Effects of theophylline and ipratropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease

Mitsuhiro Tsukino, Koichi Nishimura, Akihiko Ikeda, Takashi Hajiro, Hiroshi Koyama, Takateru Izumi

Abstract
Background—The effects of theophylline or anticholinergic agents on exercise capacity in patients with chronic obstructive pulmonary disease (COPD) remain controversial. The aim of the present study was to compare the effect of an oral theophylline with an inhaled anticholinergic agent and to examine the effects of combined therapy on exercise performance using progressive cycle ergometry.

Methods—Twenty one men with stable COPD and a mean (SD) forced expiratory volume in one second (FEV1) of 1.00 (0.40) l were studied. Theophylline (600 or 800 mg daily), ipratropium bromide (160 µg), a combination of both drugs, and placebo were given in a randomised, double blind, four period crossover design study. Spirometric data, pulse rate, and blood pressure were assessed before and at 90 and 120 minutes after inhalation. Symptom limited progressive cycle ergometer exercise tests (20 watts/min) were performed 90 minutes after each inhalation, and dyspnoea was measured during exercise using the Borg scale.

Results—The mean (SD) serum theophylline concentration was 18.3 (6.3) µg/ml, and seven patients had side effects during treatment with theophylline. Theophylline and ipratropium bromide produced greater increases in FEV1, maximal oxygen consumption, maximal minute ventilation, and several dyspnoea ratios than placebo. There were no differences between theophylline and ipratropium bromide except in maximal heart rate. A combination of both drugs produced greater improvements in pulmonary function and exercise capacity than either drug alone.

Conclusions—Both high dose theophylline and high dose ipratropium bromide improved exercise capacity in patients with stable COPD. Although data based on short term effects cannot be directly applied to long term therapy, theophylline added to an inhaled anticholinergic agent may have beneficial effects on exercise capacity in patients with COPD.

Keywords: chronic obstructive pulmonary disease; exercise capacity; ipratropium bromide; theophylline

For patients with stable chronic obstructive pulmonary disease (COPD), recent therapeutic recommendations have suggested that theophylline should be used only as a third choice drug if combined inhaled anticholinergic agents and inhaled β2 agonists fail to improve a patient’s condition.1 2 The goal of treatment in COPD is to improve exercise tolerance and decrease handicap. With respect to the beneficial effects of theophylline on exercise capacity, the results of previous studies have been conflicting.3-7 To our knowledge no study has yet demonstrated additional benefits of theophylline on exercise capacity when added to a dose optimised inhaled anticholinergic agent.

The purpose of the present study was to compare the short term effect of an oral theophylline with an inhaled anticholinergic agent and to examine the additional effect of combined therapy on exercise performance using progressive cycle ergometry in patients with stable COPD.

Methods
Twenty four men with clinically stable COPD as defined by the American Thoracic Society8 were recruited between April 1994 and July 1995. Entry criteria included age over 50 years, a history of cigarette smoking of more than 20 pack years, chest radiographs showing hyperinflation, a forced expiratory volume in one second (FEV1) of less than 70% of the predicted value, a best post-bronchodilator FEV1/forced vital capacity (FVC) of less than 0.7, and the absence of other disorders likely to affect exercise. Those with an exacerbation of their pulmonary disease within the last three months, a history of asthma, hypoxaemia defined as a PaO2 of less than 8 kPa at rest, treatment with oral bronchodilators and oral or inhaled corticosteroids in the preceding three months were excluded. Baseline pulmonary function tests were performed within the 14 day period preceding the study. Each subject underwent progressive exercise studies on at least three occasions before entering the trial. Written informed consent was obtained from all patients.

This study was performed in a randomised, double blind, placebo controlled, crossover fashion at approximately the same time on four separate days within a three week period. The interval between testing ranged from four to five days. After baseline studies had been completed, patients entered into the study underwent four separate treatment regimens: (1)
The patients were assigned to one of the four treatment regimens according to the 4 × 4 Latin square design.

Sustained-release theophylline (Slow-bid, Rhône-Poulec Rorer Japan, Tokyo, Japan) or matching placebo were each administered for three days. Patients weighing less than 60 kg received 800 mg to 16 patients and those weighing more than 60 kg received 160 µg ipratropium bromide daily were 800 mg to 16 patients and those weighing more than 60 kg received 160 µg ipratropium bromide. The doses of theophylline/placebo administered daily were 800 mg to 16 patients and 600 mg to five patients. The mean (SD) serum theophylline and ipratropium bromide; (2) theophylline and placebo; (3) placebo and ipratropium bromide; (4) placebo and placebo.

Results
Of the 24 patients enrolled, 21 completed the study. Three patients dropped out, two patients discontinued theophylline because of its adverse effect (tachycardia and arrhythmia) and one patient had an acute exacerbation during the study. Baseline values for the 21 patients who were evaluated are provided in table 1. The doses of theophylline/placebo administered daily were 800 mg to 16 patients and 600 mg to five patients. The mean (SD) serum
carbon dioxide tension.

Table 1  Baseline clinical data of the 21 patients who completed the study

<table>
<thead>
<tr>
<th>Mean (SD) Range</th>
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<tbody>
<tr>
<td>Age 65.4 (7.4) 51–77</td>
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<tr>
<td>Smoking (pack years) 58.7 (28.0) 20–120</td>
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<tr>
<td>FEV1 (l) 1.00 (0.40) 0.51–2.02</td>
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<tr>
<td>FEV1, % predicted 36.1 (13.1) 18.5–62.3</td>
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<tr>
<td>FVC (l) 2.58 (0.61) 1.35–3.78</td>
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<tr>
<td>FVC, % predicted 73.7 (16.2) 38.5–97.6</td>
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<tr>
<td>FEV/FVC (%) 38.7 (10.8) 21.2–58.7</td>
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<tr>
<td>TLC (l) 6.14 (0.99) 4.15–8.80</td>
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<tr>
<td>TLC, % predicted 110.2 (14.8) 72.7–140.8</td>
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<tr>
<td>RV/TLC (%) 51.0 (8.8) 37.5–69.1</td>
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<tr>
<td>TLCO (mmol/min/kPa) 5.77 (1.48) 2.95–8.57</td>
</tr>
<tr>
<td>TLC, % predicted 73.7 (16.2) 38.3–97.6</td>
</tr>
<tr>
<td>RV (l) 1.22 (0.19) 0.64–2.15</td>
</tr>
<tr>
<td>VO2 (l/min) 10.0 (1.2) 8.1–12.3</td>
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<tr>
<td>VCO2 (l/min) 5.5 (0.5) 4.3–6.7</td>
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</table>

The doses of theophylline/placebo administered daily were 800 mg to 16 patients and 600 mg to five patients. The mean (SD) serum theophylline and ipratropium bromide; (2) theophylline and placebo; (3) placebo and ipratropium bromide; (4) placebo and placebo.

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Theophylline concentration was 18.3 (6.3) µg/ml, but in two patients the serum concentration of theophylline was less than 10 µg/ml. Seven patients had mild side effects (nausea, insomnia and tachycardia) during treatment with theophylline.

Both theophylline and ipratropium bromide significantly (p<0.05) increased FEV1 compared with placebo (fig 1). The mean (95% CI) difference from placebo in FEV1, at 90 minutes after inhalation was 0.23 (0.17 to 0.29) l, 0.21 (0.14 to 0.29) l, and 0.40 (0.31 to 0.49) l for theophylline and ipratropium bromide, theophylline, and a combination of both drugs, respectively. A combination therapy produced greater increases in Wmax, VO2max, and VImax than either drug alone (p<0.05). The mean pulse rate at each time point with theophylline was greater than that without theophylline (p<0.05; fig 2).

The values of VO2max, VO2max and VImax increased significantly (p<0.05) with theophylline or ipratropium bromide when compared with placebo (table 2). Theophylline also showed a greater increase in Wmax than placebo (p<0.05), whereas ipratropium bromide did not. There were no differences between theophylline and ipratropium bromide in Wmax, VO2max, and VImax. A combination therapy produced greater increases in Wmax, VO2max, and VImax than either drug alone (p<0.05). The mean (SD) ratio of VImax to Vmax was 1.01 (0.35), 1.00 (0.28), and 0.98 (0.25) for placebo, ipratropium bromide, theophylline, and a combination of both drugs, respectively. The mean HRmax with theophylline was significantly greater than without theophylline (p<0.05). The mean (SD) ratio of HRmax to HRcap was 0.71 (0.08), 0.72 (0.08), 0.81 (0.10), and 0.83 (0.09) for placebo, ipratropium bromide, theophylline, and a combination of both drugs, respectively.

There were no differences between the study group in SaO2, at end of exercise, Borg score before load, and maximal Borg score. The mean (SD) maximal Borg score of placebo, ipratropium bromide, theophylline, and a combination of both drugs were 8.6 (1.6), 8.3 (1.8), 8.5 (1.7) and 8.6 (1.6), respectively. The three dyspnoea ratios (ABS-VWmax, ABS-AVO2, and ABS-AV02) with theophylline or ipratropium bromide were lower than those with placebo (p<0.05; fig 3). Combination therapy produced lower values for all three dyspnoea ratios than ipratropium bromide alone (p<0.05) and also produced a lower ratio of ABS-AV02 than theophylline alone (p<0.05).

Discussion

This study used an explanatory analysis rather than an intention to treat, and the maximum clinically permissible dosage of each drug was administered in order to produce the maximum therapeutic action. Since our previous report showed that the inhalation of ipratropium bromide at doses of 160 µg or more was necessary to improve maximal cycle exercise capacity in patients with stable COPD, we administered 160 µg of ipratropium bromide in the present study. The effect of theophylline on exercise capacity in patients with COPD has been controversial. The conflicting results of some studies may be attributed to different levels of theophylline and to different methodologies for measuring exercise capacity. The bronchodilating effects of theophylline seemed to be dose dependent in the usual therapeutic range. Moreover, Chrystyn et al showed that exercise performance assessed by six minute walking was dose dependent. McKay et al showed that high doses of theophylline (17 µg/ml) improved exercise performance as assessed by the...
treadmill test, but that low doses (10 µg/ml) did not. These findings suggested that higher doses of theophylline may be needed to achieve beneficial effects on exercise capacity, and our data support this. The use of high dose theophylline in our study resulted in a mean serum theophylline concentration of approximately 18 µg/ml, which was in the submaximal therapeutic range and was thought to produce improvements in exercise capacity.

In recommended doses theophylline has less of a bronchodilator effect than anticholinergic agents in patients with COPD. However, the results of our study show that high dose theophylline had a similar bronchodilating effect to that of ipratropium bromide and produced additional improvements even when four times the clinically recommended dose of ipratropium bromide was used. We speculate that the former effect may be due to the dose-response effect of theophylline, as discussed above, and the latter effect may be due to differences in the mechanism of action between theophylline and ipratropium bromide.

The ratio of V̇max to V̇Ecap was more than 1.0 and the ratio of HRmax to HRcap was less than 0.83 in every group. These data suggest that ventilatory rather than cardiovascular mechanisms were the limiting factor in the exercise test. Furthermore, the present study showed that all scores on the Borg scale were more than 8 at Wmax, which was greater than that shown previously. This suggests that dyspnoea may be an important limiting factor in addition to ventilatory mechanics. Ikeda et al. reported that the correlation between improvements in exercise capacity and improvements in FEV1 when anticholinergic agents were administered was significant. However, this correlation was weak and, in the present study, there was no correlation between the change in Wmax and the change in V̇E. These results support the theory that improvements in exercise capacity are not solely dependent on reductions in airflow limitation.

Several studies have reported that theophylline reduced the severity of dyspnoea in patients with COPD. Thus, theophylline may prevent the development of the sensation of dyspnoea during exercise and would therefore be expected to improve exercise tolerance. In our study three dyspnoea ratios (ABS-Wmax, ΔBS-ΔV̇O2, and ΔBS-ΔV̇E) with theophylline alone were lower than those with placebo. On the other hand, Teramoto et al. reported that anticholinergic agents possibly improved dyspnoea when they analysed the relationship between the Borg scale and oxygen uptake during exercise. In our study ipratropium bromide slightly but significantly improved the dyspnoea ratios, measured as ABS-Wmax, ΔBS-ΔV̇O2, and ΔBS-ΔV̇E, when compared with placebo. Reductions in the sensation of dyspnoea with ipratropium bromide may therefore be partly related to improvements in exercise capacity.

The results of this study represent the short term effects of theophylline administration over a period of three days and/or the effects of a single dose of ipratropium bromide. Although a single high dose of ipratropium bromide had no adverse effects in this study and a previous study, no evidence has been found of tolerance to high doses of anticholinergic agents during long-term therapy. Adverse effects of theophylline increase considerably at levels more than 15 µg/ml and thus would pose a problem in clinical practice in an elderly patient group. Furthermore, data from cycle ergometer exercise tests are not directly relevant to usual exercise patterns. The results of our study may not therefore be directly applied to long term therapy.

Although high dose theophylline was used in this study, two patients had low serum theophylline concentrations of less than 10 µg/ml. They were thought to be protocol violations. There is little difference between analyses including and excluding these subjects, and therefore the former analysis is used.

In conclusion, high dose theophylline and high dose ipratropium bromide both improved cycle exercise capacity in patients with stable COPD. In addition, high dose combinations of both drugs can produce additional improvements in exercise capacity beyond either drug alone. However, our study evaluated the short term effects of these therapeutic agents and these effects may be different with chronic dosing. Further study is therefore needed to evaluate the effects of long term therapy.

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10 Medical Section of the American Lung Association. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;136:225-44.
