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The protective effect of low-dose inhaled fenoterol against methacholine and exercise-induced bronchoconstriction in asthma: A dose-response study

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*We compared in a randomized, double-blind study the protective effect of low doses of fenoterol on the airway response to exercise during cold air breathing and an inhalation challenge with methacholine. In six asymptomatic asthmatic persons (mean age, 20.3 years) exercise and methacholine challenges were performed under control conditions and 15 minutes after the inhalation from a metered-dose inhaler of either placebo or 30, 50, 100, and 200 μ g fenoterol, resulting in 12 separate study sessions within a 3-week period. Airway response was determined by measuring specific airway resistance (sRaw). Exercise tests were standardized by maintaining a constant respiratory heat exchange, with an average (range) of 1.28 (1.15 to 1.45) kcal/min. Methacholine was inhaled at increasing doses until sRaw had doubled ($PD_{100sRaw}$). Mean postexercise increase of sRaw (SD) after control conditions, placebo, and 30, 50, 100, and 200 μ g fenoterol aerosol was 27.8 (6.9), 28.9 (10.0), 7.20 (2.7), 9.33 (3.8), 5.57 (2.3), and 5.28 (1.6) cm $H_2O \cdot s$. Fenoterol aerosol was equally effective at all doses administered, whereas methacholine-induced bronchoconstriction was attenuated in a dose-dependent manner. From these observations we suggest that low-dose fenoterol protects against bronchoconstriction induced by exercise, a naturally occurring stimulus reflecting airway hyperresponsiveness. (*J ALLERGY CLIN IMMUNOL* 1992;90:846-51.)*

Key words: Asthma, exercise, low-dose fenoterol, airway hyperresponsiveness

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Fenoterol aerosol is a selective and widely used β_2 -adrenoceptor agonist, usually inhaled from a metered-dose inhaler, with one puff containing 200 μ g (Berotec; Boehringer Ingelheim, Ingelheim am Rhein, Germany) or 100 μ g (Berotec mite). Both doses of fenoterol produce effective bronchodilation and protect against a variety of stimuli.¹⁻⁵ However, because

Abbreviations used

EIB:	Exercise-induced bronchoconstriction
sRaw:	Specific airway resistance
PD ₁₀₀ sRaw:	Cumulative provocative dose of methacholine necessary to increase sRaw by 100%
Cbu:	Cumulative breath unit

these doses may be associated with cardiovascular side effects and tremor, it would be preferable to provide bronchodilation and protection at lower doses. We therefore performed a double-blind, placebo-controlled study in subjects with mild asthma to determine, on separate study days, the effect of low doses of inhaled fenoterol against methacholine and exercise-induced bronchoconstriction (EIB). We have chosen these two stimuli because methacholine is widely used as a bronchoconstricting agent for assessing airway responsiveness in the clinical laboratory, whereas exercise during cold air breathing represents a naturally occurring stimulus for asthmatic subjects.

MATERIAL AND METHODS**Patients**

Six persons with mild stable asthma (4 women; age range, 16 to 24 years; forced expiratory volume in 1 second [FEV₁] >80% pred) participated in the study. None of them required regular medication during the course of the study, and the intermittent use of inhaled β_2 -adrenoceptor agonists was withheld at least 12 hours before the study sessions. All subjects complained of shortness of breath after physical exercise. All patients were hyperresponsive to inhaled methacholine and had an increase in specific airway resistance (sRaw) of at least 100% after standardized exercise challenge. In each individual, the dose of methacholine and the work load, necessary to increase sRaw compared with baseline by 100%, were determined before they entered the study.

Lung function measurement

Lung function was measured by a body plethysmograph (Bodytest. E. Jaeger, Würzburg, Germany) during quiet breathing. Airway resistance was determined from at least three pressure-flow loops and multiplied by the corresponding thoracic gas volume to calculate sRaw.

Methacholine challenges

Airway responsiveness to methacholine was determined according to the method of Chai et al.⁶ After inhaling saline solution, doubling concentrations of methacholine were administered, starting with 0.0075 mg/ml. Each concentration was given during five deep inhalations by a nebulizer (DeVilbiss no. 646; DeVilbiss Co., Somerset, Pa.) with an output of 0.011 ml per activation. Lung function was mea-

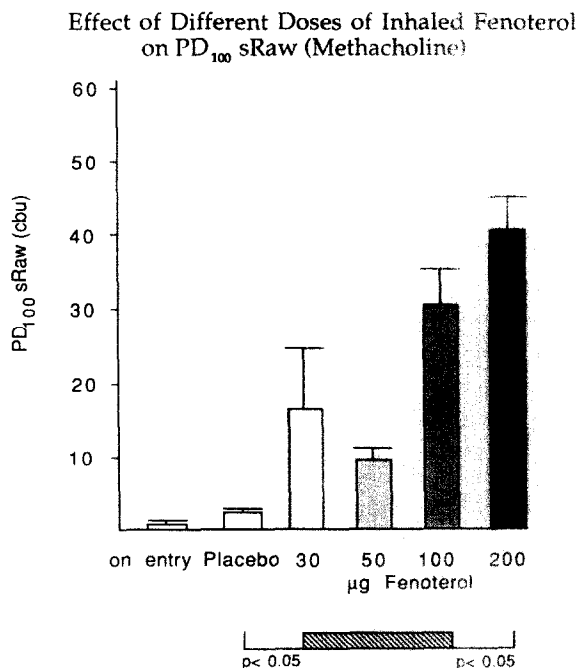


FIG. 1. Mean values of sRaw, (in cm H₂O · s) on entry into the study and before administration of fenoterol or placebo aerosol (*B*, baseline), 15 minutes after inhaling the aerosol (*P*, prechallenge), and maximum values after the standardized exercise challenge (*Max*).

sured 3 minutes after inhalation. One breath of methacholine, at a concentration of 1 mg/ml, was defined as 1 breath unit. The cumulative provocative dose of methacholine, PD₁₀₀sRaw, in cumulative breath units (cbu) necessary to increase sRaw by 100% compared with values measured after saline inhalation was determined by plotting sRaw against log of cumulative doses of methacholine.

Exercise challenge

Cold air was provided by passing room air through a heat exchanger. This set-up provided a constant temperature of inspired air (−15°C) at ventilation rates up to 80 L/min. Patients inhaled cold air through a temperature-insulated two-way valve, and expired air was directed through a pneumotachygraph (Fleisch no. 3; Gould Medical BV, Bilt-hoven, The Netherlands). Ventilation was calculated through integration of flow over time, and the temperature of inspired and expired air was measured through separate temperature probes. Respiratory heat exchange, as a measure of airway cooling and drying during exercise, was calculated from the following formula⁷:

$$\text{RHE} = V_E \cdot (\text{HC} \cdot (T_i - T_e) + \text{HV} \cdot (\text{WC}_i - \text{WC}_e))$$

RHE, respiratory heat exchange (kcal/min); V_E , minute ventilation in L/min; HC, heat capacity of air = 0.304 cal/L per °C; T_i , inspired air temperature in degrees Celsius; T_e , expired air temperature in degrees Celsius; HV, latent heat of vaporization of H₂O = 0.58 kcal/gm; WC_i , water

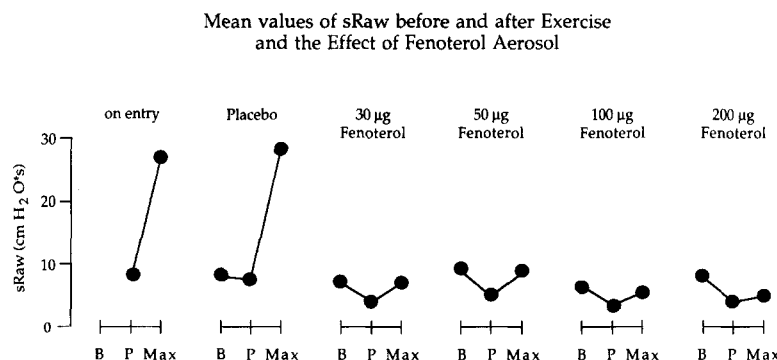


FIG. 2. Median and 75% percentile values of PD₁₀₀sRaw of methacholine (in cbu) on entry into the study and after inhalation of fenoterol or placebo aerosol. Hatched area indicates values not significantly different from each other.

content of the inspired air in mg H₂O/L air; WC_e, water content of the expired air in milligrams H₂O/L air.

After measuring prechallenge values, patients breathed cold air for 4 minutes at rest, exercised at their predetermined level for 4 minutes, and then recovered for 4 minutes while still breathing cold air. Lung function was measured 3, 10, 15, and 30 minutes after the end of the cold air breathing. Airway response to exercise was quantified as the maximum increase of sRaw measured after the challenge as compared with the prechallenge values.

Study design

The study was performed as a randomized, double-blind, placebo-controlled clinical trial. Exercise and methacholine challenges were performed in random order. Volunteers for the study signed their written consent on entry.

All medications were given as single puffs from a metered-dose inhaler. On a first selection day, the airway responsiveness to inhaled methacholine was determined. On each of the five methacholine study days lung function measurements were performed before (baseline) and 15 minutes after (prechallenge) inhalation of either placebo or one of the four fenoterol doses. Subsequently, methacholine challenges were performed.

On a second selection day the airway response to exercise was determined. Constant exercise conditions were maintained for each individual throughout the study. At each of the 5 exercise study days, after measuring baseline lung function, the test medication was inhaled, followed by another lung function measurement 15 minutes afterward (prechallenge values). Immediately afterward, the exercise challenge was performed. In all subjects recovery to baseline values was fast, and there was no need for giving an inhaled β_2 -adrenoceptor agonist aerosol for bronchodilation.

Statistical analysis

Data were analyzed by two-way analysis of variance (ANOVA). Differences between treatments were analyzed with the Newman-Keuls multiple range test and a *t* test, as linear contrast between the PD-values measured after 200 μ g and the average of the values after the lower doses of fenoterol.⁸ Log values were taken for PD₁₀₀sRaw and ab-

solute and relative values for differences between maximum postexercise and prechallenge values. Baseline values were compared by the same test, and bronchodilation was analyzed by comparing the relative changes between baseline and prechallenge values. Statistical significance was assumed for *p* < 0.05.

RESULTS

All patients in this study had a normal or slightly increased baseline sRaw (mean, 8.66 ± 2.80). On entry into the study, geometric mean (SD) PD₁₀₀sRaw of methacholine was 1.15 (5.18) cbu (Table I), and mean (SD) maximal increase of sRaw after exercise was 27.8 (6.9) cm H₂O · s (Table II). Baseline values on entry into the study and on the actual study days were not statistically different from each other.

Effect of fenoterol aerosol and placebo on airway tone

Compared with baseline, all doses of fenoterol aerosol provided a significant bronchodilation measured 15 minutes after the inhalation of the drug (*p* < 0.05). The mean (SD) decrease of sRaw after placebo was 0.5% (26%), and the mean (SD) decrease after 30, 50, 100, and 200 μ g fenoterol was 46% (15), 31% (20), 38% (19), and 41% (10), respectively. No significant difference occurred between the bronchodilator effect of the different doses of fenoterol aerosol.

Effect of fenoterol aerosol and placebo on methacholine challenges

Geometric mean (SD) PD₁₀₀sRaw after placebo, 30, 50, 100, and 200 μ g fenoterol was 2.2 (1.6), 17.3 (1.8), 10.2 (1.3), 24.2 (1.9), and 36.8 (2.0) cbu, respectively (Table I, Fig. 1). Compared with placebo, inhalation of fenoterol aerosol provided a significant protection against methacholine challenge at every dose examined (*p* < 0.05). Placebo values were not

TABLE I. Individual and geometric mean values (SD) of PD₁₀₀sRaw of methacholine (cbus)

Patient	On entry	Placebo	µg Fenoterol			
			30	50	100	200
1	1.12	1.41	6.68	11.9	28.2	39.8
2	0.08	3.16	16.8	9.72	17.8	44.7
3	0.94	2.81	15.0	8.91	42.2	42.2
4	1.58	1.26	16.8	7.94	7.94	12.6
5	1.26	1.99	37.6	15.8	35.5	99.4
6	14.1	3.98	25.1	8.91	33.5	26.6
Mean	1.15	2.24	17.3	10.2	24.2	36.8
SD	5.18	1.58	1.78	1.29	1.86	1.97

TABLE II. Maximum increase of sRaw after exercise challenge (cm H₂O*s)

Patient	On entry	Placebo	µg Fenoterol			
			30	50	100	200
1	21.9	35.9	4.76	4.52	2.59	5.31
2	27.8	38.4	5.40	11.0	7.50	6.00
3	35.0	24.8	4.25	7.76	3.49	2.73
4	24.7	23.5	6.96	13.3	5.34	7.35
5	37.1	41.2	5.61	6.09	5.96	5.95
6	20.4	15.8	7.66	13.3	8.54	4.35
Mean	27.8	28.9	7.20	9.33	5.57	5.28
SD	6.89	10.0	2.70	3.75	2.28	1.59

statistically different from those on entry of the study. No statistical difference occurred between the doses of 30, 50, and 100 µg, but 200 µg fenoterol aerosol was more effective than the three lower doses ($p < 0.05$).

Effect of fenoterol aerosol and placebo on exercise challenges

Table III summarizes the respiratory heat exchange and minute ventilation of each subject together with the work load applied on the 5 study days. The overall mean (range) respiratory heat exchange was 1.28 (1.15 to 1.45) kcal/min, and the mean (range) minute ventilation was 47.9 (43.2 to 54.9) L/min. Mean (SD) maximum increase after exercise was 28.9 (10.0) cm H₂O after placebo, and 7.2 (2.7), 9.3 (3.8), 5.6 (2.3), and 5.3 (1.6) cm H₂O · s for 30, 50, 100, and 200 µg fenoterol, respectively (Table II, Fig. 2). Placebo values were not statistically different from those on entry into the study. Compared with placebo, inhalation of fenoterol aerosol provided a significant protection against exercise challenge at every dose examined ($p < 0.05$). No statistical difference was observed between the different doses of fenoterol

aerosol, and this applied for both absolute and relative maximum changes after exercise.

DISCUSSION

Our results demonstrate that fenoterol aerosol significantly protects against methacholine-induced bronchoconstriction and EIB in persons with mild asthma, even at doses that are considerably lower than those usually recommended. Furthermore, the ability of fenoterol aerosol to protect against methacholine-induced bronchoconstriction was dose dependent, whereas similar protection against exercise challenge was seen at all doses studied, although these two challenges are probably not directly comparable.

Beta₂-adrenoceptor agonists protect against almost all bronchoconstricting stimuli,⁵⁻⁹ and they are the most effective drugs to protect against EIB.¹⁰ A number of dose-response studies on the effect of β₂-adrenoceptor agonists on models of bronchial hyperresponsiveness have been carried out,^{1, 11-15} but little information exists on low-dose ranges of β₂-agonists in EIB and hyperventilation-induced bronchoconstriction. O'Byrne et al.¹⁶ demonstrated that terbutaline has a dose-dependent effect against EIB, and Malo et

TABLE III. Individual data of exercise challenge

Patient	Work load (watt)	RHE (kcal/min)		Minute ventilation (L/min)	
		Mean	Range	Mean	Range
1	160	1.37	1.33-1.42	51.5	50.1-53.3
2	180	1.21	1.15-1.27	45.1	43.4-46.9
3	150	1.22	1.15-1.35	45.2	43.2-46.8
4	150	1.34	1.16-1.24	45.4	43.6-46.5
5	120	1.20	1.16-1.24	45.4	43.6-46.5
6	200	1.32	1.26-1.37	49.7	47.5-52.0
Mean		1.28		47.9	
SD		0.07		2.9	

al.¹⁷ described a dose-dependent duration of protection for two doses of terbutaline (500 vs 1500 μg) against hyperventilation challenges with dry cold air in eight adults with asthma. Fenoterol aerosol protects against EIB at doses of 200 μg ,³ and Bundgaard et al.¹⁸ showed that the protective effect of fenoterol dry powder or aerosol on EIB was not dose-dependent at 200 and 400 μg .

Airway hyperresponsiveness in persons with asthma is usually measured against histamine and methacholine challenges. Although EIB also reflects the hyperresponsive status of the airways, it does not represent a clinical problem in all asthmatic patients.¹⁹ It has been shown by some investigators that the degree of hyperventilation and exercise-induced asthma has only a weak correlation with airway responsiveness to histamine and methacholine,²⁰⁻²² whereas O'Byrne et al.²³ and Heaton et al.²⁴ find a strong correlation between PD₃₅ to cold air, histamine, and methacholine and the PD₁₀ RHE and PC₂₀ methacholine.^{23, 24}

The rationale of this study was to evaluate—on an intraindividual basis—the dose-response characteristics of an inhaled β_2 -adrenoceptor agonist at low doses against two different stimuli. We decided to test the protective ability of low-dose inhaled fenoterol against the naturally occurring stimulus “exercise” under standardized conditions, rather than extrapolating the usefulness of low-dose formulations from data obtained with histamine or methacholine challenges. By using this experimental approach we are fully aware of the problem that the airway response to methacholine is measured in a dose-dependent fashion, whereas exercise was always performed at the same level. Therefore the information derived from these different protocols is not strictly comparable. If the methacholine data are analyzed in a fashion similar to the exercise experiments, that is, comparing the effect of low-dose fenoterol against a fixed concen-

tration of methacholine, the protective effect is still detectable for all fenoterol concentrations ($p < 0.05$). Because low-dose fenoterol shifts the methacholine dose-response curve considerably, calculations by use of the highest comparable methacholine dose in each patient will not detect any dose-dependent effects as they become more apparent at higher methacholine doses that can only be administered in patients under fenoterol.

Although it was not intended to study the effects of low doses of fenoterol aerosol on airway tone in persons with mild asthma, we observed that fenoterol aerosol not only protects against methacholine and EIB, even at doses of 30 μg —approximately 15% of the recommended single dose for inhalation—but also provides a significant effect on bronchial tone. The effect on bronchial tone was not dose-dependent, which may seem contradictory to the findings with salbutamol by Britton et al.¹¹ and Higgins et al.¹² However, our subjects had no or mild airway obstruction, as demonstrated by a mean baseline sRaw of 8.7 cm H₂O $\cdot$ s, whereas the subjects of Britton et al.¹¹ were in the mean moderately obstructed, indicated by sRaw in the range of 0.05 to 0.06 kPa⁻¹ $\cdot$ s⁻¹. Since in subjects with mild or no airway obstruction only a small effect of bronchodilators is achievable, a dose-dependent effect is unlikely. At present much concern exists about the side effects of inhaled β_2 -adrenoceptor agonists,²⁵ in particular when administered at multiples of the recommended doses or when inhaled on a regular rather than on a symptom-oriented basis.^{26, 27} None of our patients complained of any side effects at the dose range applied, which is in accordance with the findings of Wong et al.²⁶

From our results we conclude that fenoterol aerosol is an effective measure to protect against EIB and methacholine-induced bronchoconstriction even at doses that are three to six times lower than those routinely recommended for asthma treatment. In stan-

standardized exercise challenges even low doses of fenoterol aerosol provide maximal protection, and therefore formulations of 50 and 100 µg seem sufficient for the protection of mild asthmatic patients with exercise-induced asthma.

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