Formoterol has as rapid-acting bronchodilatory effect as salbutamol on the recovery from methacholine-provocating bronchial obstruction

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Abstract

Background: Among inhaled bronchodilators, formoterol is authorized to have rapid-onset bronchodilatory effect as well as its lastingness. In methacholine bronchial provocation test, salbutamol is frequently used for the reverse medication. We compared to the rapidity of bronchodilatory effects between salbutamol in MDI (metered dose inhaler) applied via spacer and formoterol in Turbuhaler®.

Methods: A randomized and open-labeled study. Subjects were randomized to inhale salbutamol 400㎍ in MDI via spacer, formoterol 9㎍ in Turbuhaler® or placebo in Turbuhaler®, when each forced expiratory volume in 1 second falls more than 20% from baseline in bronchial provocation with methacholine. To evaluate rapidity of bronchodilatory effects, recovery times were compared.

Results: The recovery times were 5.28±3.70 min in salbutamol group, 5.78±4.16 min in formoterol group, with no statistical significance ($p=0.66$). However, in placebo group, significant delay was observed (16.88±5.30 min, $p<0.01$).

Conclusions: Formoterol in Turbuhaler® could be used as rapid-acting bronchodilatory effect as salbutamol in MDI via spacer after bronchial provocation test. (J Med Life Sci 2012;9(2):78-81)

Key Words : Adrenergic beta-2 receptor agonists; Asthma; Bronchial provocation tests; Formoterol; Methacholine chloride

Introduction

Asthma is a chronic inflammatory disorder of the airway characterized by airflow obstruction and bronchial hyperresponsiveness, which make asthmatics suffer from acute symptoms due to bronchoconstriction. Bronchodilators and anti-inflammatory medications are indicated for relieving and preventing acute asthmatic symptoms. β_2-agonists administered by inhalation are frequently indicated as the medication of choice for the treatment of acute exacerbations of asthma, due to their rapid-onset bronchodilatory effects[1]. As a controller therapy for maintenance of disease-stable periods, the bronchodilatory effects are preferred to lasting for a longer duration. The ideal characteristics of β_2-agonists for the treatment of asthma have rapid-onset bronchodilatory effect as well as its longer duration. Among β_2-agonists, formoterol is classified to have both of actions, rapid-onset and longer duration. However, the clinical usefulness of formoterol is not firmly established in practice.

Bronchial provocation tests with non-specific pharmacologic agents have frequently been used in clinical and research basis. By measuring the concentration of histamine or methacholine when forced expiratory volume in 1 second (FEV_1) is fallen 20% from baseline, the degree of bronchial hyperresponsiveness can be measured[2]. Customarily, inhaled β_2-agonist, salbutamol has been applied for the reverse of methacholine-induced bronchoconstriction.

This study was designed to investigate the clinical efficacy of formoterol in terms of rapidity of bronchodilatory effect, comparing with that of salbutamol and placebo in the methacholine-induced bronchoconstriction in asthmatics.

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Methods

1. Subjects

Subjects were enrolled under informed consents in the study, who visited the clinic with the suspicious symptoms of asthma such as recurrent events of wheezing, cough or chest tightness, particulary at night or in the early morning in Jeju National University Hospital, Jeju, South Korea

between January 2008 and December 2008. All the candidate subjects performed spirometry. Subjects with lower baseline FEV_1 (< 60% of predictive value or < 1000mL in actual value), current smokers, and subjects who had reported to have medication related to asthma (any type of corticosteroids, bronchodilators, theophyllines, and antileukotrienes) within a month were excluded.

2. Methacholine bronchial provocation test

Methacholine bronchial provocation test as described with modification[3,4] was conducted with informed consent. Briefly, basal FEV_1 was measured twice by spirometry. Normal saline (1mL, 0.9% NaCl) was nebulized by ultrasonic nebulizer, and then FEV_1 was checked in 3 min. With the doubling concentrations from 0.625 mg/mL to 25 mg/mL, each 1 mL of methacholine solutions (methacholine chloride in 0.9% saline) was nebulized for 5 min and FEV_1 was measured 3 min after the nebulization respectively. PC_{20} was calculated by the equation from dose-response curve. Patients with positive reaction, defined when PC_{20} (provocative concentration at 20% of FEV_1 fall from baseline FEV_1) is not more than 10 mg/mL, were enrolled for the study.

3. Study design

Before the provocation tests, patients were randomized to receive one of the bronchodilators (salbutamol 400㎍ in MDI via spacer / formoterol 9g in Turbuhaler®) or placebo (no bronchodilator in Turbuhaler®) immediately after the recognized positve reaction. FEV_1 was measured serially at 3 min, 5 min, 10 min, 15 min, and 20 min after the application of one of bronchodilators or placebo. The recovery time was defined when FEV_1 had recovered into more than 90% from baseline. When FEV_1 was not recovered after 20 min, additional bronchodilator (salbutamol in MDI via spacer) was applied and the recovery time was regarded as 20 min. We compared recovery intervals according to each bronchodilator to evaluate rapidity of bronchodilatory effects.

4. Statistical analysis

The data are presented as number (%) or median (IQR). Group comparisons of categorical variables were made using the chi-square test. To assess the relationship between continuous variables, the two sample t-test was used. *P* values < 0.05 were considered to be statistically significant. Analyses were performed using SPSS software version 14.0 (SPSS: Chicago, IL, USA).

Results

Fifty-six Asian patients (31 males, median age of 42 and interquartile ranging from 22 to 62) with 2389±898 mL (mean±STD) of baseline FEV_1 and 3.73±2.91 mg/mL of PC_{20} were enrolled and all had finished the study. The placebo group was discarded from randomization after enrollments of 8 cases (5 males, mean age of 45), because of the significant delayed recovery with patients' severe sufferings of breathlessness and coughing. Twenty-five patients (11 males, mean age of 45) were enrolled in the salbutamol group, and 23 (15 males, mean age of 37), in the formoterol group. Among the groups, the general characteristics, baseline FEV_1, and PC_{20} showed no significant differences. (Table 1)

Table 1. Comparison of baseline characteristics of between salbutamol group and formorterol group

	Salbutamol	Formoterol	P value
Subjects, n	25	23	
Males, n (%)	11 (44.0)	15 (65.2)	0.141
Age, median (IQR)	45 (22-63)	37 (22-55)	0.844
Baseline FEV1 (mL), median (IQR)	2030 (1450-3170)	2350 (2100-3350)	0.117
PC20 (mg/mL), median (IQR)	2.63 (0.98-6.30)	2.64 (1.81-4.69)	0.780

FEV_1: Forced expiratory volume in 1 second; PC_{20}: Provocative concentration of methacholine at 20% fall of FEV_1 from baseline

In the formoterol group, the recovery time was 5.72±4.16 min, with no statistical difference compared with that of the salbutamol group (5.28±3.70 min, *p=0.66*). However, the significant delay was observed in the placebo group (16.88± 5.30 min, *p<0.01*). Three subjects in the placebo group (37.5%) received the additional salbutamol via spacer for the relief of pharmacological bronchoconstriction and all had recovered FEV_1 within 5 min, where as no subjects received the additional bronchodilator in the formoterol and the salbutamol group. (Figure 1)

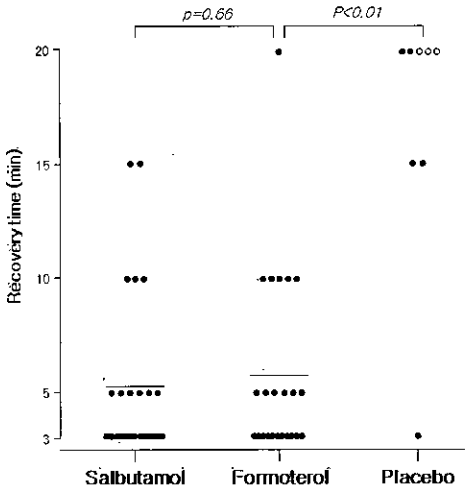

Figure 1. The recovery time of salbutamol, formoterol and placebo group. Empty dots in placebo group represent the subjects who received bronchodilator. Horizontal lines represent the mean value of each group.

Discussion

Bronchial provocation test by inhalation of methacholine solution is a simple but an informative test for the evaluation of airway hyperresponsiveness. It is a sensitive test for the diagnosis of asthma. Additionally, its PC_{20} value correlates symptom scores, response to medication, changes in lung functions and the disease severity in asthmatics[5]. Methacholine-induced bronchoconstriction and its reversal by inhaled bronchodilators have been used as a standardized model to determine the potency and the relative effectiveness of bronchodilators[6].

This investigation was designed to apply one of the two bronchodilators or placebo when provocation occurred. However, in the middle of study, it was modified, because of the lasting symptoms up to more than 20 min of dyspnea, cough and restlessness. After methacholine-induced provocation, inhaled bronchodilator should be applied for the safety of study.

For the treatment of episodic bronchoconstriction such as acute exacerbation of asthma and pretreatment of exercise-induced asthma, rapid-acting β_2-agonist is medication of choice. Traditionally, it has been used for the relief of bronchoconstriction by pharmacologic or allergenic provocation. Salbutamol in MDI is one of the most frequently prescribed medications for its recognized rapidity of bronchodilatory effect. Its bronchodilatory effect for acute exacerbation of asthma and pharmacologic bronchoconstriction is mostly valid in 5 min, consisting the result of this study[7,8].

The ideal bronchodilators for the management of asthma may have rapidity of onset for the treatment of acute exacerbation in addition to longer duration of action for the controller therapy. Although formoterol is classified to have the dual action, the former character is not firmly authorized and still on the investigation.

The bronchodilatory effect of formoterol has been compared with that of the well-known rapid-onset bronchodilators. In the treatment of stable intermittent and mild persistent asthma, formoterol in Turbuhaler® is as effective as terbutaline in Turbuhaler® with less systemic side effects[9]. In the stable mild to moderate asthmatics, formoterol in Turbuhaler® and in MDI shows identical bronchodilatory effect to salbutamol in MDI[10,11].

The rapid-acting inhaled bronchodilator is clinically indicated only for relieving symptoms in as needed basis. For the evaluation of inhaled β_2-agonist's bronchodilatory effect, the clinical investigations should be performed with symptomatic asthmatics rather than with stable asthmatic subjects. In this study, the bronchodilatory effect for the relief of methacholine-induced bronchoconstriction was investigated as a model of acute exacerbation of asthma. Formoterol in Turbuhaler® consistently showed the identical bronchodilatory response to salbutamol in MDI via spacer. Rubinfeld et al reported an open labeled comparative study, comparing the bronchodilatory effect of salbutamol in MDI and formoterol in Turbuhaler®, with asthmatic subjects who visited emergency department for acute symptoms[12]. Salbutamol showed larger FEV_1 increase than formoterol, without statistical significance. At 45 min after inhalation, both showed less than 10% increase of FEV_1 expressed in % predicted. However, in this study, the recovery of more than 90% from FEV_1 baseline was achieved within minutes after

bronchodilator inhalation in the methacholine-induced bronchoconstriction. Acute clinical symptoms of asthma are from bronchoconstriction as well as airway inflammation, but inhaled β-agonist has bronchodilatory effect without anti-inflammatory effect. Methacholine-induced bronchoconstriction has no inflammatory burdens on airway, so it is supposed to be a better model for the evaluation of bronchodilatory effect.

In conclusion, the bronchodilatory effect of formoterol in Turbuhaler® is as rapid as that of salbutamol in MDI via spacer. Formoterol can be safely used as an alternative reliever to salbutamol in the reverse of methacholine-induced bronchoconstriction and may be used as a reliever therapy in acute exacerbation of asthma. Larger randomized controlled studies are necessary to support inhaled formoterol may be an ideal β-agonist in the treatment of asthma with both of the rapid onset and longer duration of bronchodilatory effect.

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