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EFFECT OF LONG-TERM SALMETEROL TREATMENT ON EXERCISE-INDUCED ASTHMA

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ABSTRACT

Background With long-term administration of salmeterol, the extent of protection afforded by the drug against experimental precipitants of asthma such as methacholine and adenosine may decrease. Whether this effect extends to a clinically relevant stimulus such as exercise is unknown.

Methods We performed a random-order, double-blind, crossover trial in 20 patients with exercise-induced asthma. Each patient received inhaled salmeterol or placebo twice daily for a month, with a one-week washout period between treatments. The patients performed cycle ergometry while breathing frigid air 30 minutes after the morning dose and 9 hours later on the 1st, 14th, and 29th study days. The primary end point was the extent of the decrease in forced expiratory volume in 1 second (FEV₁) 10 minutes after exertion.

Results With placebo, significant airway narrowing developed at all times (mean [\pm SE] decrease from base line in FEV₁, 19 \pm 2 percent in the morning and 18 \pm 2 percent in the evening). The morning dose of salmeterol attenuated the degree of bronchoconstriction at all times (decrease in FEV₁ on day 1, 5 \pm 2 percent; on day 14, 10 \pm 3 percent; and on day 29, 9 \pm 3 percent; P=0.10). Its ability to act throughout the day, however, decreased with long-term administration (decrease in FEV₁ from morning to evening on day 1, 6 \pm 2 percent; on day 14, 15 \pm 3 percent; and on day 29, 14 \pm 3 percent; P=0.003).

Conclusions Protection against exercise-induced asthma is maintained with long-term administration of salmeterol, but the length of time that the drug remains active after a single dose decreases. (N Engl J Med 1998;339:141-6.)

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SELECTIVE β_2 -adrenergic agonists are widely used to treat acute episodes of asthma, and long-acting drugs of this type such as salmeterol are often given to prevent the bronchial narrowing that occurs at night¹ or after exercise.² However, there has been concern that long-term therapy with these agents may worsen the disease³ and minimize the body's defense against irritant stimuli.⁴⁻⁷ A multicenter trial showed that long-term treatment does not exacerbate asthma,⁸ but whether therapeutically important tachyphylaxis develops to the prophylactic action of the drugs remains to be settled.⁹ Unfortunately, studies reporting tachyphylaxis used provocations either that patients would not encounter in their daily lives (e.g., histamine, methacholine, and adenosine)⁴⁻⁶ or for which β_2 -adrenergic agonists would not be given as primary therapy (i.e., antigen).⁷ We undertook the present study to determine whether salmeterol and similar drugs lose the ability to protect against events such as exercise that initiate asthma — events for which these drugs would ordinarily be prescribed.

METHODS

We studied 20 nonsmoking patients (11 women and 9 men) with exercise-induced asthma and a mean (\pm SD) age of 29 \pm 9 years (Table 1). The patients were enrolled between November 1995 and December 1996. Exercise-induced asthma was considered to be present if a patient had symptoms of airway obstruction after exertion that were associated with a decrease in the forced expiratory volume in one second (FEV₁) of 15 percent or more from the base-line value. None of the patients had upper respiratory tract infections or had taken any glucocorticoid orally

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TABLE 1. CHARACTERISTICS OF 20 PATIENTS WITH EXERCISE-INDUCED ASTHMA.*

CHARACTERISTIC	VALUE
Sex (M/F)	9/11
Age (yr)	29±2
Workload (kilopond meters/min)	740±55
FEV ₁	
Liters	3.20±0.20
Percent of predicted value	93±3

*Plus-minus values are means ±SE. FEV₁ denotes forced expiratory volume in one second.

TABLE 2. MINUTE VENTILATION AND TEMPERATURE OF INSPIRED AIR DURING EACH CHALLENGE IN 20 PATIENTS WITH EXERCISE-INDUCED ASTHMA.*

STUDY DAY	SALMETEROL		PLACEBO	
	MORNING	EVENING	MORNING	EVENING
Minute ventilation (liters/min)				
1	56±4	55±4	61±4	58±4
14	54±3	57±3	58±4	57±3
29	53±4	55±3	53±3	52±3
Temperature of inspired air (°C)				
1	-8±1	-9±2	-7±1	-9±2
14	-9±1	-9±1	-9±1	-9±3
29	-7±1	-9±1	-5±1	-9±2

*Plus-minus values are means ±SE.

in the six weeks before the study. The investigation was a random-order, double-blind, crossover trial in which the patients took two puffs (42 µg) of salmeterol (Serevent, Glaxo Wellcome, Research Triangle Park, N.C.) twice daily or a placebo from identical canisters (Glaxo Wellcome) for one month. The study phases were separated from one another by one-week washout periods. At the crossover point, the patients were reexamined to ensure that their exercise response was similar to that recorded at base line. No significant differences were found (maximal decrease [±SE] in FEV₁ at the first screening, 24±2 percent; maximal decrease in FEV₁ at the second screening, 26±4 percent; P=0.58).

Inhaled glucocorticoid and methylxanthine therapy was permitted if the doses of these agents had been stable during the month preceding enrollment and remained constant throughout the trial. Albuterol was given to patients who had breakthrough symptoms. All treatment other than salmeterol or placebo was withheld for a minimum of 12 hours before any study day, and long-acting methylxanthine compounds were withheld for 24 hours. The protocol was approved by the institutional review board for human investigation, and all patients gave informed consent.

At base line, the patients performed four minutes of exhausting work on a cycle ergometer while breathing frigid air.¹⁰ The workloads were chosen on the basis of their ability to cause a reduction in FEV₁ of 15 percent or more at any time during the first 20 minutes after exertion, and once established, they were held constant for each patient during the study. During cycling, the pa-

tient exhaled into a calibrated dry gas meter so that minute ventilation could be continuously recorded.¹⁰ The temperature of the inspired air was also measured. Recovery occurred under ambient room conditions.¹¹

On the 1st, 14th, and 29th days of each study month, the patients came to the laboratory early in the morning without taking their study drug. Forced exhalations were performed in triplicate¹² before and 30 minutes after inhalation of the morning dose. The first exercise challenge then commenced, after which spirometry was serially recorded for 60 minutes. The degree of obstruction 10 minutes after the cessation of exercise was taken as the morning response. The curves with the largest FEV₁ were chosen for analysis. A second exercise challenge was undertaken nine hours later (in the evening). The second dose of salmeterol or placebo on this day was taken in the usual fashion when the patients returned home.

The data were analyzed with repeated-measures analyses of variance, paired t-tests, and chi-square tests.¹³ All statistical tests were two-sided. No effect of the order of treatments was found, and therefore all results were combined.

RESULTS

The mean (±SE) FEV₁ at the first visit was 93±3 percent of the predicted value, and the workload averaged 740±55 kilopond meters per minute (Table 1). At base line, 13 patients were taking nebulized albuterol as needed and 6 required both a daily β₂-adrenergic agonist and an inhaled glucocorticoid; 1 of these 6 patients was also taking a methylxanthine. The remaining patient took nedocromil daily.

The mean values for minute ventilation ranged from 52±3 to 61±4 liters per minute (P=0.69), and the temperature of inspired air ranged from -5±1 to -9±3°C (P=0.11) during the study (Table 2). Before challenge, the FEV₁ ranged from 90±3 to 98±3 percent of the predicted value (P=0.91). There were no significant differences within or among the days of study or between the salmeterol or placebo period for any of the variables shown in Table 2 and Figure 1.

The absolute effects of salmeterol and placebo are shown in Figure 2, and the relative effects are shown in Figure 3. The relative effects are provided to compensate for temporal shifts in the base-line values. With placebo, the mean decrease in FEV₁ was 19±2 percent in the morning and 18±2 percent in the evening (P<0.001 for all individual comparisons). There were no significant differences in results between challenges at any time (P=0.94). Salmeterol attenuated (P<0.001) but did not abolish the bronchial narrowing (P<0.01 for all comparisons with base-line values). The prophylactic benefit after the morning dose remained constant throughout the trial (decrease in FEV₁ on day 1, 5±2 percent; on day 14, 10±3 percent; and on day 29, 9±3 percent; P=0.10). The duration of action of the drug, however, shortened with long-term use. By the end of the second week, the extent of protection recorded in the evening was less than that on day 1 (decrease in FEV₁ from morning to evening on day 1, 6±2 percent; and on day 14, 15±3 percent; P=0.003),

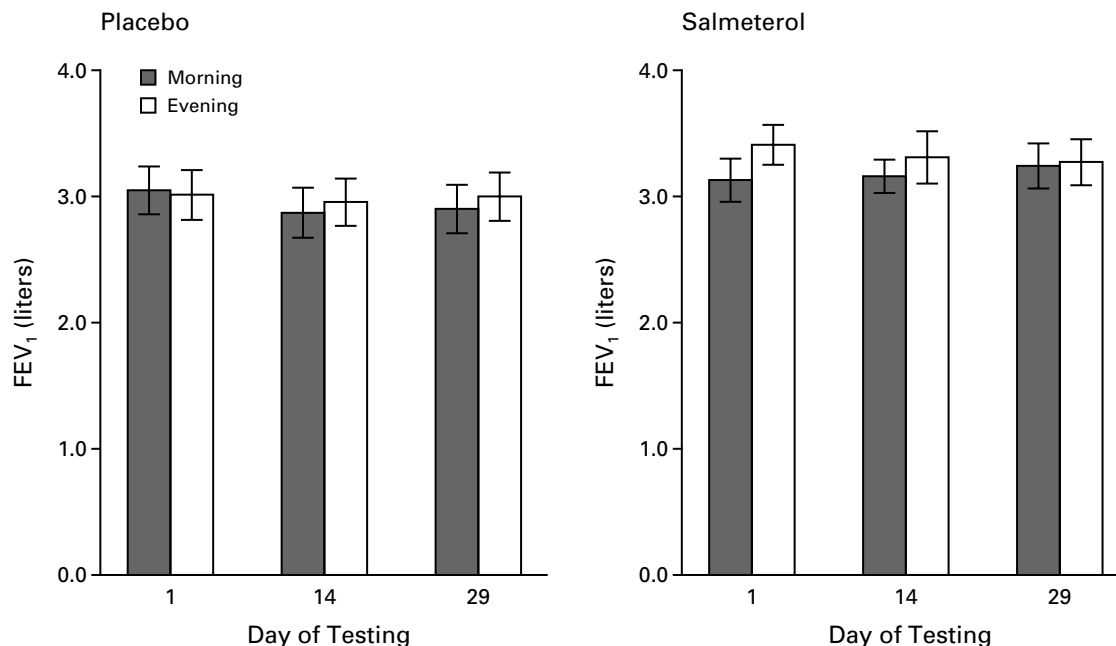


Figure 1. Mean (\pm SE) Forced Expiratory Volume in One Second (FEV_1) at Base Line on Each of the Test Days of Administration of Placebo and Salmeterol.

The morning values were recorded before the administration of the study drugs, and the evening data were obtained immediately before challenge.

but it was still slightly better than the protection afforded by placebo ($P=0.02$). Although no further changes occurred during the subsequent two weeks (decrease in FEV_1 from morning to evening with salmeterol on day 29, 14 ± 3 percent; $P=0.61$ for the comparison with day 14), the differences between salmeterol and placebo disappeared ($P=0.29$). This overall pattern held whether we analyzed the data using the maximal response irrespective of time, the first exhalation, or the mean of the three FEV_1 attempts. The number of patients for whom salmeterol did not offer protection against exercise-induced asthma later in the day (i.e., those with more than a 10 percent fall in FEV_1 after exercise) increased from 2 on study day 1 to 11 on day 29 ($P=0.02$).

DISCUSSION

We examined whether long-term therapy with inhaled salmeterol diminished the protection afforded against a clinically important, acute precipitant of asthma. The study was designed to imitate, as closely as possible, the type of situation that would be encountered in outpatient practice; hence, we studied patients who had symptomatic exercise-induced asthma superimposed on asthma of varying severity and therapeutic requirements. In some patients, exercise was the sole active trigger of their illness, whereas in others it was only one of many stimuli that caused

symptoms. This mixture of patients and the intensity of the provocation used were chosen to tax the effects of salmeterol. Generally speaking, the more aggressive the underlying asthma, the less effective any given drug is in preventing an exercise-induced component, and the more severe the challenge, the greater the opportunity for the drug to fail.¹⁴ Cold air and large workloads were used because they evoke the greatest decrements in lung function,¹⁵ yet are common natural occurrences. We found that under these circumstances the administration of standard doses of salmeterol for 30 days did not result in a clinically important decrease in protection against exertional airway obstruction.

Our findings do demonstrate, however, that the duration of action of salmeterol decreased with long-term use: by the end of the second week, the extent of protection was less in the evening, and by day 29, it no longer differed from that afforded by placebo. These observations imply that the functional activity of the airway β_2 -adrenergic receptors did not change over time, but that the rate of clearance of the drug from the tissue had accelerated or that some other phenomenon had occurred. Since a decrease in the rate of clearance is manifested by a diminution in the duration of bronchodilatation¹⁶ and since this has not been found with long-term administration of salmeterol in previous investigations,¹⁷ it seems an

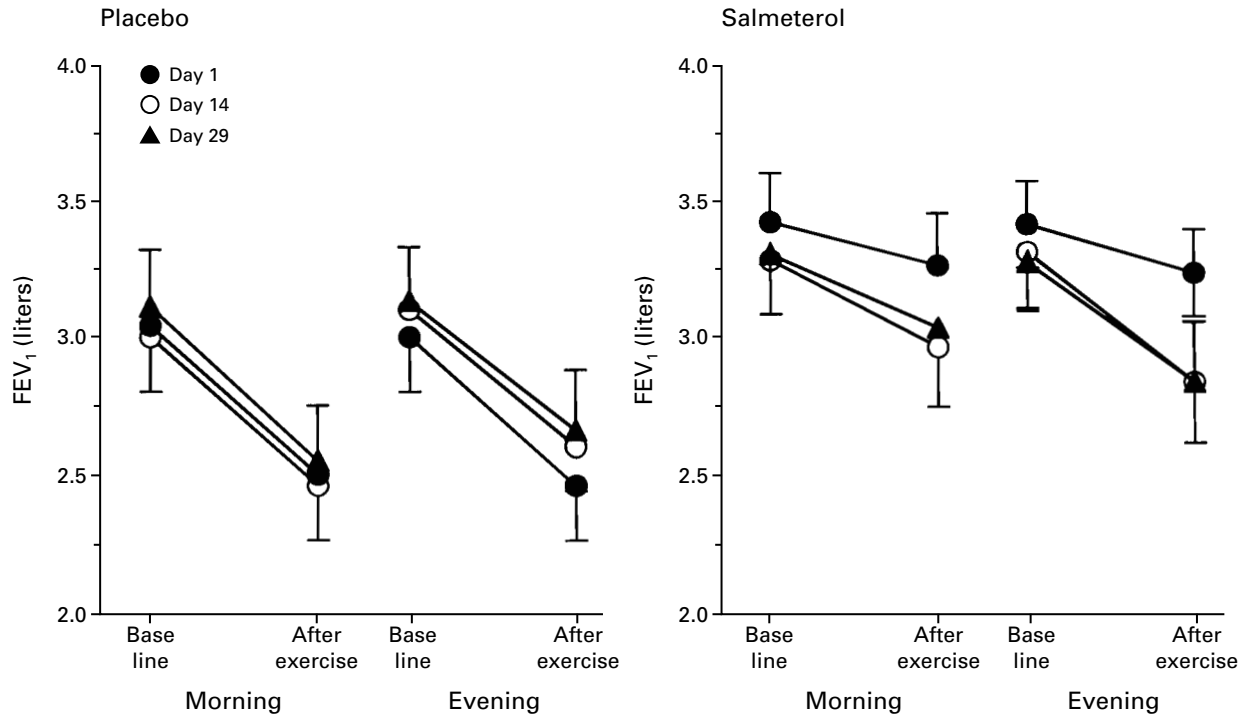


Figure 2. Absolute Effects of Placebo and Salmeterol on the Response to Exercise over Time.

The base-line data in the morning were recorded after the administration of the study drugs. FEV₁ denotes forced expiratory volume in one second. Values are means \pm SE.

unlikely explanation. However, since the protective effects of β -adrenergic drugs against exercise are independent of airway dilatation,¹⁸ the dissociation noted suggests an as yet undefined interaction between the stimulus and the drug.

It is commonly held that a single dose of salmeterol will attenuate exercise-induced bronchoconstriction in adults for 12 hours.¹⁹⁻²¹ In most short-term trials, the post-exercise decrease in FEV₁ within several hours after inhalation averages 1 to 5 percent¹⁹⁻²¹ (Fig. 2 and 3); however, as the effects of the drug begin to wear off, the benefits become less pronounced, and the proportion of patients in whom protection remains maximal at six hours ranges from 20 to 50 percent.¹⁹⁻²¹ It therefore seems possible that the temporal effects we observed may represent an exaggerated example of the normal pharmacology of the drug. Although direct proof of this postulate is lacking, it is well established that the duration of the prophylactic activities of sympathomimetic drugs are considerably less than the duration of their bronchodilator effects.^{22,23}

Our study was not designed to determine how long the protection lasted throughout the day after a month of therapy. Nonetheless, we can infer from these data that for long-term therapy with salme-

terol, either short-acting supplemental drugs or a change in dose schedule may be required to provide the greatest control toward the end of the dosing interval. Although such a requirement is clearly disadvantageous, it must be remembered that the effect of salmeterol lasts three to four times as long as the two hours offered by a standard dose of albuterol.²²

We appreciate that our work stands in contrast to several investigations that concluded that salmeterol²⁴ and its shorter-acting congener albuterol²⁵ lose their effectiveness against exercise over time. Ramage and associates²⁴ reported that the prophylaxis provided by salmeterol disappeared after a month of treatment. Unfortunately, it is unclear whether the patients actually took the drug on the test days; hence, their results are problematic. Inman and O'Byrne²⁵ administered albuterol for one week and found a diminution in the protection against physical exertion along with an inexplicable worsening of lung function. When the fluctuations in base line in these studies are taken into account by expressing the effect as a percentage change, the purported adverse effects disappear.

In summary, we found that the extended administration of a long-acting β_2 -adrenergic-agonist drug such as salmeterol does not result in a loss of

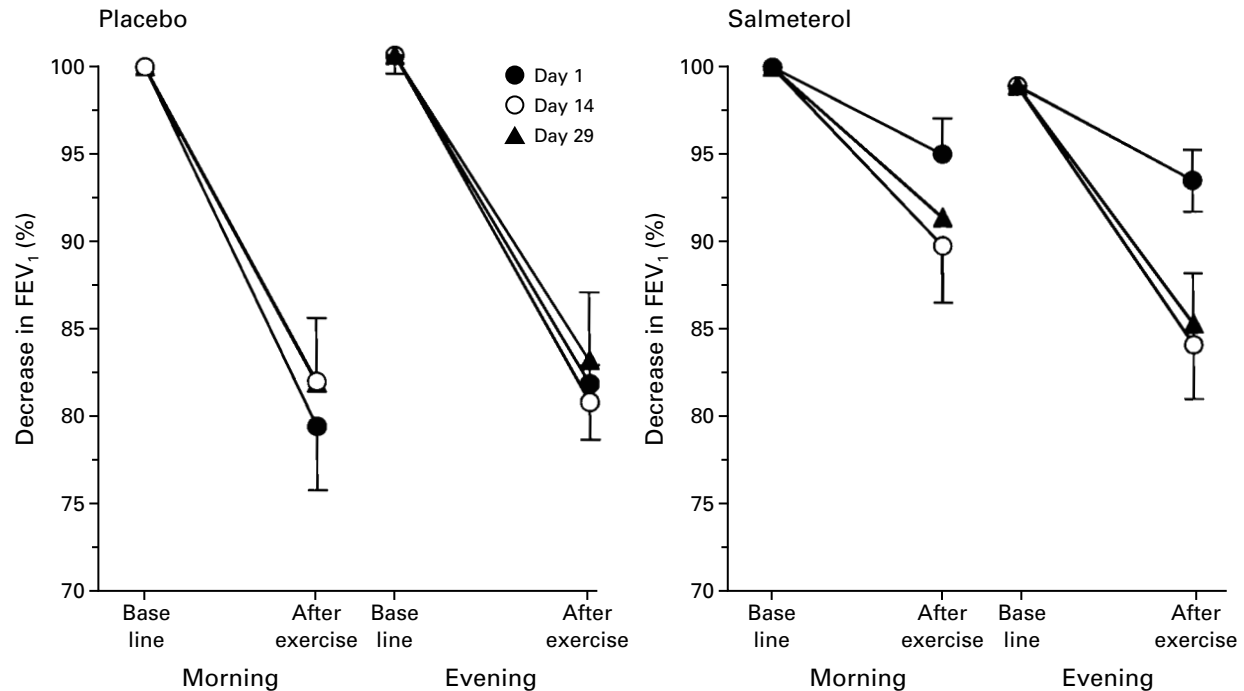


Figure 3. Relative Effects of Placebo and Salmeterol on the Response to Exercise over Time.

This presentation compensates for temporal shifts in the base-line values. The base-line data in the morning were recorded after the administration of the study drugs. FEV₁ denotes forced expiratory volume in one second. Values are means \pm SE.

protection against clinically relevant precipitants of asthma, but the duration of action of the drug is shortened.

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