The Additive Effect of Theophylline on a High-Dose Combination of Inhaled Salbutamol and Ipratropium Bromide in Stable COPD*

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**Study objective:** To determine the additive effect of oral theophylline in patients with stable COPD who received both inhaled salbutamol, 400 µg, and ipratropium bromide, 80 µg, four times daily administered with a metered-dose inhaler.

**Design:** Twenty-four male patients with stable COPD (FEV₁, 0.96 ± 0.43 L; 36.8 ± 17.0 percent predicted [% pred]) completed a randomized, double-blind, placebo-controlled crossover trial with oral theophylline for 4 weeks.

**Measurements and results:** The average serum theophylline level was 15.0 ± 5.5 µg/mL during treatment. On the whole, without inhalation of bronchodilators, FEV₁ was 0.93 ± 0.42 L during the placebo period and 1.00 ± 0.43 L (significantly different from placebo; p<0.01) during the theophylline period. At 15 and 60 min after inhalation of salbutamol, 400 µg, and ipratropium, 80 µg, the FEV₁ with placebo was 1.12 ± 0.43 L and 1.14 ± 0.46 L, respectively, and the FEV₁ with theophylline was 1.18 ± 0.45 L (p<0.01) and 1.20 ± 0.47 L (p<0.01), respectively. Daily peak expiratory flow rate also improved. Daily symptom scores were not significantly different between theophylline and placebo periods. Nevertheless, eight patients reported a subjective benefit during the theophylline administration period, and they were thus considered subjective responders. While FEV₁ after inhalation was significantly improved during the theophylline periods in subjective responders (change in FEV₁ between theophylline and placebo treatment 15 min after inhalation, 3.1 %pred; 60 min, 3.5 %pred), postbronchodilator FEV₁ was not significantly different between the placebo and theophylline periods in subjective nonresponders (15 min, 1.7 %pred; 60 min, 1.6 %pred).

**Conclusions:** On the whole, theophylline has a small bronchodilating effect but does not improve the symptoms of patients with stable COPD. However, one third of patients with COPD may respond subjectively to theophylline. The additive bronchodilating effect of theophylline may be related to the symptomatic improvement in subjective responders.

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**Key words:** bronchodilator; chronic obstructive pulmonary disease (COPD); ipratropium bromide; salbutamol; theophylline

The bronchodilating effect of oral theophylline is inferior to that of inhaled bronchodilators.1-6 Therefore, for patients with stable chronic obstructive pulmonary disease (COPD), recent therapeutic recommendations suggest that theophylline should be used only as a third-choice drug if combined inhaled anticholinergic agent and inhaled β₂-agonist fail to improve a patient's condition.7-9 However, some controversy exists as to whether the effect of theophylline is additive on that of the inhaled bronchodilators. Another complicating factor is that a single dose of theophylline may not predict the response to long-term bronchodilator therapy. Several clinical trials that compared over several weeks theophylline, inhaled β₂-agonist, and the combination of these drugs showed additive effects for these two drugs.10-18

Anticholinergic agents are often used as the first-line therapy in patients with stable COPD, and combined inhalation of an anticholinergic agent and a β₂-agonist may be more effective than inhalation of either drug alone. From the perspective of patient medical compliance, the dosage of a single inhaled bronchodilator should be maximized before a second agent is added.7-9 Nevertheless, several studies that examined the effect of theophylline in combination with an inhaled bronchodilator were performed using suboptimal doses of the inhaled bronchodilator.10-17 Our earlier study demonstrated

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718 Effect of Theophylline, Salbutamol, and Ipratropium Bromide on COPD (Nishimura et al)
that oral theophylline had an additive bronchodilating effect when used with inhaled salbutamol, 200 μg, and ipratropium bromide, 40 μg, but improvements in the symptoms were not observed.27 If larger doses of the β2-agonist and anticholinergic agent had been used, the additive bronchodilator effect of theophylline may not have occurred.

The purpose of the present study was to determine the additive effect of oral theophylline in patients who received a high-dose combination of inhaled anticholinergic agent and inhaled β2-agonist. Patients with stable COPD completed a randomized, double-blind, placebo-controlled crossover trial with oral theophylline for 4 weeks. To ensure that sufficient bronchodilators were inhaled to achieve near maximum bronchodilating effect, all patients continued to take both salbutamol, 400 μg, and ipratropium bromide, 80 μg, using a metered-dose inhaler (MDI) with a spacer device four times a day throughout the study period.

Materials and Methods

Patient Selection

Thirty-two male patients with stable COPD as defined by the American Thoracic Society28 were recruited from the patients who regularly visited the outpatient clinic at the Chest Disease Research Institute, Kyoto (Japan) University, over several months. We considered patients with no acute exacerbation of airflow obstruction within the preceding 3 months as having stable COPD. The inclusion criteria for entry into the study were as follows: age older than 55 years; a history of cigarette smoking of more than 20 pack-years; chest radiograph showing hyperinflation with or without a vascular deficiency pattern suggestive of pulmonary emphysema; a best postbronchodilator ratio of the forced expiratory volume in 1 s (FEV1) to the forced vital capacity (FVC) of less than 70%; and an FEV1 of less than 80% of the predicted value. We excluded patients with any history suggestive of asthma, heart disease, or any other illness. Patients treated with inhaled or systemic steroids in the preceding 3 weeks were also excluded.

To familiarize patients with the inhalation technique, they received detailed instructions on the use of an MDI and a spacer device (InspirEase).29 The canister was activated, the spacer with a MDI attached was held in the mouth, and after the patient had exhaled to functional residual capacity, a very slow inhalation was made until total lung capacity was reached. At this point the breath was held for at least 5 s. Patients with a poor technique were excluded from the study. Written informed consent was obtained from each patient.

Study Design

On the first day of the study, all patients underwent baseline pulmonary function tests 12 h after withdrawal of bronchodilators. Functional residual capacity was determined by body plethysmography (MBR-600, Nihon Kohden Co, Tokyo, Japan), and residual volume was calculated as functional residual capacity minus expiratory reserve volume measured by spirometric testing. Total lung capacity was determined as the sum of vital capacity and residual volume. Static compliance and airway resistance were also measured by body plethysmography. The diffusing capacity of the lung for carbon monoxide was measured by the single-breath technique (Chestac-65, Chest, Tokyo). Reversibility of FEV1 to 400 μg of salbutamol was measured after these pulmonary function tests. The drug was administered in four puffs from a MDI using the spacer device and spirometry was measured before and 15 min after inhalation.

Sustained-release theophylline and matching placebo (Rhône-Poulenc Rorer Japan, Tokyo) were each administrated for a 4-week period in a randomized, double-blind, placebo-controlled crossover fashion (Fig 1). The daily doses of theophylline were predetermined to provide average serum concentrations of more than 10 μg/mL and matching quantities of placebo were given. All of the patients continued to inhale both salbutamol (400 μg in four puffs) and ipratropium bromide (80 μg in four puffs) using an MDI four times a day throughout the study period. Treatment with other drugs was withheld for at least 2 weeks prior to and during the study period.

The patients visited the outpatient clinic around the same time at 4-week intervals. Inhalation was stopped at least 12 h before every visit. To ensure that the drugs were administered during deep inspirations, the inhalation technique was carefully observed by the same physician (K.N.). This physician also carefully observed all of the spirometric measurements. Blood samples for the assay of theophylline were collected at each visit and stored until the study was completed. Serum theophylline concentrations were determined by fluorescence polarization immunoassay using an analyzer (TDx, Dainabot, Tokyo).

Outcome Measures

Acute bronchodilator responses to the inhaled bronchodilators were measured at every visit to the clinic. Spirometry was assessed before, and 15 and 60 min after the inhalation of both salbutamol, 400 μg (four puffs), and ipratropium bromide, 80 μg (four puffs), using an MDI with a spacer device. Three consecutive flow-volume curves were recorded, according to the method described in the American Thoracic Society 1987 update,30 which requires the patient to stand during spirometry measurements. The spirometer (Autospiro AS-600, Minato Medical Science, Osaka) was calibrated with a 2.0-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 calculated according to the Japan Society of Chest Diseases’ proposal.31

Daily home measurements of peak expiratory flow rate (PEFR) were obtained during the entire study period before and 15 min after each inhalation of the bronchodilator four times a day using a flowmeter (Mini-Wright Peak Flow Meter, Airmed, Clement Clarke, London). Patients recorded the greatest value of three readings. Symptoms of cough, sputum, wheezing, and shortness of breath, rated on a scale of one to four (1=minimum to 4=severe)
vere), were noted in a diary, and side effects were also recorded during the entire study period.27 The PEFR readings, daily symptom scores, and side effects were assessed for the last 14 days of each 4-week period.

At the end of the study, all patients were asked to compare the two different treatment periods with respect to clinical well-being. If a patient did not find any difference in symptoms between the two treatment periods, he was considered a subjective nonresponder. If a patient felt much better during one side treatment period and much worse during another treatment period and his selection was compatible with theophylline treatment after the regimens were revealed, we defined him as a subjective responder. If his preference did not correspond to the theophylline treatment after the regimens were revealed, he was also defined as a subjective nonresponder.

Statistical Analysis

All data are expressed as the mean±SD. The significance of differences between values observed during treatment with theophylline and the placebo was determined by repeated measured analysis of variance. When appropriate, means were compared using the paired t test (two-tailed). Daily symptom scores were analyzed using nonparametric analysis of variance and Wilcoxon’s signed ranked test. Comparisons of baseline characteristics between responders and nonresponders were performed by unpaired Student’s t test for normally distributed continuous data, Mann-Whitney U test for nonparametric data, and χ² test for categorical data. For all tests, a p value <0.05 was considered to be statistically significant.

RESULTS

Seven patients who began the study did not finish it. One patient was withdrawn because he complained of urinary tract infection apparently unrelated to the study. Four patients dropped out of the study because of exacerbation due to respiratory tract infection: two during the theophylline period and two during the placebo period. While receiving treatment with theophylline, two patients discontinued its use because of gastrointestinal side effects. Twenty-five male patients completed the entire study. Since theophylline was not detected in the blood during the theophylline period in one patient, he was excluded from the data analysis. Consequently, a total of 24 patients were evaluated.

The baseline clinical data for the 24 patients are shown in Table 1. The average patient was elderly with a significant smoking history, severe airflow limitation, and hyperinflation. Three patients were current smokers and 21 patients were former smokers. The doses of theophylline/placebo administered daily were 400 μg for 1 patient, 600 mg for 20 patients and 800 mg for the remaining 3. Theophylline was not detected in the blood during the placebo period, but during active treatment serum theophylline averaged 15.0±5.5 μg/mL. There were only four patients with serum theophylline concentrations of less than 10 μg/mL (9.6, 7.9, 6.8, and 6.7 μg/mL).

Acute bronchodilator responses to both inhaled salbutamol, 400 μg, and ipratropium bromide, 80 μg, were measured at every visit to the clinic during the placebo and theophylline periods. Without inhalation of bronchodilators, FEV₁ was 0.93±0.42 L during the placebo period and 1.00±0.43 L (significantly different from placebo; p<0.01) during the theophylline period. At 15 and 60 min after inhalation of salbutamol, 400 μg, and ipratropium bromide, 80 μg, the FEV₁ with placebo was 1.12±0.43 L and 1.14±0.46 L, respectively, and the FEV₁ with theophylline was 1.18±0.45 L (p<0.01) and 1.20±0.47 L (p<0.01), respectively. The FVC was not significantly different between the placebo and theophylline periods before and 15 and 60 min after the inhalation of the bronchodilating agents. Both preinhalation and postinhalation values of daily PEFR were significantly higher during the theophylline period than during the placebo period (both p<0.01). No significant alteration of cough, sputum, wheezing, or shortness of breath was observed throughout the different phases of treatment (Table 2).

At the end of the study period, 15 patients did not recognize any symptomatic differences during the two crossover periods with active or placebo administration (subjective nonresponders). Nine patients reported symptomatic improvement during one of the two treatment periods. Since one of nine patients preferred the placebo period to the theophylline period, he was classified as a subjective nonresponder. The other eight patients were classified as subjective responders.

For these eight subjective responders, all the values of FEV₁ measured before and 15 and 60 min after the inhalation were significantly different between the placebo and theophylline periods (change

| Table 1—Baseline Clinical Data for 24 Patients Who Completed the Study* |
|-----------------|--------|--------|
| Age, yr         | 65.3±4.7 | 55-73  |
| FEV₁, L         | 0.96±0.43 | 0.36-1.77 |
| FEV₁, %pred     | 36.8±7.0  | 14.9-72.1 |
| FEV₁/FVC, %     | 38.4±9.0  | 23.8-57.3 |
| VC, L           | 2.91±0.62 | 1.98-4.36 |
| %VC, %          | 83.0±17.9 | 52.9-122.1 |
| Dco, mL/min/mm Hg | 18.1±5.0 | 10.2-26.7 |
| Dco, %pred      | 74.4±19.8 | 43.3-107.3 |
| Dco/Vc, mL/min/mm Hg/L | 3.66±1.11 | 2.09-6.07 |
| TLC, L          | 8.05±1.06 | 5.84-10.03 |
| TLC, %pred      | 121.2±14.2 | 100.9-155.4 |
| Cst, L/cm H₂O   | 0.50±0.19 | 0.19-0.86 |
| Raw, L/cm H₂O/L/s | 5.74±1.53 | 3.43-8.54 |
| FEV₁ reversibility, %initia | 121.1±14.5 | 93.5-151.7 |
| FEV₁ reversibility, change %pred | 6.5±4.6 | -4.0-11.5 |
| Blood eosinophils, ×10³ | 181±92 | 51-354 |

*VC=vital capacity; Dco=diffusing capacity for carbon monoxide; TLC=total lung capacity; Cst=static compliance; and Raw=airway resistance; SD=standard deviation.

†Not measured in one patient because of severe airflow limitation.

‡Not measured in four patients because of severe airflow limitation.
Table 2—Comparison of the Results of Spirometry on the Final Day of Each Treatment Period*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Theophylline</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, %pred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>35.7±16.9</td>
<td>38.5±17.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>15 min</td>
<td>42.8±17.2</td>
<td>45.0±17.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>60 min</td>
<td>43.7±18.3</td>
<td>45.9±18.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FVC, %pred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>69.3±21.6</td>
<td>72.6±18.8</td>
<td>NS</td>
</tr>
<tr>
<td>15 min</td>
<td>84.3±18.2</td>
<td>83.8±21.0</td>
<td>NS</td>
</tr>
<tr>
<td>60 min</td>
<td>85.3±19.5</td>
<td>85.4±22.4</td>
<td>NS</td>
</tr>
<tr>
<td>Daily PEFR, L/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>276±86</td>
<td>291±89</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>After</td>
<td>310±89</td>
<td>325±90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cough (1=minimum to 4=severe)</td>
<td>1.8</td>
<td>1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sputum (1=minimum to 4=severe)</td>
<td>1.4</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Wheeze (1=minimum to 4=severe)</td>
<td>1.7</td>
<td>1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea (1=minimum to 4=severe)</td>
<td>2.1</td>
<td>2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total symptom score (4-16)</td>
<td>7.0</td>
<td>6.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Daily home peak expiratory flow rate (PEFR) and symptom scores were obtained during the last 14 days of each treatment period. NS=not significant.

in FEV<sub>1</sub> between theophylline and placebo treatment 15 min after inhalation, 3.1 %pred; 60 min, 3.5 %pred) (Table 3). However, for 16 subjective nonresponders, FEV<sub>1</sub> values were not significantly different between the placebo and theophylline periods at 15 and 60 min after inhalation (15 min, 1.7 %pred; 60 min 1.6 %pred), although theophylline significantly improved FEV<sub>1</sub> at the preinhalation evaluation. When FVC, daily home PEFR, and symptom scores were analyzed separately for subjective responders and for nonresponders, the results were similar to those obtained when all patients were grouped together. Furthermore, none of the baseline clinical characteristics shown in Table 1 or the serum theophylline level was significantly different between subjective responders and nonresponders.

Sixteen patients (67%) complained of gastrointestinal side effects while receiving theophylline and 10 patients (42%) reported similar adverse effects during placebo administration. By counting the number of days that gastrointestinal side effects were reported, we found that theophylline was significantly associated with anorexia or nausea when compared with placebo administration (p<0.05). Three patients (13%) experienced irritability during theophylline treatment, whereas 2 (8%) reported a similar complaint during placebo treatment.

**Discussion**

The present report describes the first study (to our knowledge) that examined the additive effect of theophylline in patients with stable COPD who presumably received sufficient doses of both inhaled anticholinergic agent and inhaled β<sub>2</sub>-agonist. Our results indicate that the bronchodilating effect of theophylline, when used in combination with salbutamol, 400 μg, and ipratropium bromide, 80 μg, is small, but significant. This small additive bronchodilating effect does not result in symptomatic improvement. Although one third of patients reported symptomatic benefits with the administration of oral theophylline, none of the variables analyzed allowed us to predict these subjective responders.

Some clinical trials, which have compared the additive effect of combined therapy with theophylline and inhaled bronchodilators over several weeks, have reported contradictory results. Since both inhaled β<sub>2</sub>-agonists and anticholinergic agents induce dose-dependent bronchodilation in patients with stable COPD, we believe that theophylline can be determined only if these drugs are used at maximal doses. Some studies used a β-adrenergic bronchodilator administered in two puffs from an MDI, and others prescribed a heterogeneous drug mixture to set the background during the study. We used 400 μg of salbutamol and 80 μg of ipratropium bromide continuously in the present study. Since these doses are double the clinically recommended doses, we believe that maximum bronchodilation was achieved.
Dose-dependent bronchodilation also makes it difficult to discriminate between irreversible and reversible airflow limitation. Although reversibility in FEV₁ was not included as an entry criterion in the present study, we carefully selected patients with long-standing COPD. All the patients had been followed up over several months in our hospital. At the start of this study, we measured bronchodilator responses after the inhalation of salbutamol, 400 μg, using an MDI. Although FEV₁ after bronchodilator inhalation was on average 121% of the prebronchodilator value, similar bronchodilator responses have been reported in some previous studies on COPD. The clinical and physiologic improvements noted with inhaled bronchodilators are usually associated with the small but statistically significant increases in FEV₁.

Oral theophylline has been used for several decades as a bronchodilator. In addition, theophylline may improve diaphragmatic contractility and respiratory muscle performance, produce a sustained but modest enhancement of cardiac biventricular performance, and reduce the dyspnea sensation. However, none of our patients, even those who felt symptomatic benefit from theophylline (subjective responders), reported significant changes in their daily symptom scores. To our knowledge, there has been little evidence that oral theophylline treatment improved daily symptom scores. Daily symptom scores, such as the four-grade score that we used, may not be sensitive enough to monitor patient symptoms adequately. Therefore, the assessment of symptoms and subjective improvement could have been strengthened in the present study by using objective measurements of the patient's exercise tolerance such as a 6-min walk or a Borg or visual analog scale with standardized tasks to evaluate dyspnea on exercise. The inclusion of a quality-of-life scale to determine if any improvement was counterbalanced by adverse effects would have been useful.

Kirsten et al conducted a study on theophylline therapy withdrawal and found that about half of the patients with severe COPD can be considered theophylline responders. They also suggested that the clinical effectiveness of this drug cannot be attributed exclusively to bronchodilation. In the present study, while FEV₁ after inhalation was significantly improved during periods of theophylline treatment in subjective responders, postbronchodilator FEV₁ was not significantly different between the placebo and theophylline periods in subjective nonresponders. This finding suggests that the additive bronchodilating effect of oral theophylline is related to the symptomatic improvement in subjective responders and also suggests that daily symptom scores used in the present study did not reflect the symptomatic improvement in subjective responders.

Filuk et al reported that inhaled salbutamol and intravenous aminophylline are additive as bronchodilators in patients with COPD. However, Georgopulos et al found that intravenous salbutamol and aminophylline did not have a significant additive bronchodilating effect. The latter authors suggested that the distribution of the drugs could be different with inhaled and intravenous routes of administration. Thus, differential distribution of inhaled and orally administered drugs may account for our observation of an additive effect of oral theophylline when used in conjunction with a high dose of inhaled bronchodilators.

In conclusion, since theophylline has a small bronchodilating effect but does not improve the symptoms of patients with stable COPD, the usefulness of oral theophylline in combination with a high dose of inhaled bronchodilators is doubtful. However, when theophylline is used with adequate amounts of inhaled bronchodilators, our results suggest that one third of the patients with stable COPD may respond to theophylline. The additive bronchodilating effect of oral theophylline may be related to this symptomatic improvement in subjective responders. Since gastrointestinal side effects are frequently associated with theophylline administration, not all patients with COPD should receive theophylline and continuation of theophylline treatment should be considered only for patients who feel better. For individual patients with COPD, it would be worthwhile to perform a trial with theophylline to see if symptomatic improvement occurs before theophylline is continuously prescribed.

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