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Efficacy of Once-Daily Versus Twice-Daily Administration of Budesonide by Turbuhaler® in Children With Stable Asthma

Christian Möller, MD, PhD,[1]* Leif Strömberg, MD,[2] Göran Oldaeus, MD, PhD,[3] Ewa Arweström, BSc,[4] and Max Kjellman, MD, PhD[5]

Summary. We evaluated the efficacy of once-daily versus twice-daily treatment with budesonide, delivered by a Turbuhaler®, in the management of children with stable asthma in a randomized, double-blind, parallel-group study involving 206 children (age 5–15 years). After a 2-week run-in period during which the children were maintained on their usual dose of budesonide (200 µg or 400 µg/day), patients were randomized to receive the same daily dose in either two daily administrations (morning and evening) or as a single dose in the morning over a period of 12 weeks. The primary efficacy variable was morning peak expiratory flow (PEF).

The mean morning PEF during the run-in phase was 271 L/min in patients randomized to once-daily treatment and 264 L/min in those randomized to twice-daily treatment. The mean change from baseline to the last 2 weeks of the treatment period in the two groups was −0.3 L/min (95% confidence limits −6.6 to +6.0) and 2.5 L/min (−4.3 to +9.3). The estimated difference between the groups was −2.8 L/min, with 90% confidence limits of −10.4 + 4.5; these were close to the limits regarded as indicative of equivalence (−10 to +10), and hence the difference was not regarded as clinically relevant. Similarly, there were no significant differences between the groups in regard to secondary efficacy measures such as spirometric tests and symptom scores. Both treatments were well tolerated.

We conclude that once-daily administration of budesonide by Turbuhaler® is as effective as twice-daily treatment in the management of stable asthma in children treated with inhaled steroids at doses of 200–400 µg/day. **Pediatr Pulmonol. 1999; 28:337–343.**

Key words: asthma; budesonide; randomized controlled clinical trial; corticosteroids; Turbuhaler®.

INTRODUCTION

Asthma is one of the most common chronic diseases of childhood. The prevalence in developed countries is estimated to be between 5% and 18%, and studies have consistently shown that the prevalence is increasing.[1,2] Fortunately, better understanding of the inflammatory nature of the disease, increased attention to preventative measures, and the introduction of new and effective therapies have made it possible to control asthma in the majority of children.[3]

Inhaled glucocorticosteroids such as budesonide are increasingly accepted as first line treatment of chronic asthma because they inhibit the underlying airway inflammation and hence reduce bronchial reactivity and improve symptoms. Early trials in adult patients have shown that budesonide produces a significant and prolonged increase in peak expiratory flow (PEF); the effect becomes apparent within 2 hours of inhalation and reaches its peak after approximately 6–7 hours.[4] In clinical trials in asthmatic children, budesonide has been shown to produce significant improvements in lung function, airway responsiveness and asthma symptoms, with few significant adverse effects at therapeutic doses.[5] Current guidelines recommend that treatment with inhaled steroids should be started with a high dose, and the dose

[1]Department of Paediatrics, University Hospital, Umeå, Sweden.

[2]Department of Paediatrics, County Hospital Vrinnevi, Norrköping, Sweden.

[3]Department of Paediatrics, County Hospital Ryhov, Jönköping, Sweden.

[4]Draco Läkemedel AB, Lund, Sweden.

[5]Department of Paediatrics, University Hospital, Linköping, Sweden.

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*Correspondence to: Dr. C. Möller, Department of Pediatrics, University Hospital, S-901 85 Umeå, Sweden. E-mail: christian.moller.us@vll.se

should subsequently be titrated down to the lowest dose needed to control symptoms.[6]

In most patients with stable disease effective asthma control can be achieved by twice-daily dosing with inhaled corticosteroids, although four times daily dosing appears to be more effective in patients with severe asthma.[7] However, recent studies suggest that once-daily treatment may be as effective as twice-daily dosing in patients with mild to moderate disease. In adult patients, once-daily treatment with budesonide, 400 μg delivered via Turbuhaler®, has been shown to be as effective as twice-daily treatment with 200 μm in improving lung function and asthma symptoms.[8–10] Similarly, in a trial of 29 children with stable asthma, switching from twice-daily treatment to once-daily treatment was not associated with any deterioration in symptom scores or peak flow.[11] Other studies, however, have given inconsistent results,[12] possibly due to differences in the patient population studied.

Once-daily treatment offers the advantage of simplicity and hence potentially improved compliance. This is an important consideration because compliance with inhaled therapy is often poor. In one study of inhaled bronchodilator therapy, it was found that patients used their medication as instructed on only 37% of days, and only six of 34 patients showed adequate compliance.[13] Poor compliance can be a major cause of asthma morbidity.[14] There is some evidence that poor compliance may be at least partly related to dosing frequency; in a study by Mann *et al.*, compliance deteriorated when patients were switched from twice-daily to four times daily dosing.[15] This suggests that a once-daily inhaled steroid regimen might produce better compliance than a twice-daily regimen.

The aim of this study was to determine whether once-daily treatment with budesonide was as effective as twice-daily dosing in children with stable asthma.

MATERIALS AND METHODS

Study Design

The study was a double-blind, randomized, parallel-group study carried out at ten pediatric out-patient centers in Sweden. There was an initial 2-week run-in period, during which patients were maintained on their usual dose of budesonide (Pulmicort® Turbuhaler®); it was followed by a 12-week double-blind treatment period during which patients received the same dose in either one or two daily doses. The trial was approved by the ethics committee at Umeå University and the Swedish Medical Products Agency, and was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. Verbal informed consent was obtained from all patients, and written informed consent was obtained from their guardians before enrolment.

Abbreviations

ANOVA	Analysis of variance
$FEF_{25-75\%}$	Forced expiratory flow between 25 and 75% of forced vital capacity
FEV_1	Forced expired volume in 1 second
FVC	Forced vital capacity
PEF	Peak expiratory flow

Patients

A total of 206 patients (128 boys, 78 girls) aged 5-15 years (mean 9 years), with bronchial asthma of at least 6 months' duration took part in this study. They were eligible for the study if they showed at least one of the following at the time of enrollment: PEF at least 90% of the personal best value recorded during the previous 6 months; a forced expiratory volume in 1 second (FEV_1) of at least 90% of predicted values; and an FVC of at least 90% of predicted values. All patients were receiving budesonide, 100 μg twice-daily or 200 μg twice-daily via Turbuhaler® for at least 6 weeks before entry into the study. Prior to the study, the budesonide dose was maintained at the lowest level needed to control symptoms. Patients were excluded from the study if their asthma was found to be unstable during the last week of the run-in period. Unstable asthma was defined as one of the following: 15% or more diurnal variation in PEF on more than 2 days; a night-time asthma symptom score of one or more on a four-point scale (0–3); a total daytime symptom score of more than two, or a score of two for a single symptom.

Treatment

At the end of the run-in period, patients receiving a total daily dose of budesonide dose of 200 μg were randomized to receive either 100 μg twice-daily in the morning and evening, or 200 μg once daily in the morning with a placebo inhalation in the evening; similarly, patients receiving a total dose of 400 μg were randomized to receive either 200 μg twice daily or 400 μg once daily. All medication was given by Turbuhaler®; inhalers intended for morning or evening use were identified by colored labels. Compliance was checked by means of the dose indicator included in the Turbuhaler®. For use as rescue medication, if necessary, all patients were given terbutaline sulphate (Bricanyl Turbuhaler®, 0.25 mg). No other bronchodilator medication was permitted during the study; nasal corticosteroids, nasal sodium cromoglycate and antihistamines were permitted if required. Other concomitant medications considered necessary for the patient's well-being could be given at the investigator's discretion.

Assessments

Demographic characteristics and a medical history were recorded on enrolment to the study. Clinical assessments were performed at enrollment, at the end of the run-in period, and after 4 and 12 weeks of double-blind treatment. All assessments were performed at the same time of the day, and the patient was instructed not to use β_2-agonists and to avoid strenuous activity for 6 hours before the assessment.

With the patient standing, PEF was measured with a Vitalograph® peak flow meter. In addition to the clinical assessments, patients were provided with a Vitalograph® peak flow meter and asked to record PEF every day upon waking and again in the evening. These measurements were made before inhalation of the study medication and, when possible, at least 6 hours after use of terbutaline.

FEV_1, FVC and forced expiratory flow between 25 and 75% ($FEF_{25–75\%}$) of FVC were measured at each clinic visit by means of a flow volume spirometer (Vitalograph Compact®, Buckingham, UK) with the patient wearing a nose-clip and in the same position for each measurement; flow was detected by a Fleisch-type pneumotachograph and volume detection by flow integration. Spirometry was performed three times at each assessment; the highest values for FEV_1, FVC, and $FEF_{25–75\%}$ from the curve with the best FVC were recorded.

Asthma symptoms were scored on diary cards, using a four-point scale (0: no symptoms; 1: mild; 2: moderate; 3: severe). The number of inhalations from each Turbuhaler®, and the use of β_2-agonists and any other concomitant medication, were also recorded.

Information about adverse events was obtained by asking the patient or their guardian "Have you/your child had any health problems or symptoms not usually associated with your/his/her asthma since the last visit?" The onset, duration, severity and outcome of each adverse event was recorded.

Statistical Analysis

The sample size was based on the assumption that two treatments can be regarded as equivalent if the mean changes in morning PEF differ by $\leq$10 L/min. A sample size of 100 patients per group gives our study power of 80% for an equivalence test at the 5% level.

The endpoint for morning and evening PEF was the change from baseline (mean value during the last 14 days of the run-in period) to the end of the treatment period (mean value during the last 14 days). For other diary variables, the endpoint was the mean value during the last 14 days of the treatment period. For lung function variables measured at clinic visits, the endpoint was the change from baseline (at the end of the run-in period) to the end of the treatment period (value at the last clinic visit). Endpoints were analysed by means of an analysis of variance (ANOVA), which included terms for treatment, center, baseline values and initial dose. Least squares means and confidence limits were derived from the ANOVA. Comparisons of treatment effects were based on these adjusted means and their confidence intervals. For the difference between treatment effects, 90% confidence intervals were computed, whereas 95% confidence limits were computed for the within-group effects. The latter is used for descriptive purposes only. Missing data were replaced according to the principle of last observation carried forward.

For secondary efficacy measures (bronchodilator use and symptom scores), the mean values during the last 14 days of the run-in period were compared with the mean value during the 14 days before the last clinic visit (end of treatment).

TABLE 1—Patient Demographic Characteristics and Disease History

	Once-daily treatment (n = 107)	Twice-daily treatment (n = 99)
Age (years)	8.9 (5.0–12.0)*	9.0 (5.0–13.0)
Height (cm)	136.4 (112–166)	136.6 (108–172)
Weight (kg)	33.1 (19.0–63.0)	32.8 (17.0–56.0)
Duration of asthma (months)	56 (7–137)	64 (7–155)
Time since last exacerbation (months)	11 (1–50)	10 (1–44)

*Mean (Range).

RESULTS

Patient Demographics

Of the 206 patients, 107 were randomized to receive once-daily treatment and 99 to receive twice-daily treatment. The total daily dose of budesonide was 200 μg in 63 patients and 400 μg in 143. The demographic characteristics of the randomized patients, disease history, baseline lung function data and symptoms scores are summarized in Tables 1 and 2. Asthma was well controlled in all patients, and baseline symptom scores were low (mean 0.01–0.05). Morning and evening baseline PEF tended to be slightly higher in the patients receiving once-daily budesonide than in those receiving twice-daily treatment, but these differences were not regarded as clinically relevant.

A total of 15 patients (11 boys, four girls) withdrew during the course of the study. Of these, seven were receiving once-daily treatment (two receiving 200 μg, five receiving 400 μg). The most common reason for withdrawal was deterioration of asthma; it occurred in eight patients (four in the once-daily group and four in the twice-daily group); three patients withdrew because of adverse events (see below) and four because of pro-

TABLE 2—Baseline Lung Function Data and Symptom Scores

	Once-daily treatment (n = 107)	Twice-daily treatment (n = 99)
Morning PEF (L/min)	271 (142–627)*	264 (143–443)
Evening PEF (L/min)	275 (137–621)	268 (149–423)
Daytime asthma symptoms (0–3)	0.05 (0.00–0.71)	0.05 (0.00–0.57)
Night-time asthma symptoms (0–3)	0.02 (0.00–0.43)	0.01 (0.00–0.15)
β_2-agonist use (day)	0.23 (0.00–3.00)	0.10 (0.00–0.69)
β_2-agonist use (night)	0.06 (0.00–1.21)	0.01 (0.00–0.14)
FEV_1 (L)	1.82 (0.97–2.90)	1.82 (1.04–3.02)
FEV_1 (% of predicted)	89.9 (65.9–126.7)	90.4 (61.8–122.1)
FEV_1/FVC (%)	87.1 (65.6–99.5)	87.6 (57.4–100.0)
$FEF_{25–75\%}$ (L/sec)	2.06 (0.52–3.60)	2.06 (0.76–4.15)

*Mean (Range)

tocol violations. Data from one patient randomized to receive twice-daily treatment with budesonide (100 μg twice daily) were excluded from the analysis because the patient recorded exceptionally high PEF values, including some greater than 800 L/min; furthermore, there was also a wide day-to-day variation in PEF, which suggested that the patient's use of the peak flow meter was unsatisfactory.

Compliance

The numbers of doses taken by the patients are summarized in Table 3. Compliance was generally good, and there were no significant differences between groups.

Efficacy

Morning PEF was maintained throughout the study in both treatment groups and only minor differences were seen between the two groups (Fig. 1). Baseline PEF, measured during the run-in period, was similar in the two groups (once-daily: 271 L/min; twice-daily: 264 L/min). The mean change from baseline during the last 2 weeks of the treatment period was −0.3 L/min (95% confidence limits −6.6 to +6.0) in patients receiving once-daily treatment and 2.5 L/min (95% confidence limits −4.3 to +9.3) in those receiving twice-daily treatment (Table 4). The estimated difference between the two groups was −2.8 L/min, with 90% confidence limits of −10.4 and +4.5. These limits are close to those regarded as indicative of equivalence (−10 to +10); hence the difference in morning PEF between patients treated once and twice-daily was not considered to be clinically relevant.

There were no clinically significant differences between the groups for any of the secondary efficacy variables (evening PEF, FEV_1, FVC, $FEF_{25–75\%}$, daytime and night-time symptom scores, and use of rescue medication; Tables 5 and 6).

TABLE 3—Compliance in Relation to Dose Regimen

		Total compliance (% of patients)			
Treatment	Daily dose	Data not available	< 75%	75–125%	> 125%
Once daily	200 μg	6.1	9.1	78.8	6.1
	400 μg	1.4	6.8	82.4	9.5
	All	2.8	7.5	81.3	8.4
Twice daily	200 μg	6.7	3.3	80.0	10.0
	400 μg	4.3	8.7	81.2	5.8
	All	5.1	7.1	80.8	7.1

Side Effects

The incidence and spectrum of adverse events reported during the study were similar in patients receiving once-daily and twice-daily treatment. The most common adverse events were respiratory infections, which occurred in 78 patients receiving once-daily treatment and 66 patients receiving twice-daily treatment. Three adverse events were regarded as serious: constipation occurred in one patient receiving 200 μg once daily, one patient receiving 400 μg once daily suffered a fracture of a finger bone, and another patient in the same group developed transient attacks of absence. None of these events were considered related to study medication. Only three patients discontinued treatment because of adverse events; one patient receiving 400 μg once daily withdrew because of gastroenteritis, and two patients receiving 200 μg twice daily withdrew because of respiratory infection and pneumonia, respectively.

DISCUSSION

In the management of stable asthma in children treated with inhaled steroids the results of this study suggest that once-daily treatment with budesonide Turbuhaler® at doses of up to 400 μg/day, is as effective as giving the same dose in two daily administrations. For the primary efficacy variable, morning PEF, the confidence limits for the difference in treatment effects between the two groups were similar to the confidence interval indicative of equivalence; the difference was small and not clinically relevant. Similarly, there were no significant differences in any of the secondary efficacy variables between patients treated once daily or twice daily. Although the differences in treatment effects for these secondary measures tended to favor twice-daily dosing (i.e., negative differences between once and twice-daily dosing; Tables 4 and 5), these differences were very small and not clinically important.

The patients were very well controlled at baseline, with normal FEV_1 and few daytime symptoms. A weak

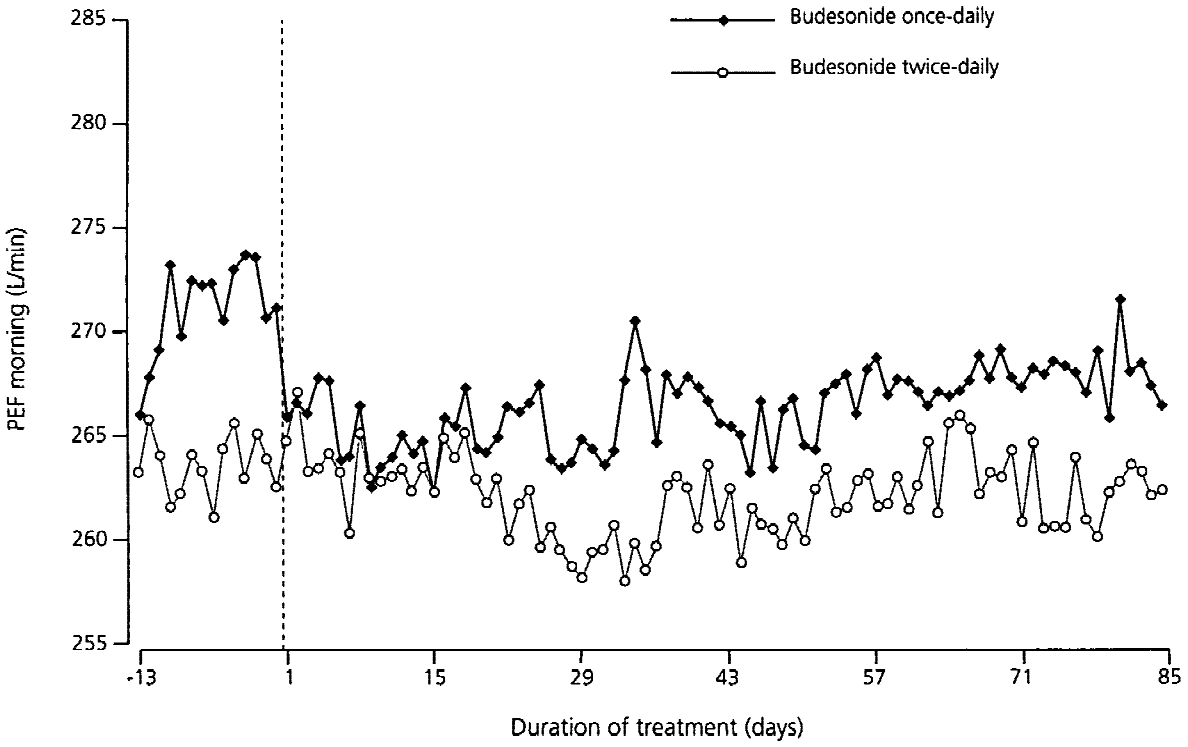

Fig. 1. Mean morning PEF in patients receiving once- or twice-daily treatment with budesonide, in total doses of 200 µg/day or 400 µg/day. Data from one patient receiving 200 µg (100 µg twice-daily) were excluded because of poor peak flow meter technique.

TABLE 4—Mean Morning PEF During the Last 14 Days of the Run-In Period and Adjusted Mean Change in Morning PEF From Baseline

			Morning PEF (L/min)				
Regimen	Daily dose	Number of patients	Run-in	Adjusted mean change from baseline	Lower 90% confidence limit	Upper 90% confidence limit	*P*-value
Once-daily	All patients	107	271 (143–627)*	−0.3	−6.6	6.0	
	200 µg	33	269 (143–432)	5.2	−5.2	15.6	
	400 µg	74	273 (160–627)	−5.8	−13.0	1.3	
Twice-daily	All patients	98	264 (143–443)	2.5	−4.3	9.3	
	200 µg	29	254 (153–443)	4.2	−7.1	15.4	
	400 µg	69	268 (143–419)	0.9	−6.7	8.4	
Difference (twice-daily–once-daily)				−2.8	−10.4	4.5	0.534

*Mean (Range).

point of the study is that we cannot be sure whether control could have been maintained with a lower dose of budesonide, although the doses were kept as low as possible prior to the study. As we wanted to enroll children with stable asthma, we could not accept low doses that would probably have been inadequate to control symptoms during the weeks immediately before the trial.

The results of this study are consistent with those of a smaller open study,[11] involving 29 asthmatic children who were switched from twice-daily treatment with budesonide to once-daily treatment; in that study no deterioration in symptom scores or peak flow occurred during the 4 weeks after the introduction of once-daily dosing. Similarly, in studies of adult patients, once-daily dosing with budesonide has been shown to be as effective as twice-daily treatments, both as initial prophylactic therapy[8] and in patients previously treated with inhaled steroids.[16,17] By contrast, however, Weiner et al. reported that twice-daily treatment with budesonide, 400 µg twice daily, was superior to once-daily treatment with 800 µg, although both regimens were effective in providing long-term control of asthma.[18] In this study, however, the drug was delivered via a pressurized metered dose inhaler with a plastic spacer device. The use of such devices can reduce drug delivery, including electrostatic charge on the wall of plastic devices, delay between actuation and inhalation, and the common practice of multiple actuation before inhalation;[19] thus, the findings of Weiner et

TABLE 5—Changes in Evening PEF, FEV_1, $FEF_{25–75\%}$ and FVC From Baseline

Variable	Change from baseline (adjusted means)		Difference (once-daily–twice-daily)	p-values
	Once-daily	Twice-daily		
Evening PEF (L/min)	0.8 (−5.4 to +6.8)	1.8 (−4.8 to +8.4)	−1.0 (−8.4 to +6.3)	0.814
FEV_1 (L)	−0.01 (−0.05 to +0.03)	0.01 (−0.03 to +0.05)	−0.02 (−0.07 to +0.02)	0.414
FEV_1 (% of predicted)	−1.1 (−2.9 to +0.7)	0.2 (−1.8 to +2.2)	−1.3 (−3.4 to +0.9)	0.331
$FEF_{25–75\%}$ (L/sec)	−0.13 (−0.21 to −0.05)	−0.05 (−0.14 to +0.03)	−0.08 (−0.17 to +0.02)	0.166
FVC (L)	0.05 (0.00 to +0.09)	0.05 (0.00 to +0.10)	0.00 (−0.06 to +0.05)	0.923

Results are expressed as the adjusted means derived from ANOVA, with 95% confidence limits.

TABLE 6—Bronchodilator Use and Symptom Scores at End of Treatment

	Once-daily treatment	Twice-daily treatment	Difference (once-daily–twice-daily)	p-values
β_2-agonist use (night)	0.06 (0.02–0.10)	0.07 (0.02–0.12)	−0.01 (−0.06 to +0.04)	0.755
β_2-agonist use (day)	0.22 (0.14–0.30)	0.19 (0.10–0.27)	0.04 (−0.06 to +0.14)	0.539
Night-time asthma symptoms (0–3)	0.04 (0.00–0.09)	0.10 (0.05–0.14)	−0.05 (−0.11 to +0.00)	0.075
Daytime asthma symptoms (0–3)	0.10 (0.05–0.15)	0.14 (0.08–0.19)	−0.04 (−0.10 to +0.03)	0.332

Results are expressed as the adjusted means derived from ANOVA, with 95% confidence limits.

al. must be interpreted with caution. In general, most studies agree that once-daily dosing is as effective as twice-daily dosing in patients with mild to moderate stable asthma. It is likely that once-daily dosing is possible in most, but not all patients with mild to moderate asthma. The present study does not, however, clarify whether once-daily dosing is possible in children with severe asthma. Patients with severe asthma may require an increase in the dosing frequency to four times daily to achieve optimal control.[7,20]

The use of once-daily inhaled steroid treatment offers convenience and improved acceptability to the patient. Evidence for this comes from a study in which patients were randomized to receive once-daily treatment with 400 μg budesonide, twice-daily treatment with 200 μg budesonide or twice-daily treatment with 200 μg fluticasone propionate.[16] This study included a crossover period to allow patients' preferences for once or twice-daily dosing to be assessed. Overall, 61% of patients expressed a preference for once-daily dosing over twice-daily treatment, and the same percentage indicated that they would perfer once-daily treatment if it were offered. Similarly, in a placebo-controlled trial of budesonide, 400 μg once daily as initial prophylactic therapy, 97% of patients expressed a preference for once-daily treatment.[21]

Once-daily treatment might also be expected to result in improved patient compliance, as there is evidence that compliance decreases as the frequency of daily dosing increases.[15] It was not possible, however, to assess potential improvements in compliance in this study, because patients receiving once-daily treatment had to use a placebo inhaler in the evening to maintain the study blinding.

The trial was not designed to detect serious side effects such as decreased growth, adrenocortical suppression or impairment of bone formation. Thus we cannot determine whether dosing once daily influences the potential risk of serious adverse events associated with glucocorticosteroids.

In conclusion, the results of this study indicate that once-daily treatment with budesonide at total daily doses of 200 μg or 400 μg is as effective as twice-daily treatment in children whose asthma was well controlled by inhaled glucocorticosteroids. Both once and twice-daily treatment were well tolerated. These findings suggest, therefore, that children with well controlled asthma and treated with inhaled steroids can be changed from twice-daily treatment to once-daily treatment with doses of up to 400 μg/day. Whether once-daily dosing is given in the morning or evening will depend on the patient's preference and circumstances; both morning and evening administration have been shown to be effective.[22] These recommendations are consistent with the recent guide-

lines issued by the US National Asthma Education and Prevention Program[6] that advocates early intervention with inhaled corticosteroids in a broad patient population, including infants and children, and recommend that treatment be started with a high dose and that the dose be titrated down to maintenance levels.

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References

1. Carlsen K-H. Epidemiology of childhood asthma. Eur Respir J. 1994;4:4–9.
2. National Institutes of Health, National Heart, Lung and Blood Institute. Global Initiative for Asthma. Publication No. 95-3659. Bethesda, Maryland: 1995.
3. International Consensus Report on Diagnosis and Treatment of Asthma. Eur Respir J. 1992;5:601–641.
4. Ellul-Micallef R, Hansson E, Johansson SÅ. Budesonide. A new corticosteroid in bronchial asthma. Eur J Respir Dis. 1980;61: 167–173.
5. Agertoft L, Pedersen S. Effects of long term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med. 1994;88:373–381.
6. Expert Report II: Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program; National Institutes of Health, February 1997.
7. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. J Allergy Clin Immunol. 1982;70:288–298.
8. Jones AH, Langdon CG, Lee PS, Lingham SA, Nankant JP, Follows RMA, Tollemar U, Richardson PD. Pulmicort® Turbohaler® once daily as initial prophylactic therapy for asthma. Respir Med. 1994;88:293–299.
9. Herjavecz I, Serrano A, Blomqvist P, Országos Korányi TBC. Budesonide Turbuhaler® once or twice daily in non-steroid using patients with asthma. Eur Respir J. 1997;10(Suppl 25):174s.
10. Stiksa G, Glennow C. A clinical comparison between budesonide given once and twice daily and beccotide four times daily. Ann Allergy. 1985;55:49–51.
11. McCarthy TP. The use of a once daily inhaled glucocorticosteroid (budesonide) in the management of childhood asthma. Br J Clin Res. 1993;4:55–61.
12. McGivern DV, Ward M, Macfarlane JT, Roderick Smith WH. Failure of once daily inhaled corticosteroid treatment to control chronic asthma. Thorax. 1984;39:933–934.
13. Mawhinney H, Spector SL, Kinsman RA, Siegel SC, Rachelefsky GS, Katz RM, Rohr AS. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. Ann Allergy. 1991; 66:294–299.
14. Horn CR, Clark TJH, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. Respir Med. 1990;84:67–70.
15. Mann M, Eliasson O, Patel K, ZuWallack RL. A comparison of the effects of *bid* and *qid* dosing on compliance with inhaled flunisolide. Chest. 1992;101:496–499.
16. Venables TL, Addlestone MB, Smithers AJ, Blagden MD, Weston D, Gooding T, Carr EP, Follows RMA. A comparison of the efficacy and patient acceptability of once daily budesonide via Turbohaler and twice daily fluticasone propionate via disc-inhaler at an equal daily dose of 400 μg in adult asthmatics. Br J Clin Res. 1996;7:15–32.
17. Campbell LM, Gunn SD, Sweeney D, Smithers AJ, Zurek AAA, Golightly L, Turbitt ML. Once daily budesonide: effective control of moderately severe asthma with 800 μg once daily inhaled via Turbohaler when compared with 400 μg twice daily. Eur J Clin Res. 1995;7:1–14.
18. Weiner P, Weiner M, Azgad Y. Long term clinical comparison of single versus twice daily administration of inhaled budesonide in moderate asthma. Thorax. 1995;50:1270–1273.
19. Barry PW, O'Callaghan C. The effect of delay, multiple actuations and spacer static charge on the *in-vitro* delivery of BUD from the Nebuhaler. Br J Clin Pharmacol. 1995;40:76–78.
20. Malo J-L, Cartier A, Merland N, Ghezzo H, Buerk A, Morris J, Jennings B. Four-times-a-day dosing frequency is better than a twice-a-day regimen in subjects requiring a high-dose inhaled steroid, budesonide, to control moderate to severe asthma. Am Rev Respir Dis. 1989;140:624–628.
21. Campbell LM, Watson DG, Venables TL, Taylor MD, Richardson PDI. Once daily budesonide Turbohaler compared with placebo as initial prophylactic therapy for asthma. Br J Clin Res. 1991;2: 111–122.
22. Andersson N, Dahl L. Effect of inhaled budesonide on the HPA axis with different dosing regimens. Abstract presented at the 5th International Conference of Chronopharmacology, Amelia Island, Florida, USA, July 12–16, 1992.