Salmeterol in exercise-induced bronchoconstriction in asthmatic children: comparison of two doses

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Salmeterol in exercise-induced bronchoconstriction in asthmatic children: comparison of two doses. F.M. de Benedictis, G. Tuteri, P. Pazzelli, A. Niccoli, D. Mezzetti, R. Vaccaro. ©ERS Journals Ltd 1996.
ABSTRACT: Since the optimal dose of salmeterol in asthmatic children has not yet been clearly defined, we compared the efficacy and duration of the protective effect of two doses of salmeterol (25 and 50 µg) against exercise-induced bronchoconstriction.

Twelve children (aged 7–14 yrs) with asthma were studied in a double-blind, cross-over, placebo-controlled design. On three separate days, exercise tests were performed 1 h and 12 h after administration of the drug. Pulmonary function measurements were performed before drug inhalation, before every exercise test and 1, 5, 10, 15 and 30 min after the end of exercise. The response was expressed as maximal decrease in forced expiratory volume in one second (FEV_1).

Both doses of salmeterol provided significant bronchodilation for up to 12 h, with no difference between them. Maximal exercise-induced decrease in FEV_1 (% fall) 1 h after pretreatment was (mean±SD) 35±16, 10±10 and 4±3% for placebo, 25 and 50 µg salmeterol, respectively. At 12 h after pretreatment these values were 31±14, 19±12 and 15±13%, respectively. Individual protection against exercise-induced bronchoconstriction at 1 and 12 h did not vary between the dosages (p<0.05), even though the protection obtained by 25 µg at 12 h was no longer significant *versus* placebo.

We conclude that 25 µg of inhaled salmeterol provides equally effective long-lasting bronchodilation and acute protection against exercise-induced bronchoconstriction as 50 µg, and may be a suitable dose for most asthmatic children.
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Exercise frequently stimulates bronchoconstriction in children, which is commonly referred to as "exercise-induced asthma" (EIA). These children are often discouraged from physical activities for fear of breathlessness. The currently available beta$_2$-adrenoceptor agonists by the inhaled route will prevent EIA in about 90% of patients when given prior to activity [1]. However, the duration of their protective effect is usually less than 2 h [2, 3], probably because of the hydrophilic nature of these agents and their rapid clearance from the airways [4].

Salmeterol xinafoate is a new, selective, long-acting beta$_2$-adrenoceptor agonist. It has a polar phenylethanolamine head which binds reversibly to the beta$_2$-receptor, and a long nonpolar side-chain which binds to the cell membrane adjacent to the receptor and to which is attributed the long duration of the effect [5].

The optimal dose of salmeterol in asthmatic children has not yet been clearly defined. The commonly recommended adult dose has been used in children [6, 7]. However, both single dose studies [8, 9] and long-term treatment [10] have shown that 25 and 50 µg of salmeterol have comparable bronchodilator effects and are equally useful in controlling symptoms in children.

As very few data are available on the efficacy and duration of the protective effect of salmeterol in EIA in

children, we compared two doses (25 and 50 µg) in order to provide guidance for an optimal dosage.

Materials and methods

Subjects

Twelve subjects (10 males and 2 females) aged 7–14 yrs (mean±SD 11±2 yrs) were recruited. All patients attended the Paediatric Asthma Clinic at Perugia General Hospital and had asthma as defined by the American Thoracic Society (ATS) [11]. They were being treated with different antiasthma regimens, such as short-acting β-agonists, cromolyn, nedocromil and inhaled steroids. These drugs were withheld for 12 h before each exercise test. None of the subjects had a history of respiratory infection in the 4 weeks before the trial. Informed consent was obtained from patients and their parents, and the protocol was approved by the Hospital Ethics Committee.

Study design

Before study entry, a screening exercise test was performed. The exercise test consisted of steady-state running

for 6 min on an inclined treadmill to produce a heart rate of at least 85% of the maximum predicted for age. Nasal clips were used when breathing ambient air during the test. The exercise workload for each subject was determined on the basis of an incremental Stage 1 exercise test, and was kept constant throughout the study [12]. Only subjects who demonstrated a drop of at least 15% from baseline in forced expiratory volume in one second (FEV1) after the exercise screening test entered the blinded phase of the study. In random, cross-over, blinded order, on three separate days, each patient was tested with different treatments inhaled by metered-dose inhaler (MDI): salmeterol (two puffs = 50 µg); salmeterol (one puff = 25 µg) plus placebo (one puff); or placebo (two puffs). Patients were randomized so that an equal number of patients received each drug as the first, second and third drug, respectively, employing a Greek-Latin square design. The drugs were administered by a trained physician, and all patients were skilled in the use of MDIs. The "closed mouth" technique was used. On each of the three study days, patients attended the laboratory between 08:00 and 09:00 h and performed the exercise tests, respectively, 1 and 12 h after inhalation of each drug. Room temperature and relative humidity were monitored in a climate room. Differences of 1°C in temperature and 0.1 kPa in vapour pressure of water on the test days of each patient were considered acceptable. Room temperatures ranged 21– 23°C and relative humidity ranged 41–58%.

Pulmonary function measurements

Pulmonary function was measured with a turbine spirometer (Pocket Spirometer I; Micro Medical Ltd, Rochester, Kent, UK) according to accepted standards [13]. Predicted normal values for spirometry were obtained from the study of KNUDSON *et al.* [14]. All children were familiar with the spirometer. Measurements were performed before drug inhalation (baseline value), before every exercise test (pre-exercise value), and 1, 5, 10, 15 and 30 min after the end of exercise. Heart rate was measured before the administration of the trial medication, before exercise, and at specific times until 30 min after the end of exercise. The exercise test was performed only if the baseline FEV1 was higher than 70% of the mean predicted for the child's height, and if the baseline FEV1 varied <10% from the values on previous test days.

Exercise challenge parameters

The following parameters were calculated from the results of the pulmonary function tests. The maximum % drop in FEV1 was calculated as follows:

$$\frac{\text{Pre-exercise } FEV_1 - \text{lowest postexercise } FEV_1}{\text{Pre-exercise } FEV_1}$$

"Complete protection" was considered to have been obtained if the percentage drop in FEV1 was within the normal range (<10%). "Clinical protection" was considered to have been obtained if the percentage fall in FEV1 after receiving the active drug was half or less of the percentage fall after the screening [15].

In addition, the time (min) for FEV1 to recover to within 10% of the pre-exercise value was determined.

Statistical analysis

The pre-treatment FEV1 values on the three study days were compared using one-way analysis of variance (ANOVA). Two-way ANOVA was used to analyse the following indices, with drug and time after treatment (at 1 and 12 h) as factors: 1) change from baseline in values of FEV1 before exercise; and 2) maximum falls in FEV1 after exercise. When appropriate, multiple comparisons were performed by means of the Tukey studentized test. McNemars change test was used to compare the number of patients who had complete or clinical protection with different drugs. Where the expected frequency for Mc-Nemars test was too small (*e.g.* <0.5) the binomial test was used.

The time to return to 10% of the pre-exercise FEV1 was analyzed nonparametrically using Wilcoxon's rank sum test. Because the FEV1 did not return to within 10% of the pre-exercise value at 30 min after the exercise test in some subjects, 30 min was used as a minimal estimate of the time for recovery.

Factors influencing the change in FEV1 after treatment and the maximum fall in FEV1 after exercise were analysed by multiple regression analysis of pretreatment FEV1, treatment, treatment order, and time-point after treat-ment. Analysis of covariance (ANCOVA) was used to assess the impact of bronchodilation on the broncho-provocative airway responses. The analysis was performed with Statistical Analysis System (SAS) software. Differences were considered significant at a p-value less than 0.05 [16].

Results

Intervals between study days ranged 2–10 days. Pretreatment (baseline) values for FEV1 on the three study days ranged 88–119% (mean±SD 94±6%) of predicted values. There was no difference between the pre-treatment FEV1 values on the three study days.

Mean (±SD) pretreatment and pre-exercise FEV1 values, and FEV1 changes from baseline in response to treatment are shown in table 1. After placebo inhalation, FEV1 at both pre-exercise times did not change significantly from the baseline. After inhalation of 25 µg salmeterol (SLM 25) and 50 µg salmeterol (SLM 50), FEV1 change

Table 1. – Pretreatment and pre-exercise FEV1 values and percentage change from baseline on the three study days

	Placebo	SLM25	SLM50
Pretreatment FEV1	2.02±0.3	2.01±0.4	2.02±0.3
Pre-exercise at 1 h FEV1 L	2.11±0.4	2.24±0.4	2.23±0.3
ΔFEV1 %	3.9±4.3	11.7±8.6	10.8±5.0
Pre-exercise at 12 h FEV1 L	2.00±0.4	2.16±0.3	2.21±0.4
ΔFEV1 %	-1.2±5.1	8.0±7.3	9.5±5.3

Values are presented as mean±SD. SLM25: salmeterol 25 µg; SLM50: salmeterol 50 µg; FEV1: forced expiratory volume in one second; ΔFEV1: change in FEV1.

Table 2. – Maximum percentage decrease in FEV1 at screening and after the first and the second exercise test with each treatment

Pt. No.	Screening	Placebo		SLM25		SLM50	
		Maximum decrease in FEV1 %					
		1 h	12 h	1 h	12 h	1 h	12 h
1	28	35	26	24	25	6	15
2	60	48	46	27	30	10	39
3	28	30	8	0	6	0	2
4	20	35	29	1	3	0	4
5	28	19	23	2	8	5	7
6	57	61	50	1	12	3	14
7	31	19	25	4	6	4	5
8	41	60	50	24	34	6	41
9	27	27	23	3	33	3	21
10	69	54	48	6	22	3	11
11	23	20	18	18	27	8	10
12	23	28	25	7	26	0	10
Mean	36	35	31	10	19	4	15
±SD	16	16	14	10	12	3	13

Pt: patients. For definitions see legend to table 1.

was significantly greater than after placebo (PL), both at 1 h (SLM 25: $p<0.02$; SLM 50: $p<0.05$) and at 12 h (SLM 25: $p<0.05$; SLM 50: $p<0.001$). No significant interdose difference emerged in the FEV1 changes at either time. Multiple regression analysis showed that treatment ($p<0.001$) and time after treatment ($p<0.02$) were significant factors for change in FEV1 after treatment.

Table 2 shows the maximum percentage decrease in FEV1 after the first and the second exercise test on each study day. Comparing the maximum percentage decreases in FEV1 showed that SLM 25 and SLM 50 were both significantly better than placebo at 1 h (SLM 25: $p<0.001$; SLM 50: $p<0.001$), but only SLM 50 was more effective than placebo at 12 h (SLM 50: $p<0.05$; SLM 25: NS). There was no statistical difference in the mean of the percentage drops in FEV1 between SLM 25 and SLM 50 at either time (fig. 1). Multiple regression analysis
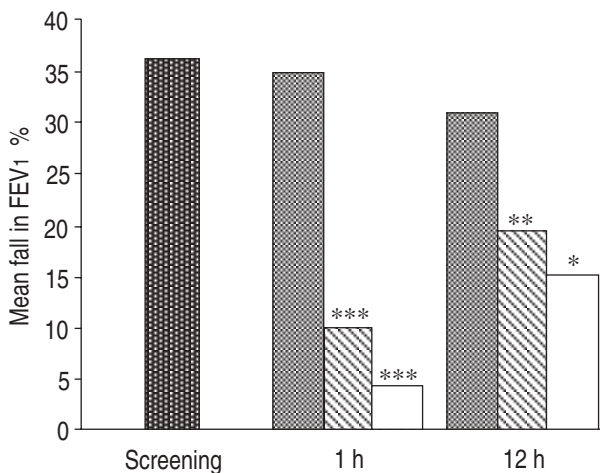

Fig. 1. – Mean percentage decrease in forced expiratory volume in one second (FEV1) at screening and after the first and second exercise test with each treatment. ▓ : placebo; ▨ : salmeterol 25 µg; ☐ : salmeterol 50 µg. *, **, ***: $p<0.05$, <0.01, <0.001 vs placebo.

Table 3. – Individual protection against exercise-induced bronchoconstriction in asthmatic children (n=12) and mean time for recovery of FEV1 to 10% of pre-exercise values

	1 h			12 h		
	PL	SLM 25	SLM 50	PL	SLM 25	SLM 50
Complete protection n	0	8**	12***	1	4	6*
Clinical (>50%) protection n	0	9**	12**	1	7*	8*
Mean recovery time min	23	5**	0**	18	13	7**

*, **, ***: $p<0.05$, <0.01, <0.001 vs placebo (PL). For definitions see legends to tables 1 and 2.

showed that significant factors for fall in FEV1 after exercise were treatment ($p<0.001$) and time after treatment ($p<0.05$). ANCOVA revealed a weak correlation ($p<0.1$) between the change in FEV1 after treatment and the fall in FEV1 after exercise at both times, that is protection from exercise-induced bronchoconstriction was not dependent on bronchodilation.

The mean time (min) for recovery of FEV1 to 10% of pre-exercise values was significantly shorter for SLM 25 and SLM 50 at 1 h and for SLM 50 at 12 h, with respect to placebo. There was no significant difference between SLM 25 and SLM 50 at either exercise challenge (table 3).

Individual protection

After the first exercise challenge, complete protection was provided in 67% of patients with SLM 25, in all patients with SLM 50, and none with placebo. The number of protected patients decreased after the second exercise test: only 33%, 50% and 8% of the subjects were completely protected by SLM 25, SLM 50, and placebo, respectively (table 3).

Clinical (>50%) protection was present in 75%, 100% and none of the patients after the first exercise challenge, and in 58%, 66%, 8% after the second challenge for SLM 25, SLM 50 and placebo, respectively (table 3).

Unwanted side-effects were not observed by the physician or referred by any patients. No significant changes were observed in heart rate with either treatment.

Discussion

Salmeterol xinafoate is a new, selective, beta$_2$-adrenoceptor agonist, which has been shown to produce sustained bronchodilation and prolonged protection against different stimuli both in adults [17–24] and in children [6, 7, 25]. Several studies have evaluated the protection of beta$_2$-adrenoceptor agents against different bronchoconstrictive challenges. Whilst a dose-response effect has been demonstrated for chemical stimuli [17, 25–27], contradictory results have been obtained with exercise [28, 29]. In the present study, 25 and 50 µg doses of salmeterol provided the same protection against EIA at 1 h. After 12 h, although no statistical difference emerged between the two dosages in the mean of the percentage

drops in FEV1, only SLM 50 was more protective than placebo. However, in drug studies on EIA individual protection is as important as the mean drop in pulmonary function parameters. Interestingly, statistical analysis of complete and clinical protection in individual patients showed no difference between the two dosages even after 12 h. It should be noted, however, that with such a small number of patients any statistical test to evaluate individual protection probably has very little power.

The effects of 25 and 50 µg salmeterol on suppression of bronchial hyperresponsiveness in children has been compared in only two studies [25, 30]. SIMONS et al. [25] demonstrated that both doses are better than placebo against methacholine challenge, but salmeterol 50 µg provides significantly greater bronchoprotection than 25 µg from 30 min to 12 h. Although the results of the present study are different, they are not necessarily conflicting. Indeed, the degree and the duration of the protective effect of any drug on airway hyperresponsiveness may vary with the stimulus [31]. Furthermore, the results of methacholine and exercise challenges are not strictly comparable, since the airway response to methacholine is measured in dose-dependent fashion, whereas exercise is always performed at the same level [32].

Very recently, CARLSEN et al. [30] evaluated the overnight protection against EIA afforded by 25 and 50 µg of dry powder salmeterol in children. No significant differences in pre- and postexercise lung function were found between the two doses 12 h after inhalation. Despite differences in times of administration (overnight vs diurnal), methods of delivery (inhaled powder vs metered dose inhaler) and cut-off values for protection (15 vs 10%), the results of the present study overlap with those of CARLSEN et al. [30], suggesting that children may benefit and obtain adequate clinical protection even from only 25 µg of inhaled salmeterol.

Tachyphylaxis to the functional antagonism of salmeterol against EIA is an emerging problem. Recent studies have shown that 2–4 weeks regular treatment with 50 µg twice daily reduced the protective effect of the drug against EIA [33] and cold air challenge [34]. The design of the present study excluded the possibility of this phenomenon, in fact no patient had used salmeterol regularly. Furthermore, the order of treatment did not influence the results. However, given the great clinical significance of this aspect, studies are urgently required to determine whether tachyphylaxis also occurs at lower salmeterol dosages.

The same bronchodilating effect for up to 12 h was provided by inhalation of 25 or 50 µg of salmeterol, confirming previous comparative dose-response results [8, 9, 25]. The present study also indicates that the protective effect induced by beta$_2$-agonists on EIA does not necessarily occur because of concomitant bronchodilation [35]. The fact that no significant correlation was found between the degree of protective effect and the bronchodilation supports the view that other factors in addition to smooth muscle inhibition play a role in salmeterol-induced protection against exercise. Evaporative water loss from the airway mucosa is considered an important mechanism in the pathogenesis of EIA, since it may cause a transient change in osmolarity of the epithelial fluid, which subsequently induces the release of inflammatory mediators [36]. In this respect, salmeterol could act by stimulating Cl$^-$ ion secretion, thus enhancing water transport to the airway epithelium [22]. Moreover, as has been suggested for other beta$_2$-agonists, salmeterol could also act by preventing the release of mediators from the lung mast cells [22]. Indeed, when compared with placebo, salmeterol significantly reduces the rise in histamine and leukotriene blood concentrations induced by exercise challenge [23].

The protection against EIA of currently available beta$_2$-agonists is usually of shorter duration than their bronchodilating effect [37, 38]; this does not seem to be the case for long-acting beta$_2$-agonists. In fact, VERBERNE et al. [7] found that a small but significant reduction of airway sensitivity to methacholine was still present 24 h after administration of 50 µg of salmeterol. Furthermore, MALO et al. [39] observed that about 40% of their patients presented no significant bronchodilation 12 h after formoterol, but that all were partially or completely protected by hyperventilation-induced bronchoconstriction. The present study was not designed to evaluate the long-term aspects of bronchodilation and protection, which undoubtedly require specific investigation.

As previously reported [17, 25], the long duration of action of salmeterol was not associated with significant side-effects, such as tremor or palpitations. Since tachycardia and tremor are known side-effects of beta$_2$-agonists, inhaled salmeterol may represent a major advance for treatment of asthma in children who require bronchodilators in addition to anti-inflammatory therapy. Furthermore, since the time when children exercise is often unpredictable, using a long-acting drug may avoid the need to administer a beta$_2$-agonist before every strenuous physical activity and removes the stigma of inhaler use at school.

In conclusion, as the present study demonstrates that both 25 and 50 µg salmeterol provide long-acting bronchodilation and protect the majority of children against exercise-induced asthma for at least 12 h, we suggest that 25 µg salmeterol may be efficacious for most asthmatic children. Nevertheless, we remain convinced that studies to determine whether tachyphylaxis arises from regular therapy at this dosage should be performed in the near future.

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