

The effect of inhaled salmeterol on methacholine responsiveness in subjects with asthma up to 12 hours

Eric Y. Derom, MD, Romain A. Pauwels, MD, and
Marcel E. F. Van Der Straeten, MD Ghent, Belgium

The duration of the protective effect of 50 and 100 µg of inhaled salmeterol against methacholine-induced bronchoconstriction was compared with that of 200 µg of inhaled salbutamol in 12 patients with asthma with a baseline FEV₁ of at least 70% and a provocative concentration of inhaled methacholine causing a 20% fall in FEV₁ (PC₂₀) ≥8 mg/ml. The study was placebo controlled, double blind, randomized, and crossover. The bronchodilating effect was no longer significant 4 hours after inhalation of salbutamol, whereas the effect was still present 12 hours after administration of 50 and 100 µg of salmeterol. All active treatments caused PC₂₀ to increase at 1 hour (p < 0.05). PC₂₀ (milligrams per milliliter) thus reached 3.7 ± 0.8 after placebo, 13.8 ± 3.0 after 50 µg of salmeterol, 23.2 ± 4.7 after 100 µg of salmeterol, and 13.9 ± 3.4 after 200 µg of salbutamol. The protective effect of 200 µg of salbutamol was no longer significant at 4 hours, whereas both doses of salmeterol protected against methacholine challenge up to 12 hours after inhalation (p < 0.01). An increased incidence of tremor (2/12) and palpitations (2/12) was recorded after inhalation of 100 µg of salmeterol. We conclude that inhalation of 50 or 100 µg of salmeterol causes a long-lasting bronchodilatation and protects against methacholine-induced bronchoconstriction for at least 12 hours. (J ALLERGY CLIN IMMUNOL 1992;89:811-5.)

Key words: Salmeterol, bronchodilation, sympathomimetics, aerosol, salbutamol, asthma, methacholine challenge, protective effect

Salmeterol, a new β₂-adrenoceptor agonist, produces bronchodilation for at least 12 hours when it is inhaled by subjects with asthma.¹ Aerosolized β₂-agonists have also been demonstrated to reduce non-specific airway responsiveness in subjects with asthma. However, a discordance in the time course of effectiveness of inhaled β₂-agonists on bronchodilation and on suppression of bronchial hyperresponsiveness has been reported. For instance, the protective effect of fenoterol² and metaproterenol³ is no longer significant at 4 hours, despite persisting bronchodilation.

Abbreviations used

PC₂₀: Provocative concentration of inhaled methacholine required to reduce FEV₁ by 20%
MDI: Metered-dose inhaler

Bronchoprovocation with methacholine is a generally accepted method to investigate the peak intensity and duration of the protective effect of aerosolized bronchodilators.³ Using this method, we have evaluated the magnitude and the duration of the protective effect of 50 and 100 µg of inhaled salmeterol by comparing it with the protective effect provided by a standard dose of 200 µg of inhaled salbutamol and placebo.

MATERIAL AND METHODS

Patient selection

Twelve patients with bronchial asthma (10 male and two female patients), aged 18 to 31 years, participated in the study (Table I). All patients had a baseline FEV₁ of at least 70% of the predicted normal value⁴ at the start of each test day. Moreover, PC₂₀ was ≥8 mg/ml in all participating

From the Department of Respiratory Diseases, University Hospital, Ghent, Belgium.

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Reprint requests: E. Derom, MD, Department of Respiratory Diseases, University Hospital, De Pintelaan, 185 B-9000 Ghent, Belgium.

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TABLE I. Patients' characteristics

Patient No.	Sex	Age (yr)	FEV ₁ baseline (L)	PC ₂₀ (mg/ml)	Smoking	Medication*
1	M	19	4.00	1.5	N	Bi; Si
2	M	23	3.38	2.6	N	Bi
3	M	30	4.40	1.9	S	Bi
4	F	31	2.90	2.3	S	—
5	F	25	3.35	2.7	N	Bi
6	M	27	3.97	0.6	N	Bi
7	M	25	5.22	1.6	S	Bi
8	M	31	3.60	1.2	N	Bi; Si
9	M	29	3.54	1.2	N	—
10	M	21	4.22	0.8	N	Bi; SCG
11	M	23	4.30	1.0	N	Bi; SCG
12	M	29	4.19	4.5	S	Bi

S, Smokers; N, nonsmokers; Bi, inhaled β_2 -agonists; Si, inhaled steroids; SCG, sodium cromoglycate.

*Medication is the current antiasthma medication.

subjects. All patients were examined during a stable period of their disease and were free of any respiratory tract infection for at least 1 month. Clinical examination and routine blood analysis of all participants were within normal limits. Informed consent of the patients and approval of the Ethical Committee of the University Hospital of Ghent was obtained.

Design of the study

On all examination days, patients always arrived at the lung-function laboratory at 7:45 AM, having stopped their treatment with inhaled β_2 -agonists for 8 hours. Baseline FEV₁ and PC₂₀ were determined, and patients were only allowed to participate if FEV₁ was within 10% of their baseline value and if the PC₂₀ was within $\pm$ one doubling dilution of that measured on the selection day. If these requirements were not met, patients were requested to return on another day. Patients were then instructed to take two doses from an MDI. On 4 nonconsecutive days (at least 2 full days between each study day were observed), the patients inhaled either placebo, 200 μ g of salbutamol, or 50 or 100 μ g of salmeterol according to a randomized, double-blind and crossover design. MDIs were identical in appearance and were tested before given to the patients. To evaluate magnitude and duration of the protective effect of the test medication, the bronchial challenge with methacholine was repeated 1, 4, 8, and 12 hours after inhalation of the test medication. The tolerance of the study medications was assessed by questioning the patient about potential adverse effects during and after the examination day. Patients were allowed to use rescue medication throughout the study (salbutamol MDIs) but were asked to report extra inhalations to the physician supervising the trial. Methacholine challenge was stopped once rescue medication had been used. Patients who needed rescue medication were neither retested nor excluded from the study.

Methacholine challenge test

Methacholine challenge was performed according to the protocol of Cockcroft et al.⁵ with some minor modifications. Increasing concentrations of methacholine were administered via a Wiesbadener doppel inhalator (Wiesbadener Inhalatoren-Vertrieb Wiesbaden, Germany) with an airflow at 6 L/min. The same nebulizer was used on all test days for a particular patient. The output of the nebulizer was 0.125 ml/min. The nebulized solutions were inhaled during 2 minutes of tidal breathing with the outlet of the nebulizer in the mouth and the nose closed by a clip. Phosphate-buffered saline solution was inhaled first, followed at 5-minute intervals by methacholine in twofold-increasing concentrations from 0.0625 to 32 mg/ml. FEV₁ was chosen as the parameter of airway caliber. It was measured with a water-sealed spirometer (Expirograph; Godart, Bilthoven, The Netherlands) 30, 60, and 90 seconds after each concentration step, each value representing the highest of three consecutive maneuvers. The provocation was terminated when the FEV₁ fell by >20% (compared to that of the postsaline FEV₁) or when the maximal concentration was reached. The PC₂₀ was obtained from the log dose-response curve by linear interpolation of the last two points.

Data analysis

FEV₁ values and changes in FEV₁ (expressed as percentage of baseline) measured at different time points are expressed as means $\pm$ standard error of the mean of 12 individual values. PC₂₀ values measured at different time points are expressed as geometric means of 12 individual values. The time course of log PC₂₀ and FEV₁ on the different test days was compared with a two-way analysis of variance. Values of FEV₁ and logarithmically transformed PC₂₀ at individual time points were compared by Student's paired *t* tests.⁶ All data obtained subsequent to the use of rescue medication were discarded and replaced by the data obtained

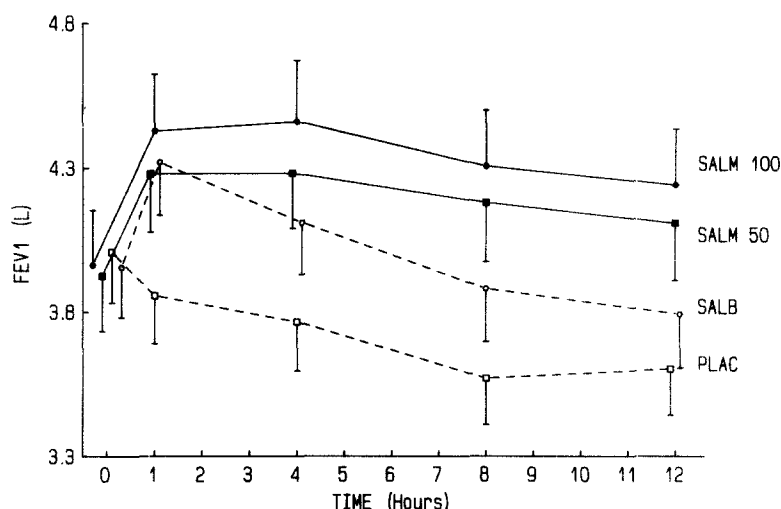


FIG. 1. Time course of FEV₁ (mean $\pm$ SEM) expressed in liters in 12 subjects with asthma after inhalation of placebo (PLAC), salbutamol, 200 μ g (SALB), salmeterol, 50 μ g (SALM 50), and salmeterol, 100 μ g (SALM 100).

just before the rescue inhalation. Whenever PC₂₀ exceeded 32 mg/ml, it was substituted by an estimated value of 40 mg/ml.

RESULTS

Effect on FEV₁

The time course of the mean FEV₁ for each treatment is illustrated in Fig. 1. Mean baseline FEV₁ on each of the 4 treatment days did not differ significantly. FEV₁ decreased slightly but significantly 1, 8, and 12 hours after administration of placebo. All active treatments resulted in a bronchodilating effect. Inhalation of salbutamol after the pretreatment methacholine challenge caused an increase in FEV₁ ($p < 0.01$, when salbutamol was compared with placebo), which had disappeared after 4 hours. The increase in FEV₁ 1 hour after inhalation of 50 μ g of salmeterol was similar to the effect of 200 μ g of salbutamol. In spite of a slight decrease over time, this increase in FEV₁ remained significant until the end of the trial compared with that of placebo ($p < 0.01$) or salbutamol ($p < 0.05$). The 100 μ g of salmeterol dose resulted in an even greater increase in FEV₁, reaching $12\% \pm 1\%$ after 1 hour. This increase remained significant throughout the trial, compared with that of placebo, 50 μ g of salmeterol, or 200 μ g of salbutamol (all $p < 0.01$).

Mean PC₂₀ response

The time course of the mean PC₂₀ for each treatment during 12 hours is illustrated in Fig. 2. All active drugs reduced airway responsiveness to methacholine. Salmeterol at both doses was more effective in pro-

tecting against methacholine-induced bronchoconstriction than placebo and salbutamol during a 12-hour period (both $p < 0.001$). Moreover, 100 μ g of salmeterol proved to be significantly more effective as a protective agent than 50 μ g of salmeterol ($p = 0.015$). The increase in PC₂₀ 1 hour after inhalation of 50 μ g of salmeterol did not differ from the increase measured 1 hour after inhalation of 200 μ g of salbutamol. In contrast, the degree of protection provided by 100 μ g of salmeterol was more than the protective effect produced by salbutamol and 50 μ g of salmeterol ($p < 0.01$). Mean PC₂₀ equaled, and even exceeded, 8 mg/ml 12 hours after inhalation of salmeterol, 50 and 100 μ g, respectively (both $p < 0.01$ compared to that of salbutamol). The initial salbutamol-induced increase in PC₂₀ had disappeared at 4 hours (Fig. 2).

Adverse effects

On a total of 48 examination days, rescue medication was only used on one occasion. One placebo-treated patient asked for two puffs of salbutamol 8 hours after the start of the trial because of shortness of breath. All treatments were generally well tolerated. Inhalation of salmeterol, 100 μ g, was associated with tremor (reported by two patients and classified as mild and not disturbing) and palpitations (reported by two patients, also classified as mild).

DISCUSSION

The present study not only confirms the long-acting bronchodilating effect of inhaled salmeterol in sub-

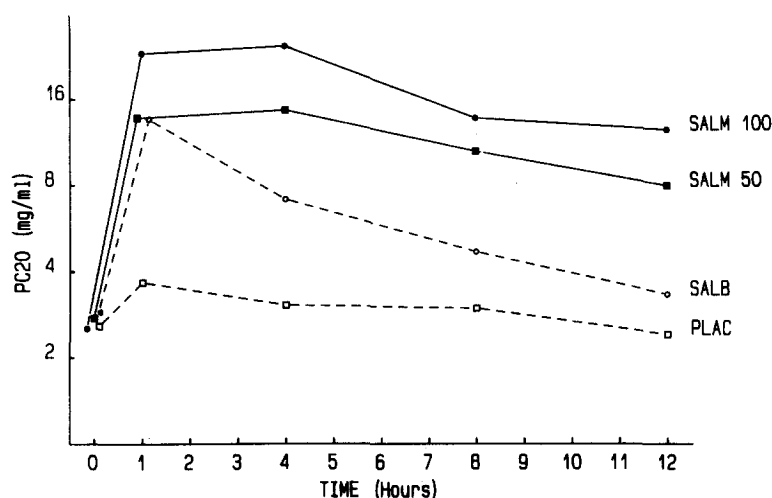


FIG. 2. Time course of PC₂₀ expressed as milligrams per milliliter in 12 subjects with asthma after inhalation of placebo, salbutamol, and two doses of salmeterol. Same conventions as in Fig. 1.

jects with asthma but is the first study to demonstrate that this drug significantly protects for at least 12 hours against methacholine-induced bronchoconstriction. Indeed, inhalation of 50 and 100 μ g of salmeterol resulted in a significant increase in PC₂₀ after 1 hour, the magnitude of which for a 50 μ g dose equaled, and for a 100 μ g dose, exceeded, the protective effect obtained with 200 μ g of salbutamol. This inhibition of direct bronchial hyperresponsiveness was still present 12 hours after inhalation of both 50 and 100 μ g of salmeterol, whereas the protective effect of salbutamol had disappeared after 4 hours. Moreover, inhalation of 100 μ g of salmeterol was clearly superior to 50 μ g in decreasing nonspecific airway hyperresponsiveness, thus exhibiting a clear dose-response effect. Both doses of salmeterol were well tolerated, and only the larger dose of salmeterol caused mild tremor and palpitations in two cases.

One factor that may have contributed to the improved protective effect of salmeterol on methacholine-induced bronchoconstriction is its bronchodilating effect. Indeed, it is well documented that as airway caliber increases, the response to inhaled methacholine decreases.⁷ In the present study, drugs producing the greatest bronchodilation also produced the greatest protection. However, the decrease in FEV₁ by 10% during 12 hours, observed on the placebo-treatment day, did not affect bronchial hyperresponsiveness to a great extent. In contrast, a rather significant difference in protective effect between the 50 μ g and the 100 μ g dose of salmeterol was observed 1 hour after the beginning of the study, in spite of the virtually equal bronchodilating effect measured at that time

point. As a consequence, other factors independent of the degree of bronchodilation appear to be involved in the mechanism of salmeterol-induced protective effect in subjects with asthma.

One of the potential disadvantages of the currently available β_2 -adrenergic agents is the short duration of their protective and bronchodilating activity, which is especially relevant for asthmatic symptoms during the night.^{2,8,9} The present study clearly demonstrates that salmeterol, along with its long-acting bronchodilating properties, also produces a significantly longer protective effect, which apparently is dose dependent (Fig. 2). The increased incidence in tremor and palpitations after 100 μ g of salmeterol, however, limits, to some extent, the relevance of this finding. Interestingly, the present observations are in line with data reported by Becker et al.¹⁰ who demonstrated that formoterol, another β_2 -agonist with a prolonged bronchodilator effect, exhibited a comparable long-lasting and dose-related protection in children with asthma.

Twelve hours after inhalation of 50 μ g of salmeterol, PC₂₀ still reached 8 mg/ml. Airway hyperresponsiveness in itself has been demonstrated to correlate well with the severity of asthmatic symptoms,¹¹ the degree of bronchospasm provoked by a standardized exercise test,¹² the severity of bronchospasm induced by hyperventilation of cold air,¹³ and medication requirements.¹⁴ Indeed, subjects with symptomatic asthma having a PC₂₀ <8 mg/ml generally use their bronchodilating drugs more frequently than patients with a PC₂₀ >8 mg/ml, whose asthma may be well controlled with occasional use of medication only.¹⁴ If salmeterol were to be as long acting in pro-

testing against bronchoconstriction caused by exercise, hyperventilation, or other stimuli encountered in daily life as it is against methacholine or allergen¹⁵ challenge, a decreased consumption of extra doses of β_2 -agonist and a better sleep quality may be expected. This finding was observed in two recently published clinical trials.^{16, 17}

Whether the development of salmeterol represents an important improvement in asthma treatment remains to be established. Indeed, long-term clinical studies are needed to evaluate the potential disadvantages of long-acting β_2 -agonists, such as a delayed detection of exacerbation and a possible development of tachyphylaxis. The demonstration that regular treatment with the short-acting β_2 -agonist, fenoterol, may have an aggravating effect on asthma warrants further caution.¹⁸ Although there is no clear evidence for development of tachyphylaxis with salmeterol after a 2-week period when it is combined with inhaled steroids,¹⁶ it is not known whether tachyphylaxis can occur when salmeterol is used for a longer period of time.

In conclusion, the present study demonstrates that inhaled salmeterol provides significantly longer protection than 200 μ g of inhaled salbutamol against methacholine-induced bronchoconstriction and that this protective effect is still present 12 hours after inhalation of either 50 or 100 μ g.

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