance in chronic obstructive pulmonary disease (COPD) patients treated with oral aminophylline may be different from those treated with high-dose inhaled ipratropium bromide. The purpose of this study was to compare the effects of therapeutic doses of oral aminophylline with high-dose ipratropium bromide on spirometry and exercise tolerance. The study was conducted on three consecutive days in a double-blind, randomized, crossover fashion. Baseline studies obtained on each study day included vital signs, simple spirometry and a symptom-limited maximal cardiopulmonary stress test, after which patients received one of the following treatments on each day: Treatment 1, inhaled ipratropium (total dose of 144 µg) with placebo tablets; Treatment 2, inhaled placebo with oral aminophylline (400 mg); Treatment 3, inhaled placebo and placebo tablets. Simple spirometry was repeated at 60 and 120 min after baseline. Vital signs and cardiopulmonary stress testing was repeated at 120 min.

Eighteen patients were enrolled in the study, and 17 of these completed the study. There was a significant (P<0.05) increase in both forced expiratory volume in 1 s (FEV₁), from 0.75 (0.21) to 0.92 (0.3), and forced vital capacity (FVC), from 1.8 (0.79) to 2.11 (0.84), with high-dose ipratropium despite prior β-agonist therapy. Lack of improvement in exercise capacity was noted with ipratropium despite improvement in spirometry.

These results suggest that elderly patients with severe COPD may have exercise limitation that is not directly dependent on severity of airflow obstruction. Ipratropium bromide and aminophylline demonstrated no acute effects on exercise capacity.

Introduction

The quaternary ammonium anti-cholinergic compound ipratropium bromide is commonly prescribed for patients with chronic obstructive pulmonary disease (COPD). In patients with stable COPD, inhalation of 36–40 µg ipratropium has been shown to produce a larger improvement in forced expiratory volume in 1 s (FEV₁) with a greater peak response and duration of action when compared to conventional β-agonist aerosols (1–3). Although the optimal dose of nebulized ipratropium in COPD has been found to be 0.4 mg (4), the dosage of ipratropium via metered dose inhaler has not been established in COPD. It has been suggested that ipratropium by metered dose inhaler in a higher than recommended (54–108 µg) dose may be used as the first-line therapy for patients with COPD (5). At these higher doses, it has not been studied whether ipratropium results in
greater bronchodilation or improved exercise tolerance.

High doses of inhaled ipratropium bromide in young, healthy adults resulted in slowing of heart rate and increased stroke volume at rest (6). In another study of patients with COPD, inhalation of 36 µg ipratropium has been shown to be a more potent bronchodilator and free of cardiovascular side-effects when compared to therapeutic doses of theophylline which resulted in increased heart rate (7). Due to this difference in the degree of bronchodilation and cardiovascular response, the authors hypothesize that the exercise tolerance in patients treated with aminophylline can be different from those treated with ipratropium. The present study was designed to compare the effects of a therapeutic dose of oral aminophylline with high-dose inhaled ipratropium bromide on spirometry and exercise tolerance in elderly patients with severe COPD. A higher than the currently recommended dose of ipratropium, equivalent to the suggested maximum dose by Gross et al. (4), was administered.

Methods

Eighteen patients were selected from the authors’ outpatient population, and the study was approved by an Institutional Review Board and a Human Studies Subcommittee. Informed consent was obtained from each patient. All patients selected had COPD based on history, physical examination, chest roentgenogram and previous pulmonary function testing. All patients had a significant history of smoking. Three patients were smokers at the time of the study and the remaining patients were ex-smokers. Additionally, patients had stable COPD without any evidence of an acute exacerbation of their lung disease for 6 weeks prior to entry into the study. In all patients, FEV₁ was less than 1.5 L, total lung capacity (TLC) was greater than 80% predicted, and carbon monoxide diffusing capacity (DLCO) was reduced (Table 1). Arterial blood gas data was obtained within 3 months prior to study entry. Patients had no personal or family history of asthma, and no blood or sputum eosinophilia. Two patients were on a daily dose of 5 mg prednisone. All 18 patients were using theophylline prior to study entry. None of the patients required supplemental oxygen.

### Table 1. Baseline patient data (n=17)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.76 (6.53)</td>
</tr>
<tr>
<td>FEV₁ (l) (% pred.)</td>
<td>26.06 (10.57)</td>
</tr>
<tr>
<td>FVC (l) (% pred.)</td>
<td>46.06 (15.09)</td>
</tr>
<tr>
<td>DLCO (% pred.)</td>
<td>28.07 (16.66)</td>
</tr>
<tr>
<td>Smoking history (no. of patients)</td>
<td>3</td>
</tr>
<tr>
<td>Current</td>
<td>14</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>14</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>70.53 (13.07)</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>43.06 (14.64)</td>
</tr>
</tbody>
</table>

Study Design

The study was conducted on three consecutive days in a double-blind, randomized, crossover fashion. A single-day trial of each medication was performed to measure the acute effects of aminophylline and ipratropium on spirometry and exercise tolerance. The patients were instructed to discontinue their aminophylline or theophylline products 48 h and their ipratropium bromide 12 h prior to entry in the study. Patients took all other medications as usual including oral and inhaled steroids and inhaled β-agonist agents. Additionally, patients were instructed to eat a light breakfast and refrain from consuming caffeine-containing beverages.

Patients took their inhaled β-agonist 1 h prior to each testing period. Baseline studies obtained 1 h after using the β-agonist aerosols included: (1) vital signs at rest; (2) simple spirometry with an FEV₁ and forced vital capacity (FVC); and (3) symptom-limited maximal cardiopulmonary stress test with continuous monitoring of the patients’ electrocardiogram, blood pressure, oxygen consumption, minute ventilation and oxygen saturation via pulse oximetry. Testing began at the same time each morning.

After the baseline studies were completed, all patients received β-agonist inhaler followed by one of the treatments listed below, given at time 0.
TREATMENT 1
(1) Inhaled ipratropium bromide 2 puffs every 2 min for four doses (time 0, 2, 4, 6 min), for a total of 144 µg.
(2) Placebo tablets.

TREATMENT 2
(1) Placebo aerosol 2 puffs every 2 min for four doses (time 0, 2, 4, 6 min).
(2) Short-acting oral aminophylline in a dose of 400 mg.

TREATMENT 3
(1) Placebo aerosol 2 puffs every 2 min for four doses (time 0, 2, 4, 6 min).
(2) Placebo tablets.

The simple spirometry was repeated at 60 and 120 min after time 0 (baseline). Resting vital signs and maximal symptom-limited cardiopulmonary stress test were repeated at 120 min after time 0. A serum theophylline level was obtained at 120 min after time 0.

Testing Procedures
Vital signs were measured with the patient seated in an upright posture in a relaxed position. Simple spirometry was obtained using a Spiromate AS-600 (Riko, Lake Success, NY, U.S.A.). For each determination of FVC and FEV₁, the subjects performed at least three FVC manoeuvres, until the two best efforts were within 5% of each other. The best FVC and the best FEV₁ were then used for analysis. Symptom-limited exercise testing was performed on a variable-speed treadmill (Quinton, Seattle, WA, U.S.A.), and the work rate was increased every minute (Figure 1). Treadmill testing was selected because it is a familiar form of exercise that allows testing of most ambulatory patients. Patients were encouraged to walk on the treadmill until they could go no longer. Cardiac rhythm and heart rate (HR) were recorded on a cardiac monitor (Hewlett Packard, Andover, MA, U.S.A.) connected to a strip chart recorder (Hewlett-Packard). Oxymoglobin saturation (SaO₂) was monitored with a pulse oximeter (Nellcor, Hayward, CA, U.S.A.). Breath-by-breath collection of expired gases was accomplished through a two-way, non-rebreathing valve, pneumotachograph, and O₂ and CO₂ analysers (SensorMedics, Yorba Linda, CA, U.S.A.) were used to obtain oxygen consumption (VO₂), minute ventilation (VE), respiratory exchange ratio (RER), ventilatory equivalent for carbon dioxide (VE/VO₂) and oxygen pulse (VO₂/HR). Anaerobic threshold was determined using the ž slope method. One patient was severely limited by his COPD and was unable to perform a treadmill test. In this patient, a 6-min walk test was performed, and SaO₂ was monitored. The tests were considered maximal if 85% pred. max VO₂, VE or HR were achieved or there was persistent desaturation of 4% or greater compared to the resting value.

Analysis of Data
Predicted normals for FEV₁ and FVC were calculated using Knudson criteria. Predicted maximum VE, HR and VO₂ were calculated using the following formulas: max VE = FEV₁ × 35 (8), max HR =210-0.65 (age) &max VO₂ =4.2-(0.3 × age in years). Resting vital signs, FVC, FEV₁, VE, VO₂, RER, VE/VO₂ and VO₂/HR done before and after administration of treatments on the three separate days were compared using analysis of variance with a SPSS statistical package. A one way repeated measures ANOVA was used. Post-hoc significance testing for differences among means was carried out using a GT2 test. A P value of less than 0.05 was considered to be significant for the
differences among means. Data is reported as mean (standard deviation).

**Results**

Of the 18 patients enrolled, 17 completed the study. The remaining one patient complained of anterior chest pain during the first cardiopulmonary stress test, and the study was discontinued. His data was not included in the analysis.

Results of spirometry on the three study days is shown in Fig. 2(a,b). The FEV\textsubscript{1} increased significantly (P<0.05) with ipratropium at 60 min, and there was no further significant change at 120 min. There was no significant increase in FEV\textsubscript{1} with theophylline. Functional vital capacity improved significantly with both ipratropium and theophylline at 60 min, and there was no further increase at 120 min. This increase in spirometry is over and above the improvement produced by β-agonists.

Comparison of the parameters at peak exercise is shown in Table 2. Peak \( \dot{V}O_2 \), maximum achieved \( V_{\text{E}} \) and HR, oxygen pulse and \( V_{\text{E}}/\dot{V}O_2 \) did not differ significantly in the three treatment groups. All patients complained of dyspnoea as a reason for termination of the exercise test. None of the patients achieved anaerobic threshold. Seventeen patients completed two cardiopulmonary stress tests daily for three consecutive days. All tests were discontinued at the patient’s request. Patients complained of severe shortness of breath as a reason for termination of exercise. Therefore, a total of 102 cardiopulmonary stress tests were performed. In 72 (71%) of these tests, patients achieved a \( V_{\text{E}} \) max of 85% of predicted or greater. Eleven of 102 (10.8%) tests had evidence of oxyhaemoglobin desaturation of greater than 4% from baseline. In four tests (3.9%), there was technical difficulty in obtaining \( SaO_2 \). There was no significant difference in \( SaO_2 \) between the three treatments. There was no significant difference observed in the duration of exercise with the three different protocols.

The resting HR with Treatment 2 (aminophylline) was significantly increased. There was no significant difference in resting HR at baseline and 120 min for ipratropium or placebo treatments. There was no change in HR max during exercise (Table 2). Figure 3 demonstrates lack of change in peak \( \dot{V}O_2 \) despite marked improvement in FEV\textsubscript{1} with ipratropium.

The serum theophylline levels with Treatments 1 and 3 remained below 2 \( \mu \)g ml\(^{-1}\). The mean theophylline level with Treatment 2 was 11.4 (2.9) \( \mu \)g ml\(^{-1}\). All but one of the patients tolerated high-dose ipratropium bromide. One patient who had history of doing poorly with ipratropium bromide inhalation prior to the study, complained of cough with Treatment 1.
TABLE 2. Heart rate, minute ventilation, peak oxygen consumption and oxygen pulse on the three study days

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rest</th>
<th>Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>VE (l min⁻¹)</td>
<td>HR (beats min⁻¹)</td>
</tr>
<tr>
<td>Treatment 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>84.3 (13.3)</td>
<td>12.2 (2.9)</td>
</tr>
<tr>
<td>120 min</td>
<td>83.3 (14.3)</td>
<td>12.8 (4.0)</td>
</tr>
<tr>
<td>Treatment 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>84.2 (14.1)</td>
<td>13.0 (3.0)</td>
</tr>
<tr>
<td>120 min</td>
<td>90.4 (13.7)*</td>
<td>13.4 (3.6)</td>
</tr>
<tr>
<td>Treatment 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>84.8 (13.8)</td>
<td>12.3 (2.9)</td>
</tr>
<tr>
<td>120 min</td>
<td>83.3 (13.8)</td>
<td>12.2 (3.8)</td>
</tr>
</tbody>
</table>

Treatment 1, placebo tablets, ipratropium bromide inhaler; Treatment 2, placebo inhaler, oral aminophylline; Treatment 3, placebo tablets, placebo inhaler.

HR, heart rate; VE, minute ventilation; VO₂, oxygen consumption.

*P<0.05.

FIG. 3. Peak oxygen consumption (VO₂) compared to forced expiratory volume in 1 s (FEV₁) on the three study days compared with baseline on each day. *P<0.05. Solid bars, time 0; hatched bars, time 120 min.

and had worsening spirometry. All other patients had improvements in spirometry with Treatment 1. No other adverse effects were noted.

Discussion

In this study, high-dose ipratropium bromide and therapeutic levels of aminophylline were compared in 17 patients with COPD. It was hypothesized that high-dose ipratropium bromide results in significant bronchodilation which may translate into increased exercise capacity as measured by oxygen consumption. The results indicate that despite significant improvement in spirometry with ipratropium bromide, there is no corresponding increase in exercise capacity. In addition, there was no significant difference in exercise response when compared to aminophylline.

Inhaled ipratropium is an effective therapeutic agent in the management of stable COPD. Recently, it has been suggested that high-dose inhalation of ipratropium can be used to optimize its potential bronchodilating effects (5). Gross et al. (4) studied the dose-response of ipratropium as a nebulized solution in patients with stable COPD, and the optimal dose in this patient population was found to be 0.4 mg. These authors noted that the recommended dose of 40 μg via metered dose inhaler was found to be equivalent to about 0.1 mg of nebulized solution, and significantly less than the optimal
dose of nebulized ipratropium (4). In view of these findings, the optimal dose of inhaled ipratropium via metered dose inhaler is 160 μg (8-9 puffs). Based on this, the authors proceeded to evaluate the therapeutic efficacy and assess the side-effects of high-dose ipratropium, equivalent to about the optimal dose suggested by Gross et al. (4). In the present study, ipratropium at this dose resulted in additional bronchodilation over and above that seen with adrenergic agents. This is in agreement with a previous study using maximal β-agonist therapy, followed by atropine, where there was further bronchodilation with atropine over and above that produced by salbutamol (9).

To the authors' knowledge, this is the first study evaluating the effects of high-dose ipratropium on exercise tolerance in COPD patients. There was no difference in exercise tolerance between placebo, ipratropium and aminophylline. Previous studies using theophylline showed similar lack of improvement in exercise tolerance in COPD patients (10). The authors suggested that a 10–15% improvement in spirometry may be too small to result in significantly improved exercise tolerance. In the present patients, despite a much larger increase in resting pulmonary functions with ipratropium, no corresponding increase in peak oxygen consumption during exercise was found (Fig. 3). Similar findings were noted in a previous trial of ipratropium in chronic bronchitis patients, in whom there was a significant increase in FEV₁ and FVC, but no improvement in 12-min walking distance (11). In a study using salbutamol, there was no correlation between FEV₁ and exercise tolerance in COPD patients (12). Lack of correlation between exercise tolerance and FEV₁ has been noted in patients with COPD who were treated with inhaled metaproterenol, in whom exercise performance improved without significant improvement in spirometry (13). Such discrepancies between exercise capacity and bronchodilation can occur if some patients were maximally bronchodilated and others were not. This is unlikely in the present study patients since all but one patient showed marked improvement with ipratropium, suggesting that they were not maximally bronchodilated prior to administration of study drug. A recent study demonstrated a decrease in resting oxygen consumption compared to baseline with ipratropium bromide (14). The authors hypothesized that the fall in $\dot{V}$O₂ could indicate reduction in the work of breathing. Resting pulmonary functions may not be representative of the dynamic changes which occur during exercise in patients with COPD. In addition, relief of airway obstruction is not the only explanation for the effect on exercise. The exercise performance in COPD is limited by factors such as changes in lung mechanics, respiratory muscle fatigue, altered pulmonary gas exchange, impaired perception of breathlessness, nutritional factors and presence of cor pulmonale (15). Additionally, particularly in the age group of the present patients with chronic disease, deconditioning may play a role.

The use of oral aminophylline in the present patients resulted in theophylline levels of 11.4 (2.9) μg ml⁻¹ (moderate theophylline levels). Previous studies have suggested that because of a log-linear relationship between bronchodilation and blood level, little bronchodilator efficacy is lost by using a target therapeutic theophylline blood level of 10 (2) μg ml⁻¹ (16). Aminophylline treatment caused resting HR to increase significantly (Table 2), even at moderate theophylline levels. Previous studies have reported similar increases in resting HR in patients with COPD with the use of theophylline (17). Some authors report no increase in peak HR during exercise (18). Others noted that the peak HR during exercise significantly increases following aminophylline (19,20). The HR increase by aminophylline is thought to be mediated by catecholamines, and this effect may be obscured by the catecholamine outpouring during maximal exercise (21). Different levels of theophylline, the level of exercise, and the fitness of the subjects are possible reasons for the differences between studies.

In the present study, all patients were treated with β-agonist aerosol 1 h before administration of the study drug. β-agonist aerosol was administered before the baseline exercise test to allow even the severely limited patients to participate in the exercise test.

All of the patients in the present study had a significant smoking history, and all except one patient had improved spirometry with ipratropium. This is similar to the findings of Braun et al. who noted that ipratropium-responsive
patients had a greater smoking history (3) and lower FEV₁. Only one of the present patients complained of cough with ipratropium, and although blinded to the study agent, this one patient correctly identified ipratropium when he received it.

Another finding of the present study is that the baseline exercise data during maximal exercise performance was significantly different on the three study days. The mean coefficient of variation was greater than 15% for peak VO₂, peak VE and HR max. However, large spontaneous variations in VO₂, VE and HR have been reported in patients with clinically stable severe COPD (22).

In summary, the present patients had a marked increase in FVC and FEV₁ following administration of a relatively high dose of ipratropium, although they had been pre-treated with β-agonist aerosol. Since different dosages of ipratropium, i.e. high dose and conventional, were not tested, it is impossible to state whether the high dose was superior to the conventional. The authors were disappointed that the study patients showed no improvement in exercise capacity despite the marked improvement in pulmonary function. It is apparent that the elderly patients with severe COPD had exercise limitation that was not directly dependent on severity of airflow obstruction. One may wonder whether their exercise capacity would have improved further if their pulmonary function improvement was maintained for a long period.

Acknowledgements

The authors wish to thank Dr J. Martz for his assistance with statistical analysis, and Ms Rosetta Reid for her assistance in preparing the manuscript for publication.

References