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ORIGINAL RESEARCH

Combined Therapy with Tiotropium and Formoterol in Chronic Obstructive Pulmonary Disease: Effect on the 6-Minute Walk Test

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Abstract

Combined therapy with tiotropium and long-acting beta 2 agonists confers additional improvement in symptoms, lung function and aspects of health-related quality of life (QOL) compared with each drug alone in patients with COPD. However, the efficacy of combined therapy on walking distance, a surrogate measure of daily functional activity and morbidity remains unclear. The aim was, therefore, to quantify the benefit of this therapy on the six minute walk test. Secondary outcomes included change in lung function, symptoms, the BODE index and QOL. In a double-blind, crossover study, 38 participants with moderate to severe COPD on tiotropium were randomised to receive either formoterol or placebo for 6 weeks. Following a 2-week washout period, participants crossed over to the alternate arm of therapy for a further 6 weeks. Thirty-six participants, with an average age of 64.3 years and FEV_1 predicted of 53%, completed the study. Combined therapy improved walking distance by a mean of 36 metres [95% CI: 2.4, 70.1; *p* = 0.04] compared with tiotropium. FEV_1 increased in both groups (160 mL combination therapy versus 30 mL tiotropium) with a mean difference of 110 mL (95% CI: –100, 320; *p* = 0.07) between groups, These findings further support the emerging advantages of combined therapy in COPD. Australian New Zealand Clinical Trials.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive debilitating disorder characterised by worsening respiratory symptoms, ongoing airway inflammation and irreversible airflow limitation. It is a major cause of morbidity and mortality—currently predicted to be the fourth-leading cause of death in the world by 2030 (1, 2). Quality-of-life studies demonstrate that COPD sufferers are mainly limited by physical function and up to 43% depend on family and friends for help with activities of daily living (3).

Key goals of COPD management include preventing disease progression, relieving symptoms, reducing exacerbations and improving exercise tolerance and health status(1, 2). Smoking cessation, annual influenza vaccination and pulmonary rehabilitation have been shown to improve these outcomes (1) as have bronchodilators (4–12), either alone or in combination with inhaled corticosteroids. Tiotropium, an anticholinergic bronchodilator, and long-acting beta 2 agonist bronchodilators (LABA) such as salmeterol, formoterol and indacaterol have been shown individually to significantly improve lung function, symptoms,

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health- related quality of life and exercise capacity in COPD compared with standard therapy (4–14).

Although comparative trials have established tiotropium to be equivalent or superior to long-acting beta 2 agonists in COPD (4, 14–16), studies have demonstrated that when these drugs are combined, there is further significant improvement in lung function and health-related quality of life measures (9, 10, 12, 17). No studies to our knowledge, have primarily examined the effects of combined therapy on walking distance a functional outcome similar to quality of life, that is important and meaningful to patients. The six minute walk test (6MWT), measuring the distance walked in 6 minutes, is a validated tool which reflects functional exercise capacity for daily physical activities (18). It has been shown to be responsive to interventions in COPD (19) and is a predictor of morbidity and mortality (20, 21).

The aim of this study was, therefore, to assess the therapeutic benefit of adding formoterol to tiotropium compared with tiotropium alone on the 6MWT in patients with COPD. We hypothesised that combined therapy would improve this patient outcome as well as lung function, symptoms and health-related quality of life measures.

Methods

Design

In this double-blind, crossover study, we randomised participants with clinically stable COPD on tiotropium for a minimum of 4 weeks, to receive either formoterol or placebo for six weeks, followed by a 2-week washout period. This washout period was considered clinically adequate to avoid drug carry over effects.

Participants then crossed over to the alternate arm of therapy for a further 6 weeks. The order of first intervention was randomised. Outcomes were measured at the beginning and end of the first 6 week treatment phase, and at the beginning and end of the second 6 week treatment phase of the study.

Participants

Participants were aged between 18 and 80 years, had COPD defined by American Thoracic Society/European Respiratory Society (ATS/ERS) criteria and were current or ex-smokers with a ≥ 10 pack-year smoking history (22). They were clinically stable without a respiratory infection or exacerbation of COPD for 4 weeks prior to entry into the study. Inhaled corticosteroids were permitted. Patients with a history of asthma, myocardial infarction within 3 months of the study, symptomatic prostatic hypertrophy or glaucoma were excluded; participants on long-term long-acting beta-2 agonists, prednisone or theophylline were excluded. The study received approval from the regional Ethics Committee and was conducted in accordance with the Declaration of Helsinki International Conference on Harmonization (ICH)/Good Clinical Practice. Participants provided written informed consent. The study was registered with the Australian New Zealand Clinical Trials Registry, number: ACTRN12608000079347.

Procedures

Patient visits were conducted at the same time throughout the study ±1 hour; all visits were conducted in the morning. Patients were advised to stop their respiratory medications as follows: tiotropium 24 hours; short-acting beta-agonists 6 hours; long-acting beta-agonists, 12 hours. Symptoms were recorded and dyspnoea was graded using the validated, modified Medical Research Council (MMRC) dyspnoea scale (23, 24).The 6MWT was performed according to ATS guidelines (18). Spirometry with reversibility was then measured according to published guidelines using predicted values from Crapo and colleagues (25–27) The **B**ody–mass index, Airflow **o**bstruction **D**yspnoea, **E**xercise capacity (BODE) index, a composite multidimensional functional grading system based on a 10-point scale, with higher scores indicative of poorer outcomes, was calculated (28). Health-related quality of life was measured by the St George's Respiratory Questionnaire (SGRQ), which measures 56 items across 3 domains: symptoms, activity and impacts (psychosocial dysfunction)(29). A total score is calculated from all three components, with zero indicating no health impairment and 100 representing maximum impairment, with a change in score of 4 units considered clinically significant (30).

Medications, both drug and placebo inhalers, were provided by an independent, accredited compounding pharmacy. Compliance was measured by weighing the turbuhalers at the beginning of the study and at the end of each treatment period. Additionally, a count of the number of inhalations taken was calculated from the number dial. As tiotropium was delivered via the handihaler device, a capsule count was performed before and after each period. Patients also self-reported medication use at each visit. Adverse events were recorded.

Participants were randomly allocated to 1 of the 2 treatment arms using a randomisation schedule generated from a random numbers table. Randomisation tables and treatment allocation codes were generated and held off site by an independent monitor. Participants, research assistants, and investigators were masked to treatment allocation.

Statistical plan and analysis

We estimated that about 35 subjects would need to be enrolled to have 80% power to detect a mean difference of 25 meters in the 6-minute walk test between the groups, assuming a 10% dropout rate.

Analytical methods

Descriptive statistics were used to summarise the clinical characteristics of participants. Normality of the

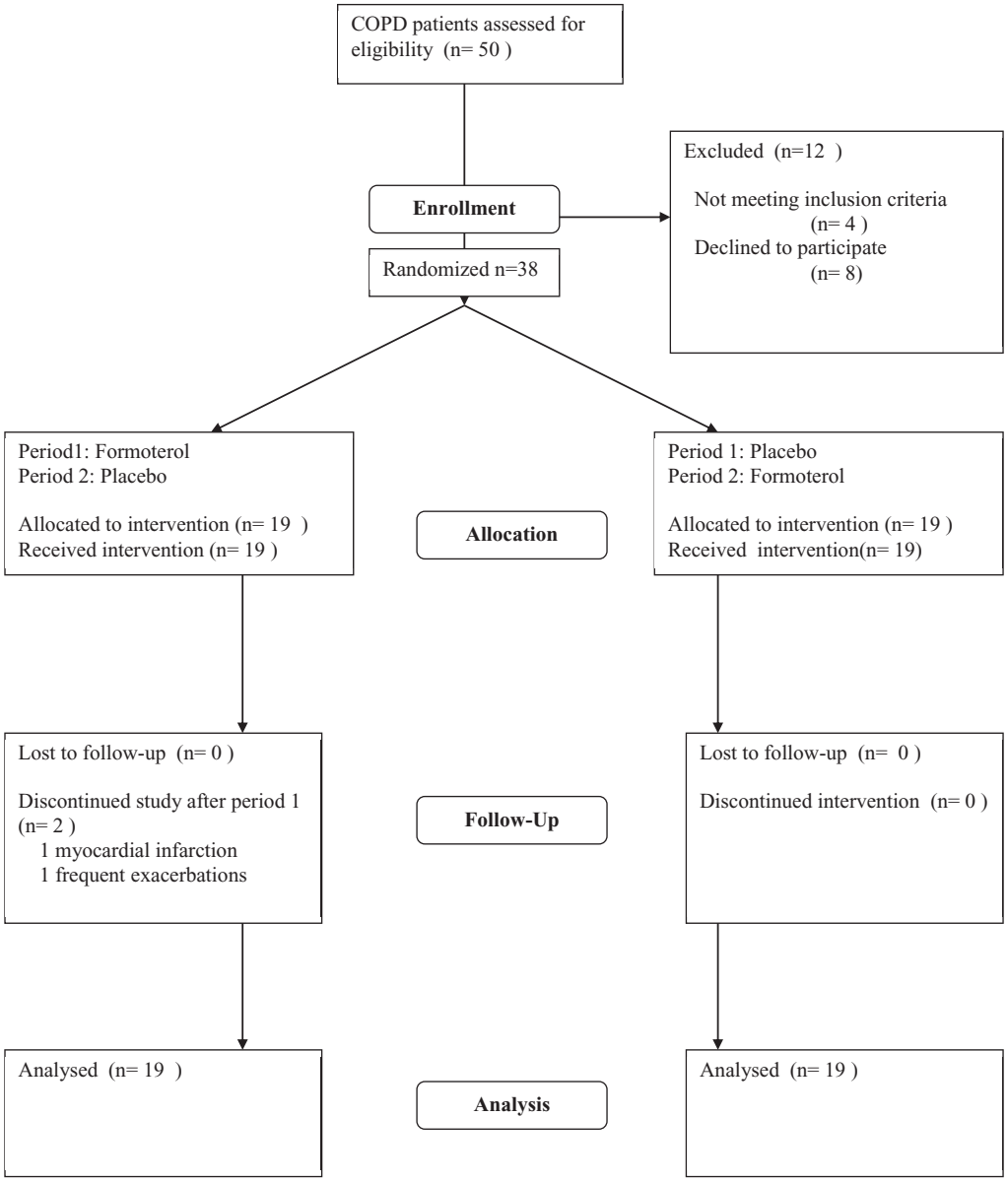

Figure 1. Flow diagram.

outcome data were tested and evaluated using the skewed statistics and visualised by box-plot and histogram. The changes in all outcome data were analysed with paired sample *t*-tests. Effects of treatment order, time period and carryover were assessed as per Hills and Armitage for a two-period crossover study (31). All analyses were done by intention-to-treat. Significance was accepted at $p < 0.05$. Data analysis was performed using SAS/STAT software, Version 9.2 of the SAS System for Windows (Copyright © 2002–2008 SAS Institute Inc.) and R software, Version 2.11 (20).

Results

Thirty-eight subjects were enrolled. Two were withdrawn after completing period 1: one due to frequent exacerbations and 1 due to myocardial infarction On unblinding, both had been assigned to combination therapy (Figure 1). Baseline characteristics are described in Table 1: participants had an average age of 64.3 (8.7) years and moderately severe COPD with a mean FEV_1 predicted of 53(16)% (32). Seventy percent were on inhaled corticosteroids, 60% had been on tiotropium for longer than 4 weeks and none were on a LABA in the preceding 4 weeks prior to study entry.

Combined therapy (tiotropium plus formoterol) improved 6-minute walking distance after six weeks compared with tiotropium alone (Table 2) by a mean of 36.3 metres [95% CI: 2.4, 70.1]. Although an improvement in FEV_1 was observed in both treatment groups over 6 weeks, greater with combined therapy, it did not achieve statistical significance (160 mL versus 30 mL; mean difference between groups: 110 mL [95% CI, –100, 320; $p = 0.07$] (Table 2). Inspiratory capacity and symptom scores were similar in both groups (Table 2). Health-related quality

Table 1. Baseline characteristics

Variable	
n	38
Men n(%)	23 (60)
Age (yrs)	64.3 (8.7)
BMI (kg·m^2)	27 (12)
Current, n	14
Ex-smoker, n	24
Pack-years	40 (17)
Medication, % ICS,	70
Mean dose in subjects receiving ICS, fluticasone equivalent, ucg	590 (265)
% on tiotropium for more than 4 weeks at study entry	60
symptoms: dyspnoea (MMRC scale) #	2 (3)
FEV_1 (L)post-BD	1.37 (0.42)
FEV_1 (%) pred, post-BD	53 (16.2)
FVC (L)post-BD	3.0 (0.80)
FEV_1/VC,%	46 (10)
IC (L) post-BD	2.26 (0.64)
6MWT distance (m)	375 (90)
SGRQ symptoms	48.7 (24.3)
SGRQ impact	29.5 (7.8)
SGRQ activity	60.7 (23.2)
SGRQ total score	42.1 (18.4)
BODE index	2.37 (1.1)

mean (sd); # median (IQR); n: number, yrs: years, % percentage, ICS inhaled corticosteroid dose, ucg: micrograms, MMRC: Modified Medical Research Council scale, FEV_1 post-BD: forced expiratory volume in one second post bronchodilator (BD), L: litres; pred: predicted, FVC: forced vital capacity, IC: inspiratory capacity, 6MWT: six minute walk test, m: metres, SGQR: St George's Respiratory Questionnaire, BODE index: Body–mass index, Airflow obstruction Dyspnoea, Exercise capacity.

of life outcomes were also similar in both groups. (Table 3). The improvement in the BODE index was greater with combined therapy compared with tiotropium alone (mean –0.27 [95% CI, –0.65, 0.11] versus 0.34 [95% CI, 0.11,0.66]; $p = 0.04$). No significant treatment period, or carry-over effect was present. Compliance with medications was 80%. Treatment with combined therapy was generally well tolerated, and no adverse events defined as ocular, oropharyngeal, cardiac, respiratory, gastrointestinal, urological, or dermatological were reported during the study. The data for the subject who was withdrawn due to a myocardial infarction were reviewed by an independent monitoring committee and not considered to be related to the study medications.

Table 3. Health-related quality of life (SGRQ)

	T+Formoterol	T+placebo	Difference in change	*p*-value
Change in activity	0.5(–2.9, 4.0)	–0.5(–3.2, 2.2)	1.6(–3.2, 6.4)	0.45
Change in impact	–0.4(–3.5, 2.6)	–0.6(–4.1, 2.9)	0.3(–4.2, 4.8)	0.90
Change in symptom	–5.5(–11.4, 0.4)	1.2(–4.2, 6.7)	–6.7(–15.7, 2.3)	0.13
Change in total scores	–1.0(–3.7, 1.7)	–0.5(–2.8, 1.7)	–0.2(–3.6, 3.2)	0.89

Data presented are mean (95% C.I.)

Discussion

This study demonstrates that adding formoterol to tiotropium therapy further increases walking distance in patients with COPD compared with tiotropium alone. The improvement in 6-minute walking distance of 36 metres obtained with combined therapy although modest, was clinically and statistically relevant; with a change of more than 25 to 30 metres considered to be the minimal clinically important difference (33, 34). Previously, tiotropium alone has been shown to improve the 6-minute walking distance by 15 to 26 metres, and the incremental shuttle walk test (SWT) by 36 metres compared with placebo, in patients with COPD (35–37); findings that are comparable to the 36 m increase noted in this study. More recently, 2 crossover studies adding tiotropium for 2 weeks in patients with

Table 2. Outcome variables: Exercise capacity, lung function and symptoms

	T + Formoterol $n = 38$	T+placebo $n = 36$	Difference in change	*p*-value
Change in exercise 6-minute walk test, metres	25.5(4.4, 46.5)	–7.6(–23.1, 7.8)	36.3(2.4, 70.1)	0.04
FEV_1, L post-BD	0.16(0.00, 0.31)	0.03(–0.11, 0.17)	0.11(–0.10, 0.32)	0.07
FVC , L post-BD	0.12(–0.01, 0.26)	0.14(–0.07, 0.34)	–0.04(–0.30, 0.22)	0.70
Inspiratory Capacity, L	–0.036(–0.13–0.0.058)	0.018(–0.056–0.093)	0.05(–0.182–0.082)	0.45
Symptoms, MMRC#	–0.1(–0.3,0.1)	0.1(–0.2,0.3)	–0.2(–0.54, 0.14)	0.13

Data presented are mean (95% C.I.) unless specified; # median (IQR); T: tiotropium, FEV_1: forced expiratory volume in one second post bronchodilator (BD), L: litres; FVC: forced vital capacity, MMRC: Modified Medical Research Council scale.

COPD receiving formoterol demonstrated a significant improvement in exercise endurance measured by treadmill and cycle ergometry compared with placebo (38, 39).

There is increasing evidence that a "walking test" is of clinical relevance, with implications for maintaining patients' independence with daily activities and reflecting disease burden (20, 40, 41). Several walking tests are utilised both clinically and in research: The SWT assesses peak walking distance or capacity; the endurance SWT (ESWT) assesses endurance time or the time taken to walk at a fixed speed (calculated as the speed corresponding to 80% of peak VO_2, predicted from the SWT), and the 6MWT assesses the distance walked over a fixed period of time (39). Although the SWT and ESWT may be more responsive to pharmacological interventions than the 6-minute walk test (38) they examine different, complimentary aspects of walking. The distance walked in 6 minutes, however, remains the easiest test to perform, and translates well into clinical practice and real life when performed with attention to the learning effect and reproducibility of the test (17, 40).

The improvement in exercise capacity was reflected by the BODE index, which incorporates the 6 MWT, lung function and symptoms into its multi-dimensional functional measurement. Worsening BODE scores have, similar to the 6-minute walk test, been shown to correlate with increasing morbidity and mortality (28, 42–44).

Significant changes were not noted in lung function, symptom scores or quality of life. The magnitude of the treatment effect obtained with these outcomes, however, was similar to that documented in previous larger, studies combining tiotropium with LABA(37). In a meta-analysis of 8 studies comparing therapy with formoterol and tiotropium to tiotropium alone, combined therapy improved lung function (FEV_1) by a mean difference (MD) of 105 mL and symptom scores assessed by the transitional dyspnoea index(TDI) by a MD of 1.5 units (12).

A recent Cochrane collaboration meta-analysis (n = 5 studies) examining the clinical benefits of combining therapy with LABA and tiotropium versus tiotropium alone showed that health-related quality of life and lung function outcomes also improved significantly with combined therapy, although the treatment effects were small: SGQR (MD) –1.61 units and FEV_1 (MD) 0.07 L (45). Last, in a crossover trial, combined therapy with tiotropium 18mcg daily and formoterol 12 mcg daily for 6 weeks increased FEV_1 by a further 100 mL, compared with formoterol or tiotropium alone (9).

Although FEV_1, reflecting airflow limitation, improved with the addition of formoterol to tiotropium therapy, inspiratory capacity (IC) and forced vital capacity (FVC), measures of dynamic hyperinflation did not. This appears to be contrary to current literature demonstrating that these variables correlate well with the 6 MWT (46) and that IC improves with bronchodilator therapy (39, 47). Possible explanations for the lack of improvement in IC include the timing of spirometric measurements to exercise and inhaled bronchodilator therapy. Studies demonstrating improvement in IC with bronchodilator therapy have assessed change immediately pre- and post-treadmill and cycle cardiopulmonary tests and at peak drug concentrations (1 to 2 hours after medication)(39, 47).

It is also unclear if the degree of clinical improvement achieved by adding tiotropium to established LABA therapy is interchangeable and comparable to that of adding a LABA such as formoterol or salmeterol to patients on regular tiotropium. As all our patients were on tiotropium, additional improvements in lung volumes with formoterol compared with placebo may have been too small to detect given the sample size. Finally, there is increasing evidence that not all patients with severe COPD experience hyperinflation at rest and dynamic hyperinflation with exercise. Other mechanical factors such as respiratory and leg muscle fatigue and "neuromuscular uncoupling" may play a role (48, 49).

Potential limitations of this study include the sample size, which likely precluded some of the results from reaching statistical significance. However, given that the treatment effect documented with combined long-acting bronchodilator therapy on the 6MWT and absolute FEV_1 is of a similar magnitude to previous studies, we propose that the benefit is genuine and clinically significant. These findings further endorse the emerging role of combined therapy in enhancing patient centred outcomes in moderate-to-severe COPD.

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Declaration of Interest Statement

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The authors alone are responsible for the content and writing of the paper.

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NOTICE OF CORRECTION:
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