For COPD a Combination of Ipratropium Bromide and Albuterol Sulfate Is More Effective Than Albuterol Base

Sammy Campbell, MD

Background: A combination metered-dose inhaler aerosol containing ipratropium bromide and albuterol sulfate has been reported to be more effective than either of its components in patients with chronic obstructive pulmonary disease. The dose of albuterol sulfate is equal in moles per liter to the dose of albuterol base used in the commercially available metered-dose inhalers.

Objective: To compare the safety and efficacy of the combination of ipratropium bromide and albuterol sulfate with a commonly prescribed albuterol metered-dose inhaler containing albuterol base alone.

Methods: Investigators at different sites performed a double-blind, 29-day trial involving 357 patients with chronic obstructive pulmonary disease. Efficacy measurements were taken at 15, 30, and 60 minutes after treatment with study medication and then hourly up to 6 hours on days 1 and 29 of the trial. The primary end point was improvement in forced expiratory volume in 1 second. Clinical status was followed up and safety monitoring was also performed.

Results: The combination produced a significantly greater peak and mean improvement in forced expiratory volume in 1 second over albuterol base alone on both test days. Similar changes were seen with forced vital capacity. Evaluations of clinical status were better for patients receiving combination therapy, and some improvements were statistically significant. The overall incidence of adverse effects was similar in the 2 treatment groups.

Conclusion: We conclude that a combination of ipratropium bromide and albuterol sulfate is more effective at improving pulmonary function than albuterol base alone, with no potentiation of adverse effects.

Arch Intern Med. 1999;159:156-160

Ipratropium bromide and β-agonist aerosols have become first-line bronchodilators for patients with chronic obstructive pulmonary disease (COPD). They produce roughly equivalent improvement in forced expiratory volume in 1 second (FEV1), although ipratropium may be more effective than β-agonist therapy for patients with COPD. The 2 medications appear to have different modes and sites of action in the lung. Ipratropium is an anticholinergic compound that blocks bronchoconstriction by competing with acetylcholine for airway binding sites. β-Agonists produce direct bronchodilation by stimulating sympathetic pathways. Barnes and coworkers report that cholinergic receptors are numerous in central airways and sparse in peripheral airways, while the highest density of β-receptors is in the bronchioles. Thus, the primary site of action of ipratropium may be in the central airways, and β-agonists in the peripheral airways.

The difference in mechanism and possibly in site of action suggests a clinical rationale for combining the 2 agents in the treatment of COPD. American Thoracic Society standards for treatment of COPD include using both ipratropium and a selective β2-agonist in patients with daily symptoms. In theory, a combination of agents that work via the parasympathetic and sympathetic airways might produce a synergistic or complementary effect.

In a multicenter trial (n = 534), a combination metered-dose inhaler (MDI) aerosol containing ipratropium bromide and the β-agonist albuterol sulfate was more effective than either of its components alone. Although albuterol base and albuterol sulfate are believed to be therapeutically equivalent, the albuterol MDI aerosols marketed in the United States are not sulfate formulations. Thus, this study was undertaken to compare the effects of combination therapy directly with a marketed albuterol base aerosol.
PATIENTS, MATERIALS, AND METHODS

The objective of the study was to compare the safety and efficacy of a combination aerosol containing ipratropium bromide and albuterol sulfate with albuterol base in patients with COPD.

Three hundred fifty-seven patients were enrolled at 17 centers in a 29-day randomized, double-blind, parallel-group trial. Patients were required to be aged 40 years or older and to have a diagnosis of COPD. Diagnostic criteria included stable airway obstruction with an FEV1 of 65% or less of predicted normal value and an FEV1/forced vital capacity (FVC) of less than 70%. Since smoking is a primary risk factor for COPD, patients were required to have a smoking history of more than 10 pack-years. They were also required to have been using at least 2 prescribed bronchodilators for control of their COPD symptoms during the 3-month period before the trial. Patients with a history of asthma, allergic rhinitis, or atopy or a total blood eosinophil count of more than 0.3 × 10^9/L were excluded.

The overall mean age of patients was 65.6 years. There were 251 men and 103 women. The mean duration of disease was 9.6 years (range, 0.3-44 years). Overall, the mean FEV1 compared with 36.2% predicted, and the mean ratio of FEV1 to FVC was 36.1%. A total of 247 (69%) of 357 patients were taking both an inhaled anticholinergic bronchodilator and an inhaled β-agonist prior to study entry.

Patients were randomized into 2 treatment groups, 177 received the combination aerosol and 180 received albuterol. They were instructed to take 2 puffs of their medication 4 times daily for 29 days. They were allowed to take up to 2 extra puff doses per day for the control of symptoms. Patients were requested to record the number of doses taken each day on medication dosing cards. One inhalation of the combination aerosol (18 µg of ipratropium bromide plus 90 µg of albuterol sulfate) delivers to the patient the same amount of albuterol as 1 inhalation from the commercial albuterol base product. The study protocol therefore resulted in a comparison of equivalent doses of the combination therapy with albuterol.

Concomitant medications were carefully monitored. Inhaled bronchodilators other than the study drugs were not allowed during the treatment period. The use of long-term oral corticosteroids were allowed if the patient was stabilized with a minimal dose for at least 1 month before the study period. Temporary increases in the steroid dose or additions of steroids required for the treatment of exacerbations were allowed for a maximum of 7 days during the 29-day treatment period. Pulmonary function testing was postponed until at least 48 hours, but not more than 7 days, after the last increase or addition of steroids.

Theophylline was allowed for maintenance therapy if the dosage was stable for 1 month before the study period. Two 5-day increases in the theophylline dose or additions of theophylline were allowed for the treatment of exacerbations. Pulmonary function testing was postponed until at least 48 hours, but not more than 7 days, after the last increase or addition of theophylline.

Before admission to the trial, informed consent was obtained and a complete medical history, a 12-lead electrocardiogram, and a physical examination were performed. Baseline laboratory evaluation included complete blood cell count; serum analyses of total protein, albumin, total bilirubin, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, urea nitrogen, creatinine, uric acid, calcium, inorganic phosphorus, and glucose levels; urinalysis, and total blood eosinophil count. Patients were then stabilized for 1 week with their concomitant COPD medications; test medications were excluded during this time to establish a baseline.

This trial conformed to the informed consent provisions and institutional review board provisions of the Code of Federal Regulations. Pulmonary function testing was carried out on days 1 and 29 of the treatment period. The patients were instructed not to use their inhaled medication for at least 12 hours before testing. Baseline spirometry was performed. Patients then took 2 puffs of their trial medication. Spirometry measurements were taken 15, 30, and 60 minutes after drug administration and hourly after that for a total of 6 hours. All pulmonary function tests were conducted in triplicate, and the results from the spirometric maneuver with the greatest sum of FEV1 and FVC was used for analysis.

The primary efficacy variable was FEV1, and the primary efficacy end points were peak change from test-day baseline duration of action and area under the curve (AUC) above test-day baseline. Analysis of AUC included the following segments: 0 to 4 hours (AUC0-4), 4 to 6 hours (AUC4-6), and well as the full 6 hours (AUC0-6). Secondary end points included AUC, peak response, and response at each time point for FVC. Biweekly physicians’ global evaluations and patients’ assessment of symptoms (wheezing, coughing, chest tightness, and shortness of breath) were used to evaluate effects of the drugs on the patients’ underlying COPD. The patients’ symptoms were graded from 0 (not present) to 3 (severe).

Safety end points were frequency of adverse events, changes from baseline physical examination findings over the 29 days, and changes from baseline in vital signs during the pulmonary function test days. Adverse events were recorded at each visit by the physician, including date of onset, number of minutes between the time of the last dose of study medication and the onset of the event, end date, intensity of the event, treatment required, outcome of the event, and the investigator’s assessment of each event’s relationship to the study drug.

The FEV1 values were adjusted for test-day baseline FEV1, center, and treatment-by-center interaction. When patients could not complete 6 hours of testing, the data were handled as follows: if testing was stopped early for reasons unrelated to COPD, the last recorded value on that test day was used for all subsequent missing values, provided at least 4 hours of testing had been completed. If testing was halted because of lack of response, the lowest value observed for that patient on that test day was used for data following testing interruption. Analysis of covariance with terms for treatment, study site, and treatment-by-site interaction was used to compare the 2 treatment groups. The baseline data were used as the covariate. Fisher exact test was used to compare adverse events and other frequency information.

©1999 American Medical Association. All rights reserved.
RESULTS

EFFICACY

Baselines for the 2 treatment groups were comparable on each of the test days and were stable over the course of the study. A total of 356 patients completed the trial and were available for efficacy analysis: 176 in the combined therapy group and 180 in the albuterol group. On each of the test days, both groups demonstrated a clinically significant response to medication; ie, a mean improvement in the FEV₁ of at least 15% over baseline. The overall response to combined therapy was superior to albuterol alone, especially during the first 4 hours of testing (Figure 1).

The mean peak response for the combined therapy group was significantly greater than for the albuterol group. Combined therapy means ranged from 26% to 28% greater than albuterol alone (Table 1). The mean AUC₀₆ and AUC₀₄₆ were significantly greater (P<.05) for combined therapy than for albuterol on both test days, and the AUC₄₆ was significantly greater on day 1.

The median onset time for each group on each test day was by 15 minutes, which was the first test point after drug administration. Median time to peak was 1 hour for combined therapy and 30 minutes for albuterol on both test days. Median duration of action for the combined therapy group ranged from 3 to 4 hours; for albuterol it was 2 hours. The duration of action for combined therapy was significantly greater than for albuterol on day 1 only.

On both test days, more patients in the combined therapy group had increases of at least 15% from baseline during the first 4 hours than in the albuterol group. Both drugs continued to be effective on day 29, with a similar number of patients demonstrating a 15% increase in FEV₁ during the first 2 hours (Figure 2).

The FVC results mirror those seen in FEV₁. The overall response to combined therapy was statistically significantly better than the response to albuterol alone on each test day. The mean peak responses were significantly higher (P<.05) for combined therapy, as shown in Table 1; means for combined therapy ranged from 16% to 18% greater than albuterol means.

Physicians’ global evaluations were higher for combination therapy than for albuterol; however, the difference was not statistically significant (P = .15). Symptom scores were mild in severity, indicating the stability of the patients’ disease despite the severity of the obstruction seen by spirometry. Although there were only minor changes in either treatment group over time (Table 2), statistically significant differences in favor of combi-

Table 1. Adjusted Mean Peak Change in FEV₁ and FVC

<table>
<thead>
<tr>
<th></th>
<th>Combination Therapy (n = 176)</th>
<th>Albuterol (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 FEV₁</td>
<td>0.37</td>
<td>0.29</td>
</tr>
<tr>
<td>Day 29 FEV₁</td>
<td>0.34</td>
<td>0.27</td>
</tr>
<tr>
<td>Day 1 FVC</td>
<td>0.77</td>
<td>0.65</td>
</tr>
<tr>
<td>Day 29 FVC</td>
<td>0.71</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*FEV₁ indicates forced expiratory volume in 1 second; FVC, forced vital capacity, measured in liters.
events that were at least possibly related to drug treat-
ingation therapy were noted for wheezing and shortness of breath throughout the study and for tightness of the chest during the first 2 weeks of treatment.

SAFETY

Adverse events were similar between the 2 treatment groups. During active treatment, 45 (25.4%) of 177 patients receiving combined therapy and 60 (33.3%) of 180 patients receiving albuterol therapy reported adverse events or worsening of the preexisting condition that was present at baseline. Lower respiratory tract system disorders were the most commonly reported adverse events. These were reported by 16 patients receiving combined therapy (9.0%) and 30 receiving albuterol alone (16.7%); the difference was not statistically significant (P = .22).

Investigators were asked to rate the probability that adverse events were drug related using the criteria by Karch and Lasagna, ie, “possible,” “probable,” or “definite.” Over the course of the 29 days of active therapy, 13 patients using combined medication and 14 patients using albuterol alone were classified as having adverse events that were at least possibly related to drug treatment (Table 3).

Fewer patients using combined therapy (25 [14%]) reported moderate to severe adverse events than with albuterol alone (40 [22.2%]). Fewer patients receiving combined therapy (7 [4.0%]) reported moderate to severe COPD exacerbations (bronchitis) than those receiving albuterol (17 [9.4%]). There was no evidence of potentiation of adverse events in the combined therapy group compared with albuterol base alone.

The current American Thoracic Society guidelines for the care of individuals with COPD contain recommendations for step-by-step pharmacological therapy. Other than patients with mild asymptomatic disease, the recommendation is to use both ipratropium and selective β-agonist aerosols. Thus, ipratropium and albuterol aerosols are frequently prescribed together. Since many patients with COPD are already using both ipratropium and albuterol, they may find it more convenient to use a single combination product. In addition, compliance may be improved by the combination of the 2 drugs into a single aerosol-dosing regimen. The wholesale cost of the combination product is less than the sum of the costs of the 2 inhalers purchased separately, even when generic albuterol is purchased.

Combination therapy has remained controversial, however. Few studies have been reported using albuterol base as the form of albuterol. A small study by Easton and coworkers (n = 11) indicated that adding either ipratropium or albuterol sequentially does not produce superior bronchodilation to maximal doses of either agent alone. Ikeda et al8 (n = 26), however, found that combination therapy was more effective than doubling the standard dose of ipratropium. Our study results confirm that a fixed-dose combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base alone in patients with COPD. The mean peak response was 26% to 28% higher for the combination aerosol than for albuterol. For the combination therapy, the mean increase in FEV1 over the 6 hours of testing was 38% to 61% greater and there were significant increases in AUC. There was a decrease in improvement in FEV1 from day 1 to day 29 for both treatments. It is possible this is because of the decrease in β-agonist efficacy because of long-term use. This is seen in all studies with β-agonist preparations and is not unexpected in this study since both treatment arms contained β-agonist therapy. Because of this decrease in efficacy, it is not surprising that the change in FEV1, AUC over the last 2 hours on day 29 was not significantly different.

The percentage of improvements in FEV1 with both MDI regimens (Figure 1) might seem high for the usual
patient with advanced COPD. However, the results seen in this study are comparable with those seen in other studies with albuterol, ipratropium, or the combination when the baseline FEV₁ is at a low level (mean of 36.2% predicted). The absolute values for change in FEV₁ are within the usual range seen in patients with COPD (Table 1).

The patients receiving combination therapy had significant improvements in their scoring of shortness of breath and chest tightness during the study. The added improvement seen with combination therapy is to be expected, since ipratropium and albuterol have different mechanisms of action. However, that combination therapy did not result in an increase in adverse effects. In fact, the overall incidence of adverse events was lower in the combination therapy group (25.4%) than in the albuterol group (33.3%). Nor was combination therapy associated with worsening of adverse effects: only 14.1% of patients using the combination aerosol reported moderate to severe adverse events, compared with 22.2% in the albuterol group.

The comparative safety of combination therapy found in a previous study involving albuterol sulfate is also confirmed by our study. The results suggest that fixed, low-dose combination therapy is a useful alternative to increasing the dosage of the β-agonist, apart from the increase in the efficacy that may be obtained. Also, there were more than twice as many patients with exacerbations who were receiving albuterol therapy alone as were receiving the combination therapy.

Patients used their study medications for rescue therapy in times of increased symptoms. This means that the group that used combination therapy 4 times daily also used it for acute symptomatic relief. Thus, combination therapy not only affords improved pulmonary function but may also be an acceptable agent to use for acute symptomatic relief. This is supported by the results in this study that also show that more than twice as many patients receiving albuterol therapy alone compared with those using the combination therapy developed exacerbations requiring treatment. Similar results were also seen in a study comparing an albuterol sulfate-ipratropium combination with albuterol sulfate, in which the study medication was also used for acute relief of symptoms. Therefore, combination therapy is at least as good as, if not better than, albuterol alone for as-needed medication. Thus, many patients with COPD could possibly carry only one inhaler to provide both routine as well as rescue medication.

A single combination inhaler would make it less confusing for a patient who is additionally prescribed an inhaled corticosteroid. The American Thoracic Society Statement on standards points out that adding inhaled steroids for COPD treatment may reduce medication compliance. However, if a combination inhaler replaced separate albuterol and ipratropium inhalers, this would no longer be applicable.

The results of our study indicate that a fixed combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base in equivalent doses, with no potentiation of adverse events. Thus, the combination aerosol should provide a useful addition to the COPD therapy armamentarium.

Accepted for publication June 12, 1998.

Reprints: Sammy C. Campbell, MD, Pulmonary Section (111A), Veterans Affairs Medical Center, 3601 S Sixth Ave, Tucson, AZ 85723.

REFERENCES