

The first 20 minutes after a single dose of inhaled salmeterol in asthmatic children

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Very little is known as yet about the effect of salmeterol in pediatric asthma, so a trial was performed on children with mild asthma to compare salmeterol with salbutamol in terms of how quickly they took effect. The double-blind study involved 11 children (mean age 13.4 years) randomly assigned to inhale salmeterol 50 µg, salbutamol 200 µg, or a placebo three times on alternate days. Peak expiratory flow (PEF), heart rate, and blood pressure were measured before and 5, 10, 15, and 20 min after administering the medication. With salbutamol, PEF was higher at 5 and 10 min, subsequently dropping off at 15 and 20 min; with salmeterol, PEF was better at 10 and 20 min. Forced expiratory volume at 1 s (FEV₁) measurements taken at the baseline and after 10 and 20 min revealed an important and consistent rise in values after salmeterol, whereas salbutamol was more effective after 10 min than after 20 min. No significant changes were recorded in heart rate or blood pressure after salbutamol; after salmeterol, there was a significant increase in heart rate after 5 min, but not at subsequent measurements. In conclusion, salmeterol begins to take effect already within 10 min of a single administration in asthmatic children, although the onset of its effect is slower than with salbutamol.

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Beta₂-agonists are the most effective bronchodilator drugs for the treatment of acute asthma, but their action is short-lived (4–6 h), giving rise to compliance problems in their long-term administration to children. The availability of a powerful and lasting beta₂-agonist would be a significant advantage in asthma therapy.

Salmeterol xinafoate, a new, long-acting beta₂ adrenoceptor agonist (13, 20, 21) for inhalation, produces a prolonged bronchodilator effect (12 h). Controlled studies have demonstrated its effectiveness in asthmatic adults both after a single dose (2, 17, 22) and after long-term treatment (1, 14, 16, 19). It has also been tested as a single-dose inhalation treatment in pediatric asthma (23) and for the prevention of exercise-induced asthma in children (5).

Animal trials with salmeterol have shown a slow onset of effect: it took about 17 min to reach half the maximal relaxation of a carbachol-contracted guinea pig trachea, as opposed to 2 min with salbutamol (10).

Experience of using salmeterol in asthmatic children is limited, and little is known about its rate of action. We therefore monitored asthmatic children for 20 min to compare a single dose of salmeterol

and salbutamol in terms of the rate of onset of their bronchodilator effect.

Material and methods

The study involved 11 outpatients (eight boys, three girls; mean age 13.4 years, range 9–17) diagnosed as having mild asthma (6–9) and atopy caused by one or more inhaled allergens (Table 1). Their asthma had been stable for at least 1 month and they had no respiratory tract infections (the study was performed during the summer, when viral infections are less common). Five patients taking inhaled corticosteroids continued to do so throughout the study, whereas patients taking oral corticosteroid therapy were excluded. Parents gave their informed consent for the children to take part in the trial. The use of beta₂-agonists was restricted to inhaled salbutamol as needed. No use of theophylline, ketotifen, or sodium cromoglycate was permitted. Salbutamol inhalations were withheld for at least 8 hours prior to testing lung function.

Patients came to the pulmonary function laboratory a total of three times, on alternate afternoons. The sequence of treatment was established on the

Table 1. Physical and allergic characteristics of children in our study

Subject	Sex	Age (years)*	Sensitization	Therapy
1. P.C.	M	15	HDM**	No
2. B.A.	M	14	HDM	No
3. G.F.	M	15	HDM-GR***	BDP
4. P.O.	F	17	HDM-GR	BDP
5. P.E.	F	10	HDM	BDP
6. B.S.	M	13	GR	BDP
7. N.A.	M	16	GR-cat-mold	No
8. D.M.	M	9	HDM	BDP
9. S.A.	M	12	HDM	No
10. C.L.	M	14	GR	No
11. C.F.	F	12	HDM	No

* Mean age = 13.4 ± 2.5 years.

** House-dust mites.

*** Grass.

BDP: beclomethasone dipropionate.

basis of a Latin square design. Double-blind conditions were maintained by giving patients three metered-dose inhalers labeled A, B, and C, containing salmeterol, placebo (normal saline solution), or salbutamol. The medication was administered to the child after a short rest (30 min) by the same physician: two puffs were given at each session (i.e., salmeterol 50 µg, salbutamol 200 µg, or placebo) from identical inhalers with no spacer. All children had been trained in the daily use of metered-dose inhalers. Puffs were administered separately, after each of which the child had to take a deep breath and hold it for 10 s (15).

Flow-volume curves were performed before and

10 and 20 min after the inhalation, using a Sensor Medics Pulmonet III System 2130, which provides BTPS (body temperature, pressure, saturated) corrected data and data expressed as a percentage of predicted values, according to Polgar & Promadath (18). The percentage of predicted values of forced expiratory volume at 1 s (FEV₁) was considered, and the highest of three technically correct measurements was recorded. Patients had to have a coefficient of variation of FEV₁ < 5% during the study period to confirm the stability of their asthma.

Heart rate, blood pressure, and PEF values were measured with an automatic digital pressure gauge (HEM400 Omrom Co., Japan) and a mini-Wright (Airmed, UK) at the baseline and 5, 10, 15, and 20 min after inhaling the drug, the best of three technically correct PEF values being recorded.

Statistical analysis

Percentage differences in FEV₁ and PEF values were calculated between the value obtained after administering the medication or placebo at 5–10 min and the baseline value, considered as 0%. These data were analyzed with Student's *t*-test on paired data; 95% confidence intervals (CI) were also calculated for the difference between the mean values obtained with each drug and the placebo (3). Each patient's heart rate and diastolic blood pressure were analyzed in the same way. A *P* value of < 0.05 was considered statistically significant.

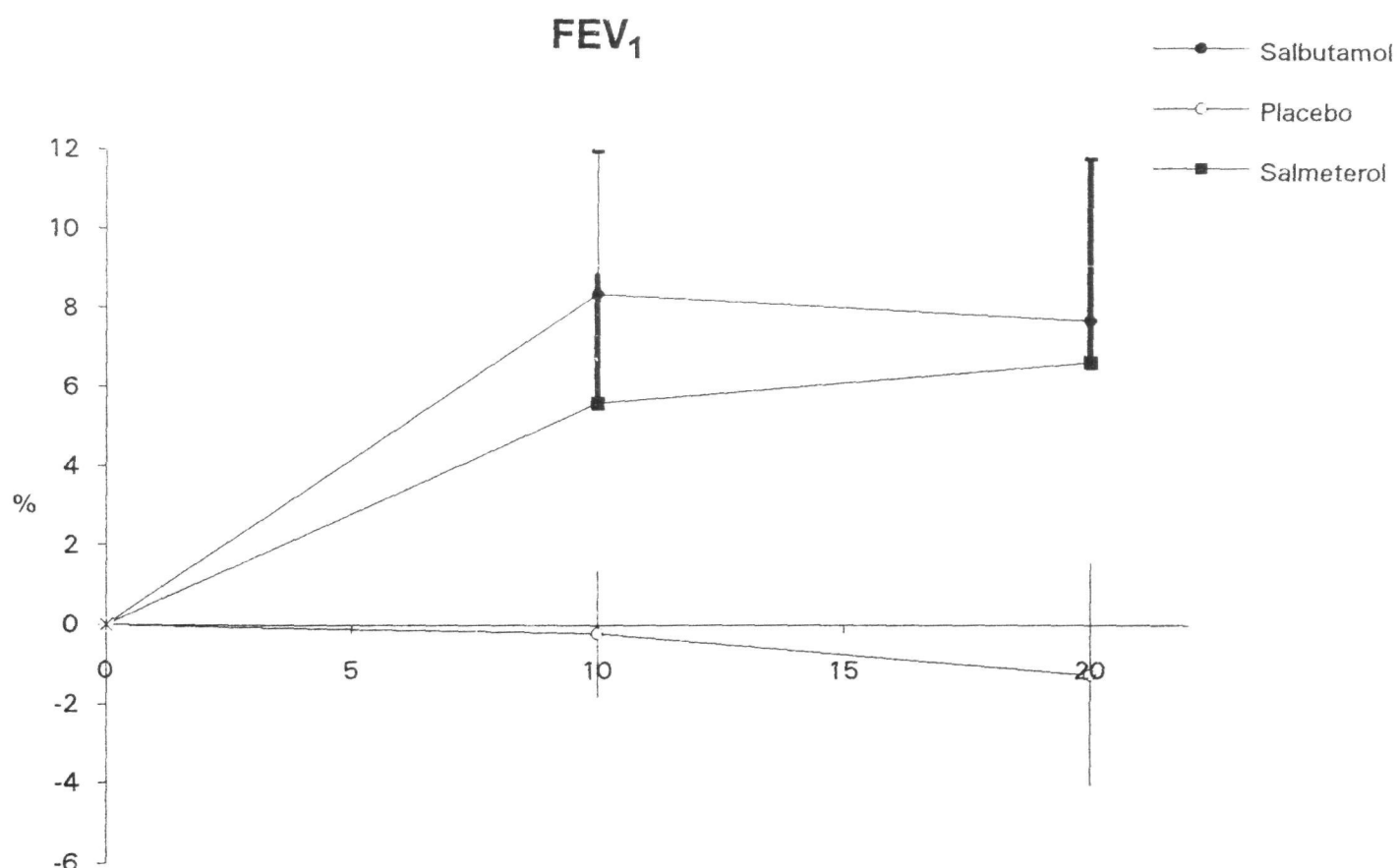


Fig. 1. Mean percent change from baseline (bars show 95% CI) in FEV₁ with salmeterol, salbutamol, and placebo.

Table 2. Pulmonary function of treatment group before drug administration

	Placebo		Salbutamol		Salmeterol	
	av.	SD	av.	SD	av.	SD
FEV ₁ (as % of predicted)	101 ± 11		99 ± 12		100 ± 11	
PEF (l/min)	433 ± 122		440 ± 115		426 ± 113	
Heart rate	84 ± 16		88 ± 11		84 ± 11	
Diastolic blood pressure (mmHg)	59 ± 9		61 ± 8		62 ± 11	

av: average; SD: standard deviation.

Results

There were no dropouts. The patients' baseline conditions at the three different inhalation sessions were similar for all variables considered; in particular,

basal values of FEV₁ and PEF for each patient revealed no statistically significant differences among the three treatment sessions (Table 2).

With salmeterol, an important rise in FEV₁ values was observed after 10 min (*P* = 0.005) and after 20 min (*P* = 0.04) (Fig. 1). After salbutamol inhalation, FEV₁ values were significantly better after 10 min (*P* = 0.003), but less so after 20 min (*P* = 0.68).

As for PEF, values rose 5 min (*P* = 0.036) and 10 min (*P* = 0.046) after salbutamol inhalation, and then fell after 15 min (*p* = 0.067) and 20 min (*P* = 0.554); with salmeterol, an improvement was achieved after 10 and maintained after 20 min (*P* = 0.012) (Fig. 2).

The CI between mean values of the sample confirms the extent of the difference between salmeterol and placebo mean values and between salbutamol

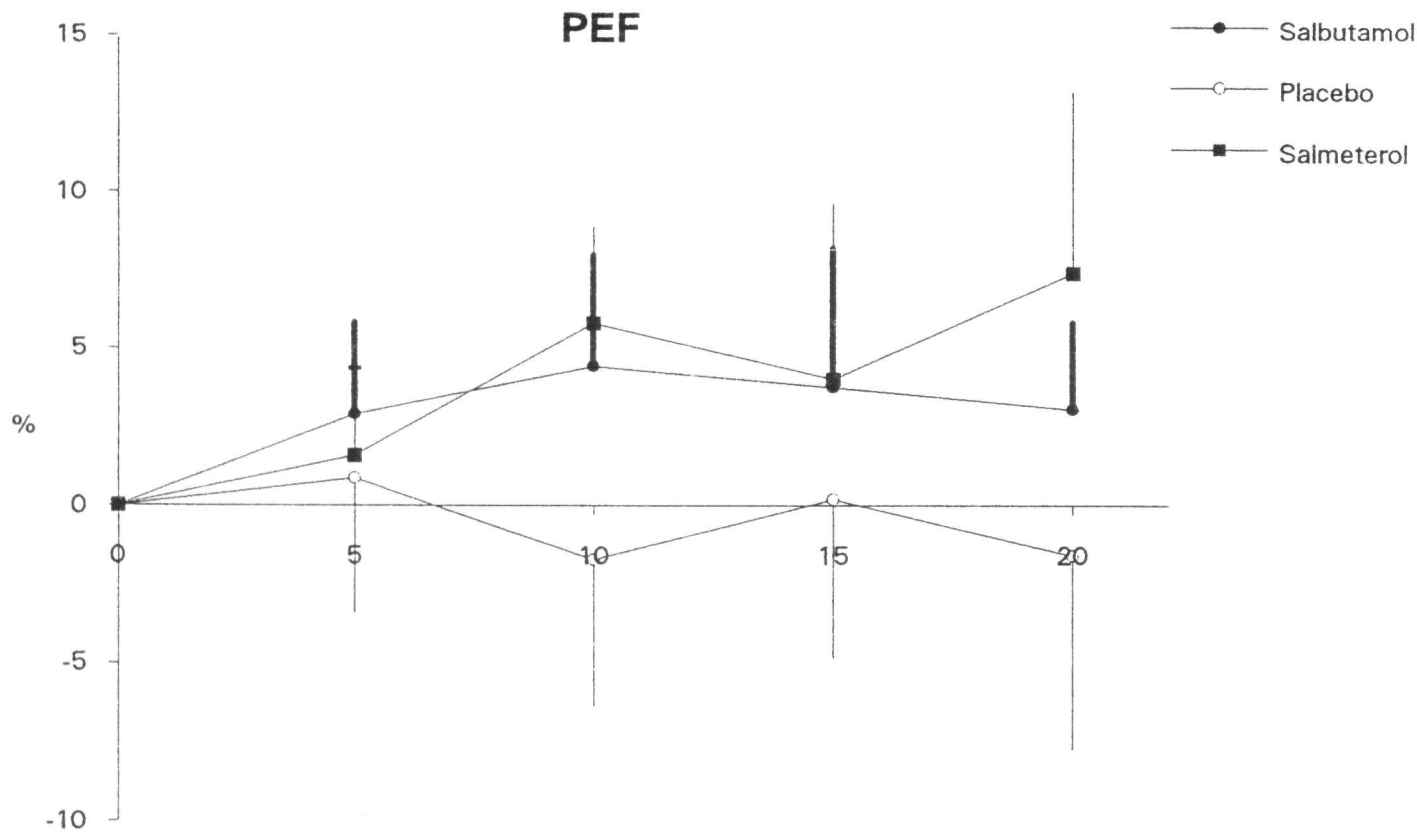


Fig. 2. Mean percent change from baseline (bars show 95% CI) in PEF with salmeterol, salbutamol, and placebo.

Table 3. Mean percent change from baseline in FEV₁ and PEF

	Salmeterol	95% CI		Placebo	95% CI		Salbutamol
		→	→		←	←	
0 min	0.00			0.00			0.00
10 min FEV ₁	5.59 ^{1,2}	2.61	9.01	-0.22	5.07	12.09	8.36 ^{1,2}
20 min FEV ₁	6.63 ^{1,2}	2.71	13.05	-1.25	4.52	13.36	7.69 ²
0 min	0.00			0.00			0.00
5 min PEF	1.59	-3.79	5.23	0.87	-2.57	6.63	2.90 ^{1,2}
10 min PEF	5.81 ^{1,2}	2.61	12.45	-1.72	0.99	11.31	4.43 ^{1,2}
15 min PEF	4.01 ²	-2.87	10.49	0.20	-2.41	9.51	3.75 ²
20 min PEF	7.42 ^{1,2}	1.62	16.42	-1.60	-1.28	10.56	3.04 ²

¹ *P* < 0.05 in comparison with the baseline value.

² *P* < 0.05 in comparison with placebo.

CI: confidence intervals.

and placebo mean values at the various time intervals (Table 3).

FEV₁ and PEF values did not change significantly after inhalation of placebo.

The heart rate and blood pressure readings at the various time intervals revealed no changes, except for a significantly faster heart rate 5 min after inhalation of salmeterol.

Discussion

Our asthma patients had a basal respiratory function within normal limits, because some of them suffered from only a mild form of asthma and the others were chronically receiving steroid inhalant treatment. The bronchodilators tested in this study consequently had a modest but still significant effect.

Our findings confirm that salmeterol (50 µg) takes effect more slowly than salbutamol (200 µg). Salmeterol is effective already within the first 5 min, although significantly less so than salbutamol, and at 15 and 20 min its effect on PEF and FEV₁ is comparable with that of salbutamol.

The finding of a raised heart rate 5 min after inhalation of salmeterol is consistent with reports in the literature of increased heart rate (22) and premature supraventricular beats (12) in adults inhaling a high single dose (100 µg) of salmeterol.

As for the dosage of the two preparations used in our study, the choice of 50 µg of salmeterol and 200 µg of salbutamol was based on their being considered equipotent in several adult studies (4, 22). A similar dose was also used in children by Verberne et al. (23). However, the PEF values we recorded suggest that 50 µg of salmeterol is more powerful than 200 µg of salbutamol, in children at least.

In adults, salmeterol is recommended for long-term use (11) as a bronchodilator with the support of short-acting beta₂-agonists (such as salbutamol) for occasional, additional relief.

There are insufficient clinical data available on children at present to recommend such use of the preparation in pediatric patients. However, our trial would suggest that the association of a short-acting beta₂-agonist (taking effect within 5 min) with another, long-lasting beta₂-agonist could ensure a prolonged bronchodilator coverage in recurrent acute asthma, thus permitting a lower overall dosage of the drug to be administered and consequently achieving better compliance from children and their families.

In conclusion, although the effect of salmeterol has a slower rate of onset than that of salbutamol, a significant response is achieved within 10 min. The preparation is clearly unsuitable for use in emergency situations with severe obstruction, but further

study would be useful to verify its potential role in children with mild symptoms.

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