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Additive efficacy of short-acting bronchodilators on dynamic hyperinflation and exercise tolerance in stable COPD patients treated with long-acting bronchodilators

Yoshiaki Kitaguchi [a], Keisaku Fujimoto [b,*], Yoshimichi Komatsu [a], Masayuki Hanaoka [a], Takayuki Honda [c], Keishi Kubo [a]

[a] First Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto 390-8621, Japan
[b] Department of Clinical Laboratory Sciences, Shinshu University School of Health Sciences, 3-1-1 Asahi, Matsumoto 390-8621, Japan
[c] Department of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto 390-8621, Japan

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Summary
The purpose of this study was to clarify the additive efficacy of short-acting β_2-agonists (SABA) or muscarinic antagonists (SAMA) on dynamic hyperinflation and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) who had been treated with long-acting bronchodilators.

Thirty-two patients with stable COPD who had been treated with long-acting bronchodilators, including long-acting muscarinic antagonists (LAMA), were examined by pulmonary function tests, dynamic hyperinflation evaluated by the method of step-wise metronome-paced incremental hyperventilation, and the incremental shuttle walking test before and after inhalation of SABA or SAMA. The additive efficacy of the two drugs was analyzed.

Inhalation of SABA and SAMA improved airflow limitation and dynamic hyperinflation in stable COPD patients who had been treated with LAMA. Inhalation of SABA decreased respiratory resistance and the difference in respiratory resistance at 5 Hz and 20 Hz. On the whole, the additive efficacy of SABA on airflow limitation and dynamic hyperinflation was superior to that of SAMA. Furthermore, inhalation of SABA resulted in relief of breathlessness during exercise and significant improvement in exercise capacity.

* Corresponding author. Tel.: +81 263 37 2393; fax: +81 263 37 2370.
E-mail address: keisaku@shinshu-u.ac.jp (K. Fujimoto).

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Inhalation of SABA resulted in significant improvement in exercise tolerance, which may have been due to improvement in dynamic hyperinflation. Single use of SABA before exercise, in addition to regular treatment with LAMA, may therefore be useful in stable COPD patients.

Introduction

Dynamic hyperinflation is attributed to air trapping during exercise, caused by a decrease in elastic recoil pressure due to destruction of the alveoli and narrowing of the small airways in patients with chronic obstructive pulmonary disease (COPD).[1,2] There is a significant relationship between dynamic hyperinflation and exertional dyspnea or decreased exercise tolerance in COPD patients,[1,3,4] thus suggesting that dynamic hyperinflation importantly contributes to exertional dyspnea and impairment of exercise tolerance in COPD.

According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines,[5] bronchodilator medications play a central role in the management of stable COPD. The types of bronchodilators most commonly used are β_2-agonists and anticholinergic agents. Of all the bronchodilators, the long-acting muscarinic antagonists (LAMA) are the most effective agents for COPD when used alone. However, COPD patients still have exertional dyspnea in their daily lives despite treatment with long-acting bronchodilators. Short-acting β_2-agonists (SABA) and muscarinic antagonists (SAMA) are recommended to use for relief of dyspnea as-needed in combination with regular use of long-acting bronchodilators.[5]

We have developed the method to evaluate dynamic hyperinflation by the metronome-paced incremental hyperventilation (MPIH) technique, and demonstrated that both SABA and SAMA are effective for reducing dynamic hyperinflation in COPD.[6] We also demonstrated that the treatment with tiotropium (LAMA) for eight weeks partially reduced dynamic hyperinflation following the incremental hyperventilation and improved exercise capacity and health-related quality of life in COPD.[7]

We hypothesized that the efficacy of SABA or SAMA on improving exercise capacity may be due to the relief of dynamic hyperinflation in stable COPD patients, and that it may also be additive to the efficacy of regular treatment with long-acting bronchodilators, including LAMA.

Methods

Subjects

Thirty-two stable COPD patients, with $FEV_1/FVC < 70\%$ and FEV_1 values less than 80% of the predicted value after inhalation of a β_2-agonist (moderate-to-very severe COPD), were recruited from the outpatient clinic of Shinshu University Hospital from February 2007 to July 2009. COPD was diagnosed based on clinical history and symptoms, and pulmonary function characterized by irreversible airflow limitation in accordance with the GOLD guidelines.[5] All subjects had smoking-related COPD without α1-antitrypsin deficiency, and had a smoking history of more than 30 pack-years. Patients with any history of asthma or asthmatic symptoms as well as patients who had walking disability, severe arrhythmia or heart failure, or had suffered from respiratory tract infection or exacerbation of COPD during the preceding three months were excluded from the study. All subjects had been treated with tiotropium (18 μg, LAMA) once daily for more than three months, while continuing their other current therapy without any changes in dose. The subjects were randomized into two groups: (1) SABA group ($n = 16$) or (2) SAMA group ($n = 16$) as stated in the study protocol. The severity of COPD, assessed according to the GOLD guidelines, was stage 2 ($n = 7$), stage 3 ($n = 6$) and stage 4 ($n = 3$) in the SABA group, and was stage 2 ($n = 3$), stage 3 ($n = 11$) and stage 4 ($n = 2$) in the SAMA group. There were no significant differences in the severity of COPD between the two groups. As the other current therapies being used in addition to tiotropium, 8 patients were being treated with long-acting β_2-agonists (LABA), 6 with inhaled corticosteroid (ICS) and 5 with oral theophylline in the SABA group, and 9 patients were being treated with LABA, 7 with ICS and 8 with oral theophylline in the SAMA group. The study was approved by the institutional research ethics committee of Shinshu University School of Medicine, and all patients gave written informed consent to participate.

Protocol

All patients received treatment with tiotropium in the morning on the day that the pulmonary function tests were performed, but did not use SABA or SAMA. Pulmonary function tests including respiratory impedance evaluated using an impulse oscillation system (IOS), dynamic hyperinflation following MPIH, and exercise capacity evaluated by the incremental shuttle walking test were performed. After completion of the baseline measurements, the subjects were then enrolled in a randomized, open-label, comparative trial to evaluate the additive efficacy of SABA and SAMA. One group inhaled 20 μg of procaterol hydrochloride (SABA; Meptin®; Otsuka Pharmaceutical, Tokushima, Japan), while the other group inhaled 0.2 mg of oxitropium bromide (SAMA; Tersigan®; Boehringer Ingelheim, Ingelheim, Germany), using a metered-dose inhaler with a spacer device. Measurements were again performed 30 min after inhalation of procaterol hydrochloride or 60 min after inhalation of oxitropium bromide.

Pulmonary function tests

Spirometry and DLCO were measured using the Chestac-8800 (Chest Co Ltd, Tokyo, Japan). Functional residual