Eur Respir J
1991, 4, 296–300

Protective effect and duration of action of formoterol aerosol on exercise-induced asthma

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Protective effect and duration of action of formoterol aerosol on exercise-induced asthma. A. Patessio, A. Podda, M. Carone, N. Trombetta, C.F. Donner.

ABSTRACT: The short-term protective effect on exercise-induced asthma (EIA) and the duration of action of formoterol, given by metered dose aerosol at a dose of 24 μg, were compared with salbutamol (200 μg) and placebo in twelve asthmatic EIA-positive patients in a double-blind, placebo-controlled, three period cross-over study. On each treatment day the patients were given one of the drugs or placebo and two exercise tests were performed at the second and at the eighth hour after dosing. Using a standard procedure, exercise was performed by treadmill in well-controlled environmental conditions. In the first test at 2 h a significant difference relative to placebo ($p<0.001$) at each incremental time after exercise (*i.e.* 5, 10, 15, 20, 30 min) was obtained with both formoterol and salbutamol, without any significant difference between formoterol and salbutamol. After the eighth hour test formoterol still protected against EIA in comparison to both salbutamol and placebo. The effect of salbutamol at this time was not different from placebo. No adverse effects were reported in any treatment group. Formoterol has a long duration of action in protecting against EIA that persisted for eight hours, removing the need to dose with β_2-agonist before every exercise.

Eur Respir J., 1991, 4, 296–300.

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Keywords: Duration of action; exercise-induced asthma; formoterol; salbutamol.

Received: March 2, 1990; accepted after revision August 29, 1990.

Exercise is a frequent trigger stimulus for an attack of asthma. In the great majority of cases, the induced bronchoconstriction is not life-threatening, lasts for a short time and is reproducible provided that the environmental conditions and the level of ventilation induced by exercise are the same [1–3]. The mechanisms involved are thought to relate to increased ventilation during exercise, leading to mucosal water loss and cooling. The consequent increase in ion concentration and decrease in the temperature of the airways [4, 5] stimulates release of mediators from the resident mast cells [6–8] leading to bronchoconstriction, increased vascular permeability and mucosal oedema.

Despite the variety of pathophysiological factors, β-adrenoceptor agonists are the most effective drugs in protecting against exercise-induced asthma (EIA), the best results being obtained after aerosol rather than oral administration [9–11]. However, their duration of action is short when used as bronchodilators and even shorter when taken for EIA protection [12–14]. A patient sustaining a useful response needs to take these drugs for every exercise.

Formoterol, a phenylethylamine derivative, is a highly potent β_2-agonist, with considerable selectivity for the pulmonary smooth muscle β_2-receptors [15, 16]. Administered orally, it is about 50 times more potent than equimolar doses of salbutamol [15] and after inhalation has a longer duration of action than other similar compounds [17–20]. It seems reasonable to suppose that its protective effect against EIA would also last longer.

This study evaluates the short-term protective effect on EIA of formoterol in comparison with salbutamol and placebo. All were administered by metered dose aerosol. The duration of EIA prevention was measured following two exercise tests at different times after dose administration.

Patients and methods

Twelve patients, eight out-patients and four in-patients, two men and ten women, (mean age 25±6.2 yrs; forced expiratory volume in one second (FEV_1) 96.9±12.5% of predicted) suffering from bronchial asthma as defined by the American Thoracic Society [21], participated in the study. The inclusion criteria rested on lung function tests defined as follows: 1) FEV_1 ≥80% of predicted normal values; 2) FEV_1 variability ±10% on 3 different spirometric tests performed on three consecutive days; 3) FEV_1 increase <15%, 30 min after the inhalation of 200 μg of salbutamol; 4) FEV_1 decrease

of 20% or more after a preliminary exercise test, carried out a week before the study, without any pharmacological pre-treatment and assessed 5–30 min after the end of exercise.

Exclusion criteria were the presence of respiratory infection during the month preceding the study, coronary artery disease or cardiac arrhythmias, systemic hypertension, diabetes mellitus, renal or hepatic disease, concomitant diseases or therapies complicating the evaluation of the drug, allergies for substances similar to those used in the study and poor co-operation. Women of childbearing potential (excluding those taking contraceptive pills or with an intrauterine device) were also excluded. All patients were to refrain from taking any medications for the 24 h before the study (48 h for antihistamines), as well as throughout the study period.

All patients gave their informed consent to the study, which was conducted in accordance with the declaration of Helsinki, and none were withdrawn from it.

Methods

This study comprised a double-blind, placebo-controlled, three period, cross-over investigation. After a run-in period during which every patient was given placebo aerosol (two puffs) on three consecutive days, two hours before testing lung function, the patients were randomized to one of the three following treatment sequences, using a 3×3 latin square design, four times replicated:

Formoterol - Salbutamol - Placebo
Salbutamol - Placebo - Formoterol
Placebo - Formoterol - Salbutamol

The treatments were given on three different days by metered dose aerosol. The single doses of formoterol and salbutamol were 24 μg (two puffs) and 200 μg (two puffs), respectively. Each treatment day was separated by a one day wash-out period. Patients were given the treatments between 08.30 and 09.00 h. Two exercise tests were performed at the second and eighth hour after dosing.

These tests, as well as the inclusion test, comprised a run on a treadmill with a 6% inclination for 7 min, to include a 1 min spell of rapid increase of the workload (= speed of the belt), to induce a target heart rate of 90% of the predicted maximum age-specific value [22], and 6 min (or less, if severe asthma occurred) of constant load [23]. During the test, the patients were monitored by continuous recording of the V5 precordial electrocardiographic lead by the telemetric method (Telecuster 36 E1; Siemens, West Germany). Room temperature (21±1°C) and relative humidity (46±4%) were maintained constant using an air conditioner. At baseline, 5, 10, 15, 20 and 30 min after the test, three successive forced expiratory manoeuvres (Pneumotachograph; EOS-Sprint Jaëger, Wuzburg, West Germany) were performed and at each time the best result was used in the analysis. From the flow-volume loop the following variables were recorded: forced vital capacity (FVC), FEV_1, forced mid-expiratory flow ($FEF_{25-75\%}$), maximal expiratory flow when 25% and 50% FVC remains ($MEF_{25\%FVC}$) and ($MEF_{50\%FVC}$) respectively. Heart rate and blood pressure were measured just before and just after exercise.

Statistical analysis

Fisher's exact test (for non-parametric data) or a one-way analysis of variance (for parametric data) were used to check the patient distribution among the three sequences. The stability of the pre-drug FEV_1 values throughout the study (*i.e.* the period effect) was checked by means of an analysis of variance for latin square designs. Since no period effect was observed, efficacy was assessed by means of an analysis of variance for a repeated measurements design, performed separately for the two exercise tests, taking into consideration the times and treatments as sources of variation. When appropriate, multiple comparisons were performed by means of the Tukey studentized test. Linear regression analysis allowed examination of relationships among physiologic variables. The SAS package was used to perform all the calculations, $p<0.05$ was considered significant. Data are given as mean values ±standard deviation.

Results

Resting lung function

All enrolled patients completed the study. FEV_1 variability was less than ±10% during the three days before entry. Patient distribution among the three sequences was satisfactory with no statistically significant differences between age, sex and baseline FEV_1 values being observed. Mean FEV_1 values at baseline (*i.e.* before drug administration) were always >80% of predicted values. Two hours after dosing and before the start of the exercise tests the mean values of FEV_1 were 99±9% of predicted for formoterol (9.1±0.4% increase in respect to baseline), 97.2±10.4% for salbutamol (5.4±0.4% increase over baseline) and 94.9±11.8% for placebo (1.7±0.4% over baseline). Both at the second (*i.e.* before the first test) and at the eighth hour (*i.e.* before the second test), the % predicted FEV_1 values were no different either between treatments or between these two times.

Lung function after exercise

Figure 1 shows the FEV_1 behaviour throughout the study. In the first test there was a significant difference ($F=9.87$; $p<0.0009$) between treatments, as well as a significant ($F=2.09$; $p<0.045$) treatment-time interaction. At this first study time, formoterol and salbutamol gave a significantly better protection than placebo, without any appreciable difference between them. In the

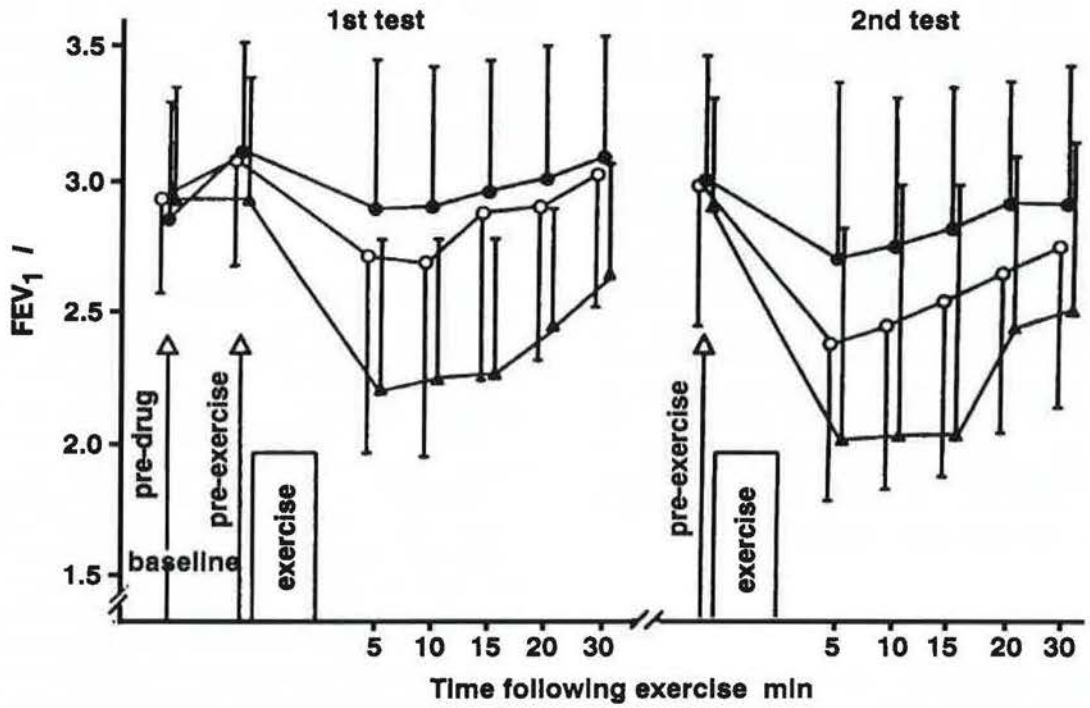

Fig. 1. – FEV_1 values (mean±SD) at baseline (*i.e.* pre-drug), just before and at different times after the two exercise tests, carried out at the second (1st test) and at the eighth hour (2nd test) after dosing. Formoterol (●- - -●); salbutamol (○- - -○); placebo (▲- - -▲). FEV_1: forced expiratory volume in one second.

second test there was still a significant difference of variance (F=8.12; p<0.002) between treatments, but the Tukey test revealed formoterol to be significantly (p<0.05) more effective than both salbutamol and placebo. No significant difference was observed between salbutamol and placebo. The change in FEV_1 was also calculated according to the following formula:

$$\% \text{ decrease} = \frac{\text{lowest post-exercise value - pre-exercise value}}{\text{pre-exercise value}} \times 100$$

Patients were retrospectively classified into three subgroups according to their exercise maximal decrease in FEV_1: <15%=negative; 15–25%=positive, but symptoms were not usually encountered; and >25%, at which point patients usually complained of breathlessness. Eight patients were still protected (*i.e.* decrease in FEV_1 <15%) at the eighth hour after formoterol *versus* only three patients after salbutamol and one after placebo (table 1).

Further analyses carried out on the other variables (FVC, $FEF_{25-75\%}$, $MEF_{25\%FVC}$, $MEF_{50\%FVC}$) again confirmed that formoterol and salbutamol had approximately the same efficacy at two hours but at the eighth hour after dosing only formoterol was better than placebo (table 2).

Finally, no adverse effects were reported or observed during the study in any of the treatment groups. In particular, no differences between treatments were observed in any of the cardiovascular variables, namely blood pressure and heart rate.

Table 1. – Absolute frequency of patients in the three treatment groups divided on the basis of the FEV_1 decrease after exercise

	Second hour			Eighth hour		
	≤15%	16–25%	≥26%	≤15%	16–25%	≥26%
Formoterol	8	4	0	8	3	1
Salbutamol	6	4	2	3	3	5
Placebo	3	3	6	1	4	7

FEV_1: forced expiratory volume in one second.

Table 2. – Summary of the significant (p<0.05) differences between treatments (multiple comparison tests) obtained at the exploratory analysis

Variable	1st test Second hour	2nd test Eighth hour
FVC	F = S > P	F > S = P
$FEF_{25-75\%}$	F = S > P	F = S > P
$MEF_{25\%FVC}$	F = S > P	F > S = P
$MEF_{50\%FVC}$	F > S = P	F > S = P

F: formoterol; S: salbutamol; P: placebo; FVC: forced vital capacity; $FEF_{25-75\%}$: forced mid-expiratory flow; $MEF_{25\%FVC}$ and $MEF_{50\%FVC}$: maximal expiratory flow when 25% and 50% FVC remains to be exhaled, respectively.

Discussion

Formoterol has a longer bronchodilating action (lasting up to twelve hours) [20] than other β_2-adrenergic compounds [17–19]. This study adds further information in that inhaled formoterol has a more prolonged effect than salbutamol in protecting against post-exertional asthma.

Both formoterol and salbutamol gave significantly better protection than placebo for EIA at 2 h, but by 8 h only formoterol remained active. Baseline values before the tests were not statistically different and no interaction between drug and drug order was observed, nor was there any period effect. Thus, the protective effect of each treatment was finished by the time the successive study was undertaken. Good stability in lung function was achieved probably because the patients were symptom-free and had a normal baseline respiratory function (FEV_1 >80% of predicted value). Nevertheless, 2 h after administration, the bronchodilating effect measured by change in FEV_1 was greater after formoterol than salbutamol demonstrating in asymptomatic patients a certain degree of bronchial tone.

The doses used may not be considered equipotent (defining equipotency as reaching the same maximum bronchodilating effect), since equipotency was shown between 6 μg of formoterol and 100 μg of salbutamol: however, the maximum bronchodilation was achieved 60 min after salbutamol and 120 min after formoterol and this time-effect relationship could have biased the observation of the equipotency between the two mentioned doses [24].

The patients were exercised at the second and eighth hours, but not at 30 min after drug administration because the effect of β_2-agonists at this time is well-known. The times selected in this study seemed the most suitable for testing the time course of effect of the new drug. After two hours most of the existing β_2-agonists begin to lose their efficacy and after eight hours there are no reported exercise tests, as the bronchodilator effect is considered finished. We did not exceed 8 h, even though some observations reveal a longer duration of action, because it is known [12] that the bronchodilating effect of these drugs lasts longer that the protective effect against EIA. The explanations are not clear but this could be related to the mechanism of EIA, such as mediator release from mast cells and the increase in mucosal osmolarity. The concentrations needed to counteract these events in the airway lumen are presumably greater than those necessary to relax bronchial smooth muscle. Lung function was measured for 30 min following exercise as the majority of responders show bronchoconstriction, which attains its peak between the fifth and tenth minutes. Almost all patients are in the recovery phase by the thirtieth minute, with recovery usually complete by the ninetieth minute [25].

Recovery from EIA raises the important question of the influence of the first test on the second. Repeated exercise induces lower degrees of bronchoconstriction [26, 27] but such response is usually over if the interval exceeds two hours. In the present study the interval was six hours, with a return of the eighth hour pre-exercise FEV_1 to previous pre-exercise values. Exercise may produce a biphasic asthmatic reaction in 30 to 60% of asthmatic patients, probably associated with elaboration of mediators of immediate hypersensitivity [28–30]. If this were true, the first test would interfere with the second but RUBINSTEIN *et al.* [31] demonstrated that the second bronchoconstriction (seen between 4–10 h after exercise) is a phenomenon limited to only a few patients. It has also been suggested that this may be a nonspecific phenomenon not related to the performance of exercise, but to the withdrawal of medication. This may also explain the more severe bronchoconstriction in the second test after placebo, but the difference between tests performed after the active drugs can only be ascribed to differences in the power and duration of the action of the drugs themselves. As far as the reduction in FEV_1 is concerned we observed a significant placebo effect as previously reported [32].

In conclusion, formoterol, given by metered dose aerosol of 0.24 μg, is able to protect the majority of patients suffering from EIA for up to eight hours removing the necessity for repeating administration before every exercise.

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Effet protecteur et durée d'action d'une aérosol de formoterol sur l'asthme induit par l'effort. A. Patessio, A. Podda, M. Carone, N. Trombetta, C.F. Donner.

RÉSUMÉ: Nous avons comparé, chez 12 asthmatiques présentant de l'asthme d'effort, dans une étude en double aveugle contrôlée par placebo, au cours de trois périodes, avec permutation croisée, les effets protecteurs à court terme et la durée d'action du formoterol en aérosol doseur à raison de 24 µg en comparaison avec 200 µg de salbutamol et un placebo. A chaque jour de traitement, les patients ont reçu un des produits ou le placebo, et ont subi deux tests d'effort à la 2e et à la 8e heure après l'administration. L'effort a été réalisé sur tapis roulant selon un protocole standard, dans des conditions environnementales bien contrôlées. Lors du premier test à 2 h, une différence significative par rapport au placebo ($p<0.001$) a été observée à chaque période d'effort, c'est-à-dire 5, 10, 15, 20 et 30 minutes, à la fois avec le formoterol et le salbutamol, sans aucune différence significative entre ces deux produits. Après la 80 heure, le formoterol protège toujours contre l'asthme d'effort, par comparaison avec le salbutamol et le placebo. L'effet du salbutamol, à ce moment, n'est pas différent de celui du placebo. L'on n'a rencontré aucun effet collatéral dans aucun des groupes traités. La longue durée de protection obtenue par le formoterol contre l'asthme d'effort (8 h) permet d'éviter l'administration de bêta$_2$-agonistes avant chaque effort.
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