The Combination of Ipratropium and Albuterol Optimizes Pulmonary Function Reversibility Testing in Patients With COPD*

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Study objectives: To determine whether the combination of ipratropium bromide and albuterol results in greater and more consistent pulmonary function test (PFT) response rates than ipratropium bromide or albuterol alone in patients with COPD.

Design: Retrospective review of two recently completed 3-month, randomized, double-blind, parallel, multicenter, phase III trials.

Setting: Outpatient.

Patients: A total of 1,067 stable patients with COPD.

Interventions: Ipratropium bromide (36 μg qid), albuterol base (180 μg qid), or an equivalent combination of ipratropium bromide and albuterol sulfate (42 μg and 240 μg qid, respectively).

Measurements and results: PFT response rates were analyzed using 12% and 15% increases in FEV1 compared with baseline values and were measured in the various treatment groups on days 1, 29, 57, and 85 in these trials. Regardless of whether a 12% or a 15% increase in FEV1 was used to define a positive response, an equivalent combination of ipratropium bromide and albuterol sulfate was superior to the individual agents (p < 0.05; all comparisons within 30 min). In addition, a 15% or more increase in FEV1 was seen in >80% of patients who received the combination of ipratropium and albuterol sulfate during the initial PFT and continued to be observed 3 months after initial testing.

Conclusions: Use of a combination of ipratropium bromide and albuterol sulfate is superior to the individual agents in identifying PFT reversibility in patients with COPD.

(CHEST 1999; 115:966–971)

Key words: albuterol; bronchodilator; COPD; ipratropium bromide; pulmonary function

Abbreviations: PFT = pulmonary function test

COPD is part of a spectrum of diseases that share in common physiologic evidence of airflow obstruction. Among these diseases, cigarette-induced COPD is the most common; it affects approximately 14 million people in the United States and is responsible for an estimated $6.5 billion in direct and indirect costs per year.1–3 Airflow obstruction in COPD occurs largely on a structural basis and is generally considered to be irreversible.2 However, assessment of responsiveness to bronchodilators in patients with COPD has been problematic both clinically and experimentally.4–9 Likewise, there is a poor correlation between current methods of assessing acute pulmonary function reversibility and long-term bronchodilator response.8 Current American Thoracic Society recommendations for defining a significant bronchodilator response state that FEV1 should increase by 12% of baseline with an absolute change of 200 mL.9 Using these criteria, as few as 30% of patients with COPD will demonstrate reversibility during a pulmonary function test (PFT).8,9 To the extent that current recommendations for assessing bronchodilator response may result in an underestimation of the true incidence of reversibility in

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Manuscript received May 20, 1998; revision accepted November 3, 1998.

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patients with COPD, they may also impact patient care, especially if negative testing results in withholding of therapy.\textsuperscript{10}

Despite remaining uncertainties, recent data obtained in patients with COPD indicates that the long-term (i.e., 3 months) use of a combination of ipratropium and albuterol at recommended doses is superior to either agent alone as assessed by improvements in FEV\textsubscript{1}.\textsuperscript{11–13} From these observations, it is reasonable to postulate that the combination of ipratropium and albuterol may also be superior to either agent alone in identifying patients with COPD who have a short-term, clinically significant response to bronchodilators. The purpose of the present study, therefore, was to test the hypothesis that the combination of ipratropium and albuterol may also be superior to either agent alone in identifying patients with COPD.

MATERIALS AND METHODS

The PFT response rates obtained during two recently completed randomized, multicenter, double-blind, parallel group, phase III clinical trials comparing the safety and efficacy of a combination of ipratropium and albuterol to either ipratropium alone or albuterol alone were reviewed\textsuperscript{11} (data on file; Boehringer Ingelheim Pharmaceuticals Inc.). Informed consent was obtained from each subject who participated in these trials.

The study groups consisted of outpatients of either sex who were 40 years or older and who had a clinical diagnosis of COPD. Study participants were required to have a smoking history of more than 10 pack-years and to be regularly using at least two bronchodilators for control of their COPD symptoms during the 3-month period immediately preceding enrollment into either trial. Study participants also had to have an FEV\textsubscript{1} ≤ 65% of predicted normal values and an FEV\textsubscript{1} ≤ 70% of FVC. Patients were excluded from participation if they had a history of asthma or allergic rhinitis, atopy, or a total blood eosinophil count > 500/mm\textsuperscript{3}. Patients were also excluded if they required long-term oxygen use or > 10 mg of prednisone per day to manage their COPD symptoms during the month before entering into the study. In addition, patients were excluded if they had a recent history (1 year or less) of myocardial infarction, heart failure (3 years or less), or a cardiac arrhythmia requiring drug therapy.

Protocol: Patients from both trials underwent a medical history and physical examination, laboratory testing, and a 12-lead ECG before enrollment.\textsuperscript{11} After this initial screen and a 2-week baseline period, qualified patients (N = 1,067) were randomly assigned to receive two inhalations of ipratropium and albuterol inhalational aerosol (Combivent; Boehringer Ingelheim Pharmaceuticals, Inc; Ridgefield, CT), ipratropium inhalational aerosol (18 µg/inhalation), or albuterol inhalational aerosol (90 µg/inhalation) four times per day for 85 days. The dose selected for the combined ipratropium and albuterol inhalational aerosol was based on the usual recommended doses for each of the individual components (i.e., ipratropium inhalational aerosol, 18 µg/inhalation and albuterol inhalational aerosol, 90 µg/inhalation). These doses are based on mouthpiece delivery and are equivalent to 21 µg and 100 µg delivered from the valve, respectively. The combination delivers 21 µg of ipratropium bromide and 120 µg of albuterol sulfate per actuation from the valve (note that 120 µg of albuterol sulfate is the molar equivalent of 100 µg of albuterol base).

Return visits were scheduled every 2 weeks throughout the 85-day treatment period to assess and record adverse events and concomitant medication use. Likewise, patients in both trials were permitted to take up to two extra doses of investigational drug per day to control exacerbations. Concomitant maintenance doses of theophylline preparations and inhaled steroids were also permitted, but only if the patient’s dosage had been stabilized for at least 1 month before the baseline PFT studies and remained stable throughout the entire study period. Oral corticosteroids were permitted if the patient had been stabilized for at least 1 month on a total daily dose that was the equivalent of 10 mg of prednisone per day or less and the patient remained stable on this dosage throughout the study.

Pulmonary Function Testing: Pulmonary function testing started at the same time each day (i.e., between 7 and 10 am) and was conducted on treatment days 1, 29, 57, and 85. On these test days, measurements of FEV\textsubscript{1} and FVC were recorded before drug administration and again at 15, 30, 60, and 120 min after drug administration. Spirometric maneuvers were conducted in triplicate and the maneuver with the greatest sum of FEV\textsubscript{1} and FVC was recorded and used in the subsequent analyses. Predicted normal values for men and women for FEV\textsubscript{1} and FVC were derived from published algorithms.\textsuperscript{14} Spirometers used in these trials were required to meet American Thoracic Society standards.\textsuperscript{15}

To ensure standardized conditions on all PFT days, theophylline preparations were required to be discontinued 24 h before pulmonary function testing (compliance was assured by measuring theophylline levels before pulmonary function testing and rescheduling patients whose levels exceeded 5.0 µg/mL). Likewise, although long-acting β-agonists were not available at the time of this study, all short-acting bronchodilators and steroids had to be stopped at least 12 h before pulmonary function testing. Finally, the study drug, when applicable, had to be stopped at least 12 h before pulmonary function testing.

Definition of Bronchodilator Response: The interpretation of bronchodilator response in patients with COPD is controversial.\textsuperscript{4,7} For this reason, PFT data were evaluated on each test day, and a significant bronchodilator response was analyzed as a 12% and a 15% improvement in FEV\textsubscript{1} compared with baseline values.\textsuperscript{8}

Statistical Evaluation: Unless otherwise specified, all data are expressed as the mean ± SD. Response rates of patients who received the combination of ipratropium and albuterol were compared with response rates from each of the other treatment groups using Fisher’s exact test.

RESULTS

Patient Demographics

A total of 1,067 patients were enrolled in the two trials with 852 patients completing the entire study. The demographic and baseline characteristics of the 1,067 randomized patients are presented in Table 1. These patients had moderate to severe COPD with an overall FEV\textsubscript{1} of 0.95 ± 0.41 L, which corresponds to an FEV\textsubscript{1} percent predicted of 35.6 ± 13.6% for the group as a whole.

FEV\textsubscript{1} Response Rate on Individual Test Days

As shown in Table 1, mean baseline values for FEV\textsubscript{1} were comparable among the three groups and
remained comparable as well as within 6% of the day 1 baseline values on each of the subsequent PFT days. A clinically significant improvement in FEV\textsubscript{1} occurred on the individual PFT days for the majority of patients from each treatment group, whether improvement was defined as a 12% or a 15% increase in FEV\textsubscript{1} (Table 2). The percentage of patients demonstrating a 15% increase in FEV\textsubscript{1} declined on test day 4 (i.e., 85 days after therapy was initiated) compared with test day 1 (i.e., initiation of therapy) for all treatment groups and was significant (p < 0.05) for the ipratropium plus albuterol combination group. However, the overall decline in the percentage of responding patients on test day 4 was small for all groups and ranged between 2% and 8% (Table 2). More importantly, despite these modest declines, a greater percentage of patients in the ipratropium plus albuterol combination group continued to demonstrate a 15% increase in FEV\textsubscript{1} compared with the individual treatment groups.

**FEV\textsubscript{1} Response Rate on Multiple Test Days**

The variability of FEV\textsubscript{1} response on repeated measurements over time is shown in Tables 3 and 4. Only those patients who completed all four test days (852 patients) were included in this analysis. It is important to note that a significantly greater number of patients responded with a 12% or a 15% increase in FEV\textsubscript{1} on 3 or more test days if they received the ipratropium plus albuterol combination compared with either agent alone (p < 0.05, all comparisons). As shown in Figures 1 and 2, these differences were significant at all time points on the various testing days in patients who received the ipratropium plus albuterol combination compared with the single agents, and was most pronounced at the 30-min point.

**Discussion**

Our study confirms the hypothesis that the combination of ipratropium and albuterol results in greater PFT response rates than ipratropium or albuterol alone in patients with COPD. Specifically, the data demonstrate that whether a significant PFT response is defined as a 12% or a 15% increase in FEV\textsubscript{1} compared with baseline values, the combination of ipratropium plus albuterol is superior to the individual agents. In addition, the superior PFT response rate observed with the combination of ipratropium and albuterol was reproducible throughout a 3-month span. These data suggest that a combination of ipratropium and albuterol at usual doses optimizes the identification of PFT reversibility in a well-defined population of patients with COPD.

### Table 1—Patient Demographics and Baseline Pulmonary Function\textsuperscript{*}

<table>
<thead>
<tr>
<th></th>
<th>Ipratropium and Albuterol (n = 358)</th>
<th>Ipratropium (n = 362)</th>
<th>Albuterol (n = 347)</th>
<th>Overall (n = 1,067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>64.1 (8.2)</td>
<td>64.0 (7.7)</td>
<td>64.6 (7.8)</td>
<td>64.2 (7.9)</td>
</tr>
<tr>
<td>% Male</td>
<td>71</td>
<td>69</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Duration of disease, yr</td>
<td>8.9 (7.1)</td>
<td>8.5 (7.0)</td>
<td>8.2 (6.5)</td>
<td>8.5 (6.9)</td>
</tr>
<tr>
<td>Baseline FEV\textsubscript{1}, L</td>
<td>0.96 (0.39)</td>
<td>0.93 (0.43)</td>
<td>0.95 (0.40)</td>
<td>0.95 (0.41)</td>
</tr>
<tr>
<td>Percent of predicted FEV\textsubscript{1}—baseline</td>
<td>35.1 (13.1)</td>
<td>34.6 (14.1)</td>
<td>35.6 (13.5)</td>
<td>33.6 (13.6)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}All data expressed as mean (SD).

### Table 2—Patients With 15% Improvement in FEV\textsubscript{1} on Individual Test Days

<table>
<thead>
<tr>
<th></th>
<th>Test Day</th>
<th>Test Day</th>
<th>Test Day</th>
<th>Test Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>30 min</td>
<td>60 min</td>
<td>120 min</td>
</tr>
<tr>
<td>Ipratropium and albuterol (n = 292)</td>
<td>75%</td>
<td>83%</td>
<td>87%</td>
<td>89%</td>
</tr>
<tr>
<td>Ipratropium (n = 283)</td>
<td>54%</td>
<td>68%</td>
<td>76%</td>
<td>80%</td>
</tr>
<tr>
<td>Albuterol (n = 277)</td>
<td>64%</td>
<td>73%</td>
<td>79%</td>
<td>81%</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Ipratropium and albuterol combination significantly better than individual agents (p < 0.05).

### Table 3—Patients With 12% Improvement in FEV\textsubscript{1} 30 Min After Drug Administration\textsuperscript{†}

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group, %</th>
<th>Ipratropium and Albuterol (n = 292)</th>
<th>Ipratropium (n = 283)</th>
<th>Albuterol (n = 277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Test Days With Positive Response\dagger</td>
<td></td>
<td>0 Test days</td>
<td>1 Test day</td>
<td>2 Test days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93%</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>82%</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63%</td>
<td>46</td>
<td>46</td>
</tr>
</tbody>
</table>

\textsuperscript{†}SEM < 3% for all data points.

\textsuperscript{†}Pulmonary function tests performed on days 1, 29, 57, and 85.

\textsuperscript{‡}Ipratropium and albuterol combination significantly better than individual agents (p < 0.05).
The results of this study differ from those previously reported in the literature. Specifically, Anthonisen et al noted that although 70% of their patient population with COPD had at least one test during which FEV\textsubscript{1} increased by 15% after bronchodilator (isoproterenol) administration, only 30% of these patients demonstrated a positive response (15% increase in FEV\textsubscript{1}) on sequential testing during a period of 2.5 to 3 years. Likewise, several other investigators have identified wide variations in PFT response rates in patients with COPD and proposed several different ways of expressing bronchodilator response in this patient group.

In contrast to these earlier studies, the data from the present study indicate that a significant improvement in FEV\textsubscript{1} (defined as a 15% increase in FEV\textsubscript{1}) is not uncommon, occurs in > 80% of patients with COPD during initial testing, and continues to be found in nearly 80% of patients 3 months after initial testing. There are several plausible explanations for these apparent discrepancies. First, as suggested by Dompeling et al, the severity of underlying lung disease as assessed by baseline FEV\textsubscript{1} may affect responsiveness to bronchodilators. Thus, it is possible that the severity of underlying lung disease in the patients with COPD from the current study may have differed substantially from those reported previously and accounted for the differences in FEV\textsubscript{1} response rates. In this context, the FEV\textsubscript{1} for the overall group in the present study was 0.95 ± 0.41 L and the baseline FEV\textsubscript{1} percent predicted was 35.6 ± 13.6%. Although these values for baseline FEV\textsubscript{1} are somewhat lower than those reported by Brand et al (baseline FEV\textsubscript{1} > 1.2 L) and Dompeling et al (baseline FEV\textsubscript{1} = 2.44 ± 0.82 L), they are comparable to those reported by Meslier et al (FEV\textsubscript{1} percent predicted = 41.3 ± 16.8%). Hence, although it is intuitive that bronchodilator responsiveness may not be the same at all stages of disease severity in patients with COPD, the values for baseline FEV\textsubscript{1} observed in patients from the present study did not differ sufficiently from those reported in the literature to account for the fact that a significant improvement in FEV\textsubscript{1} occurred in > 80% of the study patients.

It is also arguable that in patients with low baseline FEV\textsubscript{1}, variability in the measurement of FEV\textsubscript{1} may have a more confounding effect on the assessment of bronchodilator response in that the absolute change in FEV\textsubscript{1} for any given percentage change from baseline in FEV\textsubscript{1} will be smaller. However, in this large study, variability in mean baseline FEV\textsubscript{1} mea-

Table 4—Patients With 15% Improvement in FEV\textsubscript{1}, 30 Min After Drug Administration

<table>
<thead>
<tr>
<th>No. of Test Days</th>
<th>Treatment Group, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipratropium and Albuterol (n = 292)</td>
</tr>
<tr>
<td>0 Test days</td>
<td>3</td>
</tr>
<tr>
<td>≥ 1 Test day</td>
<td>97†</td>
</tr>
<tr>
<td>≥ 2 Test days</td>
<td>90†</td>
</tr>
<tr>
<td>≥ 3 Test days</td>
<td>76†</td>
</tr>
<tr>
<td>All 4 test days</td>
<td>56†</td>
</tr>
</tbody>
</table>

*SEM < 3% for all data points.
†Pulmonary function tests performed on days 1, 29, 57, and 85.
‡Ipratropium and albuterol combination significantly better than individual agents (p < 0.05).

The percentage of patients demonstrating a 12% or greater increase in FEV\textsubscript{1} (by time) compared with baseline values on 3 or more test days. Patients who received ipratropium and albuterol had the highest PFT response rates (p < 0.05 at all time points).

Figure 1. Percentage of patients demonstrating a 12% or greater increase in FEV\textsubscript{1} (by time) compared with baseline values on 3 or more test days. Patients who received ipratropium and albuterol had the highest PFT response rates (p < 0.05 at all time points).
surements was small (<6%) and did not increase during the study. Hence, it is unlikely that differences in the severity of underlying lung disease or variability in mean baseline FEV$_1$ measurements alone accounts for the higher FEV$_1$ response rates reported in the present study.

Second, it is possible that differences in study design accounted for the higher FEV$_1$ response rates observed in patients with COPD from the current study. Along this line, previous studies include medication washout protocols that vary considerably. For example, Meslier et al$^6$ required that $\beta_2$-agonists be stopped only 8 h before pulmonary function testing, but did not require theophylline be discontinued. By contrast, the medication washout protocol was much more rigorous in the present study and involved not only a 12-h washout period for even short-acting $\beta$-agonists, but also a 24-h, verifiable washout of theophylline preparations. Moreover, patients were required to refrain from caffeine-containing foods and beverages, smoking, strenuous activity, and noxious fumes during the PFT days. Clearly, this rigorous medication washout protocol accounts, in part, for the fact that baseline FEV$_1$ remained unchanged among the treatment groups on the PFT days throughout these trials, and the fact that the FEV$_1$ response rates, as assessed by a 15% increase in FEV$_1$, exceeded 60% on 3 or more test days even for the $\beta_2$-agonist-treated patients.

Finally, it is possible that the combined actions of the medications themselves contributed to the improved PFT response rates observed in the study. In this regard, bronchial smooth muscle tone depends on both the innervation of the parasympathetic system and stimulation of $\beta_2$-receptors in the lung.$^{16,17}$ Thus, it is logical to postulate that attempts to reduce bronchoconstriction through two distinct mechanisms (anticholinergic and sympathomimetic) may maximize bronchodilator response. That this postulate is true is consistent with the results of recent trials in which the combination of ipratropium and albuterol were more effective than either agent alone in improving pulmonary function in patients with COPD.$^{13,18,19}$

It must be acknowledged that there were small declines (2% to 8%) in the percentage of patients who responded to bronchodilator therapy on test day 4 compared with test day 1 in all groups, and this decline was significant for the ipratropium and albuterol combination group. The precise explanation for these modest declines is unclear, but it may be related to the small fluctuations that occurred in baseline FEV$_1$ on test days subsequent to test day 1. Likewise, although all patients were required to have a stable respiratory status for 6 weeks before entry into the study, patients in long-term trials can and do develop conditions (e.g., COPD exacerbations, upper respiratory infections) after entry into the study that can affect lung function and responsiveness to bronchodilators. Finally, although tolerance to a bronchodilator can also lead to a decline in bronchodilator responsiveness, this explanation is unlikely in that...
there was no evidence of a tolerance effect in the ipratropium and albuterol treatment group as detailed in the published report of the full phase III trial.11

It must also be acknowledged that the definition of airway responsiveness to bronchodilator therapy in patients with COPD is controversial and that regardless of the definition, it may not remain stable with time. It is for this reason that we defined response to bronchodilator therapy using standard PFT criteria (ie, a 12% or 15% increase in FEV₁), and that the conditions on dilator therapy using standard PFT criteria (of the definition, it may not remain stable with time. It is for this reason that we defined response to bronchodilator therapy using standard PFT criteria (ie, a 12% or 15% increase in FEV₁), and that the conditions on dilator therapy using standard PFT criteria (of the definition, it may not remain stable with time. It is for this reason that we defined response to bronchodilator therapy using standard PFT criteria (ie, a 12% or 15% increase in FEV₁), and that the conditions on dilator therapy using standard PFT criteria (of the reference values and interpretative strategies. Am Rev Respir Dis 1986; 105:1411–1419


In summary, the data from this study indicate that bronchodilator responsiveness can be demonstrated to occur in the majority of patients with COPD who receive either ipratropium bromide or albuterol alone or the combination of ipratropium and albuterol. However, the data also indicate that the combination of ipratropium and albuterol is superior to either agent alone at standard dosages in identifying bronchodilator responsiveness in patients with COPD. In addition, the reproducibility of responsiveness to bronchodilators in patients with COPD is improved when the PFT is performed using a combination of ipratropium and albuterol. Thus, consideration should be given to assessing bronchodilator response in patients with COPD using a combination of ipratropium and albuterol in place of the current use of a β-agonist for reversibility testing. Finally, whereas failure to demonstrate bronchodilator responsiveness on the PFT does not preclude the possibility of a clinical benefit, reversibility testing results in patients with COPD may be improved by (1) discontinuation of theophylline preparations and long-acting β-agonists 24 h before the PFT, (2) discontinuation of inhaled or oral steroids and inhaled or oral β-agonists 12 h before the PFT, (3) avoidance of smoking, strenuous activity, and caffeine-containing foods and beverages on PFT days, and (4) assessing response approximately 30 min after bronchodilator administration.

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