

Twelve months, treatment with inhaled salmeterol in asthmatic patients

Effects on β_2 -receptor function and inflammatory cells

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Salmeterol is a new β_2 -receptor agonist with a prolonged duration of action after inhalation, exceeding 12 h in most patients. We have performed a 12-month open follow-up study on 11 patients with reversible asthma. All patients were given salmeterol inhalations (50 μ g twice daily). Additional asthma treatment included inhaled corticosteroids in all patients, and oral slow-release theophylline or β_2 -receptor agonists in a minority of patients (3 and 1, respectively). Before salmeterol treatment was initiated and after 3, 6, 9 and 12 months of salmeterol treatment, a cumulative dose-response curve to inhaled salbutamol (100, 300 and 900 μ g) was performed, and FEV₁ measured. We also evaluated the effect of each salbutamol dose on finger tremor, systemic blood pressure and heart rate. Blood tests, including white blood count and electrolytes, were taken at each visit. After salmeterol treatment was initiated, morning FEV₁, measured before the morning asthma medication, was significantly improved ($p < 0.05$). The responsiveness to inhaled salbutamol was not decreased during salmeterol treatment, except in one patient with asthma worsening over the study year. Baseline finger tremor measured before salbutamol dose-response curves, was significantly lower at the 12-month visit than before treatment was initiated ($p < 0.05$). Effects of salbutamol on systemic blood pressure, heart rate or finger tremor was not significantly changed during salmeterol treatment. We found a successive and significant decrease in blood eosinophils ($p < 0.05$) during the 12 months of salmeterol treatment, when the patient with asthma worsening was excluded in the analysis. Also platelet count was significantly decreased during the treatment period ($p < 0.001$), although within the normal range for all patients. In the present study, we found no evidence that long-term treatment with inhaled salmeterol (50 μ g twice daily) produced decreased β_2 -receptor sensitivity in airways.

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β_2 -receptor agonists given by inhaled route are included in the first-line treatment of asthma, together with inhaled corticosteroids, because of their excellent bronchodilating effects (5, 10, 11, 14, 15). One problem with the commonly used shorter-acting compounds (i.e. salbutamol, terbutaline and fenoterol) is that they have a relatively short duration of action, not longer than 6 h (14, 15). Thus, addition of oral bronchodilators, such as slow-release xanthines or β_2 -receptor agonists, often has to be given for acceptable asthma management. However, in re-

cent years, new longer-acting β_2 -receptor agonists for inhalation have been developed that only have to be given with 12 h intervals to maintain bronchodilatation throughout day and night (5, 14, 15). After a single dose of salmeterol, 70% of bronchodilating effect will remain after 12 h (14). This prolonged action leads to substantial improvement of asthma symptom control, as well as low frequency of side-effects (1).

Recently, Sears et al. (9) published a study where they found that regular treatment 4 times daily with fenoterol leads to worsened asthma control, as compared with more random dosage, as required by the patient. The authors suggest that β_2 -receptor desensitization possibly was induced during regular treat-

Abbreviations: FEV₁: forced expiratory volume at 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; HR: heart rate; BP: blood pressure.

ment with β_2 -receptor agonists, and implied that this effect may be even more pronounced with the new long-acting β_2 -receptor agonists, salmeterol and formoterol. However, in a previous study, we have shown that salmeterol treatment for 2 weeks did not induce any decreased sensitivity to inhaled salbutamol (15), suggesting that bronchial smooth muscle β_2 -receptors had unchanged sensitivity after such a short treatment period with salmeterol. To further evaluate whether long-term treatment with salmeterol would lead to β_2 -receptor desensitization, we continued studying the same patients for an additional 12 months. Salmeterol was given at a dose of 50 μg twice daily. To monitor β_2 -receptor sensitivity, we performed reversibility tests with 3 doses of inhaled salbutamol (100, 300 and 900 μg), measuring FEV₁ after each dose. This procedure was performed before and 3, 6, 9 and 12 months after salmeterol treatment was initiated. In addition, we monitored finger tremor, changes in heart rate and systemic blood pressure, as well as blood cells and plasma electrolytes.

Methods

Design and patients

This study was designed as an open 12-month follow-up of 12 asthmatic patients included in a previous study with salmeterol (15). One patient withdrew after the second visit, because of personal reasons unrelated to the study. All patients had asthma in a stable phase, and had demonstrated a reversibility of FEV₁ to inhaled salbutamol of at least 15% after 200 μg or 20% after 500 μg tested earlier. The maximal reversibility with 1300 μg salbutamol at visit No. 1 in the present study is shown in Table 1. At least 3 months without treatment with long-acting β_2 -receptor agonists was allowed before inclusion in the present study. Patients receiving regular treatment with inhaled corticosteroids, and oral slow-

release theophylline or β_2 -receptor agonists were allowed to retain this medication unchanged during the present study. Salmeterol 50 μg twice daily was given to all patients. Rescue inhalation of salbutamol (100 $\mu\text{g}/\text{puff}$) was permitted as the patient required. Any changes in regular asthma treatment during the study are shown in Table 1. Prior to each study day at the clinic, slow-release theophylline or terbutaline were withheld for 36 h, salmeterol for 24 h, and inhaled salbutamol for 12 h, whereas inhaled corticosteroids were continued.

Patients were admitted to the clinic at 5 different occasions, before initiation of salmeterol treatment, and after 3, 6, 9 and 12 months of treatment. Firstly, the patients were presented with a visual analog scale (VAS) to rate general well-being, quality of night sleep, degree of dyspnea, and subjective evaluation of the duration of action of asthma medication. Secondly, routine blood tests were taken for assessment of white blood cells, platelets, and electrolytes. Subsequently, baseline FEV₁ and FVC, systemic blood pressure (BP), heart rate (HR) and finger tremor were measured. The cumulative doses of salbutamol (100, 300 and 900 μg) were given by metered dose inhaler, connected to a spacer (Volumatic®), and FEV₁, BP, HR and tremor were measured 15 min after each dose. In addition, 30 and 60 min after the highest dose of salbutamol (900 μg), 2 additional measurement procedures were performed (including FEV₁, BP, HR and tremor).

FEV₁ and FVC were measured using a Vicatest 3 spirometer connected to a Macintosh II personal computer, using specialized software (MacSpiro, Collingsworth Electronics, UK). HR was continuously monitored from ECG. BP was measured with the cuff method. Objective skeletal muscle tremor was measured from a single-plane accelerometer (Grass Instruments, Quincy, MA, USA), connected to an Analog-Digital converter board (MIO-16, National Instruments, Austin, TX, USA) and analyzed with a data acquisition software (LabView 2, Na-

Table 1. Patient history

Pat.	Sex	Age	Weight	Height	Smoker	FEV % pred	Reversib. %	Asthma med.	Change of med.
1	F	40	63	162	N	77	52	Bi, Si	
2	M	67	73	170	N	93	40	Bi, Si	
3	M	66	66	170	EX	48	39	Bi, Si, Tho	Incr. Bi at 9 m, β_2 at 9 m
4	M	70	81	184	EX	73	33	Bi, Si	
5	M	68	75	165	EX	59	29	Bi, Si, β_2	
6	F	56	62	161	S	65	13	Bi, Si, Tho	
7	M	62	80	173	EX	71	22	Bi, Si	
8	M	64	84	180	S	55	24	Bi, Si	
9	F	27	62	171	N	86	11	Bi, Si	
10	M	66	75	174	EX	42	68	Bi, Si	
11	F	62	50	145	N	76	27	Bi, Si, Tho	

Bi=beclomethasone inhalation; Si=salbutamol inhalation; Tho=oral slow release theophylline; β_2 =oral slow release terbutaline m=duration of salmeterol treatment in months.

tional Instruments). The accelerometer was attached to the middle finger of the left hand, and a recording was made for 50 s using a previously described method (12).

For 1 week after each visit, the patients measured peak expiratory flow (PEF) twice daily. PEF was measured with a mini-Wright PEF-meter before the morning and evening doses of asthma drugs, including salmeterol. The PEF values were recorded on diary cards together with the number of rescue doses of salbutamol inhalations, and possible side-effects.

Statistics

All statistics were performed using a Macintosh II computer and a standard statistical package (Stat-View II, Abacus Concept, USA). The statistical analysis used was paired Student's *t*-test. A *p* value < 0.05 was considered significant.

Results

Although 12 patients were included in the study, one patient withdrew after 3 months for personal reasons unrelated to the asthma treatment. Therefore, only data from 11 patients are presented. Asthma treatments, other than salmeterol, are shown in Table 1. All anti-asthma treatments were maintained constant for all patients, except for Patient 3, who received increased dose of inhaled corticosteroids after 9 months of salmeterol treatment, due to asthma worsening during the year.

Baseline measurements

After salmeterol treatment was initiated, baseline FEV₁ increased significantly compared to that prior to treatment ($p < 0.05$, Fig. 1), and this improvement was maintained over the 12 months. However, salmeterol treatment did not significantly affect either baseline systolic BP, diastolic BP or HR (124 ± 4 , 75 ± 3 and 66 ± 4 before treatment, and 126 ± 4 , 77 ± 3 and 68 ± 4 after 12 months, treatment, respectively). Baseline finger tremor was slightly decreased at the 12-month visit compared to before treatment (10.1 ± 1.6 , 10.2 ± 1.3 , 10.8 ± 1.4 , 10.4 ± 2.7 , 6.6 ± 1.2 [arbitrary units $\pm$ SEM] for the visits at 0, 3, 9, 12 months, respectively: $p < 0.05$ for 0 vs 12 months).

Reversibility tests to salbutamol

There were no signs of shift in FEV₁ during the reversibility test with salbutamol, as shown in Fig. 2. Inhalation of increasing doses of salbutamol (100, 300 and 900 μ g) produced a small but significant

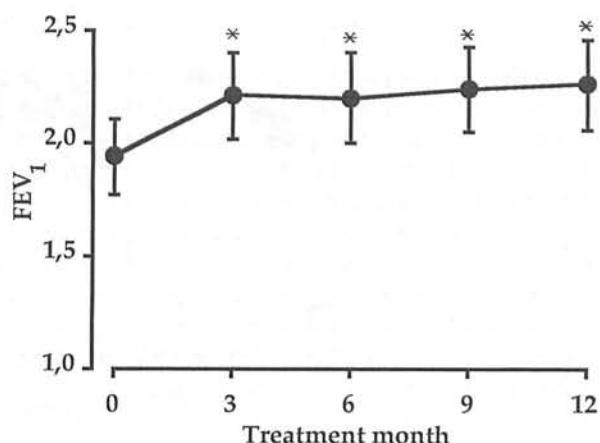


Fig. 1. Baseline FEV₁, measured 24 h after last dose of salmeterol, and 12 h after last dose of salbutamol, before and after 3, 6, 9 and 12 months of treatment with salmeterol (50 μ g $\times$ 2). During the treatment period there was a significant increase in baseline FEV₁. Data shown as mean $\pm$ SEM (**p* < 0.05).

increase in systolic BP, a decrease in diastolic BP, as well as an increase in HR (data not shown). Finger tremor also significantly increased with salbutamol (data not shown). Salmeterol treatment over 12 months did not alter these effects in any significant way.

In one patient (No. 3) a subjective worsening of asthma was also objectively observed as decreased FEV₁, and lower maximum FEV₁ after reversibility tests with salbutamol (Fig. 2). The cause of this deterioration of airway function is unknown, but led to an increase in the dosage of inhaled corticosteroids during the study period (Table 1).

PEF-measurements, rescue medication and visual analog score

The mean PEF measurements (mean for the whole week after each visit to the clinic), before each morning or evening dose of salmeterol, were not significantly changed over the 12-month treatment period for the morning values (427 ± 18 , 430 ± 24 , 429 ± 24 , 426 ± 26 and 435 ± 27 after 0, 3, 6, 9 and 12 months, respectively), or evening values (434 ± 19 , 435 ± 24 , 430 ± 24 , 432 ± 24 and 432 ± 26 after 0, 3, 6, 9 and 12 months, respectively). The use of extra inhalations of salbutamol during the monitoring weeks is shown in Table 2. Initially, 2 patients used extra salbutamol during the day, but this decreased to one patient after 3 months. During the night, 3 patients used extra salbutamol throughout the 12-month treatment period.

Visual analog scoring to rate general well-being, quality of night sleep, degree of dyspnea, and subjective evaluation of the duration of action of asthma medication are shown in Table 3. There was no significant improvement in any of these parameters,

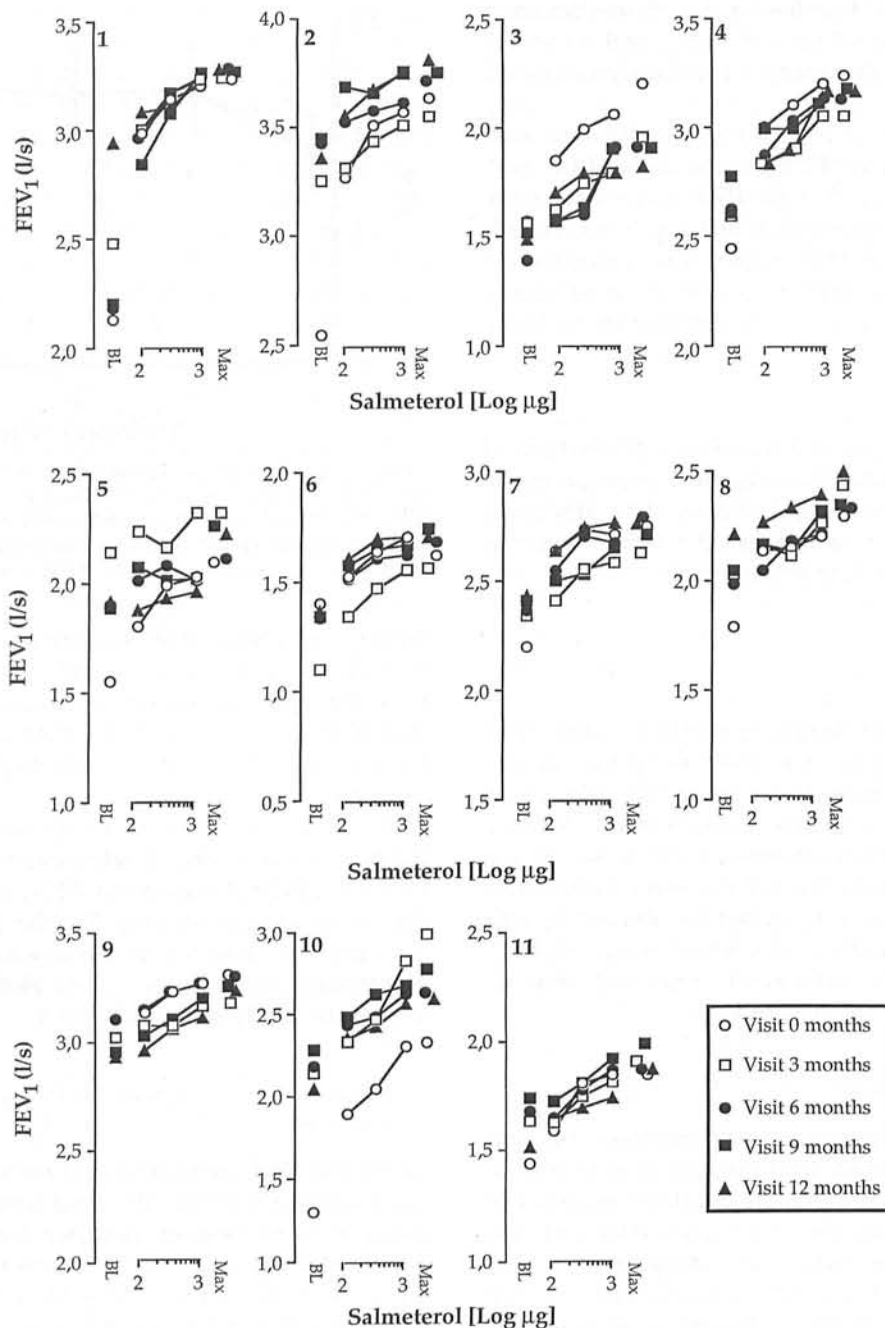


Fig. 2. Salbutamol dose-response curves from each individual patient (Patient No. as indicated), showing reversibility of FEV₁ measured before, and after 3, 6, 9 and 12 months treatment with salmeterol (50 µg × 2). There was no sign of overall shift in the reversibility of FEV₁ over the treatment period with salmeterol. BL = baseline FEV₁ before reversibility test. Max = maximum measured FEV₁ after the last dose of salbutamol.

except for dyspnea after 3 months, treatment, and increased subjective rating of long duration of action of the asthma medication (Table 3).

Effects on white blood cells and electrolytes

Over the 12-month treatment period, salmeterol had no significant effect on white blood count (WBC), %

polymorphonuclear cells (PMN), % lymphocytes, % monocytes or % basophils, but significantly decreased the % eosinophils and the number of platelets in total blood (Table 4, $p < 0.05$ and 0.001 , respectively). Although a significant decrease in total number of platelets was found, no patient acquired pathologically low values, as specified by the Sahlgrens University Hospital ($150\text{--}350 \times 10^9$ platelets/

Table 2. Rescue medication. Mean daily extra inhalations (rescue) of salbutamol over the week following the visit to the clinic (at 0, 3, 6, 9, and 12 months)

	Months of salmeterol treatment				
	0	3	6	9	12
<i>Day</i>					
No. of patients (total 11)	2	1	1	1	1
No. inhalations (mean/day)	0.5	0.9	1.1	0.6	0.9
<i>Night</i>					
No. patients (total 11)	3	3	3	3	3
No. inhalations (mean) (mean/night)	1.3	1.3	1.3	1.1	1

l). Patient 3 was excluded in the analysis of B eosinophils and platelet count, because of asthma worsening during the study year, requiring increasing dosage of inhaled corticosteroids.

Over the 12-month treatment period, there was no significant change in S-Na, S-K, or S-Ca, except for a small decrease of S-Ca at 3 months (Table 4).

Discussion

In the present open study, evaluating the effects of 12 months, treatment with salmeterol, we found no evidence that salmeterol altered airway sensitivity to salbutamol. Further, we did not find any decreased sensitivity in the circulatory responses (BP and HR), but a small decrease in baseline finger tremor. Baseline FEV₁, measured 24 h after the last dose of salmeterol, was significantly improved during the study period. The overall asthma control, measured objectively with PEF, and subjectively with VAS, was well maintained during the salmeterol treatment. Lastly, we found that salmeterol significantly diminished the relative number of eosinophils in blood, as well as the total platelet count.

When discussing this study, it is important to remember that it is an open follow-up, and does not contain a control group. Thus, the data must be considered with care. All patients had previously been treated for several years with inhaled salbutamol or terbutaline, which could have induced some

Table 3. Visual-analog scoring of general well-being, quality of night sleep, degree of dyspnea, and subjective evaluation of the duration of action of asthma medication, calculated as % highest score

	Months of salmeterol treatment					0%	100%
	0	3	6	9	12		
Well-being	81±5	89±3	79±7	84±4	80±5	very bad	very good
Night sleep	75±7	90±2	86±3	80±7	81±4	very bad	very good
Dyspnea	73±7	90±3*	81±8	88±4	81±7	very much	not at all
Duration	56±8	91±2**	80±9*	86±5**	90±2**	very short	very long

Data shown as mean±SEM. * $p < 0.05$, ** $p < 0.01$.

Table 4. Routine laboratory parameters

	Months of salmeterol treatment				
	0	3	6	9	12
WBC ($10^9/l$)	7.0±0.6	6.3±0.4	6.3±0.5	6.6±0.4	6.8±0.4
% PMN	57±2	59±2	59±2	57±1	60±2
% lymphocytes	66±4	66±3	65±3	64±3	68±4
% monocytes	7.1±0.3	7.0±0.4	7.1±0.3	6.7±0.5	7.1±0.3
% basophils	1.0±0.9	1.1±0.1	1.0±0.1	1.0±0.1	0.9±0.1
% eosinophils	9.2±0.6	5.1±0.6	5.1±0.5*	4.8±0.7*	4.3±0.4**
Platelets ($10^9/l$)	318±26	282±21	288±23*	278±23**	243±16**
<i>Electrolytes</i>					
S-Na (mmol/l)	142±1	143±1	142±1	141±1	141±1
S-K (mmol/l)	4.2±0.1	4.2±0.1	4.3±0.1	4.3±0.1	4.2±0.1
S-Ca (mmol/l)	2.36±0.03	2.27±0.02*	2.30±0.02	2.34±0.02	2.37±0.03

Data shown as mean±SEM. * $P < 0.05$, ** $P < 0.01$.

Effect of 12 months, salmeterol treatment on white blood count (WBC), differential counts of polymorphonuclear leucocytes (PMN), lymphocytes, mononuclear cells, basophils, eosinophils, and total number of blood platelets. Patient 3 was excluded from the calculation of these values because of increased dosage of inhaled corticosteroids during the study (Table 1). Also the effects on serum electrolytes are shown (S-Na, S-k and S-Ca).

degree of desensitization of β_2 -receptors in the airways (2, 10, 11, 16). We found no evidence that the more long-acting β_2 -agonist, salmeterol, produced any additional desensitization of β_2 -receptors in the airways compared to the previous asthma treatment. In this study, all patients were receiving inhaled corticosteroids, which may inhibit β_2 -receptor desensitization (11). Further, we found no desensitization of BP or HR responses to salbutamol, although a small inhibition of the baseline (or total) tremor was seen at the 12-month visit. Thus, in the present study, 50 μ g of inhaled salmeterol twice daily did not seem to induce β_2 -receptor desensitization either in the airways or systemically.

At the later visits to the clinic during this study (3, 6, 9 and 12 months), we found that baseline FEV₁ was significantly higher than at the first visit. Thus, morning lung function was better during salmeterol treatment, than before. This finding may be explained by at least two mechanisms. First, it is possible that the latest salmeterol dose, given 24 h before, the FEV₁-measurement, maintained significant bronchodilating effects. However, Twentyman et al. did not find that salmeterol had any direct bronchial relaxant effects 34 h after inhalation, although bronchial hyperresponsiveness was significantly inhibited at this time (13). Second, salmeterol may have had some anti-inflammatory effect in the airways, leading to prolonged control of asthma. The latter suggestion is supported by our findings in a previous study, where patients receiving 2 weeks treatment with salmeterol had better asthma control (PEF) during 1 week after salmeterol was discontinued (15). Also, salmeterol has been shown to have some anti-inflammatory effects in experimental animals (5) which are longer-acting than the effects of more shorter acting β_2 -receptor agonists (5, 8). These anti-inflammatory properties have recently been confirmed in asthmatics by bronchoscopy and bronchoalveolar lavage techniques (4, 7). Thus, salmeterol may lead to an increased airway caliber in asthma partly due to smooth muscle relaxant properties, but also perhaps through other, more long-acting mechanisms, such as inhibition of airway inflammation and airway wall edema. In the present study, we found that during salmeterol treatment there was a significant decrease in the relative number of eosinophils in blood, which could possibly reflect an anti-inflammatory effect, because the asthmatic inflammation is characterized by eosinophilia (3). The significant decrease in total number of platelets in blood during the study period is more difficult to explain. Possibly, this also may be an anti-inflammatory property of salmeterol, since platelets in airway walls have been implied in airway inflammation (6). We found no evidence that platelets were diminished to pathologically low values. One patient

received increasing doses of inhaled glucocorticoid during the treatment period, but was not included in the analysis of white blood cells and platelets.

Even though salmeterol may have some anti-inflammatory effects in the airways of asthmatics, there are no data available to suggest that this drug lessens the requirement of inhaled corticosteroids in asthmatics.

Overall asthma control was objectively tested with PEF curves 1 week after each visit, showing a maintained anti-asthmatic effect of the treatment. In addition, the visual scores of general well-being, quality of night sleep, degree of dyspnea were maintained high, or improved slightly during salmeterol treatment. Further, the patients found that salmeterol subjectively had a much longer duration of action compared to previous medication. We found no evidence that 12 months, treatment with regular twice daily treatment with salmeterol could produce deterioration of asthma control, as was suggested by Sears et al. (9). By contrast, long-acting β_2 -receptor agonists, such as salmeterol, seem to be of benefit to the patient, improving asthma control and possibly patient compliance, as compared with shorter-acting β_2 -agonists (1, 14, 15).

In the present study, the patients were carefully followed in the clinic, and they received general information about asthma. Thus, the compliance to prescribed asthma treatment may have been improved during the study period, and more careful administration of inhaled corticosteroids by the patients may have contributed to the general improvement and the anti-inflammatory effects.

In summary, the present 12-month open follow-up study shows no evidence of decreased β_2 -receptor sensitivity in airways during treatment with salmeterol. By contrast, overall asthma control appeared to be improved for most patients. Further studies, preferably on previously untreated asthmatic patients, may give additional information about whether β_2 -receptor desensitization develops in the airways during treatment with long-acting β_2 -receptor agonists.

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