Pulmonary Pharmacology & Therapeutics 39 (2016) 81–84

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Effect of tiotropium on mucus hypersecretion and airway clearance in patients with COPD☆

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ARTICLE INFO

Article history:
Received 21 May 2016
Received in revised form
12 June 2016
Accepted 23 June 2016
Available online 24 June 2016

Keywords:
Mucus hypersecretion
COPD
Tiotropium
CASA-Q
Mucociliary clearance

ABSTRACT

Background: Increased sputum production is an important feature of COPD, in which a large amount of secretions stagnated in the respiratory lumen may aggravate airflow limitation, impair airway mucociliary transport, and cause recurrent respiratory infection and, hence, acute exacerbations of the diseases. There is evidence that airway mucus hypersecretion is associated with the severity and prognosis of COPD, but the symptoms are generally difficult to treat.

Methods: In an open, non-controlled study, we examined the effect of the anticholinergic agent tiotropium on airway mucus hypersecretion in 22 COPD patients. After a 4-week run-in period, the patients received 18 μg of tiotropium once daily delivered through the handihaler for 8 weeks, while symptoms and their impact associated with sputum were scored according to cough and sputum assessment questionnaire (CASA-Q). At week 0 and week 8, spirometry was performed before and 30 min after the administration of albuterol. To test the effect of tiotropium on airway mucociliary transport, nasal clearance time was measured. To evaluate airway mucus production, solid composition of the sputum (dry/wet weight ratio) was measured.

Results: Treatment with tiotropium increased both prebronchodilator FEV_1 and postbronchodilator FEV_1. Tiotropium decreased cough symptom scores and provided with favorable influences on sputum-related symptoms, and none of the patients complained of worsening of the symptoms judging from the CASA-Q score. Both solid composition of the sputum and mucin contents decreased and nasal clearance time was shortened from 29.4 ± 5.1 to 20.6 ± 4.1min ($p < 0.05$) during the 8-week treatment.

Conclusions: Tiotropium decreases symptoms associated with sputum in COPD patients, an effect that may be related to the inhibition of airway mucus hypersecretion and improvement of airway mucociliary clearance.

1. Introduction

Airway mucus hypersecretion is one of the characteristic features of chronic airway inflammatory diseases including COPD and asthma. Mucus hypersecretion and difficulty in expectoration are bothersome symptoms, which frequently impair patients' quality of life (QOL) and may increase the risk of infection, but the symptoms are generally difficult to treat. There is evidence that airway mucus hypersecretion is associated with the severity and prognosis of COPD. For example, luminal occlusion by mucus exudates is negatively correlated with forced expiratory volume in 1 s (FEV_1) [1], and the decline in FEV_1 is more pronounced in COPD patients with chronic sputum production than in those without chronic sputum production, and the former group of patients are at a higher risk of acute exacerbations requiring care with hospitalization [2]. In the diagnosis and treatment of chronic airway diseases, provision of treatment for controlling mucus production taking into account possible airway stagnation of sputum, which can hardly be expectorated, is considered necessary, even in patients presenting with modest sputum production.

☆ The abstract of this paper was presented at the American Thoracic Society International Conference 2012 as a poster presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in American Thoracic Society Journal: http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2012.185.1_MeetingAbstracts.A2921.

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http://dx.doi.org/10.1016/j.pupt.2016.06.008
1094-5539/

Bronchodilators are first-line drugs for the treatment of COPD [3]. Inhaled anticholinergic agents are effective in patients with COPD, because vagally-mediated airway restriction is the sole reversible pathophysiological abnormality in this disease. Among five subtypes of muscarinic receptors (M1-M5) [4], M3 receptor are the dominant receptor subtype in the regulation of neuronally mediated airway smooth muscle contraction and mucus secretion from submucosal gland and goblet cells [5,6]. Tiotropium is a long-acting anticholinergic agent, with a high selectivity for M3 receptors [7], and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends it as a useful bronchodilator for the treatment of moderate or severe COPD [3]. It is well known that tiotropium improves pulmonary function and symptom and reduces the number of exacerbations of COPD [8,9], but the effects on sputum production and airway mucociliary function have not been elucidated.

Therefore, to determine whether tiotropium affects mucus hypersecretion and airway clearance, we studied patients with COPD who have difficulties in sputum expectoration and cough symptoms.

2. Methods

2.1. Patients

We recruited 26 patients with COPD complaining of sputum and cough at least for 8 weeks who had not been treated with anticholinergic agents. All patients were ex-smokers, and they had not smoked at least for the previous 5 years. Patients who had respiratory tract infection within the previous 4 weeks, those whose therapy regimens had been modified within the previous 8 weeks, and those who were receiving corticosteroids or macrolide antibiotics were excluded from the study. During the study period, 4 patients were withdrawn because of missed clinic visits (2 patients) and discontinuation of the treatment (2 patients). Thus, the data of 22 patients were finally analyzed (18 males and 4 females with a mean age of 67 years). Their height, body weight, and BMI were 164 ± 7 cm, 68 ± 5 kg, and 25.3 ± 3.1, respectively. Apparent low attenuation areas on CT scans were present in 17 of 22 patients. Regarding concurrent diseases, 4 patients had asthma, 2 patients had bronchiectasis, and 2 patients had chronic sinusitis. Written informed consent was obtained from each patient, and the study was approved by the Tokyo Women's Medical University Review Board. COPD was diagnosed according to GOLD criteria [3].

2.2. Study design

This study was conducted as an open, non-controlled trial. After a 4 week run-in period, all patients received 18 μg tiotropium (Boehringer Ingelheim Co., Tokyo, Japan) once daily delivered through the handihaler inhalation device for 8 weeks. Other medications continued without alterations.

2.3. Measurements

All patients were visited every 2 weeks, and at the first visit, demographic details were recorded. Symptoms and their impact associated with cough and sputum were recorded daily, which were then scored according to Cough and Sputum Assessment Questionnaire (CASA-Q) [10]. Briefly, CASA-Q score is a tool for evaluating cough and sputum and their impact on patient's QOL in COPD. CASA-Q used in the study consisted of two cough domains; the cough symptom domain (COUS, 11 items) and the cough impact domain (COUI, 8 items), and two sputum domains; the sputum symptom domain (SPUS, 3 items) and the sputum impact domain (SPUI, 16 items). All items were scored from 0 to 4, such that the score was 0–12 for COUS and SPUS, and 0 to 24 for SPUI, and 0 to 32 for COUI, and each item was summed and rescaled using the following algorithm: (sum rescored items)/(range of rescored item sum) x 100 (%). This resulted in CASA-Q scores that range from 0 to 100, with higher score associated with fewer symptoms and less impact due to cough and sputum.

To determine the effect of tiotropium on the CASA-Q score, we evaluated 4 categories according to the change in scores during the 8-week treatment period. The following definitions of therapeutic response to tiotropium, in terms of the change in the CASA-Q score as compared to the baseline (ΔCASA-Q), were used; ΔCASA-Q > +40: greatly improved, +20 < ΔCASA-Q < +40: improved, −20 < ΔCASA-Q ≤ +20: no change, −20 ≥ ΔCASA-Q: worse.

As the secondary outcomes, at the entry into the study and the beginning and end of treatment period, spirometry was performed by CHESTAC 8800 system (Chest Co., Tokyo, Japan). To test airway mucociliary clearance, we measured nasal clearance time by saccharine test, which is the time from the placement of a saccharine crystal on nasal turbinate mucosa to the patient's perception of sweet taste. Nasal clearance time has been shown to reflect airway mucociliary clearance [11].

In addition, the patients were given preweighed, covered, plastic cups, and were asked to collect sputum at home. At the beginning of run-in period and at week 0 and week 8 for the treatment period, sputum samples collected in the morning (7 a.m.–10 a.m.) were transported to the laboratory. After determination of the wet weight, they were dried in a microwave oven (500 W for 30 min) and reweighed. The percentage of solid composition was then calculated from the ratio of wet to dry weight [12]. Mucin concentrations in the sputum supernatants were also measured with the double-sandwich enzyme-linked immunoassay (ELISA) using 17Q2 antibody according to the method of Ordoñez [13].

2.4. Statistical analysis

All data are expressed as means ± SEM. Values at week 8 of the treatment were compared with those at the baseline period (week 0). Statistical analyses were performed by *t*-test, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. CASA-Q score

In patients with COPD in the present study, the average durations of sputum expectoration, cough, and shortness of breath were 45 months, 37 months, and 28 months, respectively. None of the patients smoked during the run-in and the treatment periods. After treatment with tiotropium for 8 weeks, the COUS increased from 45 ± 14 to 64 ± 16 ($p < 0.001$), and the SPUS increased from 47 ± 12 to 64 ± 17 ($p < 0.001$, Fig. 1). Likewise, COUI and SPUI also increased significantly from 44 ± 13 to 54 ± 12, and from 48 ± 18 to 57 ± 16 ($p < 0.05$. for each). The rates of great improvement and improvement were respectively 32% and 32% for the COUS domain, 14% and 28% for the COUI domain, 27% and 27% for the SPUS domain, and 23% and 27% for the SPUI domain. None of the patients developed any exacerbations. These data indicate that tiotropium therapy in patients with COPD produced improvements in the symptoms of cough and sputum, and also in their impacts. No adverse reactions, such as dryness of mouth, difficulty in urination, and cardiovascular problems, were noted in any of the patients.

With regard to the effects on pulmonary function, treatment with tiotropium for 8 weeks caused increases in the ratio of FEV_1 to the forced vital capacity (FEV_1/FVC) ($p < 0.05$) and the percentage of predicted FEV_1 (%FEV_1).