Addition of Salmeterol versus Doubling the Dose of Beclomethasone in Children with Asthma

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Studies in adults revealed that addition of salmeterol to a moderate dose of inhaled corticosteroid resulted in better symptom control and higher PEF compared with doubling the dose of inhaled corticosteroid. The aim of this three group study was to compare the effects of a moderate dose of beclomethasone, the same dose of beclomethasone with salmeterol, and a doubling dose of beclomethasone on lung function and symptoms in children with moderate asthma. A total of 177 children already treated with inhaled corticosteroids, were randomized in a double-blind parallel study either to salmeterol 50 μg twice daily (BDP400+salm), beclomethasone 200 μg twice daily (BDP800), or placebo (BDP400) in addition to beclomethasone 200 μg twice daily. No significant differences between groups were found in FEV_1, PD_{20} methacholine, symptom scores, and exacerbation rates after 1 yr. Salmeterol resulted in slightly better PEF in the first months of treatment. FEV_1, and PD_{20} methacholine significantly improved in all groups. After 1 yr mean changes in FEV_1, percent predicted were 4.3% (95% CI 1.3; 7.2), 5.8% (95% CI 2.9; 8.7), and 4.3% (95% CI 2.1; 6.5) for BDP400+salm, BDP800, and BDP400, respectively. Changes in airway responsiveness were 0.60 (95% CI 0.05; 1.14), 1.30 (95% CI 0.73; 1.87), and 0.80 (95% CI 0.33; 1.27) doubling doses. Growth was significantly slower in the BDP800 group. We conclude that no additional benefit was found of adding either salmeterol or more beclomethasone to a daily dose of 400 μg beclomethasone in this group of children with excellent compliance of medication. Verberne AAPH, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF, and the Dutch Paediatric Asthma Study Group. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma.

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Salmeterol, taken as a single dose, has a bronchodilating effect of at least 12 h in adults and children (1, 2). Protection against methacholine and histamine-induced airway obstruction lasts for 12 to 24 h (2–4). Single-dose studies show prolonged protection against other bronchoconstricting stimuli such as exercise (5), hyperventilation with dry cold air (6), and allergen (7, 8). Compared with salbutamol, twice-daily salmeterol for several weeks or months has been shown to result in fewer symptoms, less need for additional bronchodilator treatment, and better improvement in peak flow rates in studies in adults and in children (9–11). International guidelines have recommended the use of long-acting β_2-agonists, such as salmeterol, either as an addition to conventional doses of inhaled corticosteroids or as an additive treatment in patients on higher doses of inhaled corticosteroids (12–14). Two studies in adults have focused on this subject. The first study was carried out in patients treated by general practitioners who were still symptomatic on 400 μg budesonide or beclomethasone. Salmeterol 50 μg twice daily together with beclomethasone 200 μg twice daily was compared with beclomethasone 500 μg twice daily (15). This study showed better peak flow rates, less diurnal variation of peak flows, and fewer symptoms after 21 wk treatment in the group in which salmeterol was added to the inhaled corticosteroid. Similar results were obtained in a 24-wk study of patients treated in hospital, in whom addition of salmeterol 50 μg twice daily and salmeterol 100 μg twice daily to beclomethasone 500 μg twice daily was compared with beclomethasone 1,000 μg twice daily (16). We set out to investigate whether beneficial effects also occur in children with asthma. The aim of our three group study was to compare the effects of 1 yr of treatment with beclomethasone 200 μg twice daily, the same dose of beclomethasone together with salmeterol 50 μg twice daily, and beclomethasone 400 μg twice daily. The primary efficacy outcome parameters were airway caliber, measured as forced expiratory volume in one second (FEV_1) and airway responsiveness to methacholine. Symptom scores, exacerbations, additional

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use of short-acting β_2-agonists and peak expiratory flows (PEF) were secondary outcome parameters.

METHODS

Patients

One hundred seventy-seven children, 6 to 16 yr of age, with moderate asthma were selected from the outpatient pediatric clinics of nine hospitals, six university hospitals, and three general hospitals. Patients were recruited between September 1992 and May 1995. All children had mild to moderate asthma according to the American Thoracic Society criteria (17). Patients included in the study had to have: (*1*) an FEV_1 between 55 and 90% of predicted value and/or a ratio of FEV_1 to forced vital capacity (FVC) of 50 and 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), which is more than two standard deviations below the mean value in healthy children (18); (*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*) used inhaled corticosteroids between 200 and 800 μg daily for at least 3 mo before the start of the study. 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 of 2 wk. In the run-in period all patients received beclomethasone 200 μg twice a day. Salbutamol 200 μg on demand was allowed as rescue medication, with a maximum of 6 inhalations per day. In the first and the last week of the run-in period FEV_1 and FVC before and after bronchodilatation and PD_{20} methacholine were assessed. Lung function inclusion criteria had to be fulfilled at one or more of these visits. At the end of the run-in period patients were allocated to one of the three treatments by an independent randomization center. Randomization was stratified by sex, age, center, baseline FEV_1, baseline PD_{20}, and prior dose of inhaled corticosteroids, using a computerized minimization method (19). Study treatment consisted of either salmeterol xinafoate 50 μg twice daily, beclomethasone dipropionate 200 μg twice daily, or placebo twice daily, while beclomethasone 200 μg twice daily was continued in all treatment arms. 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 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 this was tapered off to zero in 7 d. During the treatment period the reversibility of FEV_1 to salbutamol (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 2-wk period patients continued with beclomethasone 200 μg twice daily and salbutamol on demand. At the end of this period PD_{20} methacholine was measured again.

At each clinic visit FEV_1, FVC, PEF, height, body weight, heart rate, 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 (Clement 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 in the morning and evening before taking study medication and all three values were recorded. The highest value was used in the analysis. Patients were withdrawn from the study if they needed 3 or more prednisolone courses within 3 mo, or if it was not ethical to continue blinded treatment according to the investigator, or if patients or parents wanted to stop.

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 6 mo 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 follow-up.

Lung Function Measurements

Lung function measurements were performed between 12 and 18 h after inhalation of the study medication. 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 does of study drug and any use of salbutamol were checked before performing measurements and, if necessary, these measurements were postponed. No lung function measurements were done within the 4-wk period 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 (20). At least three maneuvers were performed with FEV_1 and FVC within 5%. A maximum of five maneuvers were allowed and the largest FEV_1 and FVC were taken for the analysis. Reference values of Zapletal and coworkers were used (21). Postbronchodilator FEV_1 was measured 20 min after inhalation of 0.8 mg salbutamol (22). 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. PEF was measured in triplicate, using the patient's own mini-Wright peak flow meter. Methacholine provocation tests were performed using a modification of the dosimeter method by Chai, as described previously (23). 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 (24). 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 nonspecific 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 6% predicted FEV_1 between any two (of three) treatment groups using a statistical significance level of 5%. With the same power this means an increase of 91% in PD_{20}.

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 preintervention 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 preintervention 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 pairs of 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. Comparisons of heights between groups were made using analysis of covariance to adjust for preintervention levels. Heights were also expressed as standard deviation scores (SDS) using Dutch reference growth charts (25). 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. This model was extended to simultaneously investigate the effect of treatment group and puberty (pre- or postpubertal according to Tanner stages) on SDS. All reported p values are for two-sided tests and for simplicity of presentation are without formal adjustment for multiple comparisons over time or for multiple comparisons between groups. Confidence intervals for means were calculated parametrically assuming normality.

RESULTS

Between October 1992 and May 1995, 177 patients (112 boys, 65 girls) were enrolled into the study. Patient characteristics at entry (beginning of the run-in period) and at randomization were similar in the three treatment groups (Table 1).

Fifteen patients withdrew during the study period, five in the BDP400+salm treated group, six in the BDP400 group, and four in the BDP400 group. Eleven patients withdrew because of noncompliance or failure to return. Three patients withdrew as a result of an adverse event: two patients, both in the BDP400+salm group, because of alopecia or ingestion of corpus alienum, one patient in the BDP800 group because of vomiting. Only one patient in the BDP400 group withdrew because of an exacerbation.

Compliance with study treatment was slightly better in the BDP400+salm group than in the BDP800 ($p = 0.01$) and the BDP400 group ($p = 0.01$). The median number of blisters of study medication used per day were 1.88, 1.77, and 1.75 in the BDP400+salm, BDP800, and BDP400 groups, respectively; i.e., 94%, 89%, and 88% of the prescribed study medication. Compliance with maintenance beclomethasone treatment was comparable to that with study medication; the median number of blisters per day were 1.89, 1.81, and 1.75, respectively.

Airway Caliber

At the end of the 54-wk treatment period no significant differences in FEV_1 percent predicted between treatment groups

TABLE 1

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

At Start of Run-in Period	BDP400+salm (*n = 60*)	BDP800 (*n = 60*)	BDP400 (*n = 57*)
Sex, F/M	20/40	24/36	21/36
Age, yr	10.8 (2.5)	11.4 (2.9)	11.1 (2.7)
Height, cm	143.6 (15.4)	147.9 (17.0)	145.6 (15.4)
Duration of asthma, yr	7.8 (3.5)	9.0 (3.1)	8.5 (3.1)
Atopy status			
None	7/60	5/60	7/57
Housedust mite	46/60	45/60	44/57
Cat	29/60	35/60	23/57
Dog	34/60	31/60	30/57
Grass pollen	30/60	28/60	26/57
Inhaled corticosteroid treatment			
Dose, μg	490 (154)	503 (201)	488 (149)
< 400 μg	1/60	6/60	2/57
> 400 μg	21/60	22/60	20/57
Duration, yr	3.2 (2.2)	3.4 (2.1)	2.9 (2.0)
FEV_1, % predicted			
Prebronchodilator	87.2 (13.0)	85.3 (13.8)	86.5 (13.2)
Postbronchodilator	103.2 (14.1)	100.9 (12.3)	102.2 (12.0)
PD_{20}, μg†	24.5 (11–47.5)	22.5 (7.5–42.5)	26 (12–38)
At Randomization			
Height, cm	144.1 (15.4)	148.5 (17.0)	146.1 (15.4)
FEV_1, % predicted			
Prebronchodilator	89.7 (11.8)	87.4 (12.3)	89.2 (13.4)
Postbronchodilator	103.5 (13.1)	102.3 (11.4)	103.0 (13.6)
PD_{20}, μg†	29 (9–59)	20 (6–56)	27 (16.5–44)
PEF, L/min			
Morning	299 (79)	315 (90)	317 (79)
Evening	306 (82)	323 (92)	325 (80)
Days in 2 wk with symptoms†	6 (3–11)	5 (1.5–10)	4 (1–9)
Nights in 2 wk with symptoms†	6 (3–10)	4.5 (1–11)	5 (1–9)

* All values are means (SD) unless stated otherwise.
† Median and quartiles.

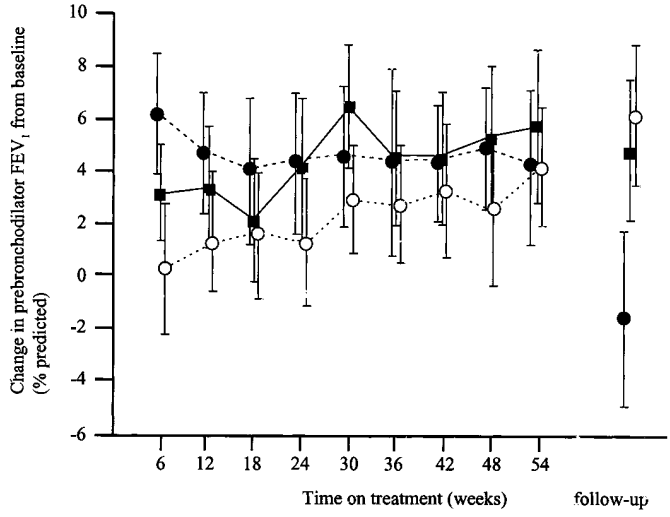

Figure 1. Changes in prebronchodilator FEV_1 percent predicted (means, 95% CI) from baseline during treatment with beclomethasone 400 μg + salmeterol (*closed circles*), beclomethasone 800 μg (*closed squares*), or beclomethasone 400 μg (*open circles*) daily.

were found. Significant changes in FEV_1 occurred in all groups. Mean changes in prebronchodilator FEV_1 from baseline to the end of the treatment period were 4.3% of predicted (95% confidence interval [CI] 1.3; 7.2) ($p = 0.005$), 5.8% of predicted (95% CI 2.9; 8.7) ($p = 0.0002$), and 4.3% of predicted (95% CI 2.1; 6.5) ($p = 0.0003$) for the BDP400+salm, BDP800, and BDP400 groups, respectively (Figure 1).

No differences between treatments were found after analyzing subgroups according to prestudy dose and duration of inhaled corticosteroid, baseline levels of FEV_1 and PD_{20}, and the numbers of daytime or nocturnal symptoms. After stopping treatment with salmeterol, there was a significant fall in FEV_1 of 5.6% of predicted (95% CI 2.1; 9.1) ($p = 0.003$). Stopping of either beclomethasone or placebo did not result in significant changes.

Mean changes in postbronchodilator FEV_1 were −0.1% of predicted (95% CI −2.3; 2.1) ($p = 0.9$), 3.5% predicted (95% CI 1.6; 5.4) ($p = 0.0005$), and 2.0% predicted (95% CI −0.6; 4.5) ($p = 0.13$) for the BDP400+salm, BDP800, and BDP400 groups, respectively (Figure 2). The difference between the levels in the BDP400+salm and BDP800 groups was of borderline statistical significance at 48 wk ($p = 0.04$) but not at any other time point.

Airway Responsiveness

At the end of the treatment period no significant differences between groups were found. Median PD_{20} values were 36, 39.5, and 35 μg for the BDP400+salm, BDP800, and BDP400 groups, respectively. All three groups showed a significant improvement in PD_{20}. Changes in PD_{20} compared with baseline were 0.60 DD (95% CI 0.05; 1.14) ($p = 0.03$), 1.30 DD (95% CI 0.73; 1.87) ($p = 0.00003$), and 0.80 DD (95% CI 0.33; 1.27) ($p = 0.001$) for the BDP400+salm, BDP800, and BDP400 groups, respectively (Figure 3). After stopping salmeterol there was a small but not significant decrease in PD_{20} (−0.28 DD), whereas after stopping placebo an increase in PD_{20} was found (0.6 DD) ($p = 0.003$) and after stopping beclomethasone no change occurred. As for FEV_1, subgroup analysis revealed no trends in favor of any of the treatments.

Peak Expiratory Flow

Morning and evening PEF improved in all treatment groups. During the first months of treatment changes were larger in the BDP400+salm group than in the other two groups with the differences between the BDP400+salm and BDP400 groups being statistically significant at some time points (Figure 4). After 1 yr mean increases in morning PEF were 41.8 L/min, 41.1 L/min, and 27.3 L/min for the BDP400+salm, BDP800, and BDP400 groups, respectively. Mean increases in evening PEF were 38.6 L/min, 37.6 L/min, and 24.9 L/min, respectively. Differences between mean follow-up levels in the BDP400 group and each of the other two groups were of borderline statistical significance for both morning and evening PEF

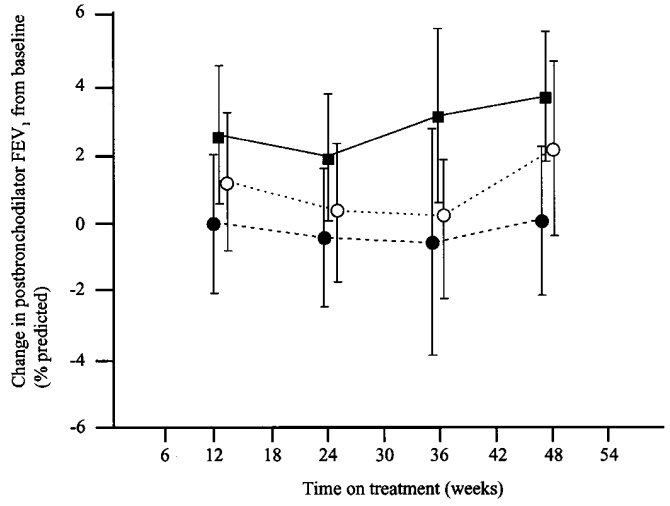

Figure 2. Changes in postbronchodilator FEV_1 percent predicted (means, 95% CI) from baseline during treatment with beclomethasone 400 μg + salmeterol (*closed circles*), beclomethasone 800 μg (*closed squares*), beclomethasone 400 μg (*open circles*) daily.

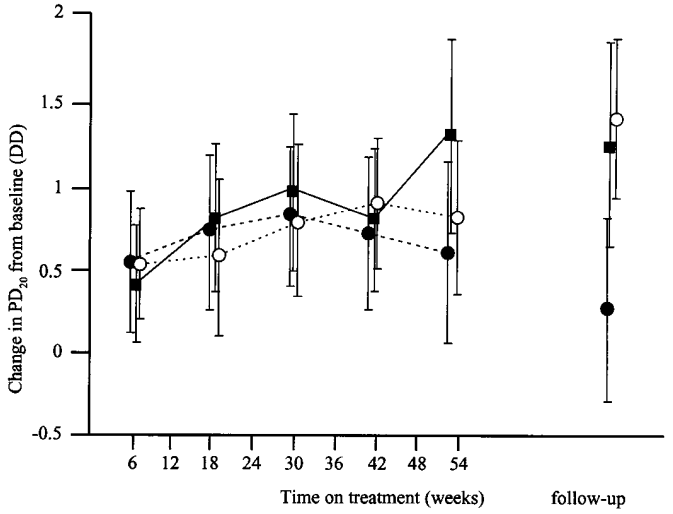

Figure 3. Changes in airway responsiveness in doubling doses (means, 95% CI) during treatment with beclomethasone 400 μg + salmeterol (*closed circles*), beclomethasone 800 μg (*closed squares*), or beclomethasone 400 μg (*open circles*) daily.

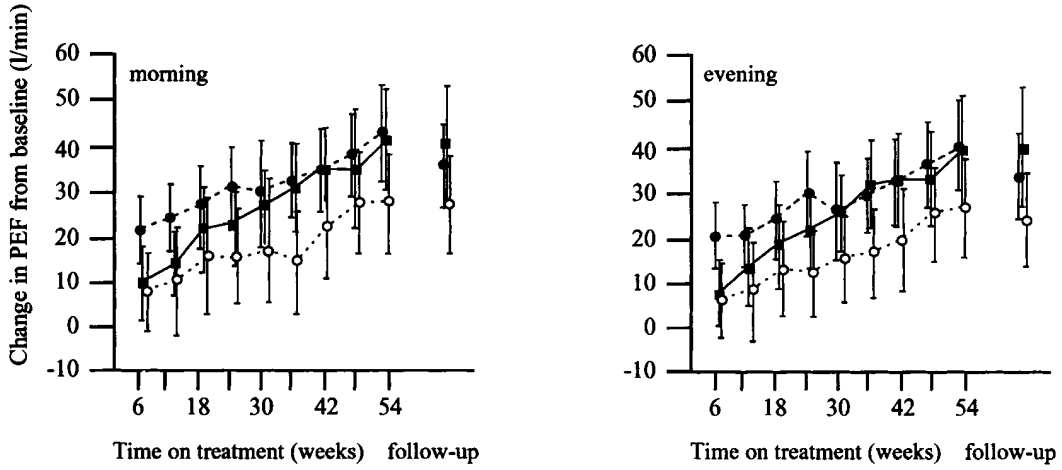

Figure 4. Mean changes in morning and evening PEF (L/min, 95% CI) during treatment with beclomethasone 400 μg + salmeterol (*closed circles*), beclomethasone 800 μg (*closed squares*), or beclomethasone 400 μg (*open circles*) daily.

($0.05 < p < 0.1$ for each comparison). There was some evidence that at the first follow-up visit, day-to-day variability was greater in the BDP800 group than in the BDP400+salm group ($p = 0.004$ A.M., $p = 0.003$ P.M.) and the BDP400 group ($p = 0.03$ A.M., $p = 0.06$ P.M.), however, especially for the morning PEF day-to-day variability at baseline was already higher in the BDP800 group. Day-to-day variability did not differ significantly between groups at any other follow-up visit.

Symptoms

Daytime and nighttime symptoms diminished in all treatment groups in a similar way. The percentage of children reporting no symptoms during the 2-wk diary card periods increased from 3%, 13%, and 11% for the BDP400+salm, BDP800, and BDP400 groups, respectively in the run-in period to 34%, 39%, and 35% after 1 yr of treatment. At no time point were there statistically significant differences in symptom scores between the groups. There was some evidence that the use of additional salbutamol, as noted on the diary cards, differed between groups; particularly during the first 2 wk of treatment this was higher in the BDP800 group than in the other groups. The median number of additional salbutamol inhalations per day during the whole treatment period, as counted from the used blisters, was 0.19, 0.33, and 0.15 for the BDP400+salm, BDP800, and BDP400 groups, respectively. The difference between the rates in the BDP800 and BDP400 group was of borderline statistical significance ($p = 0.06$).

During the treatment period 34 courses of prednisolone for exacerbations were given; 13 courses to 10 patients in the BDP400+salm treated group, 8 courses to 7 patients in the BDP-800 treated group, and 13 courses to 10 patients in the BDP-400 treated group.

Adverse Events

During the treatment period no consistently, clinically significant differences in heart rate, systolic and diastolic blood pressure were found between treatment groups. Table 2 shows the most commonly reported adverse events. The mean increase in height was 5.1 cm (95% CI 4.5; 5.7) in the BDP400+salm group, compared with 3.6 cm (95% CI 3.0; 4.2) in the BDP800 group and 4.5 cm (95% CI 3.8; 5.2) in the BDP400 group. A slightly greater proportion of patients were prepubertal in the BDP400 group (47%) than in the BDP400+salm (43%) or BDP800 (35%) groups. The reductions in SDS were greatest in the prepubertal patients. After adjustment for puberty the reduction in SDS was significantly greater in the BDP800 group than in the other two groups ($p = 0.006$ compared with BDP400+salm, $p = 0.02$ compared with BDP400). Mean changes in SDS were −0.10 (95% CI −0.19; −0.02), −0.27 (95% CI −0.34; −0.19), and −0.16 SDS (95% CI −0.24; −0.07) for BDP400+salm, BDP800, and BDP400, respectively (Figure 5).

DISCUSSION

This is the first long-term study comparing the addition of a long-acting β_2-agonist with a doubling dose of an inhaled corticosteroid in asthmatic children on maintenance treatment with inhaled corticosteroid. We selected children with moderate asthma, who had used 200 to 800 μg of inhaled corticosteroid for at least 3 mo before the start of the study. During the 6-wk run-in period they were treated with 200 μg beclomethasone twice daily, which is considered a moderate dose in the treatment of childhood asthma (14). Despite this treatment all children were symptomatic and had reversible airway obstruction and airway hyperresponsiveness. The dose chosen for sal-

TABLE 2

MOST COMMON REPORTED ADVERSE EVENTS DURING THE TREATMENT PERIOD

	BDP400+salm	BDP800	BDP400
Number of patients	60	60	57
Number of patients with adverse event	59 (98%)	52 (87%)	52 (93%)
Number of patients with:			
Headache	25 (42%)	16 (27%)	23 (41%)
Rhinitis	21 (35%)	20 (33%)	14 (25%)
Viral respiratory infection	17 (28%)	18 (30%)	14 (25%)
Asthma	16 (27%)	19 (32%)	16 (29%)
Upper respiratory tract infection	16 (27%)	15 (25%)	9 (16%)
Cough	12 (20%)	16 (27%)	13 (23%)
Fever	12 (20%)	7 (12%)	8 (14%)
Nausea and vomiting	11 (18%)	5 (8%)	7 (13%)
Diarrhea	8 (13%)	2 (3%)	4 (7%)

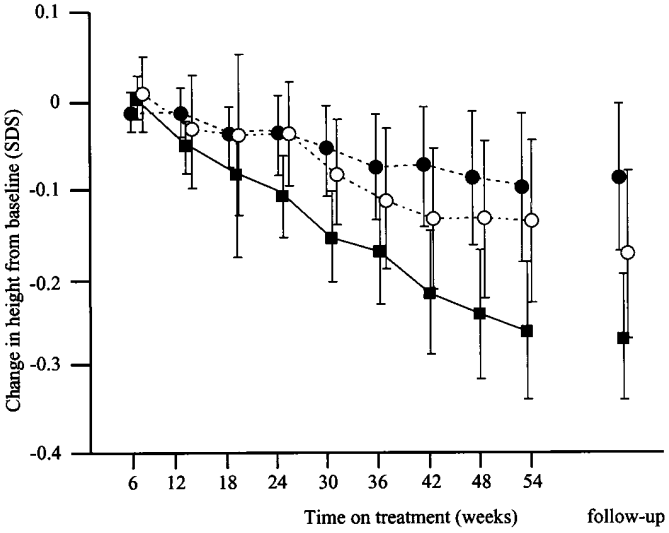

Figure 5. Change in height as SDS (means, 95% CI) during treatment with beclomethasone 400 μg + salmeterol (*closed circles*), beclomethasone 800 μg (*closed squares*), or beclomethasone 400 μg (*open circles*) daily.

meterol (50 μg twice daily) is recommended as the optimal dose in childhood asthma (11).

The data from this study show no significant differences in airway caliber, airway responsiveness, symptom scores, and exacerbation rates between 200 μg beclomethasone twice daily, 200 μg beclomethasone plus salmeterol 50 μg twice daily, or 400 μg beclomethasone twice daily. Although FEV_1 and airway responsiveness tended to be slightly better in the group on the high dose of inhaled corticosteroid, only for the postbronchodilator FEV_1 was the difference between this group and the BDP400+salm group of borderline statistical significance at the end of the treatment period. During the first months patients in the BDP400+salm group tended to have higher peak flow values.

Our results differ somewhat from those from the two adult studies which have compared the addition of salmeterol with increasing the inhaled corticosteroid dose (15, 16). Both studies lasted about 6 mo and showed a significantly better improvement in PEF with the addition of salmeterol. Symptoms were less in patients on salmeterol treatment, especially in the study by Woolcock and coworkers (16) and at some time points in the study by Greening and coworkers (15). These studies as well as our study selected patients with reversible airway obstruction. In contrast with our study, in which inclusion criteria were based on airway caliber and airway responsiveness, inclusion criteria of both adult studies were based on symptom scores in the run-in period prior to randomization and PEF variability. This may have led to the selection of highly symptomatic patients. In the study by Woolcock and coworkers (16) beclomethasone was increased from 1,000 to 2,000 μg. This dose increase may already be on the "flat part" of the dose response curve for antiasthma effects of inhaled corticosteriods (26), which could explain the better symptomatic improvement with salmeterol. In the study by Greening and coworkers (15) the beclomethasone dose increased from 400 to 1,000 μg daily. This lower dose range was probably on the "steep part" of the dose–response curve, which may explain why differences in symptom scores between salmeterol and the high dose of inhaled corticosteroid were less obvious. Based on PEF and FEV_1 data, the degree of obstruction in the adult studies is more severe than in our study: the mean baseline PEF in the study by Greening (15) was 74% predicted, the mean baseline FEV_1 in the study by Woolcock (16) was about 72% predicted compared with 86% in our study. This suggests that there might have been more room for improvement by a bronchodilator in these studies and may explain why in our study, no differences were found between salmeterol and beclomethasone in terms of FEV_1 improvement. However, subgroup analysis by FEV_1 at baseline did not reveal a larger effect of salmeterol in those asthmatic children who had more severe airway obstruction. For PEF, also in our study salmeterol was slightly superior to beclomethasone during the first 24 wk of treatment, although the differences between salmeterol and beclomethasone in our study were less than in the adult studies and not consistently statistically significant.

All treatment groups in our study showed a significant improvement in airway responsiveness compared with baseline values. For the BDP800 group this was 1.3 DD, comparable with 1.5 DD found after 1 yr of treatment with 600 μg budesonide daily in an earlier study on asthmatic children (27). However, the latter study selected children not on inhaled corticosteroids before inclusion into the study. Further data of that study showed a plateau of PD_{20} improvement after 22 mo of treatment (28). It is remarkable that a comparable improvement in PD_{20} was found in our study despite the fact that the mean duration of inhaled corticosteroid use before study entry was about 3 yr. No differences between subgroups who had used inhaled corticosteroid for less than 2 yr and those who had been on corticosteroid treatment for 2 yr or more were found. In the study by Woolcock and coworkers (16), the improvement in airway responsiveness was far less: 0.6 DD after beclomethasone 500 μg plus salmeterol 50 μg twice daily and 0.4 DD after beclomethasone 1,000 μg twice daily. However, their study population consisted of patients with longstanding asthma, who had been taking inhaled corticosteroids for several years and so their response might have reached a plateau. Furthermore, for the patients who doubled their inhaled corticosteroid dose, the plateau phase of the dose–response curve for PD_{20} may have been reached. An explanation for the relatively favorable response in our study as well as that in the study by Van Essen-Zandvliet and coworkers (28) may be that in children the inflammatory changes in the airways are more reversible by inhaled corticosteroid treatment than they are in adults, who typically have long-standing asthma. There is some evidence that a delay in the introduction of inhaled corticosteroid leads to a smaller improvement in lung function in children as well as adults (29, 30). In our study even the BDP400 group, who continued with 400 μg beclomethasone, showed a significant improvement in FEV_1 as well as in PD_{20}, an effect most likely attributable to the excellent compliance of nearly 90% of prescribed medication, which was probably better than before owing to the strict study protocol and patient control.

All treatment groups showed a decrease in height growth over the 1-yr treatment period. Several explanations are possible: growth of asthmatic children may be impaired as a result of their chronic disease or due to delayed puberty (31) or the adverse effects of the inhaled corticosteroid. The unusually high compliance with medication in this study may have resulted in effects on growth with relatively low dose of inhaled corticosteroid. Furthermore, the use of a dry powder inhaler with a high lung deposition may play a role. The effect on growth in this study appeared to be dose-dependent. The changes in SDS in the two groups treated with 400 μg beclomethasone daily (respectively, −0.10 and −0.16 SDS) were less than those found in another study in which the same dose of

beclomethasone was given for the first year (mean change in SDS was −0.28) (32). Since children had used inhaled corticosteroids for a number of years before entry into the current study, this may suggest that the effect of inhaled corticosteroids on growth diminishes during prolonged treatment. Further long-term studies are necessary to address this issue. Also it will be necessary to evaluate the long-term growth effects of other inhaled corticosteroids, such as budesonide and fluticasone; especially for this last steroid it is claimed that side effects are less.

We conclude that adding salmeterol or doubling the dose of beclomethasone gave no additional benefit over that from 200 μg beclomethasone twice daily in this selected group of children with moderate asthma, in which the compliance with medication was excellent. This study also showed that with strict monitoring of the children and frequent control visits the compliance with medication was high, which resulted in considerable improvements in lung function and symptoms. Further studies are needed in order to evaluate which of the approaches is best in children with severe asthma. The possible advantage of a higher dose of inhaled corticosteroid in suppressing airway inflammation should then be balanced against the adverse effects, especially on growth. We advocate careful monitoring of children for medication compliance and growth during treatment with inhaled corticosteroids.

The Dutch Paediatric Asthma Study Group consists of a steering committee (K. F. Kerrebijn, J. A. M. Raaymakers, S. J. Pocock, J. M. Bogaard) and members from the departments of pediatric respiratory medicine of the Emma Children's Hospital/Children's AMC, Amsterdam (J. C. van Nierop), the University Hospital of Amsterdam (A. F. Nagelkerke, B. Thio), the Sint Antonius Hospital, Nieuwegein (T. J. Schouten), the Asthma Center Heideheuvel, Hilversum (E. E. M. van Essen-Zandvliet, A. Denteneer), the Beatrix Children Clinic/University Hospital Groningen (J. Gerritsen, M. J. Grol), Hospital De Weezenlanden, Zwolle (R. J. Roorda), the University Hosptial Maastricht (J. J. E. Hendriks), the Juliana Children's Hospital, The Hague (E. J. Duiverman, J. M. Kouwenberg), the Wilhelmina Children's Hospital, Utrecht (J. van der Laag, H. J. L. Brackel), and the Sophia Children's Hospital, Rotterdam (A. A. P. H. Verberne).

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