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Budesonide/Formoterol in a Single Inhaler Versus Inhaled Corticosteroids Alone in the Treatment of Asthma

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Summary. The aim of this study was to evaluate the efficacy (expressed as effect on lung function) and tolerability of Symbicort® (budesonide/formoterol in a single inhaler) in children with asthma.

This was a double-blind, double-dummy, randomized, parallel-group, multicenter trial. After a 2–4-week run-in period, 286 asthmatic children (177 boys, 109 girls; mean age, 11 years; mean forced expiratory volume in 1 sec (FEV_1), 75% predicted normal), previously treated with inhaled corticosteroids (average dose 548 μg/day), were randomized to 12 weeks' treatment with either budesonide/formoterol 80/4.5 μg, two inhalations twice daily (n = 148), or an equivalent dose of budesonide 100 μg, two inhalations twice daily (n = 138). Efficacy variables included morning and evening peak expiratory flow (PEF), spirometery, asthma symptoms, and use of rescue medication (β_2-agonists). Serial FEV_1 assessments were carried out on a subgroup of children (budesonide/formoterol, n = 41; budesonide, n = 40) at randomization and at week 12.

Relative to baseline, morning PEF (primary variable) increased to a significantly greater extent with budesonide/formoterol than with budesonide alone (7.22% predicted normal vs 3.45% predicted normal; $P < 0.001$). Evening PEF also increased significantly with budesonide/formoterol (6.13% predicted normal vs. 2.73% predicted normal; $P < 0.001$), as did mean FEV_1 and serial FEV_1 measured over 12 hr (both $P < 0.05$). Similar improvements in asthma symptoms and rescue medication use were observed in both groups. The two treatment groups were similar in terms of their adverse-event profile and rates of discontinuation.

Budesonide/formoterol in a single inhaler provided rapid improvements in PEF and FEV_1 compared to inhaled budesonide alone. These improvements were sustained throughout the study period. Budesonide/formoterol was well-tolerated in children with moderate persistent asthma. **Pediatr Pulmonol. 2002; 34:342–350.**

Key words: asthma; children; Symbicort®; budesonide; formoterol.

INTRODUCTION

Asthma remains one of the most prevalent chronic diseases of childhood, and its worldwide prevalence is increasing.[1,2] The management of childhood asthma is similar to that in adults, with a recommended stepwise approach.[3–5]

It is widely accepted that inhaled corticosteroids are the treatment of choice in all but the mildest of asthma patients, and relatively low doses appear to be very effective in controlling most asthma symptoms in the vast majority of children.[6] The use of long-acting β_2-agonists, used as monotherapy or when added to an asthma population receiving concomitant inhaled corticosteroids with near-normal lung function, has also been reported.[7] International pediatric guidelines advocate using a long-acting β_2-agonist as add-on therapy when low-to-moderate doses of inhaled corticosteroids fail to control asthma.[8] The rationale for this comes from studies in adults which indicate that the addition of a long-acting β_2-agonist may be more beneficial than increasing the dose of inhaled corticosteroid in patients not optimally controlled with such therapy.[9,10] While there is a need for similar

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studies in children, there is nevertheless good evidence of add-on efficacy with long-acting β_2-agonists in children who remain symptomatic with less than optimal lung function despite moderate-to-high doses of inhaled corticosteroids.[11,12]

The efficacy of the corticosteroid budesonide in the treatment of childhood asthma is well-established.[6,13–15] In several studies, budesonide was well-tolerated in children with no clinically significant adrenal suppression or adverse effects related to bone growth.[13,16–18] Formoterol, a long-acting β_2-agonist, also has proven efficacy in children with asthma.[19–25] Indeed, in a 1-year study in children, formoterol was found to improve lung function as well as decrease day- and night-time symptoms, decrease the use of rescue medication, and decrease sleep disturbances due to asthma.[26]

The combination of budesonide and formoterol has the potential to provide both anti-inflammatory control and fast-onset sustained bronchodilation. In order to simplify asthma therapy and to improve adherence to a regular treatment, these agents have been combined in a single inhaler, the Symbicort® Turbuhaler® (AstraZeneca, Lund, Sweden). The present study, in which the primary endpoint was peak expiratory flow (PEF), represents the first clinical study investigating the efficacy and tolerability of budesonide/formoterol in children with asthma. This study builds on the hypothesis that the combined use of budesonide and formoterol should lead to improved lung function, compared with continued treatment with inhaled corticosteroids alone, in children with suboptimal lung function despite the regular use of inhaled corticosteroids.

MATERIALS AND METHODS

This was a double-blind, double-dummy, randomized, parallel-group study involving 48 centers in Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain, and the UK. The median number of patients per center was 5 (range, 2–26). The first patient was enrolled in November 1998, and the last patient completed the study in June 1999. The study was performed in accordance with the Declaration of Helsinki and local regulations, each study center having received ethical approval for the protocol prior to study commencement. Written informed consent was required from patients' parents/guardians and/or the patients before any study-related procedures were performed.

Study Design and Patients

Children of either sex between 4–17 years of age, with a diagnosis of asthma[4] (minimum duration, 6 months), forced expiratory volume in 1 sec (FEV_1) 40–90% of the predicted value[27] at visit 1, and $\geq$15% reversibility of FEV_1 within 15 min of inhalation of a short-acting β_2-agonist, were eligible for inclusion. In addition, patients were to have received treatment with an inhaled corticosteroid at a constant dose for at least 6 weeks prior to the study ($\geq$400 μg budesonide Turbuhaler®; $\geq$600 μg budesonide via pressurised metered-dose inhaler; $\geq$375 μg fluticasone propionate; or $\geq$600 μg CFC-beclomethasone dipropionate via any inhalation device). Asthma symptom score was not a study inclusion criterion; thus, patients with a very low or zero asthma symptom score were eligible.

Relevant exclusion criteria included unstable asthma (defined as the use of oral, parenteral, or rectal corticosteroids within 30 days of study commencement), any respiratory infection affecting disease control within the previous 4 weeks, and known hypersensitivity to study medication or inhaled lactose. Use of inhaled corticosteroids other than study medication was not allowed throughout the study. Nasal corticosteroids, however, were allowed during the study. Inhaled terbutaline or salbutamol were used as rescue medication, depending on the preference of the patient (the same brand and strength were used during the entire study). Treatment with other anti-asthma products was not permitted. Other medication that was considered necessary for the patient's well-being was given at the discretion of the investigator.

During an open, 2–4-week run-in period to collect baseline data, patients received budesonide 100 μg (via Turbuhaler®), two inhalations twice daily. Baseline values for items recorded in diary cards (including morning and evening PEF and asthma symptoms) were taken as the average of the last 10 days of the run-in period. Baseline spirometry values were determined at randomization (visit 2). Patients meeting the study randomization criteria at visit 2 of FEV_1 $\leq$100% of predicted and a reversibility of $\geq$12% (irrespective of their level of asthma symptoms) were randomized (1:1) to receive 12 weeks' inhaled treatment with either budesonide/formoterol 80/4.5 μg, two inhalations twice daily (Symbicort®), or an equivalent dose of budesonide (100 μg), two inhalations twice daily (Pulmicort®, AstraZeneca). The doses of budesonide in each group were comparable; differences are explained by labeling changes for new inhaled drugs, which require the delivered dose rather than metered dose to be reported.

Randomization was performed using a computer-generated block-randomization list, and individual treatment code envelopes were provided for each subject. The double-dummy technique was used for drug administration, since budesonide/formoterol is delivered via a new Turbuhaler® featuring a dose counter and a modified mouthpiece. Patients were trained in the correct use of the Turbuhaler® using the Turbuhaler Usage Trainer (TUT) prior to randomization, and were required to demonstrate their inhalation technique using the TUT at each subsequent visit.

Adherence to therapy was assessed by reviewing patient diary cards.

Clinical Assessments

After careful instruction, each patient measured their own morning and evening PEF, using a Mini-Wright® peak flow meter (Clement Clark, Harlow, UK). No rescue medication was to be taken in the 6 hr before recording PEF. All measurements were made while in a seated or standing position, prior to inhalation of study medication, and the best value of three consecutive measurements was recorded in patient diaries. Patients also recorded the severity of daytime and nocturnal asthma symptoms on a 4-point scale (0 = no symptoms, 3 = severe symptoms), use of rescue medication, and nocturnal awakenings due to asthma symptoms. As an overall measure of symptom control, the percentage of symptom-free days (defined as a night and a day without symptoms and no asthma-related nocturnal awakenings) was determined.

Spirometry measurements (FEV_1 and forced vital capacity (FVC)) were determined at screening, at randomization, and after 4, 8, and 12 weeks' treatment with either budesonide/formoterol or budesonide alone. Neither study drugs nor rescue medication were permitted in the 6 hr before clinic visits. Measurements were performed with the patient wearing a nose clip and in the same position (either seated or standing), according to the recommendations of the European Respiratory Society.[28] Three satisfactory tests were required, from which the highest values for FEV_1 and FVC were recorded. Although there was a 12-hr medication-free period before measurements were made, PEF and FEV_1 were measured under the influence of formoterol and budesonide or budesonide alone, depending on the treatment group.

A subgroup of 81 patients (budesonide/formoterol, n = 41; budesonide, n = 40) underwent serial FEV_1 assessments to investigate the effect of a single dose of budesonide/formoterol and budesonide alone over time. At visit 2, FEV_1 was measured over 12 hr prior to administration of study medication to provide a baseline value. Measurements were repeated at visit 5. The study period of 12 hr represented one full dosing interval. Study medication was taken at 07.00 hr, and FEV_1 was measured 15 min before, and at 3, 10, 20, and 30 min and 1, 2, 4, 6, 8, 10, and 12 hr after medication intake. Results were expressed in terms of average FEV_1 (L/min and % predicted normal) throughout the 12-hr period, maximal observed FEV_1, and the value recorded 12 hr after drug administration. The average FEV_1 during the first 10 min after drug administration was also determined.

Clinical Safety Assessments

Adverse events were recorded at visits 2–5, both those spontaneously reported and those reported in response to a standard question asked by the investigators. Diaries were also assessed for evidence of adverse events. All adverse events were recorded and evaluated in terms of intensity and causality.

Statistical Analysis

For morning PEF (the primary efficacy variable), it was estimated that with 100 patients per treatment group and a standard deviation of 30 L/min, a difference between treatments of 12 L/min could be detected with 80% power at the 5% significance level. Results were also expressed as change in % predicted normal from baseline. Assuming a residual standard deviation of 9%, expressing PEF as % predicted normal would under the same assumptions gave 80% power, detecting a true difference of 3.6%.

An intention-to-treat analysis was used with all available data. The principal model was one of analysis of variance, with the average for the entire treatment period as the dependent variable. Factors were treatment, country, and age group. For variables recorded in the clinic, the baseline value, recorded at the ramdomization visit (visit 2), was used as a covariate. For variables recorded in diary cards, the baseline value, defined as the average of the last 10 days of run-in, was used as a covariate. Change from baseline was calculated using the baseline value and the mean value for the whole of the treatment (randomization) period. Data were reviewed by age stratification (4–11 years and 12–17 years) to ensure that there was no bias by age.

RESULTS

A total of 286 patients (177 boys, 109 girls) was randomized to receive budesonide/formoterol (n = 148) or budesonide (n = 138). The two treatment groups were similar with respect to numbers and reasons for discontinuing treatment. A total of 18 patients (budesonide/formoterol, n = 9; budesonide, n = 9) discontinued the study: 11 as a result of asthma deterioration (budesonide/formoterol, n = 5; budesonide, n = 6); 2 as a result of other adverse events (budesonide/formoterol); and 5 for other reasons (budesonide/formoterol, n = 2; budesonide, n = 3). In the subgroup of children who participated in the 12-hr serial FEV_1 assessments, all but 4 patients (2 in each treatment group) completed the test at the end of the study. Adherence to treatment, as recorded in daily diary cards, was excellent, with a median use of 100% in both groups, and at least 90% of patients taking over 95% of doses.

Baseline demographics and clinical characteristics by treatment randomization are shown in Table 1. Mean morning and evening PEF were slightly higher in the budesonide group, although the mean FEV_1 percentage predicted values were similar across groups. Over the run-in period, patient self-reported asthma symptoms and

TABLE 1— Patient Demographics and Baseline Clinical Characteristics[1]

Characteristic	Treatment group	
	Budesonide/formoterol 80/4.5 μg, 2 inhalations bid	Budesonide 100 μg, 2 inhalations bid
Males:females (n)	90:58 (148)	87:51 (138)
Mean age, years (range)[2]	11 (4–17)	11 (5–17)
Mean duration of asthma, years (range)	6.5 (0–15)	7.1 (1–17)
Mean inhaled steroid use, μg/day (range)	547 (400–1,500)	548 (400–2,000)
Mean FEV_1, % predicted (range)	74 (40–114)[3]	76 (40–100)
Mean reversibility, % (range)[4]	21 (−5–54)	21 (4–62)
Mean PEF, L/min (range)		
Morning	257 (97–553)	274 (98–558)
Evening	265 (99–560)	283 (97–564)
Use of rescue medication, inhalations/24 hr	0.71 (0–3)	0.5 (0–4)
Mean total asthma symptom score (0–6)	0.67 (0–5.8)	0.58 (0–4.8)
Mean night-time awakenings, % (range)[5]	7 (0–80)	8.5 (0–90)
Mean symptom-free days, % (range)[6]	65 (0–100)	70 (0–100)

[1]bid, twice daily; FEV_1, forced expiratory volume in 1 sec; PEF, peak expiratory flow rate.
[2]Eight children were aged <6 years.
[3]Intention-to-treat analysis. One patient had a baseline FEV_1 >100% of predicted normal; this was outside the randomization criterion of ≤100%.
[4]Values represent percentage reversibility of FEV_1 at visit 2 (randomization visit), measured before and 15 min after inhalation of a short-acting β_2-agonist. Patients with reversibility <12% at randomization were included in subsequent analyses, as this was an intention-to-treat population.
[5]Values represent the proportion of patients experiencing nocturnal awakenings due to asthma over the last 10 days of the run-in period.
[6]Values represent proportion of patients who had no asthma-related nocturnal awakenings and no symptoms (night or day) over the last 10 days of the run-in period.

rescue β_2-agonist use were minimal or absent. One hundred and thirteen patients (40%) reported no asthma symptoms and 139 patients (49%) used no rescue medication, while only 20% used more than one inhalation per day, and 201 patients (70%) had no nocturnal awakenings. When baseline data were reviewed by age and treatment, there was no difference between the two treatment groups. The baseline characteristics for the 12-hr serial FEV_1 subpopulation were similar to the wider trial population; mean FEV_1 percentage predicted values at baseline were 76% and 74% in the budesonide/formoterol and budesonide groups, respectively.

Efficacy

Lung Function

Budesonide/formoterol treatment resulted in a significantly greater increase in morning and evening PEF (both $P < 0.001$) compared with those treated with budesonide alone (Table 2). Analysis of daily morning PEF curves during the study showed a rapid and large increase among those patients treated with budesonide/formoterol, which was maintained at this level for the remainder of the study (Fig. 1a). Similar findings were observed for the analysis of daily evening PEF curves for the two treatment groups (Fig. 1b, Table 2). When the data were reviewed by age, morning and evening PEF were significantly ($P < 0.05$) increased in the budesonide/formoterol group compared with the budesonide group in both age groups.

Mean clinic FEV_1 increased from baseline values (i.e., at randomization, following completion of the run-in phase) in both treatment groups (Table 2, Fig. 2), with a greater improvement in the budesonide/formoterol group compared with the budesonide group ($P < 0.05$). In the subpopulation in whom 12-hr serial assessments of FEV_1 were performed at 12 weeks, there was a 6% improvement in average FEV_1 during the first 10 min after inhalation of budesonide/formoterol compared with budesonide ($P < 0.05$). An improvement over budesonide of approximately 5% was maintained up to 12 hr after inhalation. The average improvement in FEV_1 over 12 hr and maximum improvement were statistically significant in favor of budesonide/formoterol ($P < 0.05$) (Table 3, Fig. 3).

Symptoms

A decrease in the use of rescue β_2-agonist medication was apparent in both treatment groups between the run-in and treatment periods, decreasing from 0.71 inhalations to 0.60 inhalations per 24 hr in the budesonide/formoterol group, and from 0.5 inhalations to 0.41 inhalations per 24 hr in the budesonide group. A decrease in number of nights with awakenings was also apparent in both

TABLE 2— Mean Change in PEF and Mean Spirometry Variables in All Children During Inhaled Treatment With Either Budesonide/Formoterol or Budesonide[1]

Variable	Treatment group: Budesonide/formoterol 80/4.5 μg, 2 inhalations bid	Treatment group: Budesonide 100 μg, 2 inhalations bid	Between-group difference (95% CI)
Change in morning PEF, L/min	23.1	11.1	12.0 (5.2, 18.7)
% predicted normal	7.22	3.45	3.77 (1.84, 5.70)
Change in evening PEF, L/min	20.0	8.3	11.7 (5.1, 18.2)
% predicted normal	6.13	2.73	3.4 (1.54, 5.26)
FEV_1, L/min	2.01	1.91	5.5 (1.9, 9.3)[2]
% predicted normal	86.77	83.02	3.75 (1.10; 6.40)
Use of rescue medication, inhalations/24 hr	−0.11	−0.09	−0.03 (−0.19–0.14)
Mean total asthma symptom score (0–6)	0.45	0.48	−0.04 (−0.16–0.08)
Mean night-time awakening (%)	5.5	6.6	−1.1 (−3.6–1.3)
Symptom-free days (%)	77.5	75.1	2.3 (−2.4–7.0)

[1]bid, twice daily; CI, confidence interval; PEF, peak expiratory flow rate; FEV_1, forced expiratory volume in 1 sec.
[2]Ratio of increase in budesonide/formoterol group as a percentage of budesonide response.

treatment groups, decreasing on average from 7.2% to 5.5% and from 8.5% to 6.6% in the budesonide/formoterol and budesonide groups, respectively. There was no significant increase in either group in percentage of symptom-free days.

Clinical Safety Assessments

Patients' tolerance for both budesonide/formoterol and budesonide alone were assessed in the overall population. The two treatment groups were similar in terms of adverse-event profiles. The most common adverse events (reported by ≥5% of patients) in the budesonide/formoterol and budesonide treatment groups, respectively, were: pharyngitis (8% vs. 12%); respiratory infection (8% vs. 6%); rhinitis (7% vs. 4%); coughing (5% vs. 5%); headache (6% vs. 4%); viral infection (7% vs. 3%); fever (6% vs. 2%); and aggravated asthma (5% vs. 3%).

A total of 7 patients (4.7%) in the budesonide/formoterol group had a serious adverse event (SAE) requiring admission to hospital (exacerbation of asthma, n = 5; larynx edema, n = 1; and pneumonia, n = 1). When the total number of asthma aggravations (SAEs plus non-SAEs) was analyzed, there were 8 cases (5.4%) in the budesonide/formoterol group compared with 4 cases (2.9%) in the budesonide group. Five patients discontinued treatment in the budesonide/formoterol group due to asthma deterioration, whereas 6 patients discontinued treatment in the budesonide-alone group. The asthma deteriorations that were classified as serious included 5 of the 7 SAEs in the budesonide/formoterol group, and none of these was considered treatment-related by the investigator.

DISCUSSION

Current pediatric treatment guidelines advocate the addition of a long-acting β_2-agonist, such as formoterol or salmeterol, to the treatment regimen of asthma patients not optimally controlled with inhaled corticosteroids alone.[8]

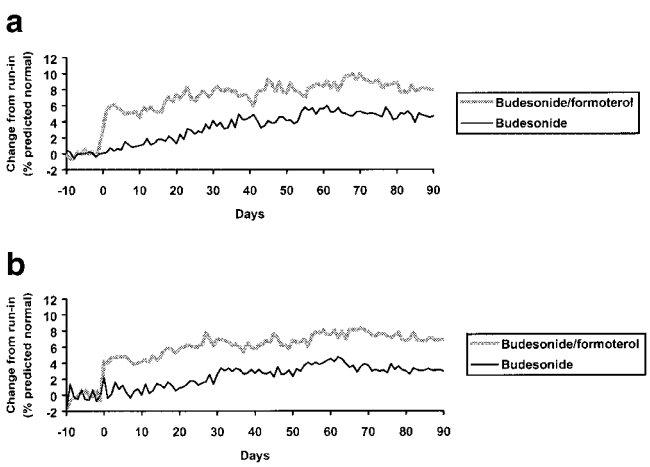

Fig. 1. Peak expiratory flow (PEF) rate, shown as daily average change in % predicted normal from run-in in (a) morning and (b) evening, in children during 12 weeks' inhaled treatment with either budesonide/formoterol 80/4.5 μg, two inhalations twice daily, or budesonide 100 μg, two inhalations twice daily.

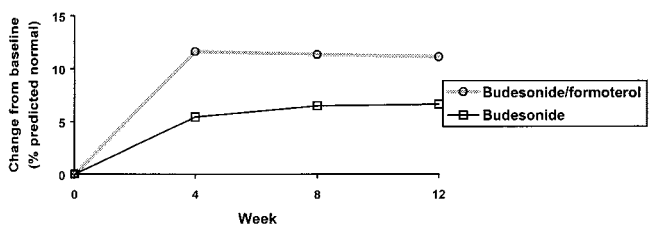

Fig. 2. Forced expiratory volume in 1 sec (FEV_1) at visits 2–5 in children treated with either budesonide/formoterol 80/4.5 μg, two inhalations twice daily, or budesonide 100 μg, two inhalations twice daily. Values are expressed as change in % predicted normal from run-in phase (taken as 100%).

TABLE 3—Mean Serial FEV_1 Variables in the Subpopulation Tested During Inhaled Treatment With Either Budesonide/Formoterol or Budesonide[1]

Variable	Treatment group: Budesonide/formoterol 80/4.5 μg, 2 inhalations bid	Treatment group: Budesonide 100 μg, 2 inhalations bid	Ratio of budesonide/formoterol: budesonide (95% CI)
Average serial FEV_1 0–10 min, L	2.24	2.11	106.3 (101.3, 111.5)
% predicted normal	90.21	84.66	5.55 (1.44, 9.66)
Average serial 12-hr FEV_1, L	2.29	2.18	105.2 (100.3, 110.3)
% predicted normal	92.18	87.40	4.78 (0.58, 8.98)
Maximum serial 12-hr FEV_1, L	2.44	2.31	105.7 (101.3, 110.3)
% predicted normal	97.81	92.42	5.39 (1.48, 9.30)
FEV_1 12 hr after inhalation, L	2.26	2.16	104.8 (99.2, 110.6)
% predicted normal	90.95	86.72	4.23 (−0.32, 8.78)

[1]bid, twice daily; CI, confidence interval; FEV_1, forced expiratory volume in 1 sec.

This study is the first to evaluate the use of budesonide and formoterol in a single inhaler in children with asthma previously treated with inhaled corticosteroids.

In adults, the addition of a long-acting β_2-agonist to inhaled corticosteroid therapy is more efficacious than increasing the dose of inhaled corticosteroid per se.[9,10] The proven efficacy of long-acting β_2-agonists as add-on therapy in adults was confirmed in a small number of studies in children.[11,12] Formoterol has demonstrated efficacy in children with asthma when added to existing inhaled corticosteroids.[23–25] To date, however, only one study has examined a combination inhaler (salmeterol/fluticasone) in children with asthma, compared with the monocomponents administered by separate inhalers.[29] Individually, the active components budesonide and formoterol have proven effective and well-tolerated in children.[6,13,30–33] The study reported here is the first in children to demonstrate the efficacy of inhaled budesonide/formoterol in a single inhaler compared with budesonide alone. In children, the beneficial effect seen in terms of improved PEF and FEV_1 with budesonide/formoterol appears at least as good as that previously observed with add-on therapy using other long-acting β_2-agonists, and greater than that reported with the leukotriene receptor antagonist montelukast.[11,34]

A prerequisite to effective treatment is the correct use of the inhaler device. This is particularly important for children. Children must be able to produce sufficient peak inspiratory flow rates through the Turbuhaler® to deliver the drug to the lung. Previous studies showed that after instruction and training, the majority of patients can use the Turbuhaler® correctly.[35,36] Ease of use makes the Turbuhaler® a suitable inhalation device for young asthmatics.

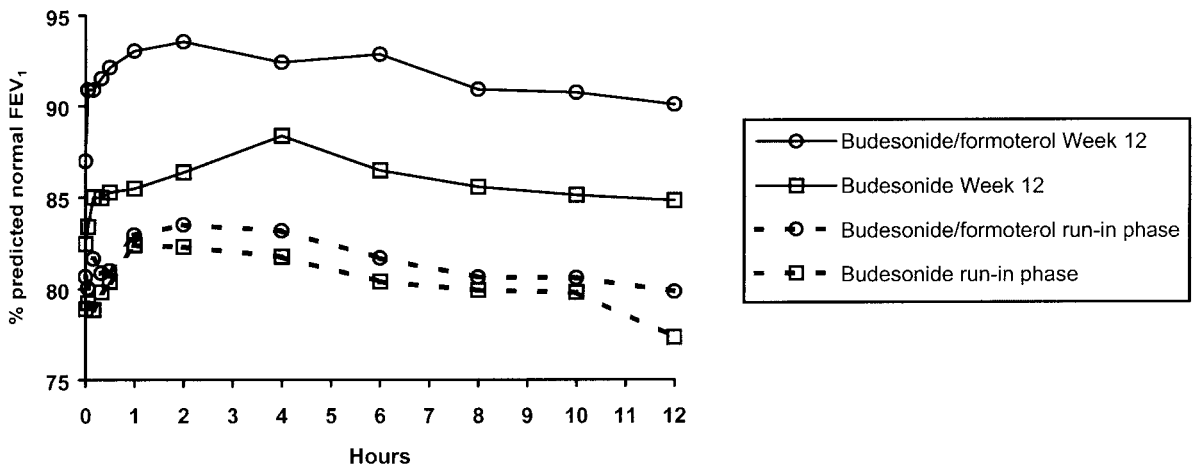

Fig. 3. Serial FEV_1 (% predicted normal) assessed in children over 12 hr following a morning dose at the last study visit (week 12), following regular treatment with either budesonide/formoterol 80/4.5 μg, two inhalations twice daily (n = 41), or budesonide 100 μg, two inhalations twice daily (n = 40). Corresponding 12-hr serial FEV_1 values are also presented for each treatment group, as observed during run-in phase prior to treatment.

Budesonide/formoterol and budesonide alone, both administered by Turbuhaler®, improved PEF and FEV_1 in children aged 4–17 years with asthma. In the overall population, there were statistically significantly greater increases in morning PEF, evening PEF, and FEV_1 with budesonide/formoterol compared with budesonide alone. The superior efficacy of budesonide/formoterol over budesonide alone, as measured by PEF, was apparent in younger (4–11 years) and older (12–17 years) patients. The significant improvements in PEF shown in this study raise the possibility that, in children as well as adults,[10] the addition of formoterol to a moderate dose of inhaled corticosteroid may reduce the need for higher doses of inhaled corticosteroid in the majority of patients. Indeed, Heuck et al.[37] showed that halving the ICS dose and adding formoterol was associated with faster short-term growth and an increase in markers of collagen turnover, with no loss of asthma control. Further studies will be required to fully determine the benefits of budesonide/formoterol in children previously requiring moderate-to-high doses of inhaled corticosteroid.

Although statistically significant improvements in morning and evening PEF were upheld when a review by age was performed, the small number of patients in the age range of 4–8 years is a limitation of the study. The small number of patients in the 4–8-year age group and the statistical powering of the study mean that the effect of treatment with budesonide/formoterol could not be assessed in these youngest patients as a separate group. Results from the present study suggest, however, that budesonide/formoterol administered via Turbuhaler® is an effective treatment for asthma in adolescents[38] and young children under age 11 years.

Adherence to treatment was excellent in both study groups. This is typical of participants in clinical studies, who tend to be well-motivated and keen to adhere to treatment, although the simplicity of the treatment regimen may have played a part in ensuring regular use. Clinical study participants, however, may not be representative of the asthma population in general, among whom adherence to medication can be poor, resulting in treatment failure and the need for oral corticosteroid rescue medication. Among the many reasons for poor adherence to asthma treatment are perceived complexity of the treatment regimen and a poor understanding of the need for continued preventive measures during periods without symptoms. Another key factor may be a need to feel an immediate effect from treatment, leading to an over-reliance on reliever medication and an underuse of inhaled corticosteroids. The use of a single inhaler that provides rapid relief of symptoms, while reducing the underlying inflammation, may improve adherence to medication and therefore provide better long-term disease control.

Mean asthma symptom scores and the need for rescue medication were reduced after both treatments. However, there was no significant difference in mean reductions for either outcome measure. The study design did not specify a value for asthma symptom score as an inclusion criterion, nor did it include a predefined need for rescue medication. During the last 10 days of the run-in period, patients enrolled in the study reported minimal or absent asthma symptoms and rescue β_2-agonist use. Given the low baseline values for both asthma symptoms and rescue medication use, a significant difference in these two outcomes would be difficult to detect. Night-time awakenings were also infrequent at the start of the study period, and the mean number of patients experiencing symptom-control days was high. It was therefore not surprising that neither group of patients reported an improvement in asthma symptoms as a result of treatment, given their favorable condition at the beginning of the study.

There was no evidence for a tolerance to budesonide/formoterol, even after 12 weeks of treatment. Indeed, in the subgroup of patients who underwent 12-hr FEV_1 assessment at the beginning and end of the study, those treated with budesonide/formoterol showed a sustained improvement in PEF compared with budesonide alone. It may be speculated that the use of budesonide/formoterol should offer added protection from bronchoconstriction induced by common triggers of childhood asthma (e.g., exercise). This speculation is supported by Grönneröd et al.,[39] who reported that a single dose of formoterol gave 12-hr bronchoprotection from repeated exercise challenge.

Most childhood asthma appears to be very responsive to relatively low doses of inhaled corticosteroids.[6,40,41] Many patients, however, are left with residual airway obstruction that may require additional treatment. Adding a second regular controller therapy (inhaler or tablet) may further complicate a treatment regimen and unduly compromise patients' adherence to the more important and potent anti-inflammatory drug. In asthmatic children, an association between treatment failure (need for rescue with oral corticosteroids) and poor adherence to inhaled corticosteroids has been seen in the presence of continued adherence to a regular β-agonist regimen.[42] Even in the absence of symptoms, prolonged and consistent anti-inflammatory therapy is required in all but the mildest intermittent asthma. Achieving adherence to budesonide/formoterol in a single inhaler will ensure treatment with both controller therapies, avoiding selective compliance with a less effective therapy (i.e., short-acting β_2-agonists).

In conclusion, budesonide/formoterol effectively improved PEF in children with asthma not optimally controlled with inhaled glucocorticosteroids alone. There was no acquired tolerance to budesonide/formoterol during the study. Moreover, the rapid onset of action and early benefit of treatment in terms of asthma control seen at the start of the study were still apparent after 12 weeks of treatment. Budesonide/formoterol was well-tolerated in

children aged 4–17 years. Overall, this study indicates a more beneficial effect (in terms of improved PEF and FEV_1) for budesonide/formoterol in a single inhaler than for continued treatment with budesonide alone.

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