Effect of Inhaled Atropine or Metaproterenol in Patients with Chronic Airway Obstruction and Therapeutic Serum Theophylline Levels*

Paul M. Passamonte, M.D.;† and Alfonso J. Martinez, M.D.‡

Twenty-one patients with stable chronic obstructive pulmonary disease (mean FEV₁ = 0.98 L) and high-normal serum theophylline levels (15-20 μg/ml) were evaluated in a randomized, double-blind fashion for additional bronchodilator response to aerosolized normal saline, atropine, or metaproterenol. Patients were classified as responders (R; n = 9) or nonresponders (NR; n = 12) to inhaled isoproterenol when they were taking no medications. Atropine and metaproterenol caused a significant additional increase in FEV₁ for R (p < .05), whereas only atropine resulted in a significant increase for NR (p < .05). For R, the increase due to atropine was significantly greater compared to metaproterenol (p < .05). We conclude that inhaled atropine (an anticholinergic drug) may be preferable to inhaled metaproterenol (a β-adrenergic agonist) when additional bronchodilation is needed in patients with chronic obstructive pulmonary disease and high-normal serum theophylline levels.

The benefits derived from administering bronchodilators to patients with chronic obstructive pulmonary disease (COPD) are inconclusive and controversial, whereas their clinical efficacy in patients with bronchial asthma is well accepted. Some authors have suggested that all patients with COPD should be given a therapeutic trial of oral or inhaled bronchodilators whether or not they acutely respond to inhaled bronchodilators as shown by spirometric testing. Others recommend long-term administration of bronchodilators only to patients demonstrating a significant response to inhaled bronchodilators.

Intravenous and oral theophylline have been shown to cause statistically significant improvement in airway function in patients with COPD, but a clearcut, corresponding improvement in dyspnea or exercise tolerance has not been demonstrated. The addition of an inhaled or oral β-adrenergic agent to a therapeutic regimen containing theophylline results in greater bronchodilation than theophylline alone in adult or pediatric patients with bronchial asthma. One group has reported that patients with COPD who had been taking oral theophylline for one month had “no clear improvement” (less than 15 percent increase) when challenged with inhaled isoproterenol on the last day of the study. This was interpreted as indicating that theophylline had already caused maximal bronchodilation.

Anticholinergic agents have been shown to cause synergistic bronchodilation when given in combination with theophylline to asthmatic patients. No similar study has been reported in adult patients with COPD.

Since we were uncertain that data obtained in asthmatic patients could be applied to COPD patients, we wished to determine if additional bronchodilation could be obtained by giving an inhaled β-adrenergic agent or an inhaled anticholinergic agent to patients with high-normal serum theophylline levels.

Method and Materials

Twenty-one male patients were selected from the outpatient populations of the Harry S. Truman Memorial Veterans Administration Hospital and the University of Missouri Medical Center. This study was approved by the Institutional Review Board of the University of Missouri-Columbia School of Medicine, and informed consent was obtained from each subject. All patients were considered to have COPD based on a history of progressive dyspnea on exertion, many years of cigarette smoking with or without sputum production, forced expired volume in the first second (FEV₁) of 500 to 1,500 ml, and no sputum or blood eosinophilia. One patient was taking oral prednisone (5 mg on alternate days) for unclear reasons, and no patient had experienced an exacerbation of symptoms within four weeks of being studied.

We made every effort to exclude asthmatic patients from our study population. Patients denied a history of asthma or atopy (allergies, dermatitis, rhinitis), but mild wheezing was noted occasionally. Most of the patients had clinical chronic bronchitis or mixed chronic bronchitis/emphysema, but four had primarily emphysema. Pulmonary function data from previous years were available in all patients and showed stable or slowly declining values.

All patients were admitted to the hospital where a complete history was obtained, a physical examination was performed, and blood was drawn for a complete blood cell count and chemistry profile. Patients were excluded if sputum (Wright stain) or blood eosinophilia (percent eosinophils × total leukocytes >500/mm³) was

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Atropine or Metaproterenol in Chronic Airway Obstruction (Passamonte, Martinez)
detected, or if an acute worsening of symptoms (cough, wheeze, dyspnea) developed when bronchodilator therapy was withdrawn.

Approximately 36 hours after stopping bronchodilator use, spirometry was performed using a 14 L water-sealed spirometer (Warren E. Collins). The response to inhaled isoproterenol (0.26 mg; two actuations of a hand-held nebulizer) was determined 15 minutes after its administration. The best of three efforts (largest FVC) was selected for measurement of forced expired vital capacity (FVC), FEV₁, and forced expiratory flow rate between 25 and 75 percent of the vital capacity (FEF 25-75%). Patients were considered to have a significant response to inhaled isoproterenol if the FEV₁ increased by 15 percent of baseline and was at least 300 ml. The latter value was included because an increase of only 75 ml could represent a 15 percent increase in a patient with baseline FEV₁, of 500 ml. Patients were classified as responders (R) if the above criteria were met and nonresponders (NR) if the increase in FEV₁ was less than 15 percent.

Patients were given an IV loading dose of aminophylline (7 mg/kg) followed by a continuous infusion for the next three days to maintain a serum theophylline level of 15 to 20 μg/ml. Spirometry testing was repeated in triplicate on each of three successive mornings at 8:30 AM, and the values were used as the baseline for calculating that day's response to inhaled test drug. The average of all three baseline values was used to compute the response to intravenous theophylline.

One inhaled test drug was administered per day in a double-blind, randomized fashion. Normal saline (S), atropine sulfate (A, made as a stock solution of 10 mg/ml from atropine powder), and metaproterenol (M, commercially available) test drug solutions were flavored with peppermint oil to disguise any recognizable taste of atropine or metaproterenol. No patient had previously been treated with atropine.

Test solutions were aerosolized with a compressor driven nebulizer (Pulmo-aide, DeVilbiss) only when the patient inhaled. Each patient took 50 inhalations (FRC to TLC) calculated to aerosolize 1.5 ml of test solution. The dose of drug administered per 1.5 ml was: S, none; A, 0.05 mg/kg; and M, 15 mg. The maximal recommended dose of atropine was chosen, and the metaproterenol dose represents a standard clinical dose. The actual amount of drug delivered to the airway surface is unknown.

Spirometric testing was repeated 20, 40, 60, 120, and 180 minutes after completion of the aerosolized drug. The best of three spirometric tracings was selected for analysis. The FEF 25-75% was corrected for changes in the FVC. Improvement in FVC, FEV₁, and FEF 25-75% over baseline values for each day was calculated in liters and percent change. The criteria for a significant response to an aerosolized drug are: FVC, increase by at least 15 percent; FEV₁, increase by 200 ml and 15 percent; FEF 25-75%, increase by at least 25 percent.

Blood pressure and pulse were measured at the time of each spirometry test. Medication side effects (nausea, headache, tremor, dry mouth, and urinary retention) were monitored by standard questionnaire. Serum theophylline levels were measured by an enzyme immunoassay method (EMIT—aad; Syva). Serum samples were obtained for analysis after withholding bronchodilators for 36 hours and on each of the three test days just prior to administering the aerosolized drugs.

**Statistical Analysis**

The linear statistical model used to test the significance of an increase in FVC, FEV₁, or FEF 25-75% was arranged as a split plot in which the main plot contained the effect of nonresponder or responder status. The subplot contained the main effects of treatment (saline, atropine, or metaproterenol), time (20, 40, 60, 120, and 180 minutes), and all possible interactions of treatment and time within each group. Mean separation was ascertained using Fisher's LSD (least significant difference) test.

Student's t test was used for other comparisons.

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### Table 1—Baseline Clinical Data*

<table>
<thead>
<tr>
<th></th>
<th>Nonresponders (n = 12)</th>
<th>Responders (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Yr</td>
<td>65.5 ± 1.9</td>
<td>59.3 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>55 - 78</td>
<td>45 - 67</td>
<td>—</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.20 ± .23</td>
<td>2.71 ± .16</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Range, L</td>
<td>0.85 ± 3.14</td>
<td>1.96 - 3.31</td>
<td>—</td>
</tr>
<tr>
<td>% Pred</td>
<td>57.8 ± 5.3</td>
<td>66.2 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.97 ± 0.12</td>
<td>1.02 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Range, L</td>
<td>0.45 ± 1.50</td>
<td>0.55 - 1.34</td>
<td>—</td>
</tr>
<tr>
<td>% Pred</td>
<td>32.6 ± 4.1</td>
<td>31.2 ± 2.2</td>
<td>—</td>
</tr>
<tr>
<td>FEF 25-75%, L/S</td>
<td>0.39 ± 0.05</td>
<td>0.39 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Range, L/S</td>
<td>0.09 - 0.65</td>
<td>0.27 - 0.49</td>
<td>—</td>
</tr>
<tr>
<td>% Pred</td>
<td>10.6 ± 1.4</td>
<td>9.8 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean ± SE.

### RESULTS

Twenty-one male patients completed the protocol (12 NR; 9 R). Baseline pulmonary function data after stopping all bronchodilators for 36 hours are shown in Table 1. There was no significant difference in age, FVC, FEV₁, or FEF 25-75% between the groups. Although the absolute value for FVC was greater for R than for NR, the percentages of predicted values were not significantly different.
Table 2—Serum Theophylline Levels

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Atropine</th>
<th>Metaproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>20.3±1.5</td>
<td>19.1±1.4</td>
<td>17.2±1.2</td>
</tr>
<tr>
<td>R</td>
<td>18.4±1.8</td>
<td>19.7±1.2</td>
<td>21.0±1.9</td>
</tr>
</tbody>
</table>

*Mean ± SE.

The mean increase in FEV₁ after isoproterenol and theophylline for each group is shown in Figure 1. The increase in FEV₁ for NR was greater after theophylline (.16±.03 L; mean ± SE) than after isoproterenol administration (.05±.02 L), but it was not statistically significant (p>.05, Student's t test). For R, the increase in FEV₁ was of similar magnitude after either drug, and the mean values were significantly greater than for NR (p<.05). Serum theophylline levels were less than 2 μg/ml for NR and R immediately prior to testing with isoproterenol.

Serum theophylline levels on the days when aerosolized saline solution, atropine, or metaproterenol were administered are shown in Table 2. There were no statistically significant differences between or within groups (p>.05, all comparisons). Two patients from each group had theophylline levels on test days that were between 12 and 15 μg/ml, but no patient had a theophylline level less than 12 μg/ml.

The increase in FEV₁ (liters) after each aerosol is shown in Figure 2. The NR group had a small, statistically significant response to atropine, but not to metaproterenol, compared to placebo (Fig 2, top). Only atropine led to 200-ml increases in FEV₁. The difference in response between atropine and metaproterenol was not significant.

The R group experienced a larger increase in FEV₁ than NR (Fig 2, bottom). Compared to placebo, the increase after atropine was statistically significant (p<.05) at all times up to three hours. In addition, the response to atropine was significantly greater than to metaproterenol (p<.05). The effect of metaproterenol was declining at three hours whereas atropine was not.

The response to atropine or metaproterenol was analyzed for increases in FVC, FEV₁, and FEF 25-75% by plotting the group mean absolute increase vs the group mean percentage of increase at each of the five testing times (Fig 3). The NR group showed greater than 15 percent increase in FVC and greater than 25 percent increase in FEF 25-75% after atropine and metaproterenol, but only atropine led to an increase in FEV₁ that was 15 percent and 200 ml (Fig 3, top center). The R group showed significant increases in FVC, FEV₁, and FEF 25-75% after atropine. Metaproterenol led to clinically significant improvement only in the FEF 25-75% (Fig 3, bottom right).

The aerosolized drugs resulted in small reductions in pulse rate, systolic blood pressure, and diastolic blood pressure that were not significantly different than baseline values. Five of 21 patients receiving atropine complained of a dry mouth, and four of 21 patients receiving metaproterenol noted tremor.

**DISCUSSION**

This study represents a systematic evaluation of inhaled bronchodilators in patients with COPD and therapeutic theophylline levels. The difference in the mechanism of action of atropine and metaproterenol allowed us to investigate whether blocking efferent parasympathetic airway nerve endings or sympathomimetic stimulation of adenylate cyclase would lead to greater bronchodilation. The use of IV theophylline allowed us to maintain a constant blood level so that changes in spirometric values were due solely to use of the aerosolized drug.

Patients were grouped based on their response to isoproterenol at a time when they were receiving no bronchodilators. Previous authors have either not stated whether their patients with COPD were responders or nonresponders, or restricted their studies to groups of responders or nonresponders. Atropine, terbutaline, isoproterenol, and albuterol have been shown to cause significant bronchodilation when administered alone to patients with COPD whose response status was unknown. Inhaled atropine caused bronchodilation in "reversible" and "irreversible" chronic bronchitis when administered alone.
The lack of comparative data for responders and nonresponders prompted us to carry out this study.

We would like briefly to address the issue of reversibility of airway function in patients with COPD. Petty has written that up to 10 percent of patients with emphysema may have reversible airway disease. Wheezing in patients with COPD may indicate bronchodilator responsiveness rather than the severity of obstruction. Other experts would categorize patients with COPD whose FEV \textsubscript{i} increased by 15 percent as asthmatic, asthmatic bronchitic, or wheezy bronchitic. We tried to exclude asthmatic subjects from our study, but we cannot totally exclude the possibility that some of our nine responders developed COPD and intrinsic asthma concurrently.

In our study, the initial response to isoproterenol correlated with response to IV theophylline similarly to results recently reported for oral theophylline. The magnitude of the increase in FVC, FEV \textsubscript{i}, and FEF 25-75% after aerosolized atropine or metaproterenol was greater in R than NR (Fig 3). These data clearly demonstrate that high-normal serum theophylline levels do not cause maximal bronchodilation in either group of COPD patients. Our data are contrary to those of Dull et al, who found no significant additional bronchodilation when isoproterenol was administered to patients taking oral theophylline. One difference may have been that the dose of isoproterenol (0.15 mg) was comparably lower than the dose of metaproterenol that we administered. Atropine, acting through a pharmacologically different mechanism than theophylline or \beta-agonists, produced the greatest amount of additional bronchodilation in both groups. Lefcoe et al recently reported that the addition of inhaled ipratropium bromide (an atropine-like drug) to fenoterol plus theophylline led to greater bronchodilation than fenoterol plus theophylline in both asthmatic and chronic bronchitic patients. Thus, anticholinergic drugs can cause improvement in airway function even when cyclic AMP levels already have been increased by two different mechanisms.

Our study demonstrates that sequential therapy with theophylline and inhaled atropine or metaproterenol led to significant cumulative bronchodilation in both groups of patients. The group that deserves more attention are the nonresponders. In our study, theophylline alone resulted in a 16 percent increase. Eaton et al obtained 40 percent increases in FEV \textsubscript{i} with "high-dose" oral theophylline, resulting in serum levels of 17 to 22 \mu g/ml. However, in a subsequent study of ten patients receiving high-dose oral theophylline, the increase was only 12 percent (a value

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**Figure 3.** Plots of group mean absolute increase vs percentage of increase above baseline for FVC, FEV \textsubscript{i}, and FEF 25-75% at each of five times after each aerosolized drug. • saline; • atropine; • metaproterenol. Increases lying to the right and/or above the dotted lines are considered significant. NR (n = 12); R (n = 9).
comparable to ours). We have no explanation for this difference in results, but the data suggest that inhomogeneity among patients with COPD is a confounding factor when trying to compare published reports.

We did not evaluate our patients for subjective improvement when they received combination bronchodilator therapy. Lefcoe et al recently reported that patients with chronic bronchitis perceived no change in breathlessness when treated with combined theophylline, fenoterol, and ipratropium compared to placebo.

Is combination bronchodilator therapy feasible or cost-effective for stable outpatients? Administration of atropine or metaproterenol in the doses used would require purchase of a compressor-driven nebulizer. Atropine solutions would have to be made weekly from atropine powder to ensure activity of the drug. Metaproterenol solutions would not constitute a problem, since it is commercially available. In addition, the FDA has not approved nebulized atropine sulfate for use in bronchospastic diseases.

Hand-held nebulizers of metaproterenol are convenient, but the dose delivered in two inhalations would be much less than the 15 mg that we administered. Ipratropium bromide, a quaternary atropine-like drug, is available as an experimental drug in a handheld nebulizer. It has been shown to be an effective bronchodilator in patients with chronic bronchitis. Few of the side effects of atropine develop because it is poorly absorbed from the lower respiratory tract.

We have shown that significant bronchodilation can be achieved by giving bronchodilators sequentially to patients with COPD in doses that are clinically relevant. Patients responsive to isoproterenol when taking no medications obtain the greatest improvement in airway function after combination bronchodilator therapy. Atropine resulted in the largest increases in both groups. This suggests that anticholinergic drugs may be preferable to β-adrenergic drugs if a second bronchodilator is to be given to patients with chronic airway obstruction and high-normal serum theophylline levels. The relative roles of anticholinergic and β-adrenergic drugs in COPD patients when serum theophylline levels are low-normal are unknown.

REFERENCES


2 Petty TL. Improving patients with advanced chronic airflow obstruction. Chest 1983; 83:713-4


10 Klein JJ, Leftowitz MS, Spector SL, Cherniack RM. Relationship between serum theophylline levels and pulmonary function before and after inhaled β2-agonist in “stable” asthma. Am Rev Respir Dis 1983; 127:413-16


17 Pak CCF, Kradjan WA, Lakshminarayan S, Marini JJ. Inhaled atropine sulfate: dose-response characteristics in adult patients with chronic airflow obstruction. Am Rev Respir Dis 1982; 125:331-4


22 Chick TW, Jenne JW. Comparative bronchodilator responses to atropine and terbutaline in asthma and chronic bronchitis. Chest 1977; 72:719-23


26 Petty TL. Chronic bronchitis versus asthma—or what's in a name? J Allergy Clin Immunol 1978; 62:323-4
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