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Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children

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*The magnitude and duration of protection against exercise-induced asthma (EIA) afforded by salbutamol and the new, long-acting β_2 -agonist, formoterol, were compared in a double-blind, placebo-controlled crossover study. Twelve children with asthma and EIA (>25% fall from baseline at a pretrial exercise test) were studied on 3 different days receiving, in random order, either formoterol, 12 μ g, salbutamol, 200 μ g, or placebo by inhalation. The effect on EIA was evaluated by standardized treadmill-exercise tests repeated at the following times after medication: 1/2 hour (test 1), 3 hours (test 2), and, if the trial drug still demonstrated an effect, 5 1/2 hours (test 3) and 8 hours (test 4). The mean (SD) maximum percent fall in FEV₁ at the pretrial test was 45% (14%). Placebo treatment had no effect on EIA. The mean (SD) maximum percent fall in FEV₁ was 44% (14%) (test 1) and 39% (13%) (test 2) (not significant). Salbutamol offered good protection against EIA after 1/2 hour (percent fall in FEV₁, 18% [18%]; $p < 0.02$) but was not significantly different from that of placebo after 3 hours, 39% (13%) fall in FEV₁. Formoterol blocked EIA in all the children and demonstrated a significant effect in most children for at least 8 hours. The percent fall in FEV₁ after the various tests were 8% (16%) (test 1), 10% (9%) (test 2), 18% (15%) (test 3), and 18% (7%) (test 4; $N = 9$) (all tests, $p < 0.001$). The mean duration of a 50% reduction in EIA was 1 1/2 hours for salbutamol and 6 1/2 hours for formoterol ($p < 0.001$). No side effects were observed. Inhaled formoterol was determined to be more effective and offered four to five times longer protection against EIA than salbutamol. (*J ALLERGY CLIN IMMUNOL* 1992;89:1176-82.)*

Key words: Children, bronchial asthma, exercise-induced asthma, β_2 -adrenoreceptor agonist, long-acting

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EIA is common in children with asthma.^{1,2} Effective treatment of the condition is important to prevent the development of physical and psychosocial problems.^{3,4}

Inhaled β_2 -agonists are the drugs of choice for acute treatment of EIA. When these drugs are taken immediately before the exercise, they can reduce/pre-

vent EIA in most patients.^{5, 6} However, the value of the currently available β_2 -agonists is limited by a rather short duration of action.^{7, 8}

Formoterol fumarate is a new, long-acting β_2 -adrenoceptor agonist for inhalation⁹ that has been demonstrated to cause bronchodilation for 8 to 12 hours,^{10, 11} to prevent EIA for 4 hours,¹² and methacholine-induced bronchoconstriction for 12 hours.¹¹

To our knowledge, no double-blind, placebo-controlled studies on the effect of formoterol on EIA in children have been published at the present time. Therefore, the aim of the present study was to compare the protective effect and duration of action of inhaled formoterol, salbutamol, and placebo on EIA in children.

METHODS

Twelve boys, aged 8 to 15 years (mean, 12.6 years), with perennial asthma and EIA were selected for the study. The inclusion criterion was a fall in PEF or FEV₁ of at least 25% after exercise challenge. This finding was established by a pretrial exercise test not later than 2 weeks before entry.

All children used inhaled β_2 -agonists, three inhaled corticosteroids (200 to 400 μ g daily), one used oral sustained-release β_2 -agonist, and one child used sustained-release theophylline. Medication was stopped 8 hours (aerosols) and 24 hours (tablets) before each test day. Use of inhaled corticosteroids were continued unchanged throughout the trial.

Informed consent was obtained from all children and their parents, and the protocol was approved by the hospital ethics committee.

Study protocol

The children attended the clinic 8 to 9 AM on 3 separate study days. After lung function and HR measurements, the test medication was administered (five inhalations from residual volume) through a 750 ml cone spacer (volumatic) that had been primed with 10 puffs of salbutamol the day before (to reduce and standardize retention of trial medication in the new spacers).

Treatments consisted of two actuations, taken 30 seconds apart, from identical-looking pressurized aerosol cans delivering 6 μ g of formoterol, 100 μ g of salbutamol, or placebo per actuation. Treatments were assigned by random allocation. After a 30-minute rest, lung function and HR were reassessed, and a standard exercise test was performed. Thereafter, exercise challenge was repeated each 2½ hours to a maximum of four exercise tests. However, if the second exercise test demonstrated no protection against EIA (i.e., a response within 10% of the pretrial test), no further exercise test was performed that day. Thus, the individual patient could be subjected to 2 to 4 exercise tests on each of the 3 study days.

To be included in the analysis, baseline lung function had to be at least 70% of the normal predicted value or of the child's own "normal" value (two subjects). Furthermore,

Abbreviations used

EIA:	Exercise-induced asthma
HR:	Heart rate
PEF:	Peak expiratory flow
FEF ₂₅₋₇₅ :	Forced expiratory flow rate between 25% and 75% of forced vital capacity
AH:	Absolute humidity

baseline was not allowed to vary >20% on the 3 study days.

The study was performed during the winter season. The treatment code was not broken until all data had been analyzed statistically.

Exercise challenge

The exercise challenge consisted of 6 minutes of continuous treadmill running with a constant work load adjusted to produce a final HR of approximately 180 beats/min, measured by radiotelemetry. Individual work loads were reproduced in all challenges. However, if PEF decreased >40% from baseline during exercise, the test was stopped. With severe EIA, a rescue, inhaled β_2 -agonist, was administered, and the child was withdrawn from further exercise tests on that day. The children wore a noseclip during exercise. The AH (gram of H₂O per kilogram of dry air) was calculated from room temperature and relative humidity before each test.

Pulmonary function

Pulmonary function was evaluated by PEF, FEV₁, and FEF₂₅₋₇₅ (best of two readings) before aerosol treatment (before drug), immediately before exercise (after drug), every second minute during exercise (PEF only) and 1, 3, 5, 10, and 20 minutes after exercise or until a maximum fall had been observed. PEF was measured by Wright peak flow meter (Airmed Ltd., Harlow, England); FEV₁ and FEF₂₅₋₇₅ was measured by a waterless spirometer (Vitalograph Ltd., Buckingham, England). The pulmonary data were transformed to percent-predicted normal values.^{13, 14}

Calculation of responses

The bronchial responses to exercise were expressed as maximum percentage fall in lung function from the preexercise (after drug) value:

$$\text{EIA} = \frac{\text{Preexercise (after drug) value} - \text{Lowest postexercise value}}{\text{Preexercise (after drug) value}} \times 100\% \quad (1)$$

The degree of protection against EIA afforded by salbutamol and formoterol was calculated as the percentage reduction in EIA on the 2 active-treatment days (EIA a) compared with that of the individual EIA (mean of exercise tests 1 and 2) on the placebo-treatment day (EIA p):

$$\% \text{Protection} = \frac{\text{EIA p} - \text{EIA a}}{\text{EIA p}} \times 100\% \quad (2)$$

TABLE I. Mean (SD) values for HR before and after medicine, at end of exercise, and AH

	n	Test No.	HR (rest)		HR (final)	AH*
			bm	am		
Placebo	12	1	78 ± 10	81 ± 14	183 ± 6	6.8 ± 0.8
	10	2			182 ± 4	7.1 ± 1.0
Salbutamol	12	1	84 ± 12	90 ± 8 [†]	183 ± 5	6.6 ± 0.8
	12	2			182 ± 5	6.8 ± 0.8
Formoterol	12	1	78 ± 10	82 ± 13	182 ± 5	6.7 ± 0.7
	12	2			182 ± 5	6.7 ± 0.7
	12	3			183 ± 6	6.6 ± 0.7
	9	4			181 ± 5	6.5 ± 0.7
<i>p</i> Value			NS	NS	NS	NS

bm, Before medicine; am, after medicine; NS, not significant.

*Gram of H₂O per kilogram of dry air.[†]*p* < 0.01.**TABLE II.** Resting mean (SEM) PEF, FEV₁, and FEF₂₅₋₇₅ values (percent predicted) before and after medication

Lung function	Placebo			Salbutamol			Formoterol		
	Before drug	After drug		Before drug	After drug		Before drug	After drug	
		½ Hour	3 Hours*		½ Hour	3 Hours		½ Hour	3 Hours
PEF	77 (4)	81 (4) [†]	81 (5)	79 (3)	90 (4) [‡]	87 (5) [†]	78 (5)	93 (4) [‡]	94 (4) [‡]
FEV ₁	73 (2)	77 (3) [†]	76 (3)	78 (3)	93 (3) [‡]	87 (3) [‡]	73 (4)	91 (3) [‡]	92 (4) [‡]
FEF ₂₅₋₇₅	58 (3)	65 (4) [‡]	60 (2)	66 (4)	92 (5) [‡]	82 (4) [‡]	58 (5)	87 (5) [‡]	91 (6) [‡]

**n* = 10; Student's *t* test (before drug versus after drug):[†]*p* < 0.05.[‡]*p* < 0.001.

Percentage protection and the duration of a ≥50% protection was calculated individually for all patients (see Fig. 2). A ≥50% protection is normally considered a good and clinically relevant protection.

Statistical analysis

Student's paired *t* tests were used for comparison of the EIA data. Resting lung-function and HR data were analyzed by two-way analysis of variance. A two-tailed 5% level of significance was used.

RESULTS

Test conditions

Work loads ranged from 3.3 to 4.4 W/kg of body weight (mean, 3.5 W/kg). Mean values for resting HR, final heart rate, and AH are presented in Table I. There was no statistically significant difference in resting HR before medication. Salbutamol, 200 µg, but not placebo or formoterol, caused a statistically significant increase in resting HR (*p* < 0.01). HR at the end of exercise and AH did not vary significantly between the various treatment days. Room tempera-

ture was constant between 21° and 23° C (mean: 22.4° [placebo treatment], 22.4° [salbutamol treatment], and 22.6° C [formoterol]).

Resting pulmonary function

Mean values for PEF, FEV₁ and FEF₂₅₋₇₅ are presented in Table II. There was no statistically significant variation in the predrug baseline values on the 3 test days. Placebo caused small, but statistically significant, increases in PEF, FEV₁, and FEF₂₅₋₇₅. Salbutamol and formoterol both caused more pronounced and highly significant (*p* < 0.001) increases in all lung-function parameters. The within-drug ½-hour and 3-hour values were not statistically different.

The individual preexercise (after drug) FEV₁ values are presented in Table III. There was no difference in bronchodilation between salbutamol and formoterol treatment after ½ hour. At 3 hours, salbutamol still demonstrated a marked bronchodilatory effect compared with that of the predrug value (*p* < 0.001), but the bronchodilation was significantly lower than the bronchodilation after formoterol treatment

TABLE III. Individual FEV₁ values (percent predicted) in relation to repetitive exercise challenge tests after pretreatment with placebo, salbutamol, and formoterol

Pt No.	Placebo				Salbutamol					Formoterol								
	Test 1		Test 2		Test 1		Test 2		Test 3		Test 1		Test 2		Test 3		Test 4	
	B	% ↓	B	% ↓	B	% ↓	B	% ↓	B	% ↓	B	% ↓	B	% ↓	B	% ↓	B	% ↓
1	74	46	76	40	80	15	74	41	ND		88	5	76	- 3	82	27	84	24
2	86	72	ND		102	7	98	42	90	71	93	2	97	6	97	9	91	26
3	100	31	90	36	113	15	102	32	ND		106	8	113	10	113	15	104	15
4	68	40	70	34	99	10	92	50	80	56	99	- 2	104	8	103	10	103	12
5	81	70	73	62	88	35	83	53	ND		83	26	84	23	85	38	ND	
6	65	38	74	37	89	38	77	43	ND		82	1	87	12	82	17	79	27
7	77	35	79	33	100	13	90	38	ND		102	4	102	4	92	23	ND	
8	81	49	71	63	86	4	91	19	86	86	86	8	86	12	81	17	79	22
9	62	40	60	38	73	15	67	40	ND		74	11	71	6	73	11	68	13
10	81	35	92	31	105	- 2	102	11	102	30	102	2	105	3	93	3	100	9
11	75	25	75	20	85	4	78	27	ND		76	- 3	81	4	81	0	88	11
12	79	44	ND		94	62	89	73	ND		96	20	98	32	97	49	ND	
Mean	77	44	76	39	93	18	87	39			91	8	92	10	90	18	88	18
± SEM	3	4	3	4	3	5	3	5			3	3	4	3	3	4	4	2

Pt, Patient; B, baseline FEV₁ measured immediately before exercise; % ↓, maximal percentage fall from baseline; ND, not done.

The first exercise tests were performed ½ hour after pretreatment. Thereafter, an exercise test was performed every 2½ hours until the individual patient was no longer protected or until a maximum of four exercise tests had been reached.

($p < 0.05$). The broncodilation after formoterol treatment was still statistically significant ($p < 0.001$) at 8 hours. The changes in PEF and FEF₂₅₋₇₅ mirrored changes in FEV₁.

Pulmonary responses to exercise

The mean (SEM) preexercise baseline and lowest postexercise PEF values are illustrated in Fig. 1. As a group, the two exercise tests performed on the placebo-treatment day, 2½ hours apart, demonstrated similar responses. Salbutamol treatment offered good protection against EIA after ½ hour, but no significant protection after 3 hours. Formoterol treatment caused good protection against EIA for at least 8 hours. The mean (SD) percent fall in PEF before entering the study was 46% (16%) (not presented). The percent fall in PEF after placebo treatment was 45% (17%) (test 1) and 47% (18%) (test 2) (not significant). After salbutamol treatment, the percent fall in PEF was 15% (16%) (test 1, $p < 0.001$) and 40% (17%) (test 2, not significant). After formoterol treatment, the percent fall in PEF was 8% (6%) (test 1), 10% (8%) (test 2), 18% (13%) (test 3), and 18% (11%) (test 4) (all tests, $p < 0.001$) compared with that after placebo.

The individual baseline and percent fall values for FEV₁ are presented in Table III. The bronchial responses to exercise were similar to responses for PEF: (1) no effect of placebo treatment and no difference between test 1 and test 2 responses after placebo treat-

ment, (2) no significant protection for salbutamol treatment after 3 hours, and (3) statistically significant effect of formoterol treatment still after 8 hours. It should be noted that at ½ hour (test 1), salbutamol was without any effect in two patients (Nos. 6 and 12). At 3 hours (test 2), some protection was demonstrated by salbutamol in only three patients (Nos. 2, 8, and 10). None of these were protected at 5½ hours (test 3).

Two patients did not perform exercise test 2 on the placebo-treatment day because they developed severe EIA after test 1 and therefore had to be treated with an inhaled β_2 -agonist.

The individual values for percentage protection against EIA are presented graphically in Fig. 2. The results are based on the FEV₁ percent fall values in Table III and calculated by means of equation No. 2. Formoterol was superior to salbutamol treatment throughout the study. At ½ hour, formoterol treatment demonstrated a mean (SD) percent protection of 83% (18%) compared with 61% (33%) for salbutamol treatment ($p < 0.02$). At 3 hours, the mean percent protection afforded by formoterol and salbutamol treatment was 76% (19%) and 17% (26%) ($p < 0.001$), respectively. Salbutamol treatment demonstrated no effect in the few patients who received exercise test 3. Formoterol treatment continued to be active against EIA for 5½ and 8 hours in most patients with a mean percent protection of 60% (30%) and 57% (14%),

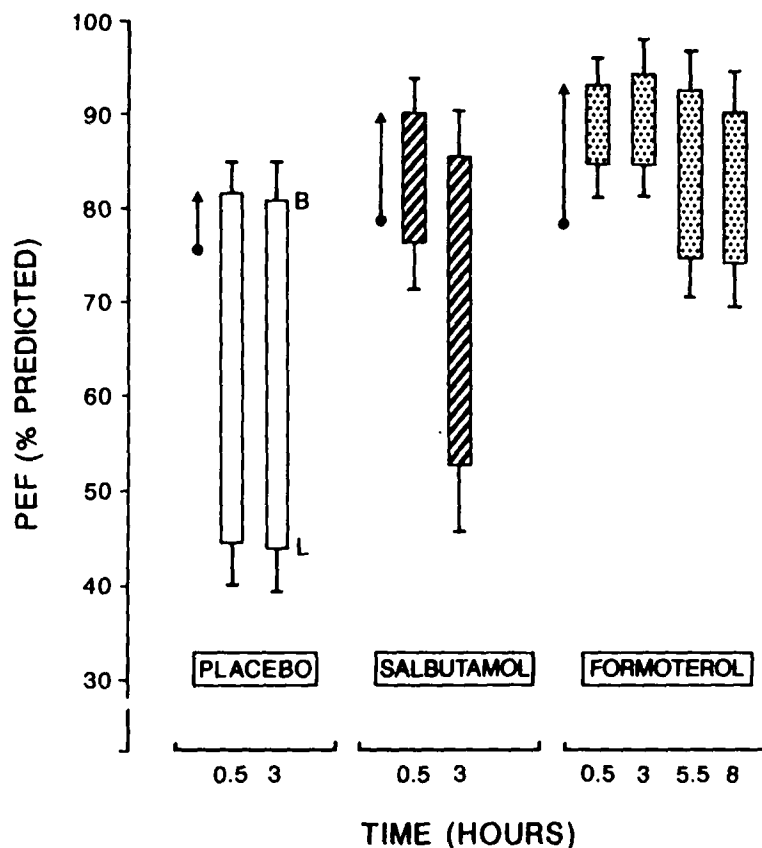


FIG. 1. Mean (SEM) PEF values before and after repeated exercise challenge in children with asthma. Results of pretreatment with inhaled placebo, salbutamol, 200 μ g, and formoterol, 12 μ g; $\uparrow$, change in baseline after drug; B, preexercise baseline value; L, lowest recorded value after exercise.

respectively. Finally, the mean (range) time for a 50% protection against EIA was 385 (80 to >480) minutes for formoterol treatment and 86 (0 to 200) minutes for salbutamol treatment ($p < 0.001$).

The exercise-induced changes in FEF_{25-75} (not presented) were similar to changes reported for PEF and FEV_1 , except that the duration of protection against EIA was $\frac{1}{2}$ to 1 hour shorter.

DISCUSSION

Potent bronchodilators are not always effective against induced bronchoconstriction, such as EIA. This finding has been demonstrated with cholinergic antagonists.^{15,16} With respect to the currently available β_2 -agonists, most studies have revealed no relationship between the bronchodilating effect and the protective effect against EIA,^{6,15,17,18} although this discordance in action may vary with the β_2 -agonist studies.¹⁹ Furthermore, with the exception of the latter study,¹⁹ the effect of β_2 -agonists on EIA is usually shorter than the duration of bronchodilation. This finding was also the case in the present study; salbutamol

treatment still caused bronchodilation after 3 hours, but the effect on EIA had disappeared. In contrast, formoterol treatment both caused long-lasting bronchodilation and protection against EIA. These effects were maintained for at least 8 hours in most patients. These findings are in agreement with the results from methacholine-induced bronchoconstriction¹¹ and extend the results of a recent study on EIA in adults.¹² In the latter study, patients with mild EIA were protected by formoterol treatment for 4 hours.

When the duration of effect of two different drugs is compared, it is important to use submaximal doses that produce the same responses; otherwise, differences in duration of action may be due solely to a difference in dose. In this respect, 100 μ g of salbutamol has previously been found equipotent to 6 μ g of formoterol.¹⁰ In the present study, we compared the usually recommended dose of salbutamol (200 μ g) with 12 μ g of formoterol. These doses of the two drugs produced the same degree of initial bronchodilation, but as with previous studies,^{10,11} formoterol

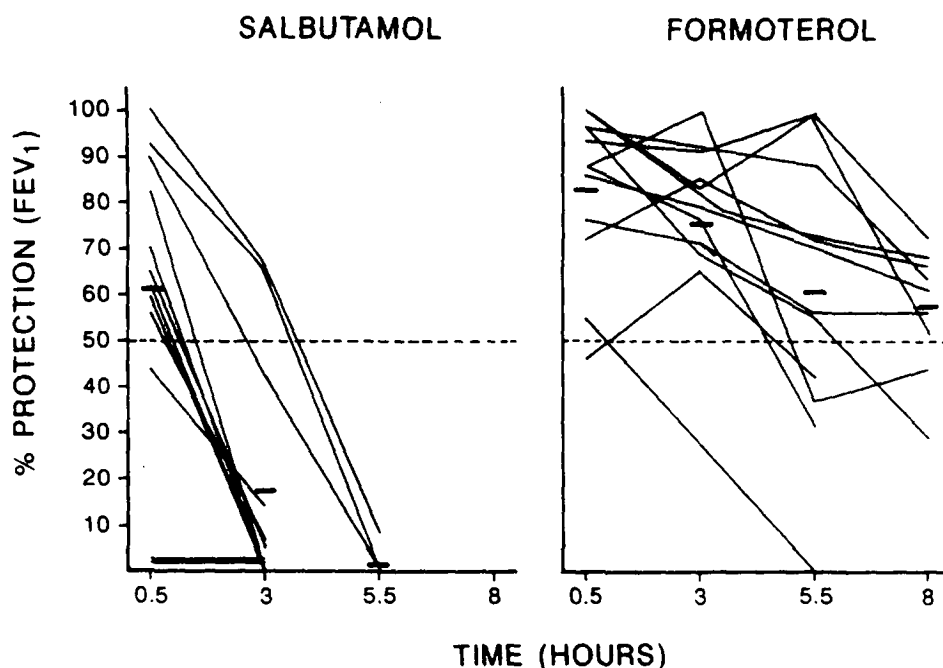


FIG. 2. Individual FEV₁ values for percentage protection against EIA afforded by inhaled salbutamol and formoterol. Time for eliciting a 50% protection can be read on the x axis by extrapolation; bars denote the mean percent protection at moments for scheduled exercise tests.

treatment maintained the bronchodilatation much longer than salbutamol treatment. No side effects were reported, but salbutamol increased HR significantly. The increase in HR after formoterol treatment was a little less and was not significant. Therefore, we believe that the different duration of action afforded by formoterol and salbutamol was due to a difference in mode of action and not to a difference in dose in favor of formoterol.

An episode of EIA may be followed by a refractory period during which repeated exercise will provoke less EIA.^{20, 21} It might be argued that the long-term reduction in EIA after formoterol treatment was due to refractoriness rather than to the effect of formoterol. However, this appears unlikely. The interval between our tests was 2½ hours, and the recovery to bronchoconstrict fully after EIA occurs normally within 2 hours.^{22, 23} Furthermore, we found no evidence of refractoriness on the placebo-treatment day or on the salbutamol-treatment day, and there is no evidence that refractoriness is more likely to occur after a fourth than after a second exercise test.^{19, 23}

We tried to blind the study by giving the medication in a randomized sequence and only studying a few patients per day. However, even if there were some improvement in lung function after placebo treatment (probably because of a spontaneous increase in airway caliber after the morning dip usually observed in sub-

jects with asthma), the magnitude of this increase was so small that it was difficult to make the placebo-treatment day completely blind. In contrast, the differences in bronchodilation between salbutamol and formoterol treatment were so small and variable that the blinding between these two drugs cannot be questioned. Even with the difficulties of blinding, we found it important to include placebo to document that the exercise challenge could be reproduced after 2½ hours without attenuation of the response. Furthermore, the placebo results also allowed us to weigh the effect of the two active drugs clinically and to determine a precise evaluation of the duration of action against EIA by means of percentage protection.

The finding of a statistically significant effect of a drug on EIA does not necessarily indicate that the effect is clinically important. Therefore, we also evaluated the duration of a 50% protection against EIA, because such protection indicates good *clinical* control of the condition. Using this measure, we found that formoterol treatment offered four to five times longer clinically relevant protection against EIA than salbutamol treatment. Salbutamol treatment failed completely in two patients and elicited a 50% protection for only 1½ hours. This time is shorter than the 3 to 4 hours found in previous studies.^{19, 24} However, if we had chosen a 20% protection level, the duration of action of salbutamol would have been 2½ hours, but

a 20% protection is definitely less important from the patients point of view.

The place of formoterol in the day-to-day management of asthma in children still remains to be established. However, the present results suggest that inhaled formoterol may become an important advance in the management of EIA.

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