Rapid Onset of Action of Inhaled Formoterol in Asthmatic Patients*

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Twelve patients with stable asthma (mean age, 39 years; asthma duration, 11 years; mean forced expiratory volume in 1 s, 65 percent of predicted; and reversibility, 31 percent) were studied in a double-blind crossover trial. The patients were studied during three test days. Airway resistance and specific airway conductance (Raw and SGaw) were measured using a body plethysmograph and pulse rate, blood pressure, tremor, and subjective effects were recorded before and 1, 3, 5, 10, 15, 30, 60, and 120 min after the test doses. A baseline Raw variability of ±20 percent was allowed between the test days. Formoterol 12 µg, 24 µg, and terbutaline 500 µg were given in a spacer (Nebulator) in a randomized double-blind crossover manner as two puffs with a 30-s interval in between. The effect of formoterol 12 µg on Raw was significantly better than terbutaline after 3, 5, 10, 60, and 120 min. Formoterol 24 µg was significantly better than terbutaline as soon as 3 min after inhalation at every point in time after that. Formoterol 24 µg tended to be better than formoterol 12 µg but the differences were not significant at any point in time. All three treatments were well-tolerated. No differences were observed for pulse rate, blood pressure, tremor, or palpitations. The overall onset of bronchodilatation after formoterol 12 and 24 µg was faster than after terbutaline 500 µg. The tolerability of formoterol was good.

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Inhaled β₂-adrenoceptor agonists are considered in most countries to be first-line treatment and a cornerstone in current asthma therapy.¹,² Because of their relatively short duration of bronchodilating effect (4 to 6 h), they must be administered up to six times per 24 h or even more. A new long-acting, inhaled β₂-agonist could thus be of great benefit to asthmatic patients, as long as its onset of action is as rapid as the commonly used β₂-agonists (salbutamol and terbutaline).

A longer-lasting bronchodilating effect of β₂-agonists has up to now been possibly only through the use of oral slow-release β₂-tablets, which, however, have a slower onset of action as well as a greater risk of side effects.¹³ Formoterol fumarate is a new potent β₂-agonist with antiallergic properties. It has been found to be at least as β₂-selective as salbutamol in animal and human studies.⁴ It is about 50 times more potent than salbutamol after oral administration but after administration by inhalation,⁶ formoterol is 5 to 15 times more potent than salbutamol. Most important, it has been shown to have a long-lasting bronchodilating effect on large and small airways for at least 12 h, both in adults⁷,⁸ and in children.¹¹ Formoterol also protects against methacholine-induced bronchoconstriction for at least 12 h.¹³ The long duration has raised the question whether formoterol has a slower onset of bronchodilating action. The aim of this study was to compare formoterol with terbutaline and focus on the onset of action during the first 15 min when the drugs were given as metered-dose aerosols to patients with stable asthma.

METHODS

Patients

Twelve patients, aged 21 to 68 years (mean, 39 years), with bronchial asthma in a stable phase (four men and eight women) were included in the study. They were all methacholine-positive (PD20) and had a mean duration of asthma of 11 years (range, 5 to 25 years), mean FEV₁ of 65 percent of predicted (range, 42 to 77), and a mean reversibility, measured as a percentage increase in FEV₁ after 400 µg inhaled salbutamol, of 31 percent (range, 15 to 70).

Eleven of the patients used inhaled β₂-agonists, five patients used oral β₂-agonists, five patients used oral theophyllines, and nine patients used inhaled steroids. Only one patient was receiving regular treatment with disodium cromoglycate (DSCG). The study was performed as a randomized, double-blind crossover study. On a day prior to the study, pulmonary function tests were carried out, and patient characteristics, case history findings, and medical examination results were recorded. It was also checked whether the patients fulfilled the inclusion criteria. The patients were then studied during three test days with at least one week between the days. Theophylline therapy was withdrawn 36 h, oral β₂-agonist therapy was withdrawn 24 h, and inhaled β₂-agonist therapy was withdrawn at least 8 h before each test day. Only inhaled steroids in stable dosage were allowed as concomitant treatment during the test period. The patients arrived at the hospital at the same time on each test day. Coffee or tea in the morning was not allowed. All assessments were made by the same physician at the same time of day. The pulmonary function tests included measurements of functional residual capacity (FRC), airway resistance (Raw), and specific airway conductance (SGaw) measured with a body plethysmograph (Siemens) of the constant volume type (Strengnost FD915 + FD40). The FRC and Raw were measured at a respiratory

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rate of 30 breaths per minute. The mean value of at least three acceptable recordings was used for calculating the FRC and Raw according to formulas described elsewhere and SGaw was calculated as (1/Raw)/FRC. Pulmonary function (Raw and SGaw), pulse rate, and blood pressure were recorded before and 1, 3, 5, 10, 15, 30, 60, and 120 min after the trial medications were given. At the same point in time, the patients were asked for subjective feeling of tremor or palpitation. A baseline variability of ±20 percent for Raw was allowed during the test days.

Formoterol 12 μg, 24 μg, and terbutaline 500 μg were given double blindly using a spacer (Nebulator) as two puffs with 30 s in between. The patients were asked to hold their breath for at least 10 s after a slow inhalation.

Informed consent was given by the patient and the study was approved by the local ethics committee.

Statistical Methods

For the purpose of analyzing the main efficacy variable, Raw, a log-transformation was employed, this transformation having been determined a priori. A general linear model was used in which treatments, patients, and periods were fitted as factors and the logarithm of Raw at baseline was used as a covariate. An independent analysis was carried out at each time point. It was assumed that the washout period was adequate and no adjustment for carryover was performed. At each time point, all three possible pairwise contrasts of treatments with their associated standard errors were estimated from the general linear model and their significance levels were obtained by referring the resulting t statistic to Student’s t distribution with 19 degrees of freedom. No adjustment for multiple testing was carried out and the results should be viewed as exploratory. The critical value for hypothesis testing was 5 percent, two-sided.

Results

All patients had an increased Raw and decreased SGaw before inhalation of the trial medication. The mean Raw was 401 Pa/(L/s), range 132 to 1154, and the mean SGaw was 0.97 1/(s·Pa), range 0.22 to 2.02. According to reference values,15,16 the mean Raw was 346 percent and the mean s-Gaw was 40 percent of the predicted values. Raw was chosen as the main efficacy parameter (Fig 1). There was no statistically significant difference among the three treatments after 1 min. Formoterol 12 μg was statistically significantly better than terbutaline 3, 5, 10, 60, and 120 min after inhalation of the trial medication. At all other points in time formoterol 12 μg showed a tendency to be better than terbutaline, but failed to reach the significance level of p≤0.05. Formoterol 24 μg was statistically significantly better than terbutaline as soon as 3 min after the trial medication and at every point in time after that. In most cases, this difference was highly significant. No statistically significant difference could be found between formoterol 12 and 24 μg. More than 25 percent change in Raw and SGaw was obtained already 1 and 3 min after formoterol 24 and 12 μg, respectively, and 10 min after terbutaline 500 μg. These results are exploratory and should be confirmed by further studies.

Specific airway conductance SGaw was a supportive variable and the results were similar to the resistance data (Fig 2).

All three treatments were well tolerated. There were no differences between the treatments at any point in time with regard to pulse rate, systolic blood pressure, or diastolic blood pressure. No other relevant adverse effects were recorded.

Discussion

Airway resistance and SGaw were selected as efficacy variables. In asthmatic patients, they probably reflect obstruction in both central and peripheral airways and can be measured during calm ventilation and are very suitable for a study with a high frequency of measurements and minimize the risk of inducing bronchoconstriction as can be made by forced expiration.

In clinical practice, terbutaline 500 μg aerosol is regarded as being equipotent to 200 μg salbutamol aerosol.17-19 On the basis of comparative studies between formoterol and salbutamol, where formoterol 12 μg was regarded as comparable to 200 μg salbutamol,7 formoterol 12 μg was considered to be equipo-
tent to terbutaline 500 μg. In our study, both formoterol doses, ie, 12 and 24 μg, seem to have a better bronchodilating effect than 500 μg terbutaline. A spacer (Nebulator) was used to optimize the deposition of the two puffs of the aerosol into the airways.\textsuperscript{20,21} In our study, formoterol 24 μg had given more than 30 percent effect on Raw after 1 min and formoterol 12 μg after 3 min, whereas terbutaline 500 μg did not produce this effect until after 10 min. In the study of Derom et al,\textsuperscript{9} a significant effect was found at 1 min after administration of 12 and 24 μg formoterol as well as after 200 μg salbutamol without the use of a spacer.

Long-acting inhaled bronchodilators would be expected to be of benefit to asthma patients.\textsuperscript{3} It has been proposed that formoterol should be used in a twice-daily dose regimen.\textsuperscript{22-24} However, the severity of the asthma varies and asthma patients frequently also need to be able to prevent or treat the bronchoconstriction caused by cold weather, exercise, etc. For that reason they need a drug that also can be used as rescue medication (as required). Our results indicate that formoterol can be used both for regular maintenance therapy and for the treatment of incidental bronchoconstriction.

Our conclusion is that the onset of bronchodilatation after formoterol 12 or 24 μg was faster than after terbutaline 500 μg. The overall tolerability of formoterol was good.

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