

Salmeterol, a new long acting inhaled β_2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients

ANDERS ULLMAN, NILS SVEDMYR

From the Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden

ABSTRACT Salmeterol is a new inhaled β_2 adrenoceptor agonist, which has been shown in animal experiments to produce a more prolonged bronchodilator effect than currently available β_2 adrenoceptor agonists. It was studied in eight adult asthmatic patients. Each patient received on separate test days salbutamol 200 μg and salmeterol 50, 100, and 200 μg according to a randomised, double blind, crossover design. FEV₁, peak expiratory flow (PEF), heart rate, blood pressure, and tremor were recorded in the clinic for six hours after drug inhalation; PEF was recorded for a further six hours at home. All three doses of salmeterol produced peak increases in FEV₁ (mean 0.5–0.8 l) and PEF (71–100 l/min) similar to those produced by salbutamol 200 μg (0.5 l and 74 l/min). After salbutamol FEV₁ and PEF had returned to baseline within six hours, but after all three doses of salmeterol more than half of the maximum bronchodilator effect remained after 12 hours. The effects of salbutamol and the two lower doses of salmeterol (50 and 100 μg) on cardiovascular measurements and on tremor were similar, whereas after salmeterol 200 μg there was a small decrease in diastolic blood pressure and an increase in heart rate and tremor. Thus inhaled salmeterol has a long acting bronchodilator action in asthmatic patients. This effect may be of value in the treatment of asthma, particularly in patients with nocturnal symptoms.

Introduction

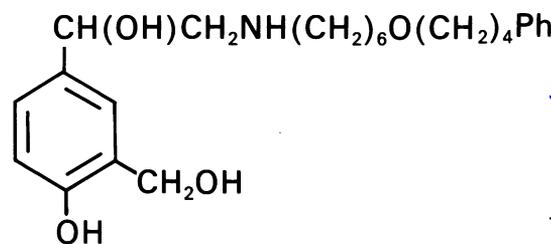
Inhaled β_2 adrenoceptor agonists have become established as first line treatment for the management of acute asthma because of their excellent bronchodilator effects, wide therapeutic range, and low level of side effects.¹⁻⁴ The major disadvantage of currently available inhaled β_2 adrenoceptor agonists is their short duration of action; none of the currently available inhaled β agonists has an effect lasting for more than six hours.^{5,6} Consequently, oral bronchodilator drugs may need to be added to other treatment for patients with early morning dyspnoea or wheeze. The availability of a longer acting inhaled β_2 adrenoceptor agonist would therefore appear to be an important therapeutic advance.

Salmeterol hydroxynaphthoate is a β_2 adrenoceptor agonist that has been shown to produce long acting bronchodilatation in both in vitro and in vivo animal

Address for reprint requests: Dr Anders Ullman, Department of Clinical Pharmacology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden.

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Salmeterol



Salbutamol

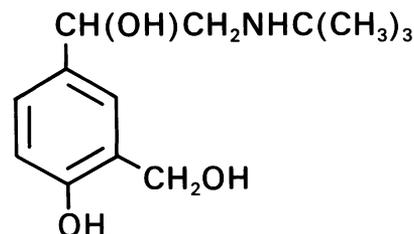


Fig 1 Chemical structures of salbutamol and salmeterol.

Table 1 Characteristics of the patients

Patient No	Sex	Age (y)	Height (cm)	Smoking history	FEV ₁			Treatment	
					l	% pred	Reversibility (%)	Oral	Inhaled
1	M	62	171	NS	1.51	49	23	th, tb	becl, sb
2	M	63	178	NS	1.41	42	33		becl, sb
3	M	67	183	NS	1.53	44	47	tb, pred, bh	becl, tb
4	M	67	184	ES	2.58	75	32	tb	sb
5	M	61	167	NS	2.26	77	25	sb	becl, sb
6	M	42	182	ES	3.12	76	25		becl, sb
7	M	64	172	NS	2.26	74	49	th	becl, sb
8	F	58	168	S	1.58	61	42	th, tb, pred	becl, sb

S, smoker; ES, ex-smoker; NS, non-smoker; th, theophylline; tb, terbutaline; becl, beclomethasone; sb, salbutamol; pred, prednisolone; bh, bromhexine.

studies.^{7,8} The β_2 selectivity of salmeterol has been shown to be similar to that of salbutamol (Glaxo, on file). On the basis of results of oral dosing and animal studies, the plasma half life of salmeterol seems to be in the same range as that of salbutamol (Glaxo, on file). The chemical structures of salmeterol and salbutamol are shown in figure 1.

The aim of our study was to compare the peak bronchodilator response and duration of action of three doses of inhaled salmeterol with those of salbutamol in adults with asthma, and to measure the effects of these drugs on blood pressure, heart rate, and skeletal muscle tremor.

Methods

We studied eight adult patients, seven male and one female, with a documented history of non-atopic asthma (table 1). Each patient had previously shown an increase in FEV₁ of 20% or more 15 minutes after inhaling salbutamol 200 μ g. On four separate study days the patients received either salmeterol 50, 100, or 200 μ g or salbutamol 200 μ g according to a randomised, double blind, placebo controlled, crossover design.

Patients arrived at the laboratory at 7.30 am, after a light breakfast. Inhaled β_2 adrenoceptor stimulants

were withheld for 12 hours before the study, oral β_2 adrenoceptor stimulants for 24 hours, and slow release theophylline for 36 hours. Patients taking inhaled corticosteroids continued this treatment at a constant dose, throughout the study. The patients rested in a semirecumbent posture for 50–70 minutes, after which the following measurements were made: (1) Heart rate, determined from continuous electrocardiographic recordings. (2) Blood pressure, determined by a sphygmomanometer. (3) Skeletal muscle tremor, recorded by means of a single plane accelerometer (Grass Instrument Co) connected to a Grass polygraph via a Grass integrator; the accelerometer was fixed to the right hand middle finger and recordings were made over 90 seconds.⁹ In addition, subjective tremor was scored by the patients. (4) Forced expiratory volume (FEV₁) measured by a Collin's survey spirometer (two recordings made and the higher value used). (5) Peak expiratory flow rate (PEF) measured by a Wright peak flow meter (two recordings made and the higher value used).

After these basal measurements either salbutamol 200 μ g or salmeterol 50, 100, or 200 μ g was administered and the above measurements were made 20, 40, 60, and 90 minutes and 2, 3, 4, 5, and 6 hours after the drug had been given. The patients were then allowed to leave the laboratory. At home patients measured PEF

Table 2 Mean (SEM) FEV₁ and peak flow (PEF) before and 0.3–12 hours after inhalation of single doses of salbutamol and salmeterol in the eight patients

Time (h)	Salmeterol							
	Salbutamol 200 μ g		50 μ g		100 μ g		200 μ g	
	FEV ₁	PEF	FEV ₁	PEF	FEV ₁	PEF	FEV ₁	PEF
0	2.2 (0.2)	417 (27)	2.1 (0.2)	398 (27)	2.2 (0.3)	428 (39)	2.1 (0.3)	408 (35)
0.3	2.7 (0.2)	487 (32)	2.5 (0.2)	459 (27)	2.6 (0.2)	481 (36)	2.6 (0.2)	488 (32)
2	2.7 (0.3)	491 (30)	2.7 (0.2)	491 (28)	2.7 (0.3)	499 (28)	2.9 (0.2)	508 (33)
6	2.2 (0.3)	426 (30)	2.6 (0.3)	481 (32)	2.6 (0.3)	479 (35)	2.7 (0.2)	494 (33)
12	—	411 (28)	—	460 (33)*	—	469 (32)*	—	489 (27)**

*p \leq 0.05 by comparison with salbutamol 200 μ g; **p \leq 0.01 by comparison with salbutamol 200 μ g.

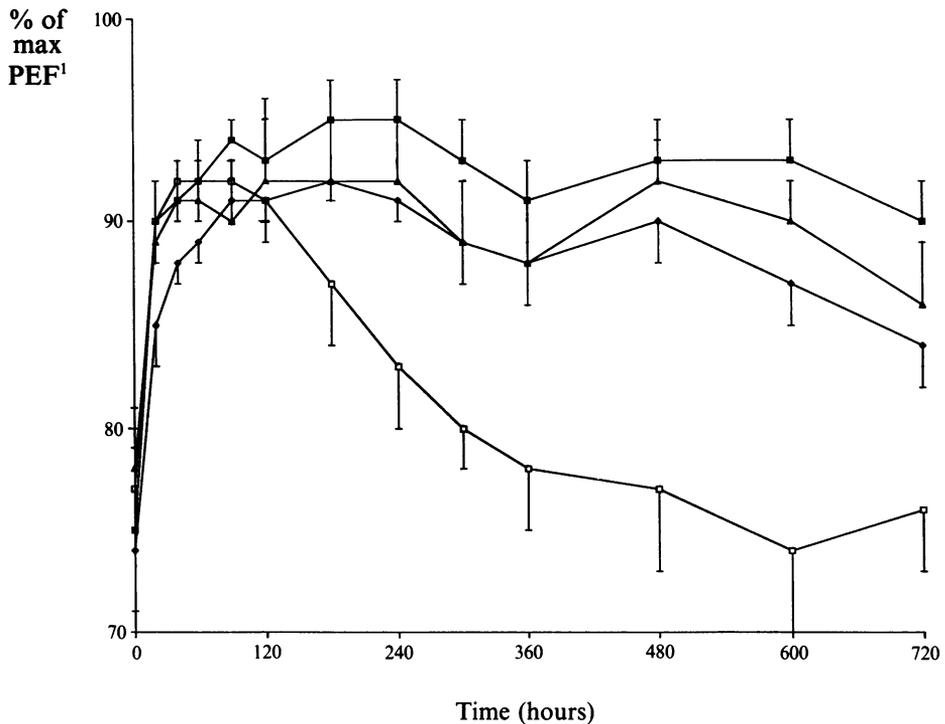


Fig 2 Peak flow (PEF) after inhalation of salbutamol 200 µg (□) and salmeterol 50 µg (◆), 100 µg (▲), and 200 µg (■). PEF is expressed as mean (SEM) percentage of the best individual registration over the four test days.

8, 10, and 12 hours after inhalation of the study drug.

For statistical comparison Friedman's test was used, followed by Wilcoxon's signed rank test when appropriate. The PEF value is expressed as a percentage of the maximum PEF for each patient during the four test days. Tremor is expressed as the ratio between measured and the basal value. Heart rate and blood pressure are expressed in terms of the change from the basal value. Basal values for blood pressure were taken as the mean of recordings carried out 10 and 30 minutes before the study drug was given. The effects of the drugs on blood pressure, heart rate, and tremor were compared by calculating the mean of the individual peak values within six hours of each treatment.

Results

Peak flow Mean basal PEF values were similar on the four study days (table 2). PEF rose after all doses of salmeterol and after salbutamol. The increase in PEF was more prolonged after all the salmeterol doses than after salbutamol (fig 2, table 2). The area under the curve (AUC) for the first two hours after adminis-

tration of the drug was similar and did not differ significantly between the three salmeterol doses and salbutamol, whereas the AUC over 12 hours was significantly greater for all salmeterol doses than for salbutamol ($p \leq 0.01$). The differences in AUC over 12 hours between the three salmeterol doses were fairly small and significant only between the 50 and 200 µg doses ($p \leq 0.01$).

FEV₁ Mean basal values were similar on the four study days (table 2). Both salbutamol and salmeterol produced a rapid increase in FEV₁. The increase over baseline two hours after administration did not differ significantly between any of the different treatments. After salbutamol the FEV₁ had returned to baseline within six hours, whereas a significant increase over baseline remained six hours after inhalation of salmeterol ($p \leq 0.05$; table 2).

Heart rate Mean basal values of heart rate for the four test days were similar. After salbutamol and salmeterol 50 and 100 µg there were small, non-significant decreases in heart rate. Salmeterol 200 µg produced an increase in heart rate with the peak effect two hours after inhalation (fig 3). The mean maximum increase over baseline was significantly higher for

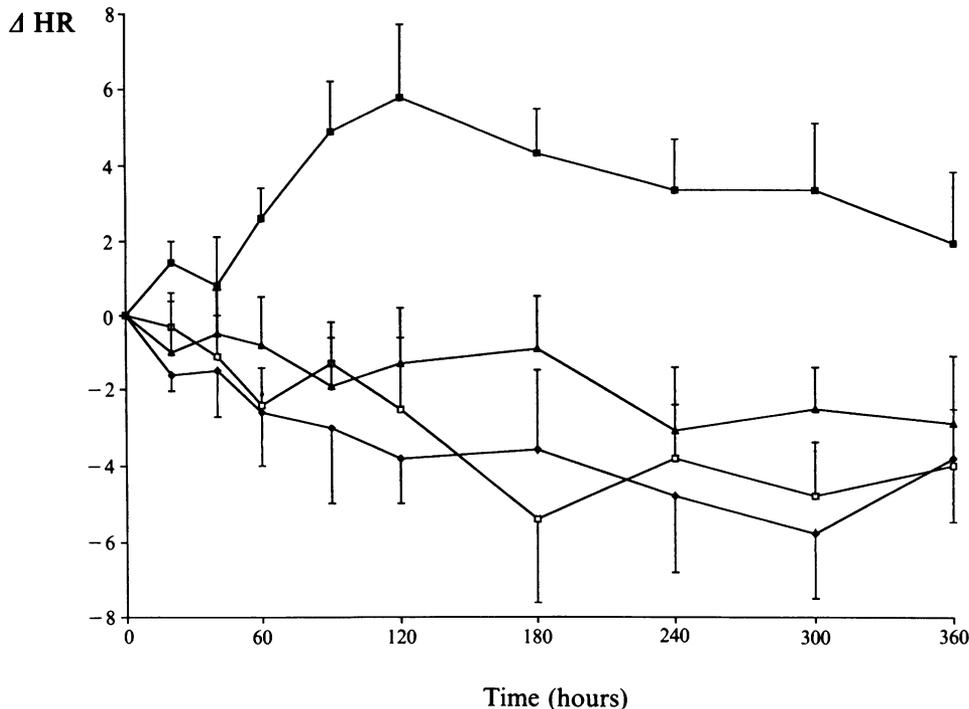


Fig 3 Changes in mean (SEM) heart rate from baseline (Δ HR) over six hours after inhalation of salbutamol 200 μ g (□) and salmeterol 50 μ g (◆), 100 μ g (▲), and 200 μ g (■).

salmeterol 200 μ g (8.2 (SEM 1.8) beats/min) than for salbutamol (1.7 (0.7) beats/min; $p \leq 0.01$).

Blood pressure Systolic blood pressure showed only minor and non-significant differences between the different treatments. The maximum fall in diastolic blood pressure was significant only for salmeterol 200 μ g (11 (SEM 3) mm Hg; $p \leq 0.05$).

Skeletal muscle tremor The ratio between the individual maximum tremor recordings and basal tremor was 1.4 (SEM 0.2) for salbutamol and 1.4 (1) for salmeterol 50 μ g, which did not differ significantly. The higher doses of salmeterol produced a greater increase in tremor ratio. It was 1.7 (SEM 0.23) for salmeterol 100 μ g ($p \leq 0.05$) and 2.2 (0.18) for salmeterol 200 μ g ($p \leq 0.01$). Subjective tremor, however, was reported by only two patients, after salmeterol 200 μ g.

Discussion

These data confirm that in asthmatic patients salmeterol is a potent long acting bronchodilator. All doses of salmeterol produced maximum bronchodilatation similar to that produced by 200 μ g salbutamol. There were no significant differences in

the time of onset between the three doses of salmeterol and salbutamol. All three doses of salmeterol had a longer duration of action than salbutamol 200 μ g and produced bronchodilatation throughout the 12 hour study period. There was a trend suggesting greater bronchodilatation by 200 μ g salmeterol than by the 50 or 100 μ g doses. Blood pressure, skeletal muscle tremor, and heart rate did not differ significantly between the 50 or 100 μ g dose of salmeterol and 200 μ g salbutamol. Salmeterol 200 μ g, however, had a more pronounced effect on heart rate, skeletal muscle tremor, and diastolic blood pressure. Our results suggest that salmeterol in doses of 50–100 μ g is approximately equipotent to 200 μ g of salbutamol, in terms of peak bronchodilator effect. These doses did not differ in their effects on the cardiovascular system or skeletal muscle tremor, but all doses of salmeterol produced bronchodilatation that lasted almost three times as long as that of salbutamol.

The pharmacological mechanism or mechanisms of the long duration of salmeterol are not clear. The plasma half life of the drug approximates to that of salbutamol (Glaxo, on file) providing further evidence that the duration of action of inhaled β_2 agonists is not closely related to their plasma half life. This is not

surprising as the bronchodilating effect of inhaled clenbuterol, a β_2 agonist with a plasma half life of about 20 hours, did not differ in duration of action from that of salbutamol, an agonist with a plasma half life of three hours (K Svedmyr, personal communication). Salmeterol was designed by modifying salbutamol to obtain a drug with much greater affinity for its receptors because of increased exoreceptor binding.¹⁰ The consequence of this would be that salmeterol would be localised to and persist in the vicinity of β_2 adrenoceptors. This may be true, but other explanations are possible. For example, it has recently been shown that the airway epithelium constitutes a diffusion barrier through which bronchodilators pass at different speeds (E Widmark and B Waldeck, paper presented to World Conference on Clinical Pharmacology and Therapeutics, 1986). Possibly therefore the airway epithelium acts as a reservoir for bronchodilator drugs.

It has been shown recently that terbutaline, when administered regularly for 14 days, produces a rebound increase in bronchial reactivity to histamine. In addition, the protection against histamine induced bronchoconstriction was found to be lower on day 14 than on day 1.¹¹ A receptor agonist with such a long lasting effect as salmeterol might produce tachyphylaxis as well as possibly affecting bronchial reactivity. Studies are required therefore to investigate the possibility that tachyphylaxis as well as changes in bronchial responsiveness may result from long term administration of salmeterol.

In conclusion, our results indicate that inhaled salmeterol produces long lasting bronchodilatation in asthmatic patients with no differences in cardiovascular effects or skeletal muscle tremor between salmeterol and equipotent doses of salbutamol. The long duration of action of this drug may be of value in the treatment of asthma, particularly in those patients with nocturnal symptoms.

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