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# In Chronic Obstructive Pulmonary Disease, a Combination of Ipratropium and Albuterol Is More Effective Than Either Agent Alone

## An 85-Day Multicenter Trial

COMBIVENT Inhalation Aerosol Study Group\*

Combination bronchodilator therapy for chronic obstructive pulmonary disease (COPD) is available widely throughout the world except in North America. Previous studies have yielded conflicting results regarding the advantages of combining anticholinergic therapy with sympathomimetic therapy in COPD. We report the results of a 12-week prospective, double-blind, parallel-group evaluation of the use of the following: albuterol, a  $\beta$ -adrenergic agent; ipratropium, an anticholinergic agent; or a combination of the two, administered by metered-dose inhaler to patients with moderately severe stable COPD. Following baseline studies, 534 patients were given one of the three test bronchodilator preparations to be used at home four times daily in addition to oral theophylline and corticosteroids as required. The doses of the latter two drugs were kept stable. Subjects were tested on days 1, 29, 57, and 85. Analysis of 1-s forced expiratory volume (FEV<sub>1</sub>) curves on those test days indicated that the combination was superior to either single agent alone in peak effect, in the effect during the first 4 h after dosing, and in the total area under the curve of the FEV<sub>1</sub> response. The mean peak percent increases in FEV<sub>1</sub> over baseline on the four test days were 31 to 33 percent for the combination, 24 to 25 per-

cent for ipratropium, and 24 to 27 percent for albuterol. The differences between the combination and its components were statistically significant on all test days. The AUC<sub>0-4</sub> means for the combination were 21 to 44 percent greater than the ipratropium means and 30 to 46 percent greater than the albuterol means. Similar changes were noted in the forced vital capacity curves. Symptom scores did not change over time and did not differ among the treatment groups. We conclude that the combination of ipratropium and albuterol, when given by metered-dose inhaler to patients with COPD, is more effective than either of the two agents alone. The advantage of the combination is apparent primarily during the first 4 h after administration. The availability of combination therapy by metered-dose inhaler should help to improve patient compliance.

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AUC=area under the curve; COPD=chronic obstructive pulmonary disease; FEF<sub>25-75%</sub>=forced expiratory flow during the middle half of forced vital capacity; FEV<sub>1</sub>=forced expiratory volume in 1 s; FVC=forced vital capacity; MDI=metered-dose inhaler; PEF=peak expiratory flow rate

Inhaled bronchodilators are widely used for symptomatic relief in chronic obstructive pulmonary disease (COPD). Studies have shown that COPD and asthma can no longer be distinguished on the basis of reversibility of bronchial obstruction.<sup>1</sup> In fact, Anthonisen et al,<sup>2</sup> measuring responses to isoproterenol

over a period of nearly 3 years in a study of 985 patients with COPD for whom asthma was a criterion for exclusion, found that the patients responded to inhalation of the  $\beta$ -agonist aerosol with an average increase of 15 percent over the initial FEV<sub>1</sub>, corresponding to an increase of approximately 5 percent of their predicted normal FEV<sub>1</sub>.

In COPD, however,  $\beta$ -agonists are surpassed in efficacy by quaternary anticholinergic bronchodilators.<sup>3,4</sup> It has been suggested by way of explanation that cholinergically mediated airway smooth muscle tone may be increased in COPD,<sup>5</sup> and/or accounts in large part for the reversible component of airway obstruction in COPD, or that patients with COPD are less responsive to adrenergic agents because these agents inhibit the smooth muscle contraction induced by mediators such as histamine and the leukotrienes, which play only a minor role in COPD.<sup>6</sup>

To date, seven studies have compared the concurrent use of ipratropium and albuterol, delivered by inhalation aerosol, in patients with COPD with use of each of the individual drugs. In five of these trials,<sup>7-11</sup>

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superior bronchodilation was obtained with the drug combination. In the remaining two studies,<sup>12,13</sup> no additive effects of the second drug were demonstrable despite the use of higher than recommended doses. All of these trials had serious design limitations. Generally, the sample sizes were too small to attain statistical significance. The studies were inadequately blinded and of short duration, and in many of them the combination was administered as the third test drug after treatment with each of the components.

A retrospective study in 296 patients with partially reversible airflow obstruction showed that in 33 percent of the patients who responded inadequately to albuterol alone, bronchodilation was increased when inhalation of this  $\beta$ -agonist was followed by inhalation of ipratropium.<sup>14</sup>

A fixed combination of a low dose of another  $\beta$ -agonist, fenoterol, and ipratropium in the same metered-dose inhaler (MDI) has been used worldwide, except in North America, for periods ranging up to 10 years. In several controlled trials, patients with COPD responded to this combination with a greater improvement in lung function than when they were treated with either fenoterol or ipratropium alone.<sup>15-18</sup> A 3-day study in 12 patients with stable COPD compared a combination of standard inhaled doses of ipratropium and metaproterenol with ipratropium alone. This combination was not found to provide any added benefit over monotherapy with the anticholinergic agent.<sup>19</sup>

The present double-blind, randomized, parallel-group trial was designed to answer the question whether long-term administration of combined albuterol and ipratropium delivered in one inhalation aerosol would result in greater bronchodilation in patients with COPD than the use of either agent alone.

## METHODS

### *Study Design and Conduct*

This trial conformed to the institutional review board and informed consent provisions of the Code of Federal Regulations. A total of 24 clinical centers participated. The safety and efficacy, including persistence of bronchodilator action, of ipratropium bromide, albuterol sulfate, and a combination of the two (COMBIVENT, Boehringer Ingelheim Pharmaceuticals, Inc) delivered by MDI were compared during an 85-day treatment period. The groups were composed of patients with a diagnosis of COPD who were at least 40 years of age. Study participants were required to have relatively stable, moderately severe airway obstruction with an  $FEV_1 \leq 65$  percent of predicted normal and  $FEV_1 \leq 70$  percent of FVC.<sup>20</sup> In addition, patients were required to have a smoking history of more than 10 pack-years and to be regularly using at least two prescribed therapeutic agents for control of their COPD symptoms during the 3-month period immediately preceding consideration for entry into this trial. Patients with a history of asthma, allergic rhinitis or atopy, or with a total blood eosinophil count above 500/mm<sup>3</sup> were excluded.

Also excluded were patients who required more than 10 mg of oral prednisone daily within a month before entry into the study.

Before admission to the trial, each patient had his or her medical history taken and underwent laboratory tests, physical examination, and a 12-lead ECG recording; these studies were repeated at the end of trial participation.

Following a 2-week baseline period, the patients were randomly assigned, by order of entry into the trial, to receive either the ipratropium-albuterol combination inhalation aerosol, ipratropium inhalation aerosol, or albuterol inhalation aerosol, using blocks of six patients. Visits to the clinic, during which adverse events and use of concomitant medication were recorded, were scheduled every 2 weeks throughout the treatment period.

While continued use of stable doses of theophylline was allowed during the study, regular use of inhaled bronchodilators other than the study drugs was not. Temporary increases or additions of corticosteroids during exacerbations were permitted but limited to two periods of up to 5 days each during the 85-day trial. The use of cromolyn sodium was disallowed.

### *Treatments*

The combination aerosol provides doses equivalent to the usual recommended doses of each of the components, namely, ipratropium 21  $\mu$ g per inhalation, and albuterol base, 100  $\mu$ g per inhalation. These doses are based on valve delivery. The recommended single dose of the combination aerosol thus consisted of two puffs each containing 21  $\mu$ g of ipratropium bromide plus 120  $\mu$ g of albuterol sulfate (equivalent to 100  $\mu$ g of albuterol base).

A majority of the patients (70 to 82 percent) reported that they took the drug four times daily during the 85-day period. The patients were allowed to take up to two extra doses of the study medication per day when required to control symptoms. The percentage of patients who reported using their drug generally more often than four times daily during any 2-week period ranged from 18 percent to 28 percent for the combination, from 15 percent to 23 percent for ipratropium, and from 20 percent to 31 percent for albuterol.

### *Observations*

Pulmonary function testing, including measurements of  $FEV_1$ , FVC, and  $FEF_{25-75\%}$ , was conducted on treatment days 1, 29, 57, and 85 immediately before drug administration, 15, 30, and 60 min after drug administration, and hourly thereafter for a total of 8 h. For standardization of bronchodilator use before testing, theophylline treatment was withheld for at least 24 h and treatment with  $\beta$ -adrenergic bronchodilators and the study drug were withheld for at least 12 h prior to pulmonary function testing. The study drug was administered between 7 and 10 AM, after baseline spirometry had been performed. All pulmonary function tests were conducted in triplicate, and the spirometric results with the greatest sum of  $FEV_1$  and FVC were recorded and used for analysis. Spirometers met American Thoracic Society (ATS) standards, and the patients were required to continue the expiratory maneuver until a maximum plateau was reached. Blood pressure and pulse rates were measured during the first 3 h of each test day, just prior to pulmonary function testing.

Peak flow measurements were performed twice daily, immediately after arising in the morning and between 4 AM and 6 PM, at least 3 h after the patient's previous dose of medication.

Severity of COPD symptoms (wheezing, shortness of breath, coughing, and tightness of chest) was reported at the end of the 2-week baseline period and every 2 weeks thereafter. This evaluation was made before the start of pulmonary function testing. A global evaluation of each patient's overall condition was made by the investigator at each visit and expressed as a numerical value, from 1 (poor) to 8 (excellent).

### Statistical Evaluation

The acute response to the bronchodilators, defined as the change in pulmonary function from baseline on each test day, served as the primary criterion of efficacy, and FEV<sub>1</sub> was chosen as the primary pulmonary function variable. The primary end points were the peak change from baseline and the area under the response-time curve (AUC) as calculated by the trapezoidal rule. The AUC was determined within the intervals of 0 to 4, 4 to 6, and 6 to 8 h as well as for the entire 8-h period after administration. The FEV<sub>1</sub> responses were also characterized in terms of onset, duration, and time to peak. The FVC and FEF<sub>25-75%</sub> were similarly evaluated as secondary pulmonary function variables.

Data from the patients who did not complete 8 h of testing were handled as follows: if testing was terminated prematurely because of a lack of response, the lowest value recorded for that patient on that test day was used to estimate data after the test interruption. If testing was discontinued early for reasons unrelated to the disease, the last observation on the test day in question was used to estimate the missing data, provided at least 4 h of testing had been completed.

The persistence of the effect over the course of the study was assessed by comparing FEV<sub>1</sub> responses on days 29, 57, and 85 with those obtained on day 1 and additionally by determining the percentages of patients who responded on each test day. Only data from patients who completed testing on all 4 days of pulmonary

function testing were included in this evaluation.

For greater precision, analysis of covariance with baseline as a covariate was used to compare the bronchodilator responses to the different treatments. Other terms in the model were treatment, center, and treatment-by-center interaction.

The primary analysis of pulmonary function was based on the evaluable data set. Patients' data were excluded from this analysis if their disease did not meet the protocol-specified criteria for COPD or if they had theophylline levels higher than 10 µg/ml at the day-1 baseline. Data were excluded for nine patients in the COMBIVENT group, three in the ipratropium group, and eight in the albuterol group. An analysis of all patients enrolled, *ie*, the intent-to-treat analysis, showed results similar to those based on the analysis of the data set with the above specified exclusions.

### RESULTS

A total of 534 patients were recruited. Their demographic and baseline characteristics as well as those of the three individual treatment groups are presented in Table 1.

The disposition of the study participants is summarized in Table 2. The rates of withdrawal from the study were similar in the three treatment groups, but

**Table 1—Demographics and Baseline Characteristics of All Randomized Patients**

	Ipratropium + Albuterol	Ipratropium	Albuterol	Overall
Total randomized and treated	182	179	173	534
Age, yr				
Mean	63.4	63.3	63.6	63.4
Range	40-88	42-82	44-82	40-88
Sex				
Male	116	120	112	348
Female	66	59	61	186
Race				
White	171	165	164	500
Black	10	10	8	28
Other	1	4	1	6
Height, cm				
Mean	167.75	167	167.75	167.5
Range	140-192.5	132-192.5	133-187.5	132-192.5
Duration of disease, yr				
Mean	8.2	8.4	8.1	8.2
Range	0.2-36.6	0.5-45.0	0.5-45.0	0.2-45.0
FEV <sub>1</sub> , L				
Mean	0.996	0.998	0.987	0.991
Range	0.38-2.31	0.29-2.78	0.32-2.43	0.29-2.78
Percent of predicted normal FEV <sub>1</sub>				
Mean	37.4%	36.6%	36.8%	36.9%
Range	11.9-76.2%	12.4-73.2%	11.5-74.1%	11.5-76.2%
FEV <sub>1</sub> /FVC				
Mean	44.0%	44.4%	43.5%	44.0%
Range	21.2-79.3%	22.6-69.4%	20.0-92.8%	20.0-92.8%
Prestudy medication for COPD, No. (%) of patients				
Anticholinergics	83 (46)	73 (41)	72 (42)	228 (43)
β-adrenergics, inhaled	170 (93)	166 (93)	158 (91)	494 (93)
β-adrenergics, oral	17 (9)	22 (12)	21 (12)	60 (11)
Steroids, inhaled	62 (34)	53 (30)	35 (20)	150 (28)
Steroids, oral	18 (10)	27 (15)	22 (13)	67 (13)
Theophylline	146 (80)	144 (80)	145 (80)	435 (81)

Table 2—Patient Disposition

	Ipratropium + Albuterol	Ipratropium	Albuterol	Overall
Total randomized and treated	182	179	173	534
Withdrawn because of				
Adverse event	7 (3.8)	16 (8.9)	13 (7.5)	36 (6.7)
Protocol violation	12 (6.6)	4 (2.2)	5 (2.9)	21 (3.9)
Unavailable for follow-up	5 (2.7)	6 (3.4)	4 (2.3)	15 (2.8)
Total	24 (13.2)	26 (14.5)	22 (12.7)	72 (13.5)
Completed all test days	158 (86.8)	153 (85.5)	151 (87.3)	462 (86.5)

fewer patients receiving the combination discontinued participation because of adverse events than did patients in either the ipratropium or the albuterol group. The most common adverse reactions leading to discontinuation were lower respiratory system events, including acute exacerbations of chronic bronchitis, cough, dyspnea, and bronchospasm that caused the withdrawal of 4 patients in the combination treatment group and 12 patients in each of the ipratropium and albuterol groups. Approximately equal percentages of patients in the three treatment groups completed all test days.

*Efficacy*

**FEV<sub>1</sub>:** The evaluable patients' mean baseline FEV<sub>1</sub> values on each of the four test days were comparable for each of the three treatment groups and remained virtually unchanged over the course of the study (Table 3). The p values denote the significance of differences between the ipratropium and albuterol groups and the group treated with the combination.

A clinically significant mean FEV<sub>1</sub> response (at least 15 percent above baseline) was observed on each of the 4 test days in all three treatment groups. On all test days, however, the magnitude of the overall response to the ipratropium-albuterol combination was greater than the response to each of the components given alone, particularly during the first 4 h after administration (Fig 1).

The mean peak responses to the combination were significantly greater than those to each of the components on all 4 test days, reflecting a combined effect of ipratropium and albuterol. The differences between the combination and ipratropium alone ranged from 16 to 30 percent, while the differences from albuterol alone ranged from 18 to 28 percent (Table 4). The mean peak percent increases in FEV<sub>1</sub> over baseline on the 4 test days were 31 to 33 percent for the combination, 24 to 25 percent for ipratropium, and 24 to 27 percent for albuterol. In all three treatment groups, the peak bronchodilator effect was obtained 1 h after administration. Analysis of the FEV<sub>1</sub> AUC values (Table 5) for the different time segments showed that the mean response to combi-

nation treatment was significantly greater than the response to each of the components during the first 4 h on all test days and during the fourth to sixth hours on the first test day. The AUC<sub>0-4</sub> means for the combination were 21 to 44 percent greater than the ipratropium means and 30 to 46 percent greater than the albuterol means. For the entire 8-h test period, the areas under the FEV<sub>1</sub> curve were larger with the combination than with each of the components on all test days. Differences from ipratropium were statistically significant on day 1 and approached significance on day 85; the differences from albuterol were statistically significant on test days 1, 57, and 85.

In each treatment group, the median time of onset of effect was 15 min, the first time point at which pulmonary function was tested after drug administration. The median duration of effect was 4 to 5 h for the combination group, 4 h for the ipratropium group, and 2 to 3 h for the albuterol group; the difference in duration between the combination and the albuterol groups was statistically significant on all test days, while the difference between the combination and ipratropium was not significant.

**FVC and FEF<sub>25-75</sub>%:** As in the case of FEV<sub>1</sub>, baseline values of these variables remained stable over the course of the study.

As shown in Figure 2, the overall FVC response to the drug combination was significantly greater than the response to either ipratropium or albuterol alone (p<0.01 to p=0.04). The peak percent increases in

Table 3—Mean FEV<sub>1</sub> Baseline Values on Test Days

Day No.	Ipratropium + Albuterol (n=173)	Ipratropium (n=176)	Albuterol (n=165)
1	0.96	0.92 (p=0.306)	0.96 (p=0.976)
29	0.98	0.95 (p=0.423)	0.96 (p=0.620)
57	0.98	0.94 (p=0.451)	0.95 (p=0.611)
85	0.97	0.95 (p=0.581)	0.95 (p=0.654)

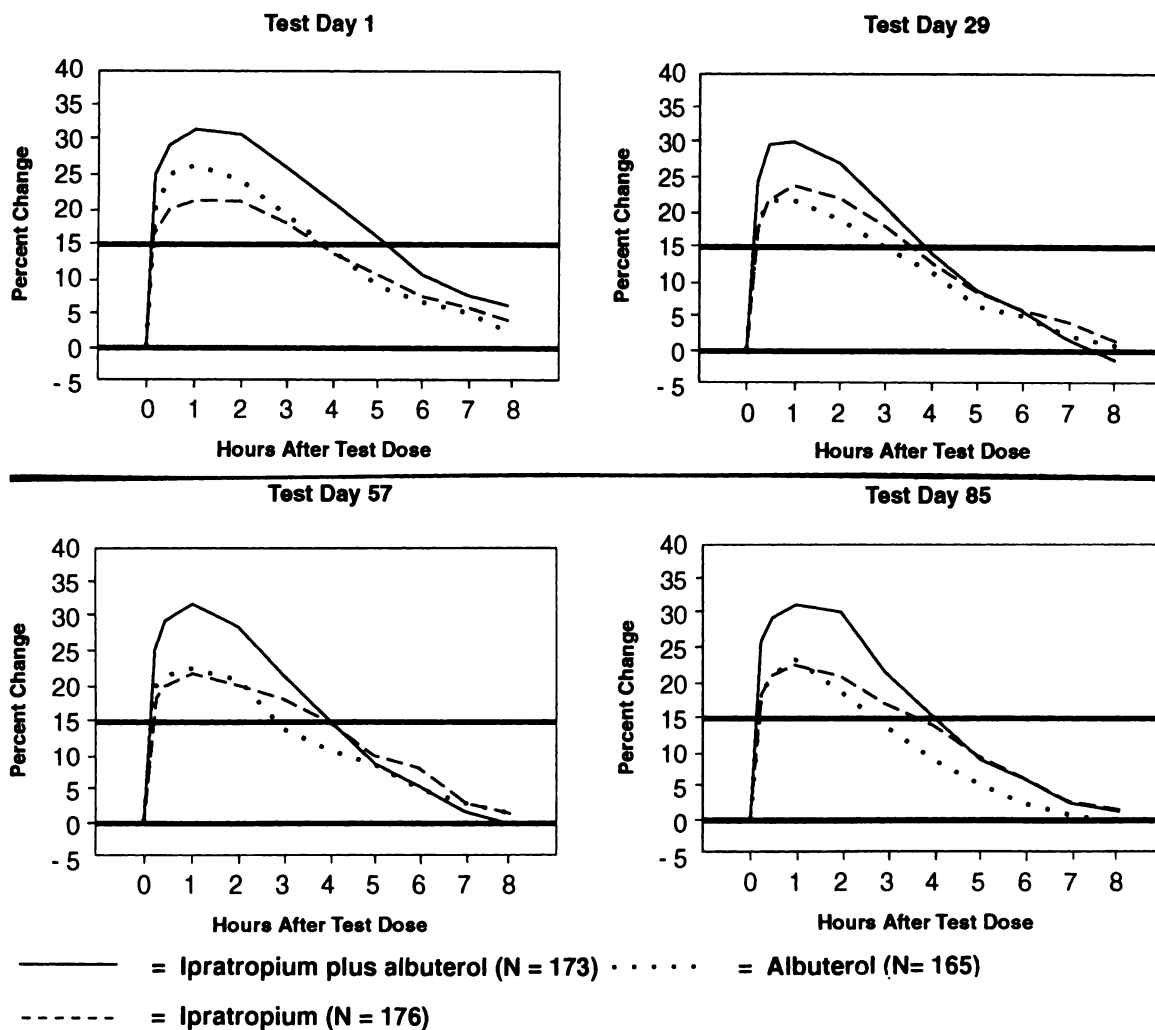


FIGURE 1. Percent changes in mean FEV<sub>1</sub> from test day baselines.

FVC over baseline on the 4 test days averaged 30 to 40 percent for the combination as contrasted with 25 to 28 percent for ipratropium and 24 to 29 percent for albuterol. The FEF<sub>25-75%</sub> results largely paralleled those obtained for FEV<sub>1</sub> and FVC. They were, however, extremely variable since the measurements were not corrected for lung volume.

**Table 4—Mean Peak FEV<sub>1</sub> Responses, L (p Values for Significance of Differences From the Combination)**

Day No.	Ipratropium +		
	Albuterol (n=173)	Ipratropium (n=176)	Albuterol (n=165)
1	0.39	0.30	0.33
29	0.36	0.31	0.30
57	0.37	0.30	0.30
85	0.37	0.30	0.29
		(p<0.001)	(p<0.001)
		(p=0.015)	(p=0.007)
		(p=0.001)	(p=0.001)
		(p<0.001)	(p<0.001)

**Table 5—Mean FEV<sub>1</sub> AUC, L×H (p Values for Significance of Differences From the Combination)**

	Ipratropium +		
	Albuterol	Ipratropium	Albuterol
AUC <sub>0-4</sub>			
Day 1	1.08	0.75	0.83
		(p<0.001)	(p=0.001)
Day 29	0.94	0.78	0.71
		(p=0.034)	(p=0.003)
Day 57	0.98	0.75	0.71
		(p=0.001)	(p<0.001)
Day 85	0.99	0.76	0.68
		(p<0.001)	(p<0.001)
AUC <sub>0-8</sub>			
Day 1	1.58	1.08	1.14
		(p<0.001)	(p=0.002)
Day 29	1.18	1.05	0.92
		(p=0.347)	(p=0.076)
Day 57	1.22	1.03	0.91
		(p=0.171)	(p=0.032)
Day 85	1.24	1.03	0.84
		(p=0.087)	(p=0.002)

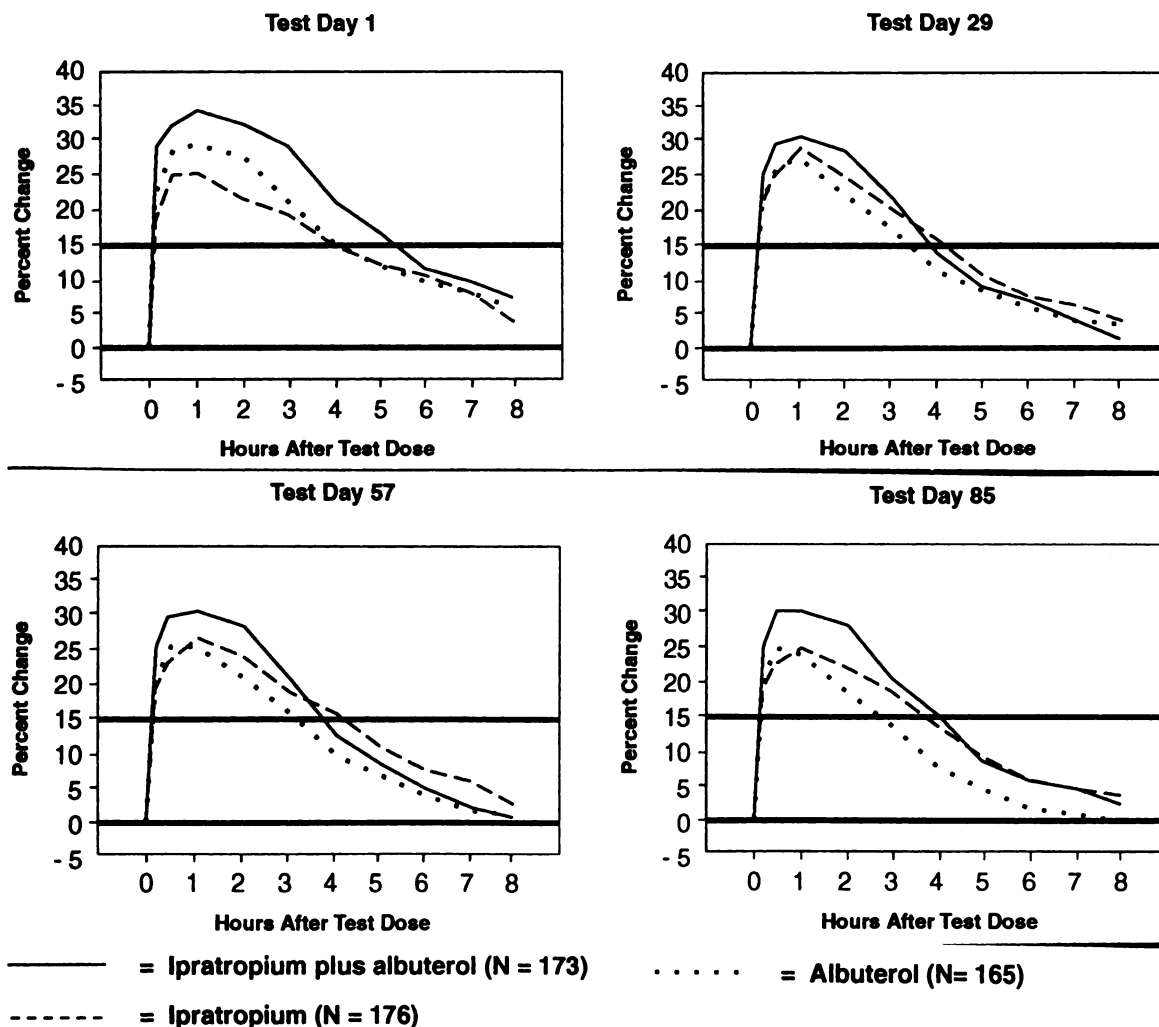


FIGURE 2. Percent changes in mean FVC from test day baselines.

### Persistence of Bronchodilating Effect

Small decreases in peak response and AUC were seen after the first test day in the combination and albuterol treatment groups, but not in the ipratropium group. All three treatment groups retained a high percentage of responding patients (80 to 89 percent) throughout the 12-week study period. A patient was considered to have responded to the treatment if the increase in FEV<sub>1</sub> over the test day baseline was at least 15 percent within 2 h after administration.

### Other Efficacy Variables

Peak expiratory flow rate (PEFR) measurements did not change during the 12-week treatment period and both baseline PEFR and PEFR responses were comparable in the three treatment groups.

The physicians' global evaluations yielded significantly better mean scores for patients in the combination group than for the other two groups on days 15 and 29, but the differences between groups were

relatively small. All mean scores fell within the range of 4.5 to 5.0, that is, "fair to good."

The COPD symptom scores did not change over time and did not differ among the treatment groups; on average, they were of mild severity. Thus, the long-term effects of the treatments on COPD symptoms were minimal and very similar in each of the three treatment groups.

Only seven (3.8 percent) patients in the combination group, as compared with 11 (6.1 percent) and 18 (10.4 percent) in the ipratropium and albuterol groups, respectively, needed to add systemic steroid medication to their regimen or to increase their steroid doses. The total number of patient days of increased steroid use was 37 (0.25 percent) among patients taking the ipratropium-albuterol combination, 66 (0.47 percent) in the ipratropium group, and 94 (0.68 percent) in the albuterol group.

Pulmonary function testing was postponed until at least 48 h but for not more than 7 days after the last increase or addition of steroids.

The numbers of patients who temporarily added,

or increased their use of, concomitant respiratory medication were small in each treatment group, and the differences between groups were not statistically significant.

### Safety

The 182 patients who were randomly allocated to the combination group were exposed to the study drugs for an average of 81 days, while those in the ipratropium group were exposed for 78 days, and those in the albuterol group were exposed for 80 days.

During the double-blind phase of the study, 95 of 182 patients receiving the combination (52.2 percent), 99 of those receiving ipratropium (55.3 percent), and 102 of 173 patients treated with albuterol (59.0 percent) reported adverse events or worsening of a pre-existing condition. Adverse experiences that were possibly drug related were reported in 19 patients (10.4 percent) taking the combination, in 22 (12.3 percent) taking ipratropium, and in 20 (11.6 percent) taking albuterol. The most common possibly drug-related adverse reactions to the combination were headache, bronchitis, and cough, which were reported by three patients each. Cough was the most common possibly drug-related adverse experience, reported by six patients, with ipratropium; headache, reported by five patients taking the most common possibly related adverse experience in the albuterol group.

Two patients died during the study, both of them in the combination group. In one, a 75-year-old white man, the cause of death was defined as arteriosclerotic cardiovascular disease. In the other case, a 60-year-old black man with a history of myocardial infarction, death was believed to have been caused by his COPD; any relationship of his death to the study medication, which he had used for 3 months, was considered doubtful.

One drug-related event led to a patient's withdrawal from the trial in the combination group, namely, severe cough experienced by a 67-year-old woman on the 65th day of treatment. In the ipratropium group, seven patients withdrew because of events that were possibly drug related. These consisted of lower respiratory system disorders in four cases, and facial edema, severe dizziness and tinnitus, and pharyngitis in one case each. The lower respiratory tract symptoms included aggravated bronchospasm and dyspnea and occasioned the withdrawal of four patients from the albuterol group. In all, lower respiratory tract disorders were reported by 41 patients in the combination group, by 43 in the ipratropium group, and by 49 in the albuterol group.

There were no clinically significant changes from baseline in any of the mean laboratory values following treatment, nor were there any clinically sig-

nificant differences in this regard among the three treatment groups.

Mean changes from baseline in blood pressure and pulse rate recorded during the first 3 h after treatment on each test day were not clinically significant in the individual groups, and there also were no significant differences among the three groups.

There were no clinically significant differences in chronic or acute ECG changes among the treatment groups. The ST-T wave changes in a patient receiving ipratropium alone, and runs of bigeminy in a patient receiving albuterol alone were the only ECG changes that were considered to be possibly drug related. The former patient discontinued participation in the study, while the patient receiving albuterol continued.

### DISCUSSION

The results of this study demonstrate that a combination of the anticholinergic agent ipratropium and the  $\beta$ -sympathomimetic albuterol elicited a statistically greater bronchodilator response in patients with stable COPD than treatment with either agent alone. The 20 to 40 percent additional bronchodilatation provided by the combination over the single entity agents is especially meaningful in this population of patients with COPD who were not required to demonstrate a bronchodilator response prior to entry into the study and who had moderately severe disease with a mean FEV<sub>1</sub> of 37 percent of their predicted normal.

It has been suggested that the regular, systematic use of inhaled bronchodilators may lower the excessive rate of decline of FEV<sub>1</sub> in patients with heightened bronchial hyperreactivity.<sup>21</sup> This rate is highest among patients with COPD with heightened bronchial hyperreactivity.<sup>22,23</sup> However, when patients with increased bronchial hyperreactivity are treated systematically and regularly with any bronchodilator, the rate of decline in their FEV<sub>1</sub> appears to be slower than that of patients having no airway hyperreactivity. Systematic and stepwise use of bronchodilators may thus be likened to therapy for hypertension: just as the responses to antihypertensive therapy are monitored by blood pressure measurements, so the administration of bronchodilators should be guided by simple objective measurements, such as peak flow or spirometry, rather than relying solely on symptomatic end points. An attempt may be made to avoid rapidly progressive and irreversible airflow obstruction, and long-term sequelae of the disease, by dint of daily or partial reversal of airflow obstruction over time.<sup>24</sup> There has been some controversy over the question whether vigorous therapy is in fact warranted in COPD.<sup>25</sup> However, in nonal-

lergic patients with COPD who regularly received another anticholinergic agent, thiazinamium, over follow-up periods of 2 to 22 years, reversibility of airway obstruction by this agent was associated with a lower rate of decline in FEV<sub>1</sub>.<sup>25</sup>

In the present study, baseline spirometry before test doses, PEFR determinations, evaluations of COPD symptomatology, and the use of concomitant medication showed that there was virtually no change in the course of the disease during the 3 months of treatment. While it might be expected that the increased bronchodilation could affect these indices over a 12-week period, the study design may have obscured this effect. The patients were allowed to continue taking their concomitant medications, notably theophylline (80 percent of patients), throughout the study except on test days. Although these patients had relatively severe disease (mean percent of predicted normal FEV<sub>1</sub> at baseline, 37 percent), their symptoms as reflected in the physician's mean global evaluation scores—ranging from fair to good—were comparatively mild. In many cases, severe symptoms were avoided by adjustments in lifestyle that the patients initiated long before their entry into the study. A proper assessment of the effect of bronchodilator therapy on the disease course would require long-term studies specifically designed for this purpose.

No additive effect on the incidence of adverse reactions was observed in our study even though the inhaler containing the fixed combination product delivered the full, standard doses of both ipratropium and albuterol. As a matter of fact, the incidence of possibly drug-related adverse events was slightly, although not significantly, lower in the combination-treated group. Only one patient in this group withdrew from the study because of drug-related adverse experiences as contrasted with four in the albuterol group and seven in the ipratropium group.

The superior effectiveness of this drug combination is hardly surprising since the combined use of the anticholinergic and the  $\beta$ -agonist bronchodilator brings to bear two different mechanisms of action: inhibition of bronchoconstriction via the parasympathetic pathway and bronchodilation by stimulation of the sympathetic pathway.<sup>26</sup> There also is some evidence that anticholinergic agents produce their bronchodilating effect mainly in the central airways, where cholinergic receptors are abundant, whereas the effective site of bronchodilation by  $\beta$ -adrenergic agents comprises both central and peripheral airways in patients with COPD.<sup>27</sup> Cholinergic nerves and receptors are only sparsely distributed in the peripheral airways.

An alternative hypothesis is that a larger dose of either ipratropium or albuterol could have produced

a similar increase in airflow and volume; however, this hypothesis has not been tested.

The availability of a single MDI that produces both anticholinergic and  $\beta$ -adrenergic bronchodilating effects should facilitate patient compliance with a regimen that, by comparison with each of its components, holds the promise of greater bronchodilation and of at least equivalent safety in regular, systematic use.

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