Efficacy of Salmeterol Xinafoate in the Treatment of COPD*

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Study objectives: **To examine and compare the efficacy and safety of salmeterol xinafoate, a long-acting inhaled β_2-adrenergic agonist, with inhaled ipratropium bromide and inhaled placebo in patients with COPD.**
Design: **A stratified, randomized, double-blind, double-dummy, placebo-controlled, parallel group clinical trial.**
Setting: **Multiple sites at clinics and university medical centers throughout the United States.**
Patients: **Four hundred eleven symptomatic patients with COPD with $FEV_1 \leq 65\%$ predicted and no clinically significant concurrent disease.**
Interventions: **Comparison of inhaled salmeterol (42 μg twice daily), inhaled ipratropium bromide (36 μg four times a day), and inhaled placebo (2 puffs four times a day) over 12 weeks.**
Results: **Salmeterol xinafoate was significantly ($p < 0.0001$) better than placebo and ipratropium in improving lung function at the recommended doses over the 12-week trial. Both salmeterol and ipratropium reduced dyspnea related to activities of daily living compared with placebo; this improvement was associated with reduced use of supplemental albuterol. Analyses of time to first COPD exacerbation revealed salmeterol to be superior to placebo and ipratropium ($p < 0.05$). Adverse effects were similar among the three treatments.**
Conclusions: **These collective data support the use of salmeterol as first-line bronchodilator therapy for the long-term treatment of airflow obstruction in patients with COPD.**
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Key words: chronic obstructive pulmonary disease; dyspnea; inhaled β_2-agonists; ipratropium; salmeterol

Abbreviations: AUC = area under the curve; BDI = baseline dyspnea index; CRDQ = chronic respiratory disease questionnaire; HRQL = health-related quality of life; 6MW = 6-min walk; TDI = transition dyspnea index

COPD, which affects approximately 14 million Americans, is the fourth leading cause of death in the United States.[1] The usual course of COPD is a slow deterioration of lung function and progressive breathlessness with activities. At the present time, only supplemental oxygen has been shown to prolong survival in hypoxemic patients with COPD,[2] and only smoking cessation has been shown to slow the accelerated decline in expiratory airflow obstruction dyspnea.[3] Treatment with bronchodilator medications is indicated to improve symptoms, particularly dyspnea, which might also enhance health-related quality of life (HRQL) in patients with COPD.

Both inhaled β_2-agonists and anticholinergic medications are considered as initial bronchodilator therapy for patients with COPD.[1,4] Randomized clinical trials have demonstrated that these medications can improve lung function and reduce the severity of breathlessness in such patients.[5–7] Most clinical experience with inhaled β_2-agonists has been with short-acting agents whose actions last 4 to 6 h. Salmeterol xinafoate is a long-acting preparation with a 12-h duration of action that has been used effectively in the treatment of asthma. Twice daily administration of salmeterol (42 μg) is the optimum dosing regimen for patients with mild-to-moderate reversible airways obstruction.[8]

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Although several studies have shown modest bronchodilation and/or reduction in dyspnea with salmeterol in patients with COPD, these investigations were all short term and involved only small numbers of patients.[9–12] In a 16-week European trial, salmeterol (42 or 84 μg) inhaled twice daily produced improvement in daytime and nighttime symptom scores, dyspnea ratings following the 6-min walk (6MW) test, use of additional bronchodilators, patient/physician assessment, number of exacerbations, and days unable to perform work compared with placebo.[13] No differences were observed between the two doses of salmeterol. Jones and Bosh[14] found that salmeterol at a dose of 42 μg taken twice daily led to a modest improvement in lung function in patients with COPD and an associated clinically significant gain in health and well-being over 4 months compared with placebo.

The purpose of the present study was to compare the efficacy and safety of salmeterol (42 μg) twice daily vs ipratropium four times a day vs placebo in the treatment of COPD. FEV_1 and dyspnea ratings were considered as primary outcome measures. To our knowledge, this multicenter study is the first comprehensive comparison of salmeterol, a long-acting β_2-agonist, vs ipratropium, an anticholinergic bronchodilator, in the treatment of COPD.[1]

Materials and Methods

Study Design

This was a 12-week, multicenter, stratified, randomized, double-blind, double-dummy, placebo-controlled, parallel group comparison of inhaled salmeterol (42 μg twice daily), ipratropium (36 μg four times a day), and placebo (two puffs four times a day) in the treatment of patients with COPD. Twenty-seven sites participated in the study. All patients provided written informed consent. Prior to assignment to treatment, patients were stratified by the bronchodilator response to 180 μg (two puffs) of albuterol measured at 30 min; this was performed to assure equivalent distribution across strata. On a separate day, bronchodilator response to 36 μg (two puffs) of ipratropium bromide was measured at 30 min. "Responsive" patients were defined as those in whom inhaled albuterol caused an increase of $\geq$ 200 mL and $\geq$ 12% in the baseline FEV_1. All other patients were considered "nonresponsive."

During a 14- to 21-day baseline period, pulmonary function, dyspnea and other symptoms, 6MW distance, and HRQL were measured. Patients returned for evaluations at 2-week intervals during the treatment period. Treatment with theophylline and short-acting bronchodilators was stopped 36 and 6 h, respectively, prior to initiating study treatment. However, albuterol was allowed for acute symptomatic relief. During the treatment period, patients on a stable regimen of oral ($\leq$ 10 mg prednisone [or equivalent] per day) or inhaled corticosteroids continued these regimens.

Study Patients

Inclusion criteria were as follows: $\geq$ 35 years of age; a $\geq$ 10 pack-year history of smoking; a diagnosis of COPD as defined by the American Thoracic Society[1]; a baseline FEV_1 of $>$ 0.70 L and $\leq$ 65% of the predicted normal values (or, if $<$ 0.70 L, $\geq$ 40% of predicted normal value)[15]; an FEV_1/FVC ratio of $\leq$ 70%; and a baseline severity of breathlessness of grade 1 (shortness of breath when hurrying on the level or walking up a slight hill) or higher on the modified Medical Research Council dyspnea scale. Exclusion criteria included the following: unstable respiratory status within the previous 4 weeks; a known history of asthma or chronic respiratory disease other than COPD; any clinically significant concurrent disease; oxygen therapy other than nocturnal use; a change in medications for COPD within 4 weeks prior to the screening visit; and inability to discontinue treatment with theophylline, ipratropium bromide, or oral β-agonist therapy after the screening visit.

Efficacy Evaluations

Pulmonary function and dyspnea ratings were the primary efficacy measures. Area under the 12-h curve for FEV_1 (FEV_1 AUC) was calculated from the pretreatment measurement for each time interval from 0 to 12 h by the trapezoidal method and summed for each of the four 12-h visits. Pulmonary function was measured at weeks 0 (following first administration of study drug), 4, 8, and 12. The severity of dyspnea was measured at week 0 with the multidimensional baseline dyspnea index (BDI), and changes in the severity of dyspnea were assessed every 2 weeks with the transition dyspnea index (TDI).[16] The 6MW was conducted on alternate visits (weeks 2, 6, and 10) within 4 h of the morning dose of study medication, and patients rated their intensity of breathlessness on the Borg dyspnea scale[17] (a 0 to 10 scale with 0 = no breathlessness and 10 = maximal breathlessness) before and after the 6MW. Other efficacy measures included spirometric measures over 12 h (FEV_1, FVC), patient self-rating of symptoms (daytime symptom scores ranging from 0 = no symptoms to 4 = symptoms so severe you were not able to do most daily activities; nighttime symptom scores ranging from 0 = no symptoms to 4 = symptoms so severe that you did not sleep), nighttime awakenings, supplemental albuterol use, and time to first COPD exacerbation.

Any patient who experienced worsening of symptoms during the washout or baseline periods was withdrawn from the study. An individual remained in the study if the exacerbation could be treated successfully using an oral antibiotic and/or up to 14 days of an oral or parenteral corticosteroid. Anyone who required more than two courses of such treatment was withdrawn from the study.

HRQL Evaluations

HRQL was assessed at weeks −2, 0, 2, 6, 8, and 12 weeks using the chronic respiratory disease questionnaire (CRDQ), a 20-item, interviewer-administered, disease-specific questionnaire that considers the domains of dyspnea, fatigue, emotional function, and mastery.[18]

Safety Evaluations

The following safety data were collected: adverse events and vital signs at 2-week intervals; clinical laboratory evaluations, physical examinations, and medical history at screening and end of treatment; a 12-lead ECG at weeks −2, 0, 4, 8, and 12; and continuous ambulatory ECG for 24 h at approximately half the study sites at weeks −2, 0, 4, 8, and 12.

Statistical Analysis

Statistical comparisons among treatment means were performed using analysis of variance, except for Borg dyspnea scores (van Eltern test) and clinical laboratory data (Wilcoxon sign rank test). Comparisons among treatment groups were performed using Cochran-Mantel-Haenszel test except for adverse events (Fisher's Exact Test), and time to exacerbation was compared using the Kaplan-Meier test. Analyses were performed on three groups of patients: all patients, responsive, and nonresponsive strata.

Results

Demographics

Three hundred sixty-one of the 411 patients enrolled completed the study. Patient demographics and characteristics were similar among the three treatment groups (Table 1). The groups were comparable with respect to type of COPD, smoking history, duration of COPD, self-assessment of dyspnea, and diffusing capacity (Table 2), as well as the average number of hospitalizations and emergency department visits due to COPD. Information on the 50 subjects who were withdrawn from the study is included in Table 1. More patients were withdrawn from the placebo group (n = 23) compared with the ipratropium group (n = 18) and the salmeterol group (n = 9).

Table 1—*Patient Demographics*

	Placebo	Salmeterol, 42 μg bid	Ipratropium, 36 μg qid	p Value
Gender, No. (%)				
Male	109 (76.2)	97 (71.9)	97 (72.9)	0.6884
Female	34 (23.8)	38 (28.1)	36 (27.1)	
Race, No. (%)				
White	130 (90.9)	124 (91.9)	122 (91.7)	0.9540
Black	9 (6.3)	9 (6.7)	10 (7.5)	
Asian	2 (1.4)	0 (0.0)	0 (0.0)	
Hispanic	2 (1.4)	1 (0.7)	1 (0.8)	
Other	0 (0.0)	1 (0.7)	0 (0.0)	
Age, yr				
Mean	63.19	63.21	64.02	0.6658
SE	0.72	0.73	0.74	
Height, inch				
Mean	68.01	67.84	68.10	0.8418
SE	0.31	0.32	0.29	
Weight, lb				
Mean	174.63	175.59	171.96	0.7339
SE	3.23	3.58	3.22	
Withdrawn	23	9	18	
Adverse event	8	1	7	
Lack of efficacy	3	3	2	
Failed to return	2	0	2	
Other*	10	5	7	

*Other reasons for withdrawal included COPD exacerbation (n = 4), noncompliance with study medication (n = 1), protocol violation (n = 7), voluntary withdrawal from the study (n = 6), and use of exclusionary medications (n = 4).

Table 2—*COPD History and Screening Pulmonary Function Tests**

	Placebo	Salmeterol, 42 μg bid	Ipratropium, 36 μg qid
COPD type, No. (%)			
Chronic bronchitis	35 (24.5)	33 (24.4)	30 (22.6)
Emphysema	63 (44.1)	66 (48.9)	63 (47.4)
Both	45 (31.5)	36 (26.7)	40 (30.1)
Smoking, pack-yr			
Mean	60.2	60.2	68.3
SE	2.8	2.7	3.5
COPD duration, yr			
Mean	8.0	7.5	7.3
SE	0.7	0.6	0.6
Dyspnea (MMRC)			
Mean	1.6	1.5	1.6
SE	0.07	0.07	0.07
DLCO, mL/min/mm Hg			
Mean	13.8	15.8	14.8
SE	0.7	1.2	1.0
FEV_1, % predicted			
Mean	40.8	42.1†	37.0†
SE	1.12	1.08	1.14
FEV_1/FVC			
Mean	0.49	0.49	0.46
SE	0.01	0.01	0.01
Chest radiograph, No. (%)			
Normal	109 (76.2)	95 (70.4)	102 (76.7)
Abnormal	33 (23.1)	38 (28.1)	30 (22.6)

*MMRC = Modified Medical Research Council scale; DLCO = carbon monoxide diffusing capacity of the lung.
†Salmeterol vs placebo (p = 0.0014); salmeterol vs ipratropium (p = 0.0157).

Pulmonary Function Tests

At screening, the FEV_1 (percent predicted) was significantly higher for the salmeterol group than the placebo group (p = 0.0014) and the ipratropium group (p = 0.0157) (Table 2). Approximately 65% of the patients in each treatment group responded to inhaled albuterol as defined above (Table 3). For all patients and for those patients reversible to albuterol, the magnitude of the bronchodilator response was greater for albuterol than for ipratropium bromide; for those patients nonreversible to albuterol, the magnitude of bronchodilator response was greater for ipratropium bromide than for albuterol (Table 3). However, there were no differences in the number of responsive patients or the magnitude of response for either bronchodilator among the three treatment groups (Table 3).

At week 0, mean predose baseline FEV_1 values were significantly lower in the ipratropium group (1.16 L) than in the placebo (1.30 L) and salmeterol (1.28 L) groups (p = 0.0006 and p = 0.018, respectively). The FEV_1 response to a single dose of salmeterol at each time interval was significantly superior to placebo (p = 0.001) at weeks 0, 4, 8, and

Table 3—*Reversibility to Albuterol and Ipratropium Bromide*

	Placebo	Salmeterol, 42 μg bid	Ipratropium, 36 μg qid	p Value
All Patients				
No.	143	135	133	
Mean prealbuterol FEV_1, L	1.31	1.36	1.18	
Mean postalbuterol FEV_1, L	1.56	1.62	1.42	
Mean ± SE (% change)	22.7 ± 1.1	23.5 ± 1.6	24.5 ± 1.6	0.6794
Mean preipratropium bromide, L	1.31	1.36	1.19	
Mean postipratropium bromide, L	1.54	1.59	1.41	
Mean ± SE (% change)	19.4 ± 1.4	17.6 ± 1.3	18.6 ± 1.2	0.6141
Patients reversible to albuterol				
No.	93	87	86	
Mean prealbuterol FEV_1, L	1.34	1.40	1.21	
Mean postalbuterol FEV_1, L	1.67	1.79	1.53	
Mean ± SE (% change)	28.2 ± 1.3	31.3 ± 1.9	31.3 ± 2.1	0.3552
Mean preipratropium bromide, L	1.38	1.42	1.26	
Mean postipratropium bromide, L	1.64	1.71	1.51	
Mean ± SE (% change)	20.3 ± 1.7	21.3 ± 1.7	20.8 ± 1.4	0.8939
Patients nonreversible to albuterol				
No.	50	48	47	
Mean prealbuterol FEV_1, L	1.24	1.27	1.12	
Mean postalbuterol FEV_1, L	1.35	1.32	1.22	
Mean ± SE (% change)	12.5 ± 1.1	9.4 ± 1.3	12.2 ± 1.1	0.1103
Mean preipratropium bromide, L	1.18	1.26	1.07	
Mean postipratropium bromide, L	1.36	1.38	1.22	
Mean ± SE (% change)	17.7 ± 2.4	10.9 ± 1.6	14.6 ± 2.0	0.0612

12 and to the two doses of ipratropium at hours 4 and 6 at week 0 and at hours 0, 4, and 6 at week 12 (Fig 1). Although the results in the responder and nonresponder strata were qualitatively similar, the magnitudes of the FEV_1 responses to salmeterol and ipratropium were greater in the responsive patients (Fig 1). The mean change from baseline for the FEV_1AUC revealed that the response to salmeterol was significantly superior to placebo ($p < 0.001$) at weeks 0, 4, 8, and 12. Salmeterol was also statistically superior to ipratropium at weeks 4 and 8 ($p < 0.005$). There was no difference in the mean change of FEV_1AUC from day 1 to day 84 in the salmeterol group, but there was a reduction noted over the same period in the ipratropium group. At the end of 12 h, the mean FEV_1 in the salmeterol group remained >12% above baseline, and the morning predose FEV_1 values at weeks 4 through 12 remained elevated from the previous evening's doses (Fig 1).

FVC responses were similar to FEV_1 responses. At baseline, FVC values ranged from 2.54 to 2.74 L across the treatment groups, with no significant differences between the treatment groups. Serial FVC response to salmeterol was significantly superior to placebo at all time points during weeks 4, 8, and 12 of the study with increases from baseline ranging from 0.26 to 0.48 L. Changes from baseline for FVC in the ipratropium group were significant at all time points during all treatment weeks except for hour 6 and hour 12 at week 4 and hour 6 at weeks 8 and 12. Significant differences in FVC between patients treated with salmeterol and with ipratropium were noted at hour 6 at all serial assessments and at hour 0 for the serial assessments at week 4 and week 12.

Dyspnea Ratings

The mean BDI scores for the placebo, salmeterol, and ipratropium groups were 6.3, 5.9, and 6.0, respectively, indicating a moderate level of dyspnea for all patients at the start of the study. The mean TDI scores demonstrated a greater improvement in patients treated with either salmeterol or ipratropium compared with placebo (Fig 2). For all patients, statistically significant improvements for salmeterol and ipratropium vs placebo were observed at weeks 2, 4, 8, and 10, and for ipratropium vs placebo also at weeks 6 and 12. For responsive patients, improvements in TDI scores were similar to those obtained in the total population; for the nonresponsive strata, there were no significant treatment differences except for ipratropium vs placebo at week 8.

Mean baseline prewalk Borg dyspnea scores in the placebo, salmeterol, and ipratropium treatment groups were 1.4 ± 0.1, 1.4 ± 0.1, and 1.3 ± 0.1, respectively, indicating "very slight" dyspnea. After the 6MW, dyspnea scores increased to 3.1 ± 0.1,

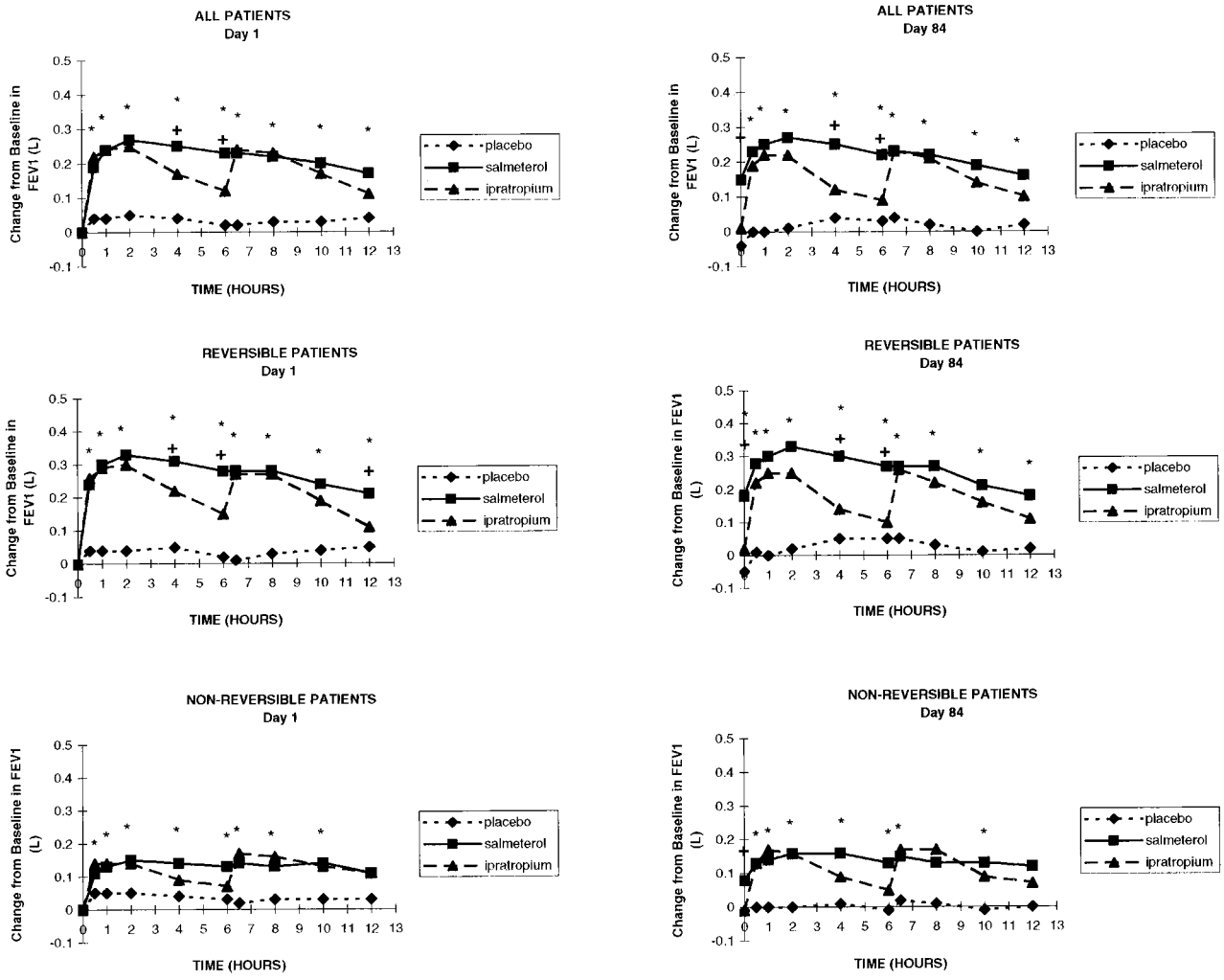

FIGURE 1. Change from baseline was analyzed within each group and by responsivity strata over a 12-h period of serial pulmonary function testing at day 1 (left) and day 84 (right). The mean change from baseline in FEV_1 in the salmeterol group (combined population) was significant (indicated by asterisk; $p < 0.001$) for each serial assessment at all visits. Within the ipratropium group, change from baseline was significant ($p \leq 0.026$) for all serial assessments except for hour 0 (predose) at day 84. Significant differences in serial FEV_1 between salmeterol and ipratropium treatment groups are indicated with a plus sign.

3.1 ± 0.2, and 2.9 ± 0.1, respectively, indicating "moderate" dyspnea. Over the 12-week period, there were no significant changes in the prewalk or postwalk dyspnea scores or the 6MW distance for any treatment group (except at week 10 when the increase of 14.0 ± 7.0 yards in the ipratropium group was significantly greater than the placebo group [$p < 0.018$]).

Patient Self-assessment

Mean baseline daytime symptom scores (shortness of breath, chest tightness, and cough) were not significantly different among treatment groups in the total group or in either stratum (responsive and nonresponsive). Mean daytime symptom scores in all three treatment groups decreased (improved) over the 12-week treatment period. With the exception of ipratropium vs placebo for shortness of breath in the responsive stratum, there were no significant differences between ipratropium or salmeterol and placebo. However, paired comparisons (baseline vs subsequent weeks) for nighttime shortness of breath showed significantly greater improvement in the salmeterol group (0.59 ± 0.07 to 0.46 ± 0.07) than in the placebo (0.59 ± 0.07 to 0.59 ± 0.07; $p = 0.042$) and ipratropium groups (0.434 ± 0.07 to 0.39 ± 0.06; $p = 0.037$) from weeks 5 to 8, and there was a trend toward significance ($p = 0.087$) over the 12 weeks of treatment. Comparison between groups for nighttime shortness of breath showed that salme-

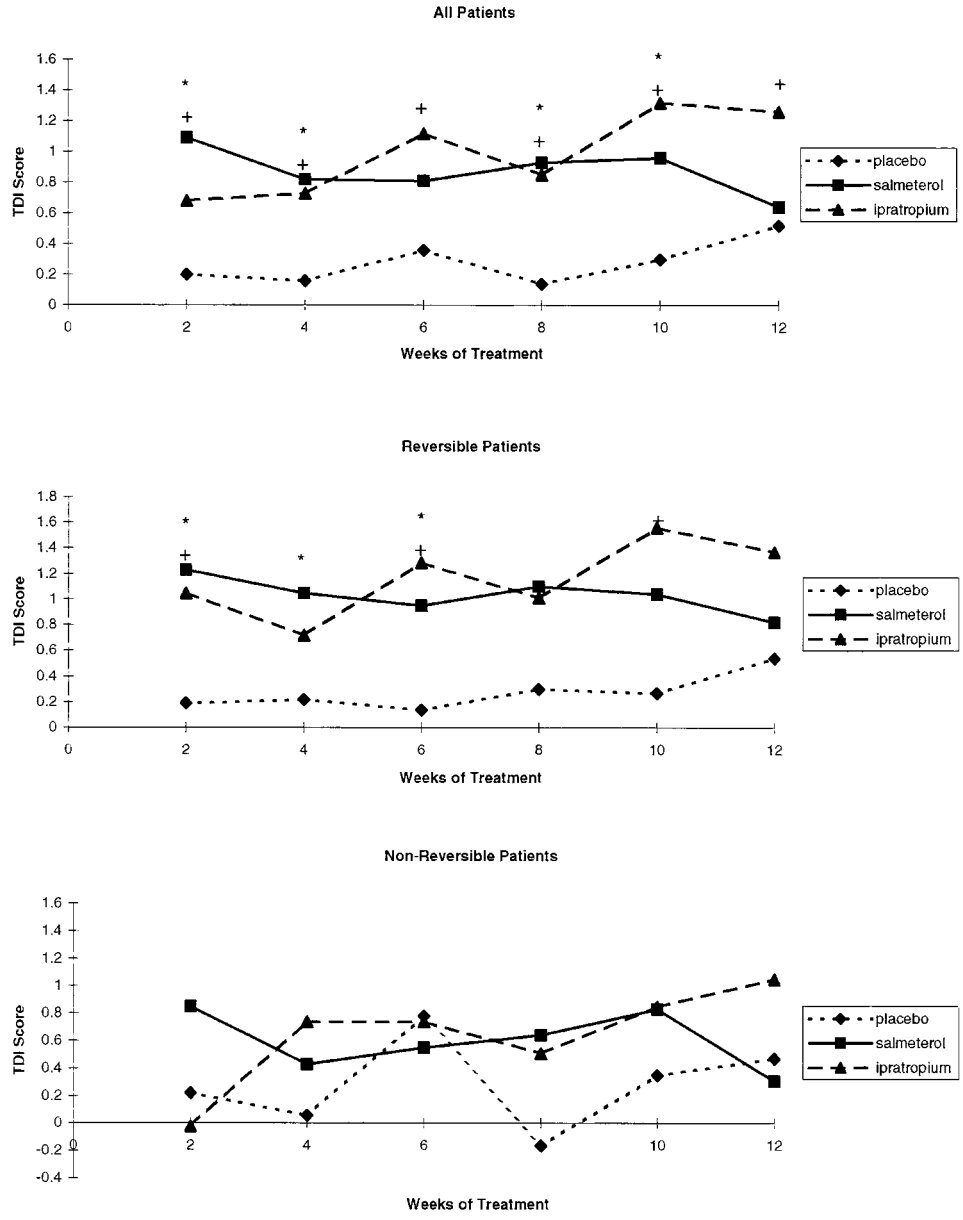

FIGURE 2. Mean TDI scores by treatment group and albuterol responsivity strata. An asterisk denotes statistical significance of salmeterol over placebo; a plus sign denotes statistical significance of ipratropium over placebo.

terol was statistically superior to ipratropium ($p = 0.043$) over the entire 12-week period. Results for daytime and nighttime cough and chest tightness were similar for all three treatment groups.

Supplemental Albuterol Use

At baseline, there was no significant difference among the three treatment groups in the daytime use of supplemental albuterol: 4.3 ± 0.3, 4.6 ± 0.3, and 4.5 ± 0.3 puffs per day for placebo, salmeterol, and ipratropium, respectively. There was a significant decrease in mean puffs per day of albuterol (to 2.0 ± 0.3 and 2.4 ± 0.3 puffs per day, respectively) in the salmeterol ($p < 0.001$) and in the ipratropium ($p < 0.047$) groups compared with placebo at every interval. Similar findings were observed in the responsive stratum. There were no significant differences in albuterol use in the nonresponsive subgroup among treatment groups.

COPD Exacerbations

The percentages of patients experiencing one or more exacerbations over the 12-week treatment pe-

riod were 32.9%, 20.7%, and 30.8% for the placebo, salmeterol, and ipratropium groups, respectively. Analysis of the time to first COPD exacerbation demonstrated salmeterol to have a delayed onset of exacerbations compared with placebo ($p = 0.0052$) and ipratropium ($p = 0.0411$) (Fig 3). More patients in the placebo group ($n = 21$) experienced their first exacerbation during week 1 than did patients in the salmeterol ($n = 7$) and ipratropium ($n = 7$) groups.

Health-Related Quality of Life

Baseline values for the total CRDQ scores were similar for the three groups. At week 12, the mean CRDQ overall score was significantly higher for salmeterol (7.1 ± 1.4; $p = 0.007$) and for ipratropium (6.8 ± 1.2; $p = 0.007$) than for placebo (2.1 ± 1.3). The proportion of patients who achieved an increase of ≥ 10 points in overall score (the minimum change indicative of an important difference)[18] was significantly higher at week 12 in the salmeterol (46%, $p = 0.002$) and ipratropium (39%, $p = 0.041$) groups than in the placebo group (27%). Both salmeterol and ipratropium showed a progressive increase from weeks 2 to 12 in the proportion of patients achieving an overall increase of 10 in the CRDQ score, which is reflected in both strata. Both salmeterol and ipratropium demonstrated a statistically higher proportion of patients who achieved an increase of 10 points in overall CRDQ score in the nonreversible stratum at week 12. In the responsive stratum, statistical significance was observed only for salmeterol.

Safety

No major differences were seen in the incidence of adverse events across treatment groups (Table 4).

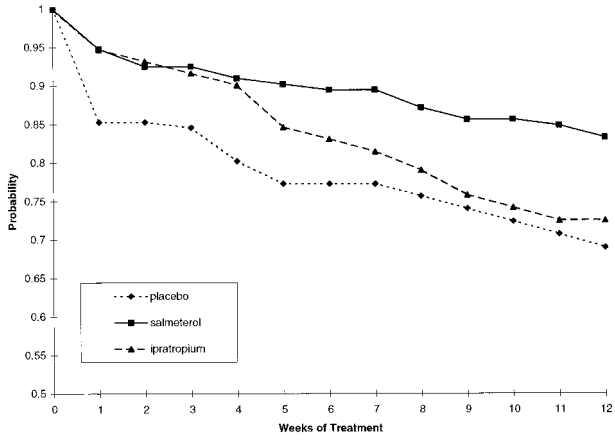

FIGURE 3. Kaplan-Meier survival analysis of time to first exacerbation. A significantly higher percentage of salmeterol-treated patients completed the study without experiencing a COPD exacerbation than did either ipratropium-treated ($p = 0.0411$) or placebo-treated ($p = 0.0052$) patients.

Table 4—*Adverse Events Occurring in ≥ 3% of Patients*

	Placebo, n = 143 (%)	Salmeterol, 42 μg bid, n = 135 (%)	Ipratropium, 36 μg qid, n = 133 (%)
Ear, nose, and throat			
Common cold	19 (13.3)	14 (10.4)	15 (11.3)
Upper respiratory tract infection	9 (6.3)	11 (8.1)	11 (8.3)
Sore throat	6 (4.2)	7 (5.2)	6 (4.5)
Rhinorrhea	4 (2.8)	4 (3.0)	1 (0.8)
Nasal congestion	5 (3.5)	1 (0.7)	2 (1.5)
GI			
Heartburn	2 (1.4)	4 (3.0)	2 (1.5)
Diarrhea	5 (3.5)	3 (2.2)	5 (3.8)
Nausea	2 (1.4)	3 (2.2)	4 (3.0)
Vomiting	1 (0.7)	0 (0.0)	4 (3.0)
Lower respiratory			
Cough	11 (7.7)	9 (6.7)	10 (7.5)
Chest congestion	1 (0.7)	5 (3.7)	1 (0.8)
Influenza	3 (2.1)	2 (1.5)	4 (3.0)
Bronchitis	8 (5.6)	1 (0.7)*	1 (0.8)*
Cough exacerbation	5 (3.5)	1 (0.7)	3 (2.3)
Neurology			
Headache	13 (9.1)	9 (6.7)	6 (4.5)
Nonsite specific			
Pain in body	1 (0.7)	4 (3.0)	1 (0.8)

*Salmeterol ($p = 0.037$) group and ipratropium ($p = 0.037$) group significantly lower than placebo.

There was a significantly reduced incidence of bronchitis in both the ipratropium ($p = 0.037$) and salmeterol ($p = 0.037$) groups compared with placebo. Twenty-three patients reported an adverse event considered related to the study drug (10 placebo, 6 salmeterol, 7 ipratropium). There were no significant differences between treatment groups by body system or individual events. A total of 16 patients withdrew from the study due to adverse events (8 placebo, 1 salmeterol, and 7 ipratropium). There were no deaths during the study.

There were no clinically significant changes in clinical laboratory values, vital signs, 12-lead ECG, or physical examination findings during treatment. As measured by 24-h ECG monitoring, there were no significant differences at baseline between treatment groups in the total number of ventricular and supraventricular ectopic events or the mean number per 1,000 beats. The number of events was highly variable between treatments and from visit to visit. At week 4, the incidence of total ventricular events was lower for salmeterol and ipratropium than placebo, and at week 8, the frequency of supraventricular events was higher in the ipratropium group than placebo ($p = 0.015$). At study completion, there were no significant differences for ECG abnormalities among treatment groups.

Discussion

In this 12-week multicenter clinical trial in patients with COPD, both salmeterol and ipratropium provided significant increases in lung function, improved dyspnea ratings using the multidimensional BDI/TDI, reduced the use of supplemental albuterol, and enhanced disease-specific quality of life on the CRDQ compared with placebo treatment. These findings not only substantiate previous data, but also expand our understanding about the relative efficacy of both inhaled bronchodilators in a large population of patients with COPD.

At the present time, ipratropium bromide is considered first-line therapy for the treatment of continuous symptoms due to COPD.[1,4] However, in this double-dummy, parallel group investigation, a single administration of salmeterol produced greater sustained bronchodilation over 12 h as measured by the FEV_1AUC than two administrations of ipratropium given four times a day. It is unlikely that the slightly higher baseline FEV_1 percent predicted in the salmeterol group influenced these results. Rather, this effect appeared to be due to the longer duration of action of salmeterol because the peak responses for salmeterol and ipratropium were similar. Although higher doses (four to six puffs) of ipratropium have been used in clinical practice, we studied the recommended starting dose (two puffs [36 mg]) given four times a day. The bronchodilator activity of salmeterol was maintained throughout the 12-week study period; in fact, mean FEV_1 levels on each of the testing days remained elevated in the morning as a result of the doses administered 12 h earlier (Fig 1). There was no evidence of the development of tolerance to the bronchodilator activity of salmeterol over the 12-week period.

Any improvement in airflow in patients with moderate-to-severe COPD may be of important clinical benefit. We observed similar reductions in breathlessness (higher TDI scores) with both salmeterol and ipratropium that were evident at 2 weeks and were generally sustained over the entire 12-week period (Fig 2). The improvement in dyspnea throughout the study was supported by the observed significant decrease in supplemental albuterol use with both salmeterol and ipratropium. The relief of dyspnea may be due in part to the reduced resistive work of breathing due to even modest bronchodilation. In addition, the known effects of bronchodilators in reducing end-expiratory lung volume[12,19] would be expected to lead to a decrease in the inspiratory elastic work of breathing.[20] Thus, both bronchodilation and/or decreased hyperinflation may contribute to the clinical benefits of salmeterol and ipratropium.

Despite these clinical benefits, neither medication altered the 6MW distance or led to a decrease in prewalk or postwalk Borg dyspnea ratings. A timed walking test is a measure of functional exercise capacity that is clearly dependent on the effort of the individual.[21] Although the patients who received salmeterol or ipratropium had less dyspnea with daily activities (as observed with the BDI/TDI), this benefit may not result in an increase in walking distance unless the patient was motivated to walk faster during the test. Furthermore, some patients with COPD are limited in their exercise capacity by leg discomfort and general fatigue rather than by breathlessness.[22] Therefore, bronchodilator therapy may not alter a timed walking test. Although dyspnea ratings increased after completion of the walking test in all three groups, there were no differences among the treatment groups. Previous studies of bronchodilator therapy in COPD have shown similar improvements in lung function and reductions in dyspnea, but no significant change in walking distance or peak exercise performance.[19,23,24]

Our results confirm a previous report that salmeterol improves HRQL in patients with COPD. Jones and Bosh[14] reported that salmeterol at a dose of 50 μg twice a day was associated with significant increases in the "total" and "impact" scores for the St. George's Respiratory Questionnaire, a disease-specific instrument, compared with placebo. We used the CRDQ, a different disease-specific instrument focused on four domains (dyspnea, fatigue, emotional function, and mastery) that affect patients with COPD. Benefits in quality of life were achieved with both salmeterol and ipratropium compared with placebo in both responsive and nonresponsive strata. However, direct comparisons showed that salmeterol provided greater improvements in mean CRDQ overall scores than those observed in the ipratropium group. Furthermore, the time to first COPD exacerbation was significantly longer with salmeterol than with either placebo or ipratropium bromide. Whether prolonged bronchodilation with salmeterol or another mechanism contributed to this benefit is unclear.

In summary, salmeterol was significantly better than placebo and ipratropium in improving lung function at the recommended doses over the 12-week period. Both salmeterol and ipratropium reduced dyspnea related to activities of daily living compared with placebo; and this improvement was associated with reduced use of supplemental albuterol. As provided in this study, patients should use a short-acting β-agonist, such as albuterol, as a rescue medication. The safety profile of salmeterol was similar to ipratropium and placebo in this trial. Compared with ipratropium, salmeterol exhibited a

significantly lower COPD exacerbation rate and led to significantly greater improvements in HRQL. Furthermore, the twice-daily dosing schedule of salmeterol should enhance compliance. These collective data support the use of salmeterol as first-line therapy for the long-term treatment of airflow obstruction in patients with COPD.

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