Original Article

Efficacy of inhaled formoterol in reversing bronchoconstriction*

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ABSTRACT

Objective: To evaluate the effectiveness and onset of action of formoterol delivered by dry-powder inhaler in reversing methacholine-induced bronchoconstriction. **Methods:** Patients presenting a drop in forced expiratory volume in one second > 20% after methacholine inhalation were included. A total of 84 patients were evaluated. All of the participating patients presented respiratory symptoms of unknown origin, which were being investigated. The patients were randomized to receive 200 µg of spray fenoterol (n = 41) or 12 µg of dry-powder inhaler formoterol (n = 43), both administered in order to achieve immediate reversal of methacholine-induced bronchoconstriction. We evaluated the decrease in forced expiratory volume in one second (in relation to the baseline value) after methacholine challenge and the dose of methacholine required to provoke a drop of 20% in forced expiratory volume in one second, as well as the increase in forced expiratory volume in one second (in relation to the baseline value) at five and ten minutes after bronchodilator use. **Results:** There were no significant differences related to gender, age, weight, height or dose of methacholine required to provoke a drop of 20% in forced expiratory volume in one second. Nor were there any significant differences in terms of baseline or post-methacholine forced expiratory volume in one second. In the fenoterol group, the mean postbronchodilator increase in forced expiratory volume in one second increase was 34% (at five minutes) and 50.1% (at ten minutes), compared with 46.5% (at five minutes) and 53.2% (at ten minutes) in the formoterol group. **Conclusion:** The bronchodilator effect of formoterol at five and ten minutes after methacholine-induced bronchoconstriction was similar to that of fenoterol. Despite being a long-acting bronchodilator, formoterol also has a rapid onset of action, which suggests that it could be employed as a relief medication in cases of bronchoconstriction occurring during asthma attacks.

Keywords: Asthma; Formoterol; Fenoterol; Inhalation therapy; Bronchodilation, Methacoline

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INTRODUCTION

Inhaled β2-agonists play an important role in the treatment of asthma due to their excellent bronchodilator effect. Short-acting β2-agonists, such as salbutamol and fenoterol, are usually used in the reversion of acute bronchoconstriction attacks. Formoterol and salmeterol, however, are classified as long-acting β2-agonists, since they present a prolonged bronchodilator effect. Long-acting bronchodilators have proven efficacious and have been well tolerated in the maintenance treatment of patients with asthma who present nocturnal symptoms or who require frequent use of short-acting β2-agonists.[1-4]

The effect of long-acting β2-agonists persists for at least twelve hours. Formoterol acts faster than salmeterol and has been compared to salbutamol, regarding the onset of action, in some studies.[5-9] Consequently, formoterol may be an alternative for the management of acute asthma attacks, facilitating treatment compliance due to the use of only one device. The use of formoterol in the maintenance treatment of patients with asthma has been associated with the concomitant use of inhaled corticoids. However, due to its rapid onset of action, formoterol can be recommended as a potential aid in the management of acute bronchoconstriction attacks.

The present study was designed in order to evaluate the effectiveness and onset of action of formoterol delivered by dry-powder inhaler in immediately reversing methacholine-induced bronchoconstriction.

METHODS

This was a prospective study involving 84 patients referred to the Pulmonary Function Laboratory of the *Pavilhão Pereira Filho da Santa Casa de Misericórdia de Porto Alegre* for the investigation of symptoms related to bronchial hyperresponsiveness, especially cough, dyspnea, and wheezing. In the spirometric results, all of the patients presented a baseline flow-volume curve with a relationship between forced expiratory volume in one second (FEV_1) and forced vital capacity greater than 70%. None of the patients made use of bronchodilators or inhaled corticoids. All patients presented bronchoconstriction after methacholine challenge in accordance with the protocol devised by the Brazilian Society of Pulmonology and Phthisiology (administering methacholine via jet nebulizer for two minutes).[10] All of the selected patients presented a decrease of at least 20% of FEV_1 in relation to the baseline value as a consequence of the administration of various concentrations of methacholine.

After the induction of bronchoconstriction, patients were randomized into two groups. Group 1 comprised 41 patients, all of whom received, immediately after the bronchoprovocation test, 200 µg of fenoterol by means of a metered-dose inhaler with a 50-mL spacer. The technique was carried out in accordance with the guidelines established by the Sociedade Brasileira de Pneumologia e Tisiologia.[1] Group 2 comprised 43 patients, all of whom received, also immediately after the bronchoprovocation test, 12 µg of dry-powder inhaler formoterol (aerolizer - Foradil®). The patients were instructed to exhale all of the air from their lungs, keeping the inhaler slightly inclined, and inhale as deep as possible, holding their breath for at least ten seconds after inhaling the medication. Spirometry was always carried out during the morning hours and was conducted by a laboratory technician who had no knowledge of which inhaler device had been used by any given patient. Patients were submitted to two additional determinations of FEV_1, at five and ten minutes after bronchodilator use. A Koko spirometer (Ferraris Respiratory Europe, Hertford, UK) was used for the determinations.

The following variables were studied: gender, age, height, weight, the dose of methacholine required to provoke a drop of 20% in FEV_1, baseline FEV_1, FEV_1 after bronchoprovocation test, FEV_1 five minutes after the use of the bronchodilator, and FEV_1 ten minutes after the use of the bronchodilator.

We used Pearson's chi-square test for the comparison between proportions. We used Student's t-test for the comparison between means. The level of statistical significance was set at 5%. The number of patients allocated to each group was randomly defined. Nevertheless, after data analysis, we calculated the statistical power of the comparisons, finding values greater than 90%, which guaranteed that the size of the sample was sufficient for the objectives of the study.

The Ethics Research Committee of the Complexo Hospitalar da Santa Casa de Misericórdia de Porto Alegre approved this study. All patients gave written informed consent.

RESULTS

There were no statistically significant differences between group 1 (fenoterol) and group 2 (formoterol) related to age, gender, weight, height, or dose of methacholine required to provoke a drop of 20% in FEV_1 (Table 1).

Table 2 shows the comparison between the groups related to the values of baseline FEV_1 and FEV_1 after methacholine-induced bronchoconstriction, as well as FEV_1 at five and ten minutes after the administration of the bronchodilators studied. It can be seen that, although absolute FEV_1 values in group 1 were always higher than those in group 2, there were no statistically significant differences in any situation. In addition, the percent of increase or drop in FEV_1 in relation to baseline values after the administration of medication was similar in both groups.After methacholine-induced bronchoconstriction, group 1 showed a mean drop in FEV_1, in relation to baseline values, of 34.9%, whereas group 2 showed a mean drop of 38.1% for the same parameter (p = 0.51). After the use of the bronchodilator, the mean increase in FEV_1 in group 1 was 34% (standard deviation of ± 10.3%) at five minutes and 50.1% (standard deviation of ± 23.5%) at ten minutes, compared with 46.5% (standard deviation of ± 16.1) at five minutes and 53.2% (standard deviation of ± 24.9%) at ten minutes in group 2. There were no significant differences between the two groups (p = 0.52 at five minutes and p = 0.72 at ten minutes) (Table 2; Figures 1 and 2).

TABLE 1

Characteristics of the patients submitted to methacholine-induced bronchoconstriction

	Fenoterol	Formoterol	p
N	41	43	-
Gender	28 M, 13 H	35 M, 8 H	0,17
Age (years)	41,9 ± 17	44,3 ± 22,1	0,57
Weight (kg)	66,5 ± 11,6	65,4 ± 13,9	0,69
Height (cm	170,5 ± 47	161,3 ± 8,95	0,21
PD20 (mg/dl)	0,77 ± 0,9	0,60 ± 0,7	0,32

F: female; M: male; PD20: provocative dose causing a drop of 20% in forced expiratory volume in one second. Results expressed as means ± standard deviation.

TABLE 2

Functional characteristics of the patients submitted to methacholine-induced bronchoconstriction and variation after the use of bronchodilators

	Fenoterol	Formoterol	p
Initial FEV_1 (L)	3.21 ± 0.99	2.81 ± 0.88	0.11
Post-methacholine	(110% previsto)	(106% previsto)	
metacolina (L)	2.09 ± 0.82	1.74 ± 0.6	0.13
FEV_1 (L)	(↓ 34.9%)	(↓ 38.1%)	0.51
Post-BD	2.80 ± 0.93	2.46 ± 0.74	0.07
FEV_1 at 5 min (L)	(↑ 34 %)	(↑ 46.5%)	0.52
BD - 10min (L)	2.95 ± 0.94	2.58 ± 0.79	0.051
FEV_1 at 10 min (L)	(↑ 50.1%)	(↑ 53.2%)	0.72

Results expressed as means ± standard deviation. The arrows show the percent of increase or decrease in FEV_1 in relation to baseline FEV_1. FEV_1: forced expiratory volume in one second; BD: bronchodilator.

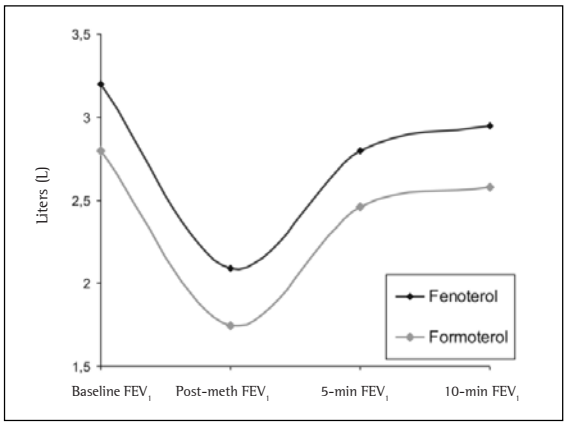

Figure 1 -Absolute variation curve of FEV_1 after methacholine-induced bronchoconstriction and bronchodilator response in the two groups. FEV_1: forced expiratory volume in one second; baseline FEV_1: FEV_1 prior to methacholine bronchoprovocation; post-meth FEV_1: FEV_1 after methacholine bronchoprovocation; FEV_1 5 min: FEV_1 five minutes after the administration of the bronchodilator; FEV_1 10 min: FEV_1 ten minutes after the administration of the bronchodilator.

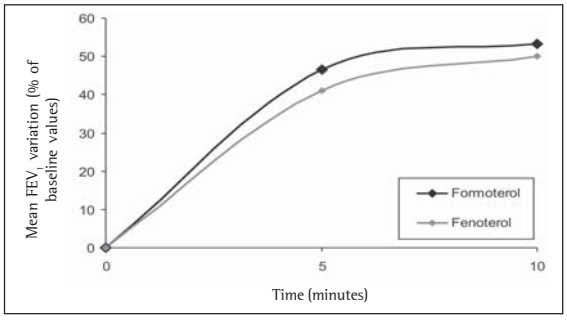

Figure 2 - Percent variation of FEV_1 after bronchodilator administration. Values expressed as percent of increase in relation to values after methacholine-induced bronchoconstriction. FEV_1: forced expiratory volume in one second.

DISCUSSION

The results of the present study show that the bronchodilator effect of dry-powder formoterol occurs rapidly, as does that of spray fenoterol. In patients submitted to methacholine-induced bronchoconstriction, the degree of bronchodilation achieved with dry-powder formoterol was practically identical to that achieved with metered-dose inhaler fenoterol. The bronchodilator response, measured by the increase in FEV_1 at five and ten minutes after the administration of the medications, was similar in both groups, with a tendency, albeit less than significant, toward an increase in the group that made use of formoterol.

The present study presents a limitation related to the fact that the two bronchodilators compared had different equipotent doses and were administered using different devices. However, these are the formulations typically available on the market and commonly used by patients with asthma.

There are few studies in the literature comparing the effect of formoterol in the immediate reversion of bronchoconstriction to that of short-acting β2-agonists.[2-5] This is one of the few studies that compared fenoterol to formoterol. In addition, we used a larger patient sample than did the authors of previous studies.

Among the long-acting β2-agonists, formoterol has the fastest onset of action, especially if compared to that of salmeterol.[5,8,11-12] However, the use of long-acting β2-agonists for the immediate reversion of bronchoconstriction or for the relief of acute symptoms has not been recommended in any asthma management consensuses or guidelines.

The model of methacholine-induced bronchoconstriction used in this study simulates an acute asthma attack and has been employed in various studies with the objective of evaluating immediate bronchodilator response.[5,7,12-13] In this study, the mean drop in FEV_1 after the use of methacholine was greater than 30% from baseline values, and most patients presented an FEV_1 lower than 2L, which represents significant bronchoconstriction and the onset of bronchial hyperresponsiveness.

The results of this study are in agreement with the conclusions found in the literature. Some authors,[7] in a randomized study comprising 16 patients with asthma, compared the speed of the onset of bronchodilation, as well as its degree, achieved with the use of 12 µg and 24 µg of powder-dry formoterol to those achieved with the use of 400 µg metered-dose inhaler salbutamol after methacholine-induced bronchoconstriction. The authors found no significant differences between the two groups. In another study,[12] 17 patients with asthma were randomized to receive, after methacholine-induced bronchoconstriction, 12 µg of dry-powder formoterol, 50 µg of dry-powder salmeterol, or 50 µg of dry-powder salbutamol. There were no statistical differences in the onset of action between salbutamol and formoterol. However, the onset of action of these medications was faster than that of salmeterol. Identical results were found in another study,[5] which compared the bronchodilator effect of 12 µg of formoterol, 50 µg of salmeterol, and 200 µg of salbutamol (delivered using a metered-dose inhaler) in patients diagnosed with moderate or severe asthma.

Two comprehensive studies were conducted in order to evaluate whether the regular use of formoterol as a rescue medication in bronchoconstriction attacks would cause systemic adverse effects in patients with asthma. In a randomized, double-blind study,[14] the clinical efficacy and safety of the regular use of dry-powder formoterol and dry-powder terbutaline, as rescue medications for patients with moderate or severe asthma, was compared. The authors found no statistical differences between the two groups in the number or severity of adverse effects. In addition, the to use rescue medication was lower among patients in the group using formoterol, who also presented longer periods of time between attacks and better results in pulmonary function tests. Later, a comprehensive population study comprising more than 18,000 patients with asthma was conducted, and the results ratified those of the previous study. Formoterol proved to be safe for use as a rescue medication in bronchoconstriction attacks, as well as being associated with better control of asthma symptoms.[15]

The immediate bronchodilator action of formoterol has also been associated with the choice of the inhaler device used for its administration. Dry-powder inhalers present better pulmonary deposition than do spray devices, and better pulmonary deposition is related to greater efficacy. In addition, the facility to administrate dry-powder formoterol (aerolizer) allows its use by both children and elderly patients who find it difficult

to perform the necessary maneuvers required by the use of metered-dose inhalers, and this results in better compliance with the treatment.[16]

The results obtained in this study show that the bronchodilator formoterol is not only long-acting but is also fast-acting. This finding suggests that formoterol may also be used as rescue medication against bronchoconstriction attacks in patients with asthma. The use of only one bronchodilator formulation, which provides both immediate relief and longer action, would surely increase patient compliance with the proposed therapeutic regimen.

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