One Year Treatment with Salmeterol Compared with Beclomethasone in Children with Asthma

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The aim of this study was to compare the effects of salmeterol and beclomethasone on lung function and symptoms in children with mild to moderate asthma. Sixty-seven children not treated with inhaled corticosteroids were randomized in a double-blind parallel study either to salmeterol 50 μg b.i.d. or beclomethasone 200 μg b.i.d. After one year, FEV_1 significantly increased in the beclomethasone group, whereas in the salmeterol group there was a small reduction. Differences between groups were 14.2% predicted ($p < 0.0001$) and 7.0% predicted ($p = 0.007$) for pre- and postbronchodilator FEV_1 values, respectively. PD_{20} methacholine decreased by 0.73 DD ($p = 0.05$) in the salmeterol group and increased by 2.02 DD ($p < 0.0001$) in the beclomethasone group. Morning and evening PEF and symptom scores improved in both groups, although more in the beclomethasone group. Asthma exacerbations, for which prednisolone was needed, were more frequent in the salmeterol group (17 versus two), as were the number of withdrawals due to exacerbations (six versus one). However, growth was significantly slower in the beclomethasone group (−0.28 SDS) compared with that in the salmeterol group (−0.03 SDS) ($p = 0.001$). We conclude that treatment with a moderate dose of beclomethasone is superior to salmeterol in children with mild to moderate asthma and recommend that salmeterol should not be used as monotherapy. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF and the Dutch Paediatric Asthma Study Group. One year treatment with salmeterol compared with beclomethasone in children with asthma.

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Short-acting inhaled beta-agonists offer rapid and effective symptom relief for asthmatic children (1). Their limited duration of action, however, makes them less suitable for controlling symptoms throughout the entire 24-hour period. Furthermore, asthma is now recognized as a chronic inflammatory disease of the airway wall; hence, recent guidelines have focused on anti-inflammatory treatment by either cromoglycate or inhaled corticosteroids (2, 3). Despite this daily prophylactic treatment many children still suffer from asthma symptoms (4). In particular, exercise-induced and nocturnal symptoms result in substantial discomfort to children as well as to their parents (5). Taken as a single dose salmeterol, a new long-acting inhaled beta-2-agonist has a bronchodilating effect of at least 12 hours in adults as well as children (6, 7). Protection against methacholine- and histamine-induced airway obstruction lasts for 12 to 24 hours (7, 8). Single-dose studies show prolonged protection against other broncho-constricting stimuli such as exercise (9), hyperventilation with dry cold air (10), and allergen (11). Twice daily dosing of salmeterol may result in a 24-hour protection against various bronchoconstricting stimuli and therefore lessen symptoms in asthmatic patients. Compared with salbutamol, twice daily salmeterol for several weeks or months in adults as well as children results in fewer symptoms, less need for additional bronchodilator treatment and better improvement in peak-flow rates (12, 13). However, in these studies, some of the patients were already on treatment with either cromoglycate or inhaled corticosteroid, making it difficult to estimate the true therapeutic potential of salmeterol. The aim of our study was to compare the effect of 1-year treatment with salmeterol with the effect of treatment with an inhaled corticosteroid. The primary efficacy outcome parameters were airway caliber, measured as forced expiratory volume in 1 second (FEV_1) and airway responsiveness to methacholine. Symptom scores, exacerbations, additional use

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of short-acting beta-2-agonists, and peakflow rates were considered as secondary outcomes.

METHODS

Patients

Sixty-seven children aged 6 to 16 yr with mild to moderate asthma were selected from the outpatient pediatric clinics of nine hospitals, six university hospitals, and 3 general hospitals. Patients were recruited between September 1992 and October 1994. All children had mild to moderate asthma according to the American Thoracic Society criteria (14). Patients included in the study had to have: (*1*) a FEV_1 that was 55–90% of predicted value and/or a ratio of FEV_1 to forced vital capacity (FVC) that was 50–75%; (*2*) an increase of at least 10% in FEV_1 after inhalation of 0.8 mg salbutamol; (*3*) airway hyperresponsiveness to methacholine, i.e., a 20% fall in FEV_1 after inhalation of 150 μg or less methacholine (PD_{20} methacholine); this being more than 2 SD below the mean value in healthy children (15); (*4*) an ability to produce reproducible lung function tests, i.e., a variation in three consecutive measurements of FEV_1 of less than 5%; (*5*) a history of stable asthma for at least 1 mo without exacerbations or respiratory tract infections; (*6*) not used inhaled corticosteroids in the previous six mo or cromoglycate in the previous 2 wk. The study was approved by the medical ethics committees of the participating centers. Written informed consent was obtained from all patients and their parents.

Study Design

The study was a double-blind, randomized clinical trial. It consisted of a 6-wk run-in period, a treatment period of 54 wk, and a follow-up period after treatment of 2 wk. In the run-in period the only medication allowed was salbutamol 200 μg on demand, with a maximum of six inhalations per day. In the first and the last week of the run-in period measurements of FEV_1 and FVC before and after bronchodilatation and measurements of PD_{20} methacholine were performed. Lung function inclusion criteria had to be fullfilled at one of these visits. At the end of the run-in period, patients were allocated to one of the two treatments by an independent randomization center. Randomization was stratified for sex, age, center, baseline FEV_1-value, baseline PD_{20}, and prior use of inhaled corticosteroids more than 6 mo before starting the study, using a computerized minimization method (16). Using this method a patient is allocated to a treatment so as to minimize any imbalance between the treatment groups for each stratification factor. Study treatment consisted of either salmeterol xinafoate 50 μg b.i.d. or beclomethasone dipropionate 200 μg b.i.d. All drugs were administered as Rotadisks® in combination with a Diskhaler® (Glaxo Wellcome, Greenford, UK). All children were instructed in the use of this inhalation device prior to entry into the study and their inhalation technique was checked at every visit. For relief of symptoms during the treatment period the use of salbutamol 200 μg Rotadisk was allowed, with a maximum dose of six inhalations per day. Asthma symptoms, which did not sufficiently improve with the maximum dose of rescue salbutamol, were treated with a standard course of prednisolone. On the first day, this started with a dose of 30 or 35 mg, depending on the weight of patients, and was tapered off to zero in 7 days. During the treatment period the response to a bronchodilator (at 12, 24, 36, and 48 wk) and PD_{20} methacholine (at 6, 18, 30, 42, and 54 wk) were measured alternately at intervals of 6 wk. After 54 wk all patients stopped taking randomized treatment for a period of 2 wk. During this follow-up period the only medication allowed was salbutamol on demand. At the end of this period PD_{20} methacholine was measured.

At each clinic visit FEV_1, FVC, PEF, height, body weight, heart rate, and systolic and diastolic blood pressure were measured. Height was measured using a stadiometer in centimeters, corrected to one decimal place. Furthermore, the patients were asked about adverse events and the number of used blisters of study medication and rescue salbutamol were counted.

Throughout the study period patients kept diary cards on which symptoms and additional use of rescue medication were recorded. They also measured PEF using a mini-Wright peak flow meter (Clemente Clarke International Ltd., Harlow, Essex, UK) at home. Symptoms and PEF measurements were recorded during the first 2 wk of each 6-wk period between clinic visits. Dyspnea, wheeze, and cough in the morning and the evening were scored separately, using a scale from 0 to 3. PEF was measured in triplicate morning and evening before taking study medication and all three values were recorded.

Patients were withdrawn from the study if they needed three or more prednisolone courses within 3 mo, if according to the investigator it was not ethical to continue blinded treatment, or if patients or parents wanted to discontinue.

All data were collected and checked by the coordinating center in Rotterdam to ensure completeness. Interim analyses of the study data were made by an independent statistician every year and reviewed by a data monitoring committee. Investigators were kept blind to the results of the interim analyses. The data monitoring committee allowed the study to continue until all patients had completed.

Lung Function Measurements

All lung function measurements were performed between 12 and 18 h after inhalation of the study drug. For each patient the time of measurement was constant throughout the study period. Patients were instructed to take their last dose of study drug before the clinic visit at a fixed time the previous evening. Rescue salbutamol was not allowed in the 8 h before lung function measurement. The time of inhalation of the last dose of study drug, and any use of salbutamol was checked before taking measurements, and, if necessary, lung function measurements were postponed. No lung function measurements were performed less than 4 wk after a course of prednisolone.

FEV_1 and FVC were measured according to the recommendations of the European Community for Steel and Coal, by using a water sealed or dry rolling seal spirometer or pneumotachometer (17). At least three maneuvers were performed with FEV_1 and FVC within 5%. Maximal five maneuvers were allowed and the largest FEV_1 and FVC were taken for the analysis. Reference values of Zapletal and coworkers were used (18). Postbronchodilator FEV_1 was measured after inhalation of 0.8 mg salbutamol in order to obtain maximal bronchodilatation (19). Salbutamol was administered by a Volumatic spacer (Glaxo Wellcome, Greenford, UK) as four puffs of 0.2 mg, one at a time, inspiring slowly from functional residual capacity to total lung capacity and holding each breath for about 10 s. FEV_1 was measured 20 min after inhalation of the last puff. PEF was measured in triplicate, using the patient's own Mini Wright peakflow meter (Clemente Clarke International Ltd, Harlow, Essex, UK). Methacholine provocation tests were performed using a modification of the dosimeter method by Chai, as described previously (20). Preparation of methacholine solutions was standardized in all centers. Nebulized methacholine bromide in unbuffered saline solution was given in doubling concentrations (0.125 to 39.2 mg/ml). The aerosol was generated by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA) attached to a Rosenthal dosimeter (Laboratory for Applied Immunology, Fairfax, VA), driven by air at 137.8 kPa (20 psi) with a timing adjustment of 0.6 s. Output of the nebulizers was measured before the start of the study. All parts of each nebulizer were marked with waterproof paint to prevent interchanging. Nebulizers were cleaned after each measurement to prevent precipitations, and orifices were checked weekly according to recommendations (21). Aerosolized solution was delivered to the mouth in four consecutive breaths. Mouth doses were 2.5 to 784 μg of methacholine. Saline was inhaled before methacholine to exclude a non-specific response. The effect of each dose was determined by measuring FEV_1 in triplicate 3 min after administration. PD_{20} methacholine was calculated by a computer program from a log-dose-response plot by linear interpolation. Airway responsiveness was only measured if FEV_1 before methacholine provocation was 80% or more of the individual's baseline value at entry into the study.

All centers used written guidelines for lung function measurements. Technicians attended a training course before the start of the study. Site visits were made once a year by the primary investigator and a pulmonary physiologist to inspect the equipment and the methods used.

Statistical Analysis

The study was designed to have 90% statistical power to detect a difference of 8% predicted FEV_1 using a statistical significance level of 5%.

Changes in FEV_1 and the logarithm of PD_{20} within each group over the study period were assessed using paired *t* tests for matched data. Changes in PD_{20} were reported as numbers of doubling doses

(DD). Comparisons of FEV_1 and the logarithm of PD_{20} between groups at each clinic visit were made using analysis of covariance to adjust for mean pre-intervention levels. Comparisons of both morning and evening PEF measurements recorded during the 2-wk diary periods were made using analysis of covariance to adjust for mean pre-intervention levels. Morning and evening PEF variability for each patient was expressed as the standard deviation of the PEF measurements. Each measure of day-to-day variability was compared between treatment groups using the Mann-Whitney test. Distributions of symptoms during the 2-wk diary periods were compared using the Mann-Whitney test, as were the numbers of blisters of rescue salbutamol used over this period. Where patients failed to complete their daily record cards for more than 7 d in any 14-d period such assessments were not included in the analysis. Otherwise, when there were missing days in the record, pro rata adjustment was made to give a 2-wk assessment. Comparison of heights between groups were made using analysis of covariance to adjust for pre-intervention levels. Heights were also expressed as standard deviation scores (SDS) using Dutch reference growth charts (22). Changes in SDS over time within each group were assessed using paired *t* tests for matched data, and comparisons between groups at each clinic visit were made using analysis of covariance to adjust for mean preintervention levels. The analysis of covariance model was extended to allow for the effect of puberty on SDS and to test for a possible interaction between puberty and treatment. All reported p values are for two-sided tests and for simplicity of presentation are without formal adjustment for multiple comparisons over time. Confidence intervals for means were calculated parametrically assuming normality. Confidence intervals for medians were calculated to be consistent with the results of the Wilcoxon test (23).

TABLE 1

BASELINE CHARACTERISTICS AT THE START OF THE RUN-IN PERIOD AND AT RANDOMIZATION BY TREATMENT GROUP

At Start of Run-in Period	Salmeterol (*n = 32*)	Beclomethasone (*n = 35*)
Sex	9F/23M	13F/22M
Age, years		
Mean (SD)	10.6 (2.9)	10.5 (2.3)
Duration of asthma, yr (mean)	6.6	6.3
Atopy status		
None	0/32	6/35
Housedust mite	30/32	28/35
Cat	18/32	14/35
Dog	19/32	20/35
Grasspollen	25/32	18/35
Previous treatment		
Cromoglycate	15/32	15/35
Inhaled corticosteroids	5/32	6/35
FEV_1 % predicted		
Mean (SD)		
Prebronchodilator	85.6 (15.0)	86.3 (13.6)
Postbronchodilator	100.8 (10.9)	99.7 (14.0)
PD_{20}, μg		
Median, quartiles	13.5 (6–35.5)	18 (8–40)
Height, cm (SD)	144.9 (16.4)	144.8 (12.6)
At randomization		
FEV_1 % predicted		
Mean (SD)		
Prebronchodilator	82.0 (13.9)	84.4 (16.7)
Postbronchodilator	99.2 (13.8)	99.2 (15.3)
PD_{20}, μg		
Median, quartiles	18 (6.5–46)	20.5 (8–39)
PEF (l/min) mean (SD)		
Morning	297 (96)	284 (69)
Evening	301 (94)	299 (71)
Days in 2 wk with symptoms		
Median, quartiles	6 (3–11)	6 (2–12)
Nights in 2 wk with symptoms		
Median, quartiles	7 (4–10)	6 (2–13)
Height, cm (SD)	145.6 (16.5)	145.3 (12.5)

RESULTS

Between October 1992 and October 1994, 67 patients (45 boys, 22 girls) were enrolled into the study. Patient characteristics at entry (beginning of the run-in period) and at randomization were similar in the two treatment groups (Table 1).

Ten patients withdrew during the study period. Seven patients withdrew because of exacerbations (six in the salmeterol group), two because of non-compliance (both in the beclomethasone group), and one because of dizziness and nausea (salmeterol group).

Compliance with study treatment did not differ between the groups: the median number of blisters used per day were 1.82 and 1.84 in the salmeterol and beclomethasone groups, respectively; i.e., 91 and 92%, respectively, of the prescribed study medication was used.

Airway Caliber

At the end of the 54-wk treatment period, the mean difference in FEV_1 between treatment groups was 14.2% predicted (95% confidence interval [CI]) 8.3; 20.0) ($p < 0.0001$) in favor of the beclomethasone treated group. On average FEV_1 levels declined in the salmeterol treated group over the course of the study. However, at no time point was the reduction from pretreatment values significantly significant. At the end of treatment, the average change was 4.5% predicted (95% CI −9.0; 0.1). In the beclomethasone-treated group average FEV_1 levels significantly increased ($p < 0.0001$) by about 10% predicted at all visits (Figure 1). Two weeks after discontinuation of beclomethasone treatment, a significant reduction in FEV_1 was noted ($p = 0.02$). Despite this reduction FEV_1 levels at the end of the follow-up period were still significantly higher ($p < 0.0001$) in the beclomethasone group than in the salmeterol group.

Postbronchodilator results of FEV_1 were similar to the prebronchodilator results. After 1 yr, the mean treatment differences was 7.0% predicted (95% CI 2.0; 11.9) ($p = 0.007$). On average FEV_1 levels declined in the salmeterol treated group and increased in the beclomethasone treated group. At the end of treatment the changes were −4.0% predicted (95% CI −8.2; 0.2) and 3.2% predicted (95% CI 0.2; 6.3), respectively.

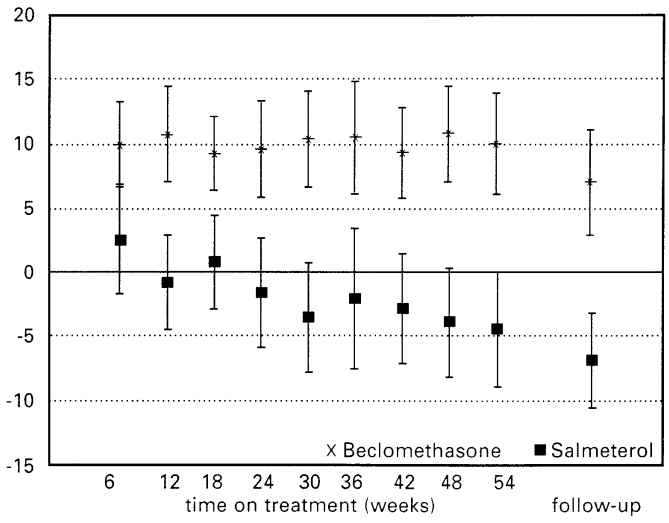

Figure 1. Changes in FEV_1 % predicted (mean, 95% CI) from baseline during treatment with salmeterol (*closed squares*) or beclomethasone (*asterisks*).

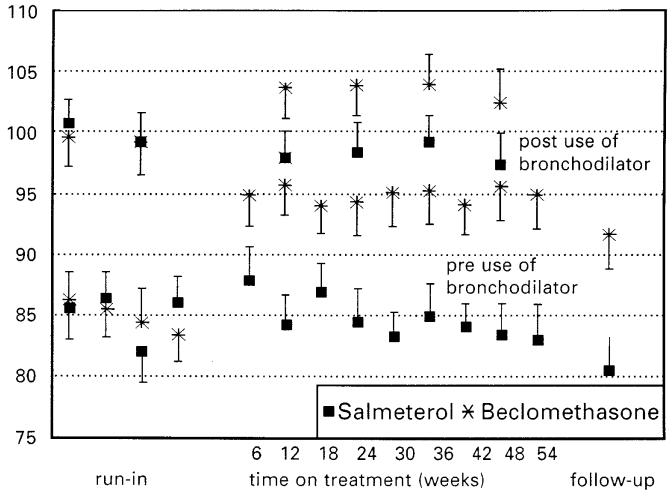

Figure 2. FEV_1 % predicted (mean, SEM) before and after bronchodilatation with 0.8 mg salbutamol during treatment with salmeterol (*closed squares*) or beclomethasone (*asterisks*).

Figure 2 shows the mean levels of FEV_1 before and after bronchodilatation.

Airway Responsiveness

At the end of the treatment period the difference between groups was 2.79 DD (95% CI 1.75; 3.84) ($p < 0.0001$). On average, PD_{20} methacholine declined in the salmeterol treated group over the course of the study. At the end of treatment the average reduction was −0.73 DD (95% CI −1.46; 0.00) ($p = 0.05$). Airway responsiveness gradually improved in the beclomethasone treated group. At the end of treatment the average increase in PD_{20} methacholine was 2.02 doubling dose (95% CI 1.26; 2.78) ($p < 0.0001$) (Figure 3). After 1 yr median PD_{20} values were 7 and 58 μg for the salmeterol- and beclomethasone-treated groups, respectively. Two weeks after discontinuation of beclomethasone PD_{20} methacholine dropped an average 0.76 DD ($p = 0.004$) to a median of 47 μg, whereas after stopping salmeterol it dropped 0.4 DD ($p = 0.09$).

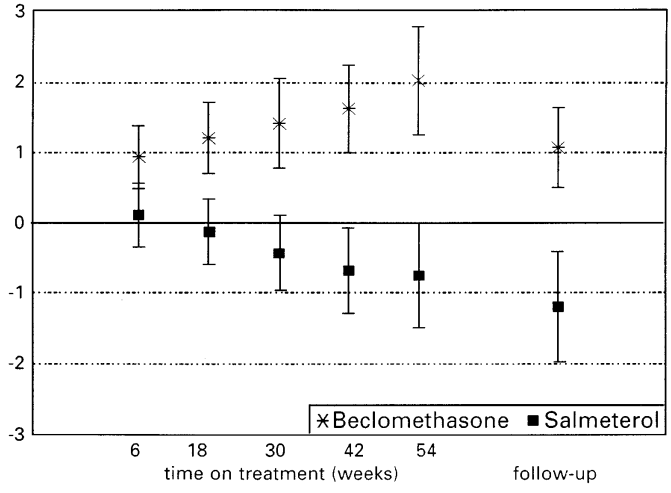

Figure 3. Changes in airway responsiveness (PD_{20}) in doubling doses (mean, 95% CI) during treatment with salmeterol (*closed squares*) or beclomethasone (*asterisks*).

TABLE 2

PERCENTAGE OF PATIENTS SHOWING AN IMPROVEMENT IN FEV_1 (PRE- AND POSTBRONCHODILATOR) AND PD_{20} BY TREATMENT GROUP

Treatment Week	6	12	18	24	30	36	42	48	54	Follow-up
Salmeterol										
FEV_1 pre	61	53	58	45	34	48	35	30	46	24
FEV_1 post		44		35		45		30		
PD_{20}	58		52		37		25		26	26
Beclomethasone										
FEV_1 pre	91	86	88	85	88	88	85	85	88	77
FEV_1 post		74		79		79		67		
PD_{20}	77		76		76		82		81	77

The differences in improvement between treatment groups for FEV_1 and airway responsiveness are also reflected in the difference in the percentage of patients improving (Table 2).

Peak Expiratory Flow Rates

Morning and evening PEF improved in both groups, with a tendency for more improvement in the group treated with beclomethasone (Figure 4). However, at the end of treatment there were no significant differences between groups. Mean increases in morning PEF were 48.8 l/min and 60.9 l/min for salmeterol and beclomethasone, respectively, mean increases in evening PEF 48.9 l/min and 54.3 l/min. Day-to-day variability in both morning and evening PEF was also lower in the beclomethasone group (Figure 5).

Clinical Symptoms

Daytime and nighttime symptoms diminished in both treatment groups, with fewer symptoms in the patients treated with beclomethasone. However, the difference between salmeterol and beclomethasone was only significant at some time points. The percentage of children in the beclomethasone treated group reporting no symptoms during the 2-wk diary card periods increased from 6% in the run-in period to 55% after 1 yr of treatment (Figure 6). In comparison, 3% and 36% were asymptomatic during the corresponding periods in the salmeterol treated group. The need for additional salbutamol during daytime and nighttime, as noted on the diary cards, significantly diminished throughout the treatment period in the beclomethasone group (Figure 7). The median number of additional salbutamol inhalations per day, as counted from the used blisters, during the treatment period was 0.44 in the salmeterol treated group and 0.07 in the beclomethasone treated group ($p = 0.0001$).

During the treatment period 19 courses of prednisolone were given, 17 of these to 15 patients in the salmeterol group (two patients received two courses).

Adverse Events

At no point during the treatment period were any significant changes in heart rate and systolic and diastolic blood pressure found in either treatment group. Table 3 shows the most common reported adverse events.

The mean increase in height was 6.1 cm (95% CI 5.3; 6.9) in the salmeterol treated group, compared with 4.7 cm (95% CI 4.0; 5.3) in the beclomethasone treated group ($p = 0.007$). SDS showed a change of −0.03 SDS in the patients treated with salmeterol compared to −0.28 SDS in the patients treated with beclomethasone ($p = 0.001$) (Figure 8). No interaction was found with gender. A significant interaction ($p = 0.03$) was found with puberty; the mean difference in SDS be-

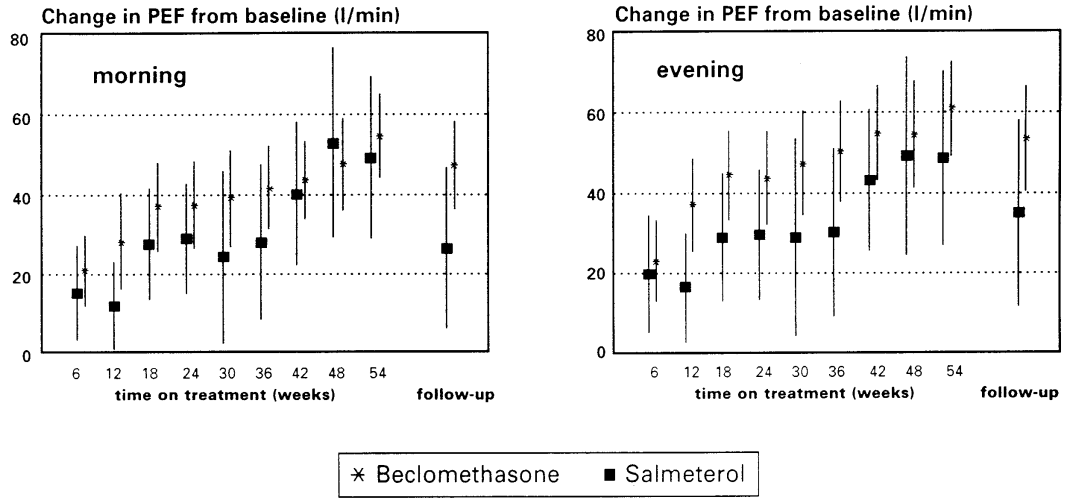

Figure 4. Mean changes in morning and evening PEF (l/min, 95% CI) during treatment with salmeterol (*closed squares*) or beclomethasone (*asterisks*).

tween groups was −0.10 (95% CI −0.29; 0.10) for patients with puberty stages 2 and more and −0.37 (95% CI −0.58; −0.16) for prepubertal patients.

DISCUSSION

This is the first long term study to compare treatment with a long-acting beta-2-agonist with treatment with an inhaled corticosteroid. We selected children with mild to moderate asthma, who were not treated with an inhaled corticosteroid, as this is the category of patients for whom monotherapy with a long-acting beta-2-agonist may be considered. For salmeterol twice daily 50 μg is recommended as the optimum dose in childhood asthma (13). Inhaled corticosteroids are the most effective asthma treatment currently available and so they were chosen as the comparator treatment. A daily dose of 400 μg beclomethasone was chosen, as this is considered to be a moderate dose in the treatment of childhood asthma (2).

The data from this study show that treatment with beclomethasone is superior to treatment with salmeterol in terms of airway caliber, airway responsiveness, symptoms and exacerbations. Two short-term studies have compared inhaled corticosteroid with salmeterol treatment. In an open uncontrolled study 23 children received either twice daily 100 μg budesonide or twice daily 50 microgram salmeterol for 3 wk (24). FEV_1 values after budesonide were not significantly higher than after salmeterol. Both treatments improved symptoms and peakflow rates. A randomized study in 46 adults showed no significant difference in the effect on FEV_1 and PC_{20} after 6 wk of treatment with salmeterol 50 μg twice daily, fluticasone 250 μg twice daily or the combination (25). No differences may have been found in these studies because of the small number of patients included and/or the short duration of treatment. However, in our study significant differences between treatments in FEV_1 and airway responsiveness were apparent already after 6 wk. The rapid improvement in FEV_1, which occurred within 6 wk after the start of beclomethasone

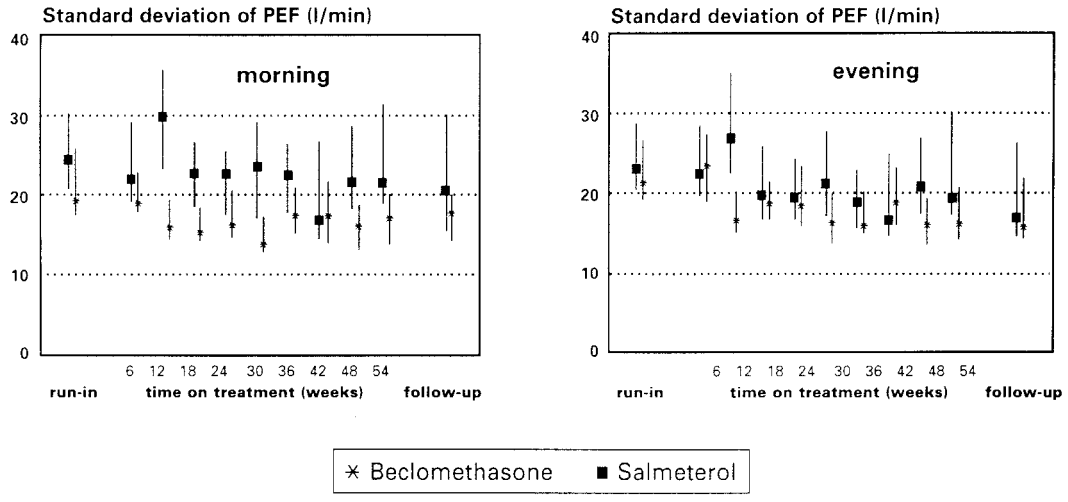

Figure 5. Standard deviation between days in morning and evening PEF (l/min, median, 95% CI) during treatment with salmeterol (*closed squares*) or beclomethasone (*asterisks*).

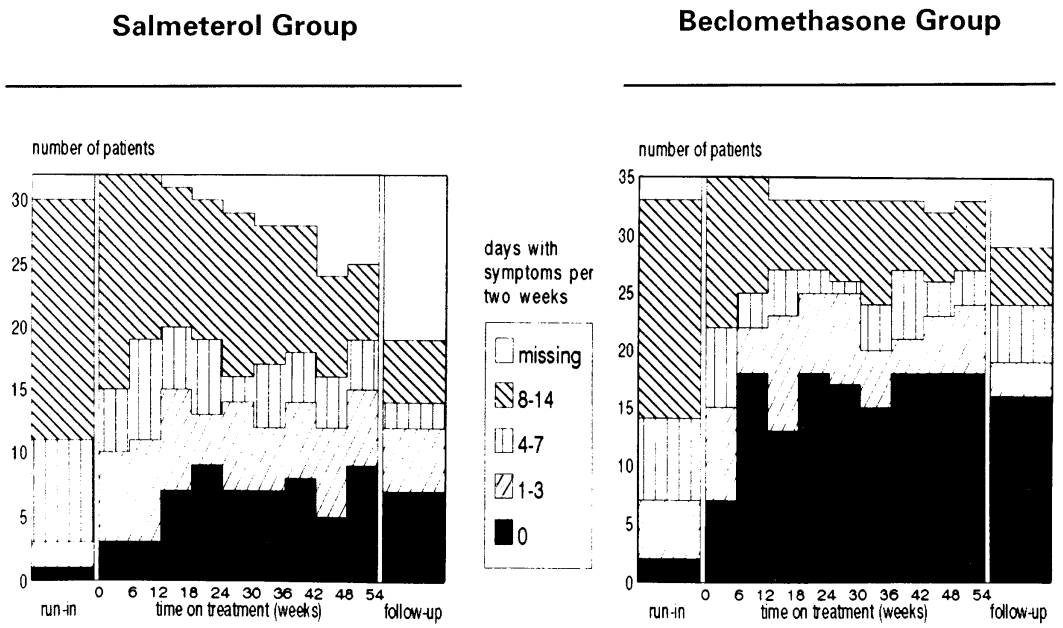

Figure 6. Number of days out of 14 with symptoms during salmeterol (*left panel*) and beclomethasone (*right panel*) treatment.

treatment compares well with the data found by Van Essen and colleagues in a three year follow-up study, in which budesonide 600 μg daily was given (26). In that study, airway responsiveness also improved, but more gradually than in the current study. After 12 mo inhaled corticosteroid treatment PD_{20} increased, on average, by less than 1.5 DD, whereas in this study it improved by 2 DD. It is likely that the patients in Van Essen's study had more severe asthma; their mean baseline FEV_1 was 76% of predicted, compared to 86% in the current study. Although baseline PD_{20} values were similar to the PD_{20} values in this study, more than half of their patients had recently been treated with inhaled corticosteroids and it is

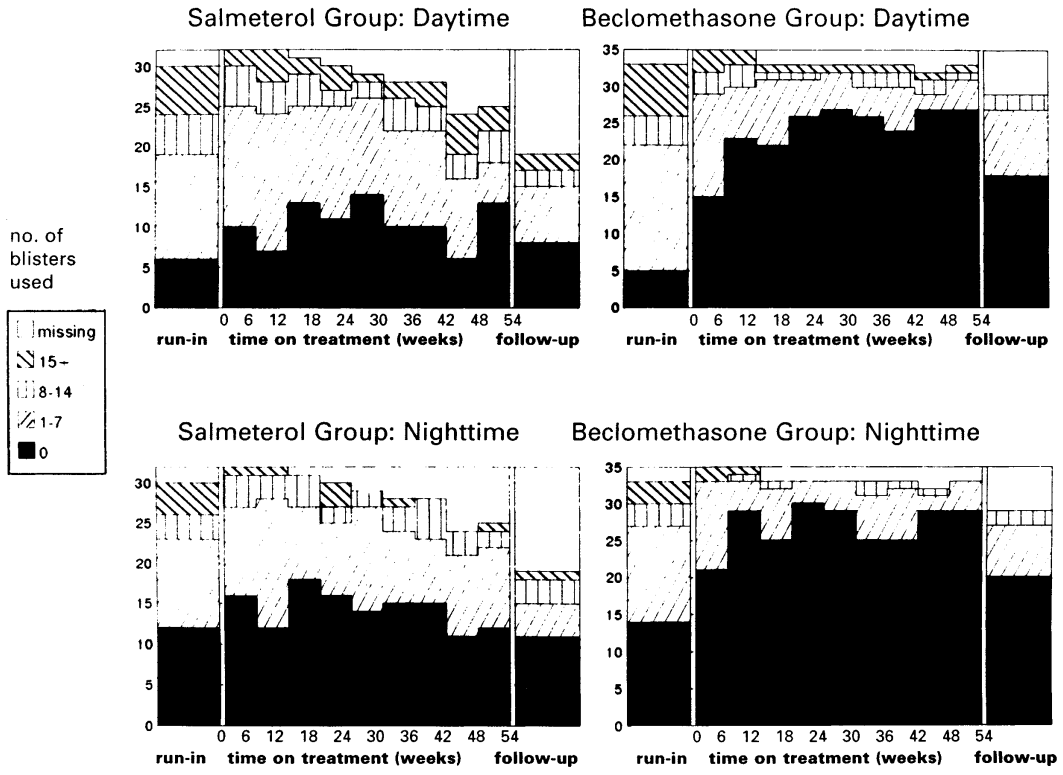

Figure 7. Number of blisters of salbutamol used in the 14-d period during daytime (*upper panel*) and nighttime (*lower panel*) for the salmeterol group (*left*) and beclomethasone group (*right*).

TABLE 3

MOST COMMON REPORTED ADVERSE EVENTS DURING THE TREATMENT PERIOD

	Salmeterol	Beclomethasone
Number of patients	32	35
Number of patients with any adverse event	30 (94%)	31 (89%)
Number of patients with:		
asthma	18 (56%)	3 (9%)
rhinitis	9 (28%)	5 (14%)
fever	8 (25%)	4 (11%)
nausea and vomiting	7 (22%)	4 (11%)
headache	6 (19%)	11 (31%)
malaise and fatigue	4 (13%)	10 (29%)
viral infections	4 (13%)	3 (9%)
breathing disorders	4 (13%)	3 (9%)
cough	3 (9%)	8 (23%)
upper respiratory tract infection	3 (9%)	5 (14%)
viral respiratory infection	2 (6%)	10 (29%)
throat irritation	2 (6%)	3 (9%)
injuries	0	4 (11%)

therefore possible that part of the potential improvement had already taken place. Another difference is that in Van Essen's study the inhaled corticosteroid was combined with an inhaled short-acting beta-2-agonist and one might hypothesize that regular use of beta-2-agonist reduces the improvement caused by the inhaled corticosteroid. This has been suggested in a study by Sears and coworkers (27), who found a negative effect of regular use of fenoterol on several outcomes of asthma, compared to its use on demand. However, a later publication indicated that the differences were small (28).

With salmeterol we observed a tendency to gradual deterioration in FEV_1 and PD_{20}. This became more pronounced at the end of the 1 yr treatment period. In a previous study, of 4 mo duration with salmeterol 50 μg b.i.d. we did not observe such a decline in FEV_1 or PD_{20} (29). However, in that study lung function measurements were performed exactly 12 h after inhalation of salmeterol and it could be argued that a negative effect was masked by the residual bronchodilator effect of salmeterol. This seems unlikely, because in the present study

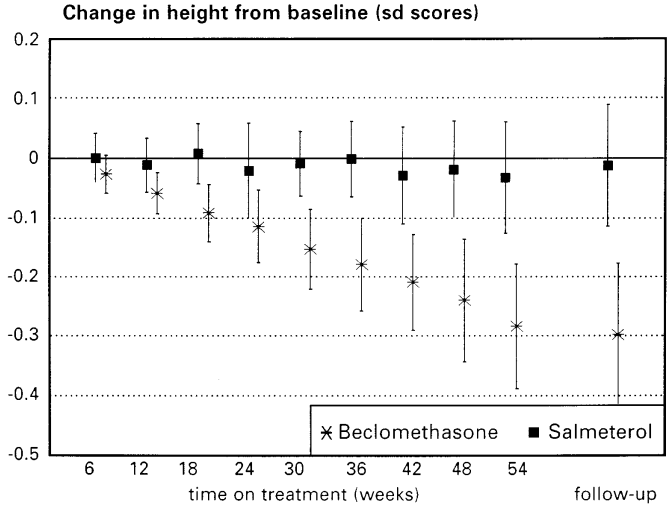

Figure 8. Change in height as SDS (mean, 95% CI) during treatment with salmeterol (*closed squares*) or beclomethasone (*asterisks*).

comparison of subgroups according to the measurement interval after salmeterol inhalation did not reveal any differences in the magnitude of the decrease in FEV_1 or PD_{20}. Tolerance to the bronchoprotective effects of salmeterol has been described and seems to occur within a period of a few days after starting daily treatment (29, 30). In the longest follow-up study so far (29), there was no evidence for a progressive decline of protection after 4 mo, and therefore it is unlikely that increasing tolerance explains our results. Salmeterol, in contrast to inhaled corticosteroid treatment, does not reduce airway wall inflammation (31). We think it likely that ongoing inflammation might be the cause of the decrease in FEV_1 and PD_{20} in the salmeterol group. Thickening of the airway wall due to inflammatory changes will result in a lower airway diameter and might also explain the increase in airway responsiveness (32). This is consistent with the finding that postbronchodilator FEV_1 during salmeterol treatment tends to decrease. Whether ongoing inflammation is the result of the underlying disease itself or whether it is negatively influenced by the use of a regular beta-2-agonist could only have been shown by incorporating a control group with placebo treatment into the study design. This was considered not feasible. The drop in FEV_1 and PD_{20} after stopping salmeterol treatment suggests that during treatment there was a beneficial effect of salmeterol on airway caliber and airway responsiveness.

Despite a deterioration in FEV_1 and PD_{20} symptoms diminish and peak flow rates increase in the patients on salmeterol. This is in agreement with the clinical improvement found in previous studies in which salmeterol was compared to salbutamol (12, 13). However, in our study, salmeterol was compared with treatment with inhaled corticosteroid and improvements were less in the salmeterol group. Asthma exacerbations were rare in the children treated with beclomethasone. In contrast, they were the most frequent reason for withdrawal in the children treated with salmeterol. In most other studies with salmeterol a significant reduction of asthma exacerbations was not observed, despite reductions in symptoms (12, 13).

In this study treatment with 400 μg beclomethasone daily, administered as dry powder, resulted in decreased growth compared to salmeterol treatment. So far, most studies with inhaled corticosteroids have not shown an effect on long- and intermediate-term growth in children (33). Recently a study by Doull and coworkers (34) revealed growth impairment during 7 mo of treatment with beclomethasone 400 μg as dry powder in children with mild asthma. Compared with placebo, a growth difference of 1.0 cm was found. This is consistent with our observed difference of 1.4 cm over a 12-mo period. In both studies no differences were found between boys and girls. The study of Doull and coworkers only included prepubertal children. In our study, the effect on growth was more marked in prepubertal children. Doull's study as well as this study used dry powder inhalators, compared to former studies in which usually metered dose inhalers were used (33). Differences in delivery systems and thereby in lung and oropharyngeal deposition may account for the differences in effect on growth. From the scarce data available, children with asthma usually grow to their predicted height (35). It is unlikely therefore, that a negative effect of inhaled corticosteroids on height will continue for years during treatment. One might speculate that it is a transient effect which will be followed by a catch-up growth later on. Further prospective long-term studies are necessary to address this issue.

From the results of this study we conclude that treatment with inhaled corticosteroid in a moderate dose provides better asthma control and lung function improvement compared with monotherapy with a long-acting beta-2-agonist in chil-

dren with mild to moderate asthma. This study shows that a reduction in symptoms and an increase in PEF may well occur during treatment with salmeterol without a corresponding improvement in airway caliber and airway responsiveness. Monotherapy with a long-acting beta-2-agonist therefore carries a risk of masking the severity of the disease and probably allow ongoing inflammation. We suggest that salmeterol should not be used as a monotherapy in children with asthma. We further advocate the careful monitoring of individual growth during treatment with inhaled corticosteroids.

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