Effects of Short-Acting Bronchodilators Added to Maintenance Tiotropium Therapy*

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Background: **Combining bronchodilators has been shown to be beneficial in patients with COPD. The additive effects of short-acting bronchodilators added to maintenance tiotropium therapy, however, are unknown.**

Methods: **Following 3 weeks of tiotropium pretreatment, 60 patients with COPD (FEV_1 40% of predicted) participated in a randomized, placebo-controlled study to assess add-on bronchodilator effects of ipratropium bromide (40 μg) or fenoterol (200 μg). Short-acting bronchodilators were added as a single dose 2 h and 8 h after tiotropium dosing. Serial lung function tests were performed over 9 h.**

Results: **The peak FEV_1 add-on response within 6 h with fenoterol was significantly greater than with placebo (137 mL) or ipratropium (84 mL); the response with ipratropium was slightly but significantly larger than with placebo (52 mL). One hour after the second dose of the test drugs, a similar order of treatment responses was found. The peak FVC add-on response was significant for fenoterol (249 mL) but not for ipratropium (42 mL).**

Conclusions: **In conclusion, both short-acting bronchodilator classes were effective when added to maintenance treatment with tiotropium. The addition of the β_2-adrenergic fenoterol provided greater additional bronchodilatation than the short-acting anticholinergic ipratropium. This is consistent with the expected effects of combining bronchodilators with different pharmacologic mechanisms.**

This randomized controlled trial was registered at www.clinicaltrials.gov (NCT00274066).

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Key words: COPD; fenoterol; ipratropium bromide; short-acting bronchodilators; tiotropium

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; MDI = metered-dose inhaler; PFT = pulmonary function test; Raw = airway resistance; sGaw = specific airway conductance

COPD is characterized by a progressive airflow limitation that is not fully reversible and by dyspnea, decreased exercise endurance, and poor health-related quality of life. Bronchodilators constitute the major component in the pharmacologic management of COPD. The European Respiratory Society/American Thoracic Society and the update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advise a stepwise increase in pharmacotherapy, depending on the severity of COPD.[1,2] Bronchodilators can be prescribed as needed or on a regular basis to prevent or reduce symptoms and increase exercise capacity.[1,3] When the disease progresses to GOLD stage 2 or higher ($FEV_1 < 80\%$ of predicted), it is recommended to supplement as-needed short-acting agents with maintenance therapy of long-acting bronchodilators.

Anticholinergic and β_2-adrenergic agents achieve their bronchodilatating effects by different pharmacologic mechanisms. Several clinical studies[1,4] have established that a combination of ipratropium or oxitropium and short- or long-acting β_2-adrenergic

agents result in additive bronchodilator effects. Furthermore, as the risks of side effects increase with increasing doses of any drug, an important additional rationale for combination therapy is the more favorable ratio of efficacy and safety.

Tiotropium is a once-daily inhaled anticholinergic bronchodilator that provides sustained bronchodilatation for 24 h.[5,6] Based on comparative clinical data vs placebo,[7] ipratropium,[8] salmeterol,[9–11] and formoterol,[12] tiotropium is an attractive agent for first-line treatment in COPD. As advocated by the GOLD report, combining bronchodilators with different modes of action in COPD should be beneficial. Only a few studies[12–14] of adding another bronchodilator to tiotropium have been conducted.

To date, no combination studies of tiotropium with short-acting bronchodilators have been performed. Therefore, given the role of short-acting bronchodilators in the emergency department and at home for the treatment of acute COPD exacerbations, we investigated the pulmonary and extrapulmonary effects of a short-acting anticholinergic agent and of a short-acting β_2-adrenergic agent when added to pharmacodynamic steady state of tiotropium in patients with moderate-to-severe COPD.

Materials and Methods

Patients

Outpatients with COPD according to GOLD guidelines[1] aged $\geq$ 40 years with a smoking history $\geq$ 10 pack-years were required to have a baseline $FEV_1 \leq 60\%$ of predicted[15] and an FEV_1/FVC ratio $< 70\%$. Patients with asthma, atopy, allergic rhinitis, or an elevated blood eosinophil count were excluded. In addition, patients were excluded who had received oxygen therapy, or had a COPD exacerbation requiring medical treatment in the 6 weeks prior to screening, had symptomatic prostatic hypertrophy and narrow-angle glaucoma, were receiving β-blocker therapy, or had some other clinically significant disease. The study (BI No. 205.258) was approved by the hospital medical ethic committee, and all patients gave written informed consent prior to participation in the study. The first patient was entered in October 2002, and the last was entered in September 2003.

Study Design

Eligible patients entered a 3-week run-in period with tiotropium inhalation powder, 18 μg qd, via inhalation device (HandiHaler; Boehringer Ingelheim; Alkmaar, the Netherlands) to reach pharmacodynamic steady state.[16] While tiotropium was continued, on separate days two single doses of ipratropium, 40 μg, via metered-dose inhaler (MDI) [two puffs of 20 μg]; fenoterol, 200 μg, via MDI (two puffs of 100 μg); or placebo MDI (two puffs) were added with a time interval of 6 h using a randomized, double-blind, three-way crossover design (Fig 1). The short-acting bronchodilator was added under supervision 2 h after tiotropium in the clinic. Test days were separated by at least 1 day. Fenoterol has similar bronchodilating properties as salbutamol[17] and was selected as representative of the short-acting β_2-adrenergics due to convenience of blinding. Stable doses of inhaled steroids, oral steroids up to 10 mg/d of prednisone, or mucolytics were allowed throughout the study. Salbutamol via MDI was provided for acute symptom relief and withheld 8 h prior to each pulmonary function test (PFT); other bronchodilators were not allowed. Prior to screening, short-acting bronchodilators were withdrawn for 8 h, long-acting β_2-adrenergics for 48 h, and tiotropium for at least 3 days. Oral β_2-adrenergics, antihistamines, or theophyllines were not allowed 1 month prior to and during the study.

Assessments

Following the qualifying lung function test (FEV_1 and FVC), and assessment of airway resistance (Raw) and specific airway conductance (sGaw) at screening, patients inhaled two puffs of 100 μg of fenoterol, and the response in FEV_1 and FVC was assessed 1 h later. On each test day, baseline lung function measurements were performed between 8:00 AM and 10:00 AM; afterwards, tiotropium was inhaled. Two hours later, the test drug was administered and lung function (FEV_1, FVC, Raw, and sGaw) and safety (pulse rate, BP, and ECG) were assessed from 30 min to 6 h after dose. Six hours after the first dose, another dose of the same bronchodilator was administered followed by the same measurements (Fig 1). Lung function was measured according to American Thoracic Society criteria.[18]

Statistical Analysis

The primary objective was to compare the effect of the first single dose of both bronchodilators to placebo. The primary end point was the peak FEV_1 response in the 6-h observation period after the first dose of randomized treatment (ipratropium, fenoterol, or placebo). Peak FEV_1 response was defined as the highest FEV_1 minus the steady-state baseline FEV_1 (that day measurement, 10 min prior to tiotropium). Secondary end points were peak FVC response (similar to peak FEV_1) and FEV_1 and FVC responses 1 h after the second dose of randomized treatment, individual FEV_1 and FVC measurements at each time point during the 9-h test day observation period, and sGaw and Raw at 1 h and 6 h after the first dose and at 1 h after the second dose of randomized treatment. The study was powered to include a total of 60 patients required to detect a difference in mean FEV_1

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