Three Regimens of Inhaled Bronchodilators for Chronic Obstructive Pulmonary Disease: Comparison of Pulmonary Function and Cardiopulmonary Exercise Test Parameters

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Abstract

This study aimed to compare that effects of tiotropium combined with formoterol, ipratropium combined with formoterol and formoterol alone on cardiopulmonary exercise testing and pulmonary function test parameters in patients with GOLD stage II and III chronic obstructive pulmonary disease (COPD). Thirty-seven patients who had been classified according to the GOLD as stage II and III participated in this randomized, prospective study. Three groups were created: patients in group 1 (FEV_1%: 55.07±9.36%) received tiotropium and formoterol; in group 2 (FEV_1%: 50.08±13.87%) they received ipratropium and formoterol, and in group 3 (FEV_1%: 62.27±7.34%) they received formoterol alone. Patient demographics were similar among the 3 groups ($p>0.05$). Prior to treatment, data were recorded for all patients for symptom-limited cycle exercise tests and pulmonary function tests. After 28 days of treatment, exercise test and spirometry were repeated, and data regarding the bronchodilator effects of the various treatments were compared. Three treatment regiments of inhaled bronchodilators were compared in terms of spirometry and cardiopulmonary exercise test parameters. Ipratropium combined with formoterol was more effective (Mean percentage changes in FEV_1%: 33.30±22.97%) than tiotropium combined with formoterol or formoterol alone as a means of improving lung flow in our patients. We found that ipratropium combined with formoterol was superior to tiotropium combined with formoterol and formoterol alone in subjects with stage II and III COPD. We suggest that combining the anticholinergics and β-agonists, especially ipratropium combined with formoterol, is more preferable than monotherapy with β-agonists in these subjects.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) have impaired lung function due to structural narrowing of the airways and cholinergic vagal bronchoconstrictive tone. The goals for clinical management of COPD are to prevent lung damage, preserve lung function, reduce the severity of symptoms, and improve exercise capacity (1-3). Cessation of smoking is considered the essential first step. After this, the American Thoracic Society (ATS), the British Thoracic Society (BTS), and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend bronchodilators as the pharmacotherapy of choice (4-6). The three major classes of bronchodilators are β-agonists, anticholinergics, and methylxanthines. Inhaled anticholinergic agents and

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β-agonist bronchodilators are the preferred treatments for COPD (7). These two groups of inhaled agents achieve their bronchodilating effects via different mechanisms: the β-agonists by stimulating adrenergic receptors, and the anticholinergic agents by inhibiting the action of acetylcholine at muscarinic receptors. When used together, these drugs may have additive effects (8,9). The GOLD guidelines and other current international guidelines recommend combination therapy with these drugs for patients who do not respond satisfactorily to monotherapy. Strong evidence from recent studies suggests that long-acting inhaled forms of β-agonists (such as salmeterol or formoterol) and the anticholinergic tiotropium bromide should be used in combination with short-acting inhaled forms (such as salbutamol or ipratropium bromide) (10,11). Recent findings also indicate that the combination of salbutamol and ipratropium affects better bronchodilation than does either of these drugs alone (12). Although several investigators have compared the bronchodilating effects of ipratropium bromide, tiotropium bromide, salbutamol, and salmeterol, there are no reports which compare the combination of tiotropium bromide and formoterol with the combination of ipratropium bromide and formoterol (7,10,13).

A report by O'Donnell and coworkers revealed that improved exercise capacity is a conspicuous feature of bronchodilator usage in COPD, and that this parameter can be used to assess bronchodilator efficacy (14). We sought to compare 4-week courses of three different drug regimens for COPD with respect to impacts on airflow obstruction, dyspnea, and exercise performance. The three regimens assessed were ipratropium bromide and formoterol, tiotropium bromide and formoterol, and formoterol alone.

Methods

Patients

The study included clinically stable patients who were newly diagnosed with COPD. All patients were assessed as having GOLD stage II and III COPD. This was defined as the percentage of forced expiratory flow in one second (FEV_1%) being between 30% and 80%, and FEV_1/forced vital capacity (FVC) less than 0.7, with or without symptoms (such as cough and sputum) (6). Reasons for exclusion were: a history of asthma, atopy, or other systemic conditions that could contribute to dyspnea or exercise limitation; a recent history of myocardial infarction, heart failure, or cardiac arrhythmia; inability to pedal for cycle ergometry; a positive response to reversibility test over 10%, or a history of an upper respiratory tract infection in the 6 weeks prior to the study. Subjects with known symptomatic prostatic hypertrophy or narrow-angle glaucoma were also excluded.

Study Design

This randomized, prospective study was approved by the Başkent University Research Ethics Committee. During an initial screening visit, each subject was assessed for study eligibility when they visited the outpatient clinic. Specifically, the first investigator identified subjects with GOLD stage II and III COPD and selected them for the study. The eligible subjects all gave written informed consent to participate. All tests were performed by the first investigator as blind to inhaled treatment modalities. Each patient was referred to a second investigator who randomly assigned medication regimens using a blind draw lot. In total, 45 GOLD stage II subjects were enrolled and assigned to three treatment groups: group 1 (n: 15) received a combination of tiotropium and formoterol (T+F), group 2 (n: 15) received a combination of ipratropium and formoterol (I+F), and group 3 (n: 15) received formoterol (F) alone. Dosage and administration details are given below.

After 4 weeks of treatment, each subject was re-examined by the first investigator, who was blinded to their therapy regimen. At both the pre- and post-treatment examinations, the investigator performed pulmonary function testing (PFT, detailed methods below) and cardiopulmonary exercise testing (CPET) to evaluate treatment efficacy. Subjects who returned to the clinic with persistent symptoms before the end of the 4-week course of treatment and were prescribed other medications in addition to inhaled anticholinergic and β-agonist drugs for COPD (such as theophylline, antibiotics, systemic or inhaled corticosteroids, and/or oxygen) were excluded from the study. Patients who developed acute exacerbations of COPD during the study period were also excluded.

The CPET evaluations were done using a cycle ergometer (detailed methods below) and each patient's test was done at the same time in the afternoon. Maximum work rate (Wmax) was recorded. After the initial exercise test (at the pre-treatment visit), the same nurse instructed each subject on how to use a Spiriva® HandiHaler® (tiotropium bromide inhalation powder; Boehringer Ingelheim Corp., Ridgefield, CT, USA). The training for the use of inhalers was as follows: Subjects were instructed to exhale to functional residual capacity, then inhale slowly until total lung capacity was reached, and then hold their breath for at least 10 seconds. To ensure that the drugs were administered correctly, the inhalation technique was carefully observed.

The inhaled bronchodilators were administered in the following dosages and forms: formoterol, 12 mg dry powder b.i.d. by HandiHaler®; tiotropium bromide 18 mg dry powder q.d. by HandiHaler®; and ipratropium bromide 40 mg (two puffs of 20 mg each) from a pressurized metered dose inhaler via a spacer two puffs every 6 hours.

Pulmonary Function Testing

As noted, spirometry was performed prior to exercise testing at the first and second visits (pre- and post-treatment). A clinical spirometer (SensorMedics™ Vmax spectra 229, Bilthoven, The Netherlands) was used, and a laboratory technician demonstrated each respiratory ma-

Table 1. Demographic characteristics and baseline PFT findings in the three groups			
Variable	T+F (n = 14) Mean±SD	I+F (n = 12) Mean±SD	F (n = 11) Mean±SD
Age (yrs)	60.1±9.5	59.2±8.3	58.7±10
Sex, n (%)	11 (78.6) M	10 (83.4) M	9(81.9) M
	3 (21.4) F	2 (16.6) F	2 (18.1) F
Body mass index	26.44±2.98	26.61±4.04	25.76±3.06
FEV_1%	55.07±9.36	50.08±13.87	62.27±7.34
FEV_1/FVC%	59.21±10.78	56.58±10.29	57.81±6.61

Table 2. Spirometry and cardiopulmonary exercise test results						
Variable	T+F group		I+F group		F group	
	Baseline	Day 28	Baseline	Day 28	Baseline	Day 28
FEV_1 (%)[1]	55.07±9.36	61.35±14.29	50.08±13.87	60.66±12.84	62.27±7.34	63.90±7.56
FEV_1/FVC(%)[1]	59.21±10.78	65.57±9.56	56.58±10.29	60.91±9.68	57.81±6.61	59.54±10.78
IC (l)[2]	1.99±0.57	2.07±0.62	2.14±0.70	2.42±0.64	2.33±0.38	2.25±0.46
PVO_2 (ml/kg/min)	18.97±4.45	17.87±4.21	16.03±2.95	16.07±2.90	16.63±2.93	16.26±3.82
W_{max}/watt	98.92±37.83	98.85±37.72	92.08±37.85	96.58±29.81	89.36±33.47	83.45±35.95
VE_{max} (l)	60.57±27.14	59.72±21.11	52.76±14.38	58.53±14.28	58.13±11.36	52.40±10.34
VT (l)	1.40±0.39	1.41±0.45	1.44±0.40	1.53±0.35	1.41±0.29	1.45±0.25
Exercise duration/min	10.15±1.60	10.01±1.31	10.94±2.46	11.55±2.88	10.02±1.64	9.43±1.79

[1] $p < 0.05$ for comparison of FEV_1% of per and FEV_1/FVC at baseline vs on day 28 of treatment in all groups.
[2] $p = 0.028$ for comparison of IC at baseline vs IC on day 28 of treatment in the I+F group.

neuver for the subject before testing each PFT parameter. All subjects performed a maximal expiratory flow maneuver in the sitting position. The number of liters of forced expiratory flow in one second FEV_1, FEV_1%, FVC, inspiratory capacity (IC), and maximal voluntary volume (MVV) were measured. At least three reproducible tests were carried out for each measurement, and the best result was recorded. Predicted values were calculated according to the European Community for Steel and Coal, as described by Quanjer (16).

Exercise Testing

As noted, symptom or maximal-heart-rate-limited CPET was performed using a cycle ergometer (ergo-metrics 900, SensorMedics™, Bilthoven, The Netherlands) and a spirometer. Subjects were told not to eat or drink for two hours before exercise testing. The gas analyzer was calibrated just before the study with air and with two standard reference gas mixtures (26% O_2 + balanced N_2 and 4% CO_2 + 16% O_2 + balanced N_2). Arterial oxygen saturation was measured via pulse oximetry (NONIN 8600 pulse oximeter™, Plymouth, Minnesota USA). A face mask connected to a low-resistance unidirectional valve (Rudolph Face Mask for Exercise Testing™; Hans Rudolph Inc., Kansas City, MO, USA) was placed on the subject's face and fit snugly to ensure no leakage. The incremental exercise test consisted of a 3-minute baseline resting period, followed by a 3-minute warm-up period (up to 60 rpm pedaling), and subsequent periodic work rate increases of 15 W each minute.

The exercise data were recorded with an automated exercise testing system (Desktop Diagnostics/CPX™; Medical Graphics Corporation, St. Paul, MN, USA) that converts breath-by-breath analog input to digital form in an on-line fashion. Wmax was recorded as the maximum work rate sustainable for 20-30 seconds. Each subject's electrocardiogram, arterial pressure, and oxygen saturation were monitored continuously during the evaluation. The testing was terminated at the point of maximal heart rate or symptom limitation (1). Reasons for terminating the test (*i.e.*, fatigue, chest pain, leg pain, dyspnea) were recorded. Maximal oxygen uptake (VO_2), peak CO_2 output (PCO_2), gas exchange ratio (VCO_2/VO_2), minute ventilation (VE-max), and tidal volume (VT) were recorded. Predicted values were calculated according to the reference values as described by Jones (17).

Statistical Analysis

All analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 9.0; SPSS; Chicago, IL, USA). The paired samples Student *t*-test was used to examine the statistical significance of differences among groups. Multivariate analyses were performed with one-way analysis of variance. *Post hoc* testing (Tukey HSD) was used to compare the group findings for changes in FEV_1%. A p value less than 0.05 was considered to indicate statistical significance. Unless indicated otherwise, data are expressed as mean±SD.

Results

Subjects

Of the 45 subjects who were initially enrolled, 37 completed the study. Six subjects failed to attend the second round of cycle ergometry testing, and two had to be removed from the study and switched from monotherapy with F to combined therapy with antibiotics and β-agonists due to acute exacerbation and unimproved dyspnea. Thus, 37 data sets were analyzed (14 from group 1 [T+F], 12 from group 2 [I+F], and 11 from group 3 [F alone]). At the end of the study we had to add an anticholinergic inhaled agent to the treatment of 9 subjects due to persistent symptoms in group 3. Table 1 shows the demographic characteristics and baseline PFT values (mean±SD) for the 37 subjects. There were no statistically significant differences among the mean values of the groups for the demographic parameters and baseline spirometric variables.

Effects of Treatment

The baseline values for FEV_1%, FEV_1/FVC, and IC were compared with values on the 28th day of treatment. Group 1 showed significant improvements in these parameters (FEV_1%: for baseline vs day 28, $p = 0.015$). In group 3, there was no difference between the baseline and day 28 values for FEV_1% ($p > 0.05$). Group 2 also showed significant improvements in FEV_1% (for baseline vs day 28, $p < 0.001$)

The group responses to treatment as reflected by FEV_1% values at baseline vs the 4-week stage. The group means for percentage change in FEV_1% were as follows; 10.91± 14.49% in group 1, 33.30±22.97% in group 2, 3.06±10.08% in group 3. Analysis showed that the three means were significantly different ($p = 0.001$), and that the percentage change in group 2 was significantly greater than the degrees of change noted in groups 1 and 3 ($p = 0.007$ for group 2 vs group 1; $p = 0.001$ for group 2 vs group 3).

As Table 2 shows, none of the three treatment groups showed a significant rise in VO_2max, or significant improvement in Wmax or exercise time from baseline to day 28. Similarly, none showed at the 4-week stage.

Group 2 showed significant improvements in VEmax (52.76±14.38 l/min vs 58.53±14.28 l/min for baseline vs day 28, respectively; $p = 0.005$) and in VT (1.44±0.40 l vs 1.45±0.25 l for baseline vs day 28, respectively; $p = 0.004$), but neither of the two other groups showed significant changes in these parameters.

Discussion

Many investigators have compared the activity of I, F, and T alone in patients with COPD (10,18-22). Combinations of short-acting β-agonists with anticholinergics have been reported to be more effective than either of these agents used alone (8,11,12,14,23). The potential additive effects of these agents are still unknown. The acute effects of the T+F combination have been investigated but, no study to date has compared T+F versus I+F in patients with COPD. The aim of this study was to compare the effects of these combinations with respect to pulmonary function and exercise test performance. We recorded data for 37 clinically stable COPD patients who underwent spirometry and CPET before and after a 4-week course of treatment with one of the three different drug regimens (T+F, I+F, or F alone).

There was a major limitation in our study. According to our study design, we planned to distribute the selected 45 patients equally to all groups by the randomized blind draw lot method (described above). However, one patient in group 1, three patients in group 2 and two in group 3 claimed they were uncomfortable while performing CPET. Hence they decided not to do a second CPET and these patients had to be excluded from the study. Therefore the number of the subjects in the study groups ended not being equal at the termination of the study.

In this study, we observed that I+F and T+F led to greater improvement in FEV_1% than the F regimen. Several other studies have also indicated that there was a potential for the combined treatment to have a synergistic effect when β-agonists and anticholinergics were used together (11-13,24-27). At the end of this study, we had to add an anticholinergic inhaled agent to the F treatment in 9 (82%) patients in group 3 due to persistent symptoms (sputum, cough, dyspnea). In this group, on the 28th day of treatment, we also found that exercise performance and exercise duration were worse than baseline findings. Based on these results, we believe that anticholinergic and β-agonist inhaled agents should be used together instead of monotherapy in patients with stage II and III COPD though the GOLD 2003 guideline recommends regular treatment with one or more bronchodilators when treating patients with stage II and III COPD (6).

Our results indicate that for a bronchodilator effect, the addition of I 40 µg qid, to treatment with F, 12 µg bid, is more effective than the addition of T 18 µg q.d., suggesting that the combination of I and F may have more pronounced additive or synergic effects than the combination of T and F in this patient group. To our knowledge, such an observation has not been previously reported in patients with COPD. Further studies are needed to examine this effect in greater depth.

Hyperinflation is an important factor for exercise limitation in patients with COPD and improvement of exercise capacity is a major goal of treatment (3). This study revealed a significant decrease in lung hyperinflation during exercise in group 2 after 4 weeks of treatment because there was significant increase in mean of IC at the end of I+F treatment. In support of this idea, O'Donnell and coworkers also highlighted increased IC as an index of reduced resting lung hyperinflation (28). We speculate that the increase in IC was due to decreased end expiratory lung volumes after the course of I+F. We conclude that I+F is a preferable combination to T+F for reducing exertional lung hyperinflation in patients with COPD.

In this study, none of the three treatment groups showed a significant increase in maximal work, oxygen uptake, and maximal exercise duration on the 28th day of treatment. We believe that the lack of significant improvement in the exercise performance of subjects was due to two probable factors: 1. Potential negative effects such as an increase in V/Q (the ratio of ventilation to perfusion) mismatch have been reported (29). We did not evaluate the V/Q mismatch of subjects on exercise and these factors may be the cause of insufficiently improved oxygen uptake and exercise performance despite an increase in ventilatory parameters, 2. In this study the maximal exercise test might not have been sensitive enough to estimate such minor changes in maximal work, oxygen uptake and maximal exercise time. A similar argument was made in the study of Oga et al (30). We believe that their study was supported by our results in that both studies failed to detect the effect of inhaled agents on exercise capacity during maximal exercise tests. Then, it might be more suitable to measure the effects of I+F on exercise capacity using an endurance test or 6-minute walking test instead of cycle ergometry and to perform these tests on larger patient series.

Our findings indicate that inhaled bronchodilators do not significantly improve exercise capacity in patients with GOLD stage II and III COPD. We believe that in addition to other treatment modalities these patients should undergo a pulmonary rehabilitation programme to increase their exercise capacity, similar to that recommended for patients in the advanced stages of COPD (Gold stage III and IV) (6). Liesker et al outlined a stepwise approach to evaluating the effect of bronchodilators on exercise capacity (31). Our study compares to that study as follows; 1) we too administered inhaled bronchodilator drugs at recommended dosages (160 μg I, 18 μg T, and 12 μg F), 2) the subjects who were unable to pedalling cycle ergometry were also excluded from our study, 3) patient groups in both studies were smaller than those of other studies. We believe that the small size of our study groups and insufficient improvement in the oxygen uptake of our patients may have been factors in the lack of improvement noted on the exercise testing in our three treatment groups.

In conclusion, we found that I combined with F was superior to T combined with F and F alone with respect to improving lung flow and exertional hyperinflation in patients with GOLD stage II and III stable COPD; however, we observed no improvement in exercise capacity in any of the three treatment groups. Thus, we suggest that combined therapy with anticholinergics and β-agonists, and in particular I+F, is preferable to monotherapy with β-agonists in this patient group. Controlled studies are needed to further assess how different combinations of inhaled bronchodilators affect CPET performance in the setting of COPD.

Abbreviations: COPD= Chronic obstructive pulmonary disease; ATS= American Thoracic Society; BTS= British Thoracic Society; GOLD= Global Initiative for Chronic Obstructive Lung Disease; FEV_1%= percent of forced expiratory flow in one second; FVC = forced vital capacity; PFT= pulmonary function test; CPET= cardiopulmonary exercise testing; T+F=tiotropium and formoterol; I+F= ipratropium and formoterol; F= formoterol; IC= inspiratory capacity; MVV= maximal voluntary volume; PVO_2= peak oxygen uptake; PCO_2= peak CO_2 output; VCO_2/VO_2= gas exchange ratio; VEmax= maximal minute ventilation; VT= tidal volume

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