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Effects of tiotropium on lung function in current smokers and never smokers with bronchial asthma

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ABSTRACT

The effects of tiotropium, an inhaled long-acting muscarinic antagonist, on lung function were investigated in current smokers and nonsmokers with asthma treated with inhaled corticosteroids (ICSs) and other asthma controllers: inhaled long-acting β_2 agonists, leukotriene receptor antagonists, and/or theophylline.

We conducted a double-blind, placebo-controlled study of an inhaled single dose of tiotropium in 9 asthmatics currently smoking and 9 asthmatics who have never smoked in a crossover manner. Lung function was measured before and 1, 3, and 24 h after inhalation of 18 μg of tiotropium or a placebo. The primary outcome was a change in forced expiratory volume in 1 s (FEV_1) from the baseline, and the secondary outcomes were changes in peak expiratory flow rate (PEFR), $\dot{V}_{50}$, and $\dot{V}_{25}$.

At baseline, asthmatics with and without a smoking history had a mean FEV_1 of 2590 ml and 2220 ml and were taking a mean dose of ICSs of 1208 and 1000 μg/day, respectively. The increase from the baseline FEV_1 was 169 ml and 105 ml higher at 3 h after tiotropium than after the placebo in current smokers and nonsmokers, respectively.

PEFR, $\dot{V}_{50}$, and $\dot{V}_{25}$ were also significantly increased after tiotropium as compared with the placebo in both study groups. Changes in FEV_1 and PEFR tended to be greater in asthmatics currently smoking than in subjects who have never smoked, although there were no statistical differences at any time points.

Tiotropium resulted in improved lung function and symptoms both in current smoker and nonsmoker asthmatics. These findings suggest that tiotropium will provide a new strategy for the treatment of bronchial asthma.

1. Introduction

Bronchial asthma is emerging as a heterogeneous disease, and there is significant variability in response to treatment. Despite treatment with an inhaled corticosteroid (ICS) plus a long-acting β_2 agonist (LABA), many patients have uncontrolled asthma that requires more intensive therapy.

One of the phenotypes that is difficult to control is represented by smoking asthmatics [1–3]. Asthmatics who smoke are reported to have a more rapid decline of lung function [4], higher asthma severity scores [5], more frequent visits to the emergency room [6], and a higher risk of death from asthma [7] than nonsmokers. In addition, a shortage of evidence on asthma in smokers is a serious problem, because smoker asthmatics have been excluded from most of systemic clinical studies in order to avoid recruiting subjects with chronic obstructive pulmonary disease (COPD) [8].

Poor response to asthma controllers is one of the problems in smoking asthmatics. Steroid resistance is observed in smoking asthmatics. Impaired response is reported not only with ICSs [9–11] but also with systemic steroids [12] and in combination with LABAs [13]. Evidence on other asthma controllers in smoking asthmatics is limited. As the urine leukotriene E_4 level is reported to be elevated, leukotriene receptor antagonists (LTRAs) are expected to be effective in smoking asthmatics [14]. However, there is a scarcity of

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studies investigating the advantage of LTRAs in smokers, and there are no studies showing a significant advantage for smokers as compared with nonsmokers [11]. Theophylline is expected to restore the response to corticosteroid by reversing the impaired histone deacetylase activity, which leads to steroid resistance in smokers [15]. However, in spite of the add-on effect of theophylline on ICSs, the histone deacetylase activity in sputum macrophages was unchanged in asthmatics who smoke [16].

Recently, evidence of long-acting muscarinic antagonists (LAMAs) as an asthma controller has been accumulating [17,18]. However, it is not well known which phenotype(s) of asthma will receive more benefit from treatment with LAMA [19]. We previously reported that a single dose of inhaled tiotropium improved lung function in asthmatics both with and without emphysematous changes [20]. In this study, we found that the improvement of lung function was greater in asthmatics with emphysematous changes. Although the difference in efficacy could be explained by the presence of COPD, a difference in smoking status could also lead to different outcomes, as the subjects we recruited consisted of nonsmoker asthmatics without emphysematous changes and smoker asthmatics with emphysema. Lower lung function at the baseline in subjects with emphysema may also affect the outcome. In order to elucidate these questions from our previous study, we compared the effect of a single dose of tiotropium on lung function in current smokers and nonsmokers with asthma without COPD, treated with an ICS and other asthma controller(s) in a randomized, double-blind, placebo-controlled, crossover design.

2. Methods

2.1. Study subjects

The study was conducted in the outpatient clinic of the Department of Respiratory Medicine of the National Hospital Organization Fukuoka Hospital. Patients with moderate to severe asthma who did not suffer from other disorders, such as liver, kidney, or metabolic diseases, were recruited. The diagnosis of asthma was based on a history consistent with asthma, diffuse expiratory wheezes heard on auscultation of the chest, eosinophils over 3% of total cells in sputum, and the demonstration of an increase of 12% or more in addition to 200 ml or more in forced expiratory volume in 1 s (FEV_1) following the inhalation of 2 puffs of albuterol. All participants had been treated with an ICS and other asthma controller medication including an LABA, an LTRA, or theophylline. Patients with any of the following were also excluded from the study: totally controlled asthma assessed by Asthma Control Test (ACT) with score of 25, supplemental oxygen therapy, upper respiratory tract infection within 6 weeks prior to screening, known hypersensitivity to muscarinic antagonists, known symptomatic prostatic hypertrophy, and narrow-angle glaucoma (Table 1).

Table 1
Inclusion and exclusion criteria.

Common inclusion criteria for all subjects
History consistent with asthma
Diffuse expiratory wheezes heard on auscultation of the chest
Eosinophils over 3% of total cells in sputum
β_2-agonist reversibility to 2 puffs of albuterol with an increase of 12% or more and 200 ml or more in forced expiratory volume in 1 s (FEV_1)
Poorly controlled symptomatic asthma despite treatment with a high-dose ICS (dose of 800 μg/day, equiv. BDP or more) and an inhaled LABA
Inclusion criteria for current smokers
Smoking history of >5 pack-years
Currently smoking >5 cigarettes per day
Inclusion criteria for nonsmokers
No smoking history at all
Common exclusion criteria for all subjects
FEV_1 <= 70% of forced vital capacity (FVC) after 2 puffs of albuterol
Presence of low attenuation area on the chest HRCT
Decreased D_{LCO} <= 80% of predicted normal values
Supplemental oxygen therapy
Short-acting β_2 agonist within 6 h prior to study-drug inhalation
Oral corticosteroid within 6 weeks prior to screening
Upper respiratory tract infection within 6 weeks prior to screening
Known hypersensitivity to muscarinic antagonists
Known symptomatic prostatic hypertrophy
Narrow-angle glaucoma

Exclusion of comorbid COPD was based on the following criteria: FEV_1 > 70% of forced vital capacity (FVC) following the inhalation of 2 puffs of albuterol, absence of low attenuation area on the chest HRCT, and D_{LCO} within the normal range (>80% of predicted normal values).

Ten asthmatics who have never smoked and 10 asthmatics who currently smoke 5 cigarettes per day or more, with a total smoking history of over 5 pack-years, were enrolled. The patient background of each group is listed in Table 2. The smoking history of current smokers ranged from 7 to 60 pack-years. None of them used β blockers.

2.2. Study design and conduct

To investigate the bronchodilating effects of a single dose of inhaled tiotropium or placebo, the study had a double-blind, crossover, placebo-controlled design. Each patient received two treatments on different study days, with a washout period of 1–2 weeks between them; the patients in random order were allocated to 18 μg of tiotropium or a placebo (Fig. 1). Tiotropium and the placebo were administered using a HandiHaler. Patients were prohibited from inhalation of a short-acting β_2 agonist 24 h before and after the treatment. Lung function (FVC, FEV_1, peak expiratory flow rate (PEFR), $\dot{V}_{50}$, and $\dot{V}_{25}$), pulse oximetry (SpO_2), pulse rate, and blood pressure were taken at the baseline condition and at 1 h, 3 h, and 24 h after inhalation of the trial drug.

The primary efficacy outcome was the absolute change in FEV_1 from baseline to 3 h after tiotropium inhalation. The secondary outcome was the relative change in PEFR, $\dot{V}_{50}$, and $\dot{V}_{25}$ from the baseline to 3 h after tiotropium inhalation. Spirometry was performed using a dry rolling-seal spirometer (Chestac-33, Chest Co., Tokyo, Japan).

The study was approved by the Institutional Board of Studies and by the Ethical Committee with an approval number of 24–27 in March 2013. All patients provided written informed consent. The registration number is R000012094, and the UMIN study ID is UMIN000010352.

2.3. Statistical analysis

The sample size was calculated for the primary endpoint, FEV_1, with 9 patients in each group completing the study; the experiment had 80% validity at the 5% significance level to detect differences between the treatments using a crossover design with the results of a previous study [20]. The increase in FEV_1 after tiotropium is estimated to be 143 ml, which is calculated as the maximal change reported in the previous study.

Data were expressed as mean ± SEM. Comparisons were made using a two-way repeated measures ANOVA and *post hoc* analysis. All comparisons were two-tailed, and probability values < 0.05 were considered significant.