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Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma[1]

Petr Pohunek[1], Piotr Kuna[2], Carin Jorup[3] and Kris De Boeck[4]

[1]University Hospital Motol, Prague, Czech Republic, [2]Barlicki University Hospital, Medical University, Lodz, Poland, [3]AstraZeneca R&D Lund, Lund, Sweden, [4]University Hospital of Leuven, Leuven, Belgium

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We aimed to compare the efficacy and safety of budesonide/formoterol (Symbicort®) with budesonide alone (Pulmicort®) or budesonide (Pulmicort) and formoterol (Oxis®) administered via separate inhalers in children with asthma. In a 12 wk, double-blind study, a total of 630 children with asthma (mean age 8 yr [4–11 yr]; mean forced expiratory volume in 1 s (FEV_1) 92% predicted; mean inhaled corticosteroid dose 454 μg/day) were randomized to: budesonide/formoterol (80/4.5 μg, two inhalations twice daily); a corresponding dose of budesonide alone (100 μg, two inhalations twice daily); or a corresponding dose of budesonide (100 μg, two inhalations twice daily) and formoterol (4.5 μg, two inhalations twice daily) (budesonide + formoterol in separate inhalers). The primary efficacy variable was the change from baseline to treatment (average of the 12-wk treatment period) in morning peak expiratory flow (PEF). Other changes in lung function and asthma symptoms were assessed, as was safety. Budesonide/formoterol significantly improved morning PEF, evening PEF and FEV_1 compared with budesonide (all $p < 0.001$); there was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers for these variables. All other diary card variables improved from baseline in all treatment groups; there were no significant between-group differences. Adverse-event profiles were similar in all groups; there were no serious asthma-related adverse events in any treatment group. Conclusion: budesonide/formoterol significantly improved lung function in children (aged 4–11 yr) with asthma compared with budesonide alone. Budesonide/formoterol is a safe and effective treatment option for children with asthma.

Key words: asthma; budesonide; budesonide/formoterol; Pulmicort; Symbicort

P. Pohunek MD PhD, Head of Division of Pediatric Respiratory Diseases, Pediatric Department, University Hospital Motol, Vúvalu 84, CZ-15006 Prague, Czech Republic
Tel.: +42 022 443 2018
Fax: +42 022 443 2217
E-mail: petr.pohunek@lfmotol.cuni.cz

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Asthma is one of the most common chronic conditions to affect children, and its prevalence is increasing (1). For children presenting with persistent asthma, treatment with inhaled corticosteroids (ICS) is widely accepted as the optimum therapeutic approach, with budesonide, in particular, having well-established efficacy (2) and safety (3, 4). International guidelines for the treatment of paediatric patients with asthma advocate the use of a long-acting β_2-agonist (LABA) as add-on therapy for those children in whom ICS fail to provide adequate asthma control (5, 6). However, evidence supporting the use of this treatment regimen in children is less compelling than in adults (7).

The beneficial effects of therapy with an ICS and a LABA have been demonstrated in children

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with asthma (8–11). Inhalers containing both an ICS and a LABA provide both anti-inflammatory and bronchodilator medications with each inhalation and may thereby simplify the treatment regimen. In a trial involving 286 children with asthma aged between 4 and 17 yr, Tal et al. (12) showed that budesonide/formoterol improved lung function – as measured by morning and evening peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1) – compared with budesonide alone.

The present study was designed to compare the efficacy and safety of budesonide/formoterol with budesonide alone or budesonide and formoterol administered via separate inhalers in children with asthma. As the study by Tal et al. (12) included children with very low asthma-symptom scores at study entry, we examined the effects of treatment on symptomatic children aged 4–11 yr who were undergoing treatment with ICS.

Patients and methods

Patients

Patients were recruited from 80 centres in Austria, Belgium, the Czech Republic, France, Hungary, Poland, Spain and Switzerland. Outpatients aged 4–11 yr who had been diagnosed with asthma [as defined by the American Thoracic Society (13)] for a minimum period of 6 months were included in the study. All patients were required to have a prebronchodilatory PEF ≥ 50% of predicted normal and had received treatment with an ICS (any brand) for at least 3 months before entry into the study, with the dose remaining constant (375–1000 μg/day) during the 30 days immediately prior to enrolment. In addition, patients had to have a history of an average of ≥1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study. All subjects needed to demonstrate the ability to use a Turbuhaler® device and peak flow metre correctly.

Patients were excluded if they had: used oral, parenteral or rectal corticosteroids within 30 days of inclusion in the study; any respiratory infection affecting asthma control within the 30 days before enrolment; any significant disease or concomitant disorder; known or suspected hypersensitivity to the study medication or inhaled lactose. The use of inhaled anticholinergics, β-blockers (including eye drops), xanthines and other anti-asthma products was not permitted during the study. Other medication considered necessary for the patients' wellbeing was given at the discretion of the investigator.

To be randomized, patients had to have a total asthma-symptom score [sum of night-time and daytime symptom scores, both ranging from 0 to 3, where 0 = no symptoms and 3 = unable to perform normal activities (or to sleep) because of symptoms] of at least one on a minimum of four of the last 7 days of the run-in period. In addition, during the last 7 days of the run-in, patients had to have a mean morning PEF of 50–85% of the postbronchodilatory PEF obtained 15 min after inhalation of terbutaline at enrolment.

Study design

This was a 12 wk, double-blind, double-dummy, randomized, parallel-group, active-controlled multi-centre study (Study 0688). The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations, each study centre having received ethical approval of the protocol before study commencement. Parents/guardians of all patients were required to give written informed consent before any study-related procedures were performed and all children gave written or oral consent.

During the 10–14 days run-in period, patients continued with the same dose of ICS that they had used before enrolment in the study, using terbutaline (Bricanyl®, AstraZeneca, Sweden) as needed for symptom relief. Following run-in, patients were randomized to one of three treatment groups (Fig. 1): budesonide/formoterol (Symbicort® Turbuhaler, AstraZeneca, Sweden; 80/4.5 μg, two inhalations twice daily); a corresponding dose of budesonide (Pulmicort® Turbuhaler, AstraZeneca, Sweden; 100 μg, two inhalations twice daily); or a corresponding dose of budesonide (Pulmicort Turbuhaler, AstraZeneca, Sweden; 100 μg, two inhalations twice daily) + formoterol (Oxis® Turbuhaler, AstraZeneca, Sweden; 4.5 μg, two inhalations twice daily) in separate inhalers. The budesonide doses

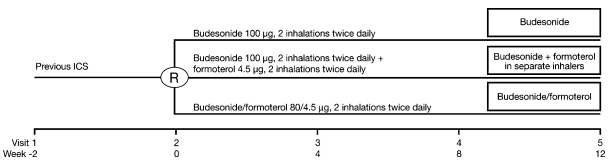

Fig. 1. Design of a 12 wk study comparing treatment with budesonide/formoterol, budesonide alone or budesonide and formoterol administered via separate inhalers. ICS, inhaled corticosteroids; R, randomization.

in each group were comparable; differences are explained by labelling changes for new inhaled drugs, which require the delivered dose rather than the metered dose to be reported.

Terbutaline (0.5 mg) was used as needed for symptom relief throughout the study.

Efficacy assessments

The primary efficacy variable was the change from baseline (average of the last 10 days of the run-in period) to treatment (average of the 12-wk treatment period) in morning PEF. Secondary efficacy variables included the change from baseline in: evening PEF; total asthma-symptom score (sum of night-time plus daytime symptom scores); night-time awakenings due to asthma symptoms; use of reliever medication; reliever-free days; and symptom-free days. Other secondary efficacy variables included the change from baseline (Visit 2 value) to treatment (average of the 12-wk treatment period) in FEV_1 and the change from baseline (Visit 2 value) to the end of treatment in health-related quality of life, as measured by the overall score and each domain score of the standardized version of the Paediatric Asthma Quality of Life Questionnaire [PAQLQ(S)] (14).

Patients used diary cards to record morning and evening PEF [measured using a Mini-Wright® PEF metre (Clement Clark, Harlow, UK)], asthma-symptom scores, night-time awakenings, reliever medication use and intake of study medication. Parents or guardians completed diaries for children who were unable to read or write.

FEV_1 was assessed by the investigator at each clinic visit. This was measured by spirometry according to European Respiratory Society recommendations (15).

The PAQLQ(S) was administered via interview at Visits 1, 2, 3 and 5. The interview at Visit 1 was for training purposes only. The domain and overall scores were assessed on a scale from 1 to 7, where one represents the greatest possible impairment and seven represents the least impairment. The overall PAQLQ(S) score was calculated as the mean value for all questions. The outcome variables for PAQLQ(S) were the change in overall and domain scores from Visit 2 to the end of treatment. The minimal important difference (MID) was defined as 'the smallest difference in score in the domain of interest that patients perceive as beneficial and would mandate, in the absence of troublesome side effects or excessive cost, a change in the patient's management'. For the overall PAQLQ(S) score the MID was determined to be a change of 0.5 (16).

Safety assessments

Adverse events were recorded throughout the study. These were classified as mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities) or severe (incapacitating with inability to perform normal activities). Deterioration in the signs or symptoms of asthma was not recorded as an adverse event unless it resulted in withdrawal from the study or was considered to be serious. A serious adverse event was one that: resulted in death, disability or significant incapacity; was immediately life-threatening; required hospitalization; jeopardized the patient; or required medical intervention to prevent one of the above outcomes. Safety data were collected for all patients who received at least one dose of study medication and for whom data were available after randomization.

Safety was also assessed by physical examination, clinical laboratory analysis (plasma and urinary cortisol) and vital signs (pulse and blood pressure). Blood samples for morning plasma cortisol analysis were taken at Visits 2 and 5 (at 8.00 AM $\pm$ 30 min). Assessment of urinary cortisol was to be performed in a subpopulation of 25 patients in each treatment group who were enrolled from selected centres in Poland. Urine was collected during the 24 h before Visits 2 and 5.

Statistical methods

A sample size of 180 in each treatment group was required to give 80% power to detect a true difference of 8.9 l/min in the mean change for morning PEF, assuming a common standard deviation of 30 l/min (5% significance level, two-group *t*-test). It was planned to enrol approximately 800 patients, as it was estimated that 600 patients needed to be randomized in order to reach 540 evaluable patients.

Intent to treat analysis was performed using data from all randomized patients. Diary card variables, spirometry and the change in PAQLQ(S) score were analysed by use of analysis of variance (ANOVA), with treatment and country as fixed factors and the baseline value (run-in period average or Visit 2 value) as a covariate. Changes in plasma and urinary cortisol were evaluated using a multiplicative ANOVA model with treatment and country as fixed factors for plasma cortisol and treatment as a fixed factor for urinary cortisol; the Visit 2

assessment was included as a covariate for both plasma and urinary cortisol. All tests were performed using two-sided alternative hypotheses and p-< 5% were considered statistically significant.

Adverse events and vital signs were evaluated using descriptive statistics.

Results

Patients

Patients were enrolled and treated between March 2002 and 2003. From a total of 809 enrolled patients, 630 were subsequently randomized to treatment with budesonide/formoterol (n = 216), budesonide (n = 213) or budesonide + formoterol in separate inhalers (n = 201). The full analysis set comprised a maximum of 630 patients. However, the primary analysis – morning PEF – was based on 627 patients, as relevant data were not available for three patients. The safety population comprised all 630 randomized patients.

A total of 38 patients (budesonide/formoterol, n = 14; budesonide, n = 13; budesonide + formoterol in separate inhalers, n = 11) discontinued the study: 27 as a result of the eligibility criteria not being fulfilled; three as a result of adverse events; and eight for other reasons. A total of 592 patients completed the study.

The three treatment groups were comparable in terms of baseline demographics and clinical characteristics (Table 1). Overall, the patients had a mean FEV_1 of 92% of predicted normal and a mean ICS dose of 454 μg/day. The mean age of all patients was 8 yr; 12% of the patients were aged 4–5 yr. Patients in all groups showed high self-reported adherence to the study medication; overall, >98% of the doses were taken.

Efficacy

Lung function. For the primary efficacy variable of morning PEF, statistically significantly greater changes from baseline (average of the last 10 days of the run-in period) were apparent in patients treated with budesonide/formoterol compared with budesonide (Fig. 2a). The mean difference between the treatment groups was 10.9 l/min ($p < 0.001$). There was no significant difference in morning PEF between patients treated with budesonide/formoterol and those who received budesonide + formoterol in separate inhalers ($p = 0.14$).

As seen with morning PEF, statistically significantly greater changes from baseline were evident in evening PEF for patients treated with budesonide/formoterol compared with budesonide (mean difference 9.1 l/min; $p < 0.001$) (Fig. 2b). There was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers with regard to evening PEF.

Improvements in PEF were apparent from the beginning of treatment with budesonide/formoterol and budesonide + formoterol in separate inhalers, and were sustained over the 12-wk treatment period.

Patients treated with budesonide/formoterol had statistically significantly greater changes in FEV_1 compared with budesonide (mean difference between the treatment groups 0.078 l; $p < 0.001$) (Fig. 3). There was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers.

Table 1. Demographic and baseline characteristics of patients receiving budesonide/formoterol, budesonide alone or budesonide and formoterol administered via separate inhalers

Characteristic	Budesonide (n = 213)	Budesonide + formoterol (n = 201)	Budesonide/formoterol (n = 216)
Male/female (no.)	147/66	137/64	140/76
Age, years (range)	8.2 (4–11)	8.1 (4–11)	8.1 (4–11)
Asthma duration, years (range)	2 (1–11)	3 (0–10)	3 (0–10)
FEV_1, l (range)	1.65 (0.6–3.4)	1.66 (0.6–3.3)	1.64 (0.7–3.0)
FEV_1, % predicted normal (range)	91.3 (52–132)	93.0 (45–169)	91.9 (50–166)
ICS dose at entry, μg (range)	446 (200*–1000)	450 (200*–1000)	465 (320*–1000)
Inhaled LABA use at entry, n (%)	88 (41)	82 (41)	86 (40)
Inhaled ICS/LABA use at entry, n (%)	5 (2)	7 (3)	13 (6)
Asthma-symptom score, 0–6 (range)	1.4 (0.0–4.9)	1.5 (0.3–5.0)	1.5 (0.1–3.9)
Reliever use, inhalations/24 h (range)	0.82 (0.0–6.0)	0.89 (0.0–7.4)	0.96 (0.0–8.8)
Night-time awakenings, % (range)	17.3 (0–100)	17.3 (0–100)	18.3 (0–100)

All values are presented as absolute numbers or as means, except for asthma duration where the median value is given.
FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist.
*Deviation from inclusion criterion not considered significant to justify exclusion of data from the analysis.

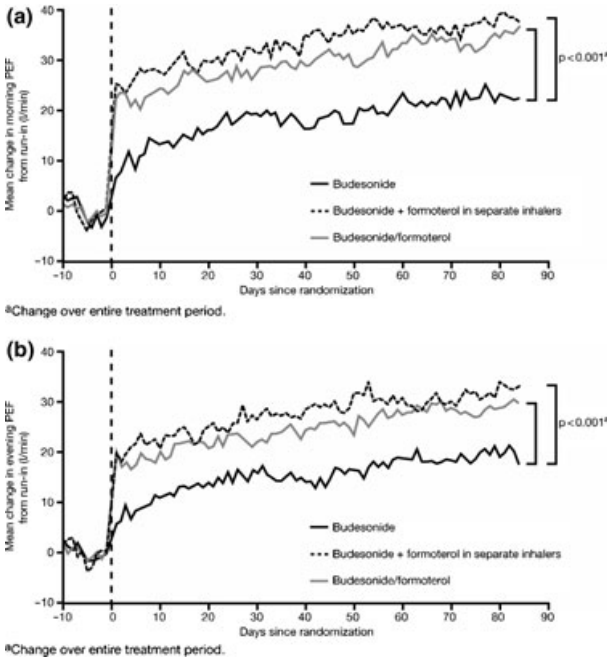

Fig. 2. Change in (a) morning and (b) evening peak expiratory flow (PEF) in patients receiving budesonide/formoterol, budesonide alone or budesonide and formoterol administered via separate inhalers.

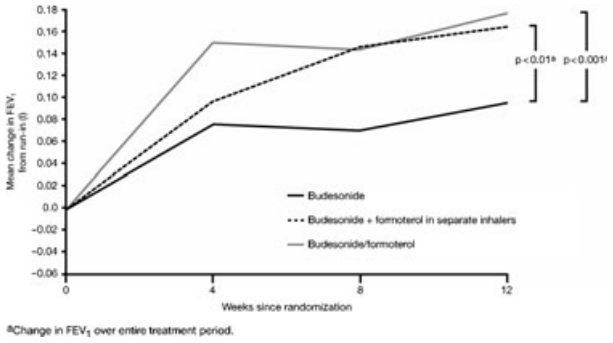

Fig. 3. Change in forced expiratory volume in 1 s (FEV_1) in patients receiving budesonide/formoterol, budesonide alone or budesonide and formoterol administered via separate inhalers.

Asthma symptoms

Asthma symptoms improved from baseline with all treatments (Table 2), with no significant between-group differences. Patients in all three treatment groups had fewer night-time awakenings, more symptom-free days and a reduced need for reliever medication, compared with baseline.

Health-related quality of life

Overall PAQLQ(S) scores improved in all treatment groups, with adjusted mean changes of 0.437, 0.494 and 0.501 for the budesonide/formoterol, budesonide + formoterol in separate inhalers and budesonide treatment groups, respectively. No significant between-group differences were observed and all three treatment groups had mean changes close to the MID (0.5). Scores were also improved for the individual domains, indicating improvements with regard to symptoms, emotional function and activity limitation; there were no differences between the treatment groups.

Safety

Adverse events. Overall, 39% of patients reported at least one adverse event. These were mostly mild or moderate in intensity, and had a similar incidence in all the treatment groups (budesonide/formoterol, 39%; budesonide, 40%; budesonide + formoterol in separate inhalers, 37%). Respiratory infection and rhinitis were the most frequently reported adverse events. The incidence of well-known class effects of ICS and β_2-agonists was low and similar between the treatment groups (Table 3).

A total of three patients discontinued the study owing to adverse events – two patients who were receiving budesonide + formoterol in separate inhalers (one as a consequence of asthma aggravated and laryngitis, and the other owing to asthma aggravated and pneumonia) and one who was being treated with budesonide (as a result of pharyngitis). There were no discontinuations attributed to adverse events in the budesonide/formoterol treatment group.

Serious adverse events after intake of the study medication were experienced by a total of 11 patients: three patients in the budesonide/formoterol treatment group (one report each of fracture, laryngitis and torticollis); three patients in the budesonide treatment group (gastroenteritis and infection viral were reported for one patient in whom gastroenteritis and fever were also recorded, enteritis was reported in another patient and a third patient experienced a fracture); and five patients in the group who received budesonide + formoterol in separate inhalers (with reports of appendicitis, vomiting, laryngitis and pneumonia being recorded for individual patients, and both abdominal pain and appendicitis being recorded in another patient). None of these events were considered to be causally related to the study drug. No deaths occurred during the study.

Clinical laboratory evaluations and vital signs

Of the 593 patients for whom an assessment of plasma cortisol was performed, 83% of the

Table 2. Clinical outcomes in patients receiving 12 wk of treatment with budesonide/formoterol, budesonide alone or budesonide and formoterol administered via separate inhalers

	Budesonide (n = 213)		Budesonide + formoterol (n = 201)		Budesonide/formoterol (n = 216)	
Variable	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
PEF (l/min)						
Morning	216	235	216	250**	212	241**
Evening	224	240	225	253**	220	245**
FEV_1 (l)	1.68	1.76	1.71	1.84*	1.66	1.82**
PAQLQ(S) score, range 1–7	5.8	6.2	5.8	6.2	5.7	6.2
Asthma-symptom score, 0–6	1.4	0.8	1.5	0.8	1.5	0.8
Reliever use, inhalations/24 h	0.82	0.36	0.88	0.41	0.96	0.37
Symptom-free days (%)	20.8	52.8	17.7	50.6	19.5	52.5
Reliever-free days (%)	54.8	78.2	53.8	77.0	52.4	79.4
Night-time awakenings (%)	16.9	6.6	17.0	7.1	18.4	6.8

All values are presented as means. Baseline means – calculated for the number of patients for whom efficacy data were available, not all randomized patients – are the mean values for the run-in period, except for FEV_1 and PAQLQ(S), which are the Visit 2 means. Treatment means are the treatment period means (average for the 12-wk treatment period), except for FEV_1 (mean of Visits 3–5) and PAQLQ(S) (mean of Visit 5).

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; PAQLQ(S), standardized version of the Paediatric Asthma Quality of Life Questionnaire.

*$p < 0.01$ for change over treatment period versus budesonide. **$p < 0.001$ for change over treatment period versus budesonide.

Table 3. Pharmacological class effects of inhaled corticosteroids and β_2-agonists in patients receiving 12 wk of treatment with budesonide/formoterol, budesonide alone or budesonide and formoterol administered via separate inhalers

	Number of patients (%)		
Adverse event	Budesonide (n = 213)	Budesonide + formoterol (n = 201)	Budesonide/formoterol (n = 216)
Inhaled corticosteroids			
Dysphonia	3 (1)	1 (<0.5)	2 (1)
Hoarseness	0	0	0
Oral candidiasis	0	0	0
β_2-agonists			
Tremor	0	2 (1)	0
Tachycardia	1 (<0.5)	0	0
Cramps	0	0	1 (<0.5)
Palpitations	0	0	0

budesonide/formoterol group and 87% of both the budesonide and budesonide + formoterol groups had plasma cortisol levels β150 nmol/l at the end of treatment. In addition, urinary cortisol was assessed in a subpopulation of 89 patients (29, 26 and 34 patients in the budesonide/formoterol, budesonide and budesonide + formoterol groups, respectively). There were no clinically important differences between the treatment groups in plasma or urinary cortisol, and there were no statistically significant between-group differences.

Discussion

This study evaluated the efficacy of budesonide/formoterol (80/4.5 μg, two inhalations twice daily) for the treatment of asthma in symptomatic children aged 4–11 yr who were undergoing therapy with ICS. A significant proportion of this group (12%) were aged 4–5 yr. Budesonide/formoterol was superior to budesonide for the primary efficacy variable – change in morning PEF over the 12-wk treatment period. Improvements in evening PEF and FEV_1 after treatment with budesonide/formoterol provided additional evidence for the greater efficacy of this treatment regimen over budesonide. These improvements in lung function were evident from the beginning of treatment and were sustained throughout the trial period.

The improvements in lung function seen in this study confirm previously reported results. Tal et al. (12) described a difference of 12.0 l/min ($p < 0.001$) in mean morning PEF between children treated with budesonide/formoterol and budesonide. In the present study, a comparable improvement was observed (10.9 l/min; $p < 0.001$ vs. budesonide). Previous studies in adult patients with asthma have also shown budesonide/formoterol to produce statistically significant improvements in lung function compared with budesonide (17, 18), with no difference between budesonide/formoterol and budesonide + formoterol treatment regimens (17). In these studies, as in the present study, the improved effects of budesonide/formoterol on lung function were apparent from the beginning of treatment and were sustained throughout the study periods. In adults, budesonide/formoterol treatment has been shown to significantly improve the percentage of asthma-control days

compared with budesonide alone (17). Despite the fact that a considerable proportion (12%) of patients in our study was aged 4–5 yr, there was little evidence of incorrect use of Turbuhaler. This is consistent with previous studies, which have shown that the majority of patients aged 4 yr and over can generate a sufficient inspiratory rate to use Turbuhaler (19–21). In addition, the ability to use both Turbuhaler and the peak flow metre correctly was a requirement for inclusion in the study.

Unlike the study by Tal et al., in which patients were not required to be symptomatic at study entry (patients had a mean total asthma symptom score at baseline of 0.63 on a scale of 0–6), patients in our study were required to have a minimum level of asthma symptoms, with a total asthma-symptom score ≥1 on at least four of the last 7 days of the run-in period. All treatments improved asthma symptoms compared with baseline; no statistically significant differences were seen between the treatment groups. While statistically significant differences in improvements in lung function were apparent between treatment groups, the absence of any corresponding differences in asthma symptoms may be a consequence of the difficulties associated with recording asthma symptoms in children. In a study of 110 asthma patients aged >6 yr, Bheekie et al. reported mean daily symptom scores as recorded by patients to be significantly lower than researcher-estimated values (22). Similarly, although patients in our study showed improvements from baseline in PAQLQ(S) scores, no differences were apparent between any of the treatment groups.

There were no discontinuations owing to asthma being aggravated in patients treated with either budesonide/formoterol or budesonide; only two patients receiving budesonide + formoterol in separate inhalers discontinued as a result of asthma aggravated. However, studies in adult patients show that, although treatment with ICS and LABA improves asthma control compared with ICS alone, many patients continue to experience asthma exacerbations (23–25). Recent studies using budesonide/formoterol for both maintenance and relief of symptoms have shown significant reductions in the risk and rate of exacerbations compared with fixed dosing with ICS/LABA or ICS for maintenance plus a short-acting β_2-agonist for symptom relief (26–28).

The study reported by O'Byrne et al. (26) included 341 children aged 4–11 yr. A significant reduction in severe exacerbations was apparent in those children treated with budesonide/formoterol for maintenance and relief compared with those receiving budesonide/formoterol plus as-needed terbutaline or a fourfold higher dose of budesonide plus terbutaline as needed – a finding not previously seen in studies of ICS/LABA therapy in children (7). The use of budesonide/formoterol for symptom relief is possible because of the rapid onset of effect of both formoterol: bronchodilation occurs within the first minute of administration of both formoterol (29) and budesonide/formoterol (30). In addition, Balanag et al. have shown that budesonide/formoterol is as fast and effective as salbutamol in providing relief from acute severe airway obstruction in asthma (31).

In our study, no patients in the budesonide/formoterol group discontinued owing to asthma aggravated or any other adverse event. These results demonstrate ICS/LABA therapy to be suitable for use in children and do not support concerns raised by Bisgaard (7) regarding findings in previous studies [e.g. (12)], in which using LABA therapy in addition to ICS was of questionable benefit in protecting against exacerbations.

In the study we report here, all three treatment regimens were well tolerated and no new safety concerns were identified. Only 39% of patients reported an adverse event, most of which were mild to moderate in intensity; the overall incidence of adverse events was similar for all treatment groups. Measurement of plasma cortisol showed no differences for all treatment groups, although as budesonide was used in all three treatment arms, plasma cortisol levels could not be compared with untreated patients.

In conclusion, budesonide/formoterol is a safe and effective treatment for children with asthma, providing significantly greater improvements in lung function than budesonide alone.

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References

1. Myers TR, Chatburn RL. Pediatric asthma disease management. Respir Care Clin North Am 2000: 6: 57–74.
2. Shapiro G, Bronsky EA, LaForce CF, et al. Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. J Pediatr 1998: 132: 976–82.
3. Tinkelman DG, Bronsky EA, Gross G, Schoenwetter WF, Spector SL. Efficacy and safety of budesonide

inhalation powder (Pulmicort Turbuhaler) during 52 weeks of treatment in adults and children with persistent asthma. J Asthma 2003: 40: 225–36.
4. Szefler SJ, Lyzell E, Fitzpatrick S, Cruz-Rivera M. Safety profile of budesonide inhalation suspension in the pediatric population: worldwide experience. Ann Allergy Asthma Immunol 2004: 93: 83–90.
5. Warner JO, Naspitz CK, for the International Pediatric Asthma Consensus Group. Third international pediatric consensus statement on the management of childhood asthma. Pediatr Pulmonol 1998: 25: 1–17.
6. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (updated 2004). National Institutes of Health [NIH] publication No. 02-3659. Bethesda, MD: NIH (Accessible at http://www.ginasthma.org).
7. Bisgaard H. Effect of long-acting β_2 agonists on exacerbation rates of asthma in children. Pediatr Pulmonol 2003: 36: 391–8.
8. Langton Hewer S, Hobbs J, French D, Lenney W. Pilgrim's progress: the effect of salmeterol in older children with chronic severe asthma. Respir Med 1995: 89: 435–40.
9. Russell G, Williams DAJ, Weller P, Price JF. Salmetetrol xinafoate in children on high dose inhaled steroids. Ann Allergy Asthma Immunol 1995: 75: 423–8.
10. Akpinarli A, Tuncer A, Saraçlar Y, Şekerel BE, Kalayci O. Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomized controlled trial. Arch Dis Child 1999: 81: 45–8.
11. von Berg A, Papageorgiou Saxoni F, Wille S, et al. Efficacy and tolerability of formoterol Turbuhaler® in children. Int J Clin Pract 2003: 57: 852–6.
12. Tal A, Simon G, Vermeulen JH, et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol 2002: 34: 342–50.
13. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987: 136: 225–44.
14. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Grith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res 1996: 5: 35–46.
15. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party: standardization of lung function tests. European Community for Steel and Coal. Eur Respir J 1993: 6 (Suppl. 16): 5–40.
16. Juniper EF, Guyatt GH, Willan A, Grith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994: 47: 81–7.
17. Zetterström O, Buhl R, Mellem H, et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. Eur Respir J 2001: 18: 262–8.
18. Buhl R, Creemers JP, Vondra V, Martelli NA, Naya IP, Ekstrom T. Once-daily budesonide/formoterol in a single inhaler in adults with moderate persistent asthma. Respir Med 2003: 97: 323–30.
19. Agertoft L, Pedersen S. Importance of training for correct Turbuhaler use in preschool children. Acta Paediatr 1998: 87: 842–7.
20. Goren A, Noviski N, Avital A, et al. Assessment of the ability of young children to use a powder inhaler device (Turbuhaler). Pediatr Pulmonol 1994: 18: 77–80.
21. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. Arch Dis Child 1990: 65: 308–10.
22. Bheekie A, Syce JA, Weinberg EG. Peak expiratory flow rate and symptom self-monitoring of asthma initiated from community pharmacies. J Clin Pharm Ther 2001: 26: 287–96.
23. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994: 344: 219–24.
24. Pauwels RA, Löfdahl C-G, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997: 337: 1405–11.
25. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001: 164: 1392–7.
26. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005: 171: 129–36.
27. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004: 20: 1403–18.
28. Rabe KF, Pizzichini E, Ställberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild to moderate asthma: a randomized, double-blind trial. Chest 2005: in press.
29. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lötvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. Eur Respir J 1997: 10: 2489–99.
30. van der Woude HJ, Boorsma M, Bergqvist PBF, Winter TH, Aalbers R. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. Pulm Pharmacol Ther 2004: 17: 89–95.
31. Balanag VM, Yunus F, Yang P-C, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. Pulm Pharmacol Ther 2005: Jul 8: [Epub ahead of print].