

Budesonide delivered by Turbuhaler is effective in a dose-dependent fashion when used in the treatment of adult patients with chronic asthma

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Background: Airway inflammation is a hallmark of asthma, therefore current treatment recommendations include the use of inhaled glucocorticosteroids (GCS). However, there is little evidence that the effects of inhaled GCS are dose dependent. **Objectives:** The objective of this study was to assess the efficacy and safety of a second-generation GCS, budesonide, delivered by Turbuhaler, in adults with chronic asthma.

Methods: In a 12-week, randomized, double-blind, multicenter, parallel-group study, 473 subjects 18 to 70 years of age received either placebo or budesonide (200, 400, 800, or 1600 µg total daily dose) administered twice daily. Primary efficacy end points were mean change from baseline for FEV₁ and morning peak expiratory flow. Safety was assessed by reported adverse events and by a cosyntropin-stimulation test.

Results: The mean baseline FEV₁ was 63% to 66% of predicted normal value between groups. All doses of budesonide were more effective than placebo ($p < 0.001$). The mean changes in morning peak expiratory flow were 12, 22, 27, and 30 L/min in the 200, 400, 800, and 1600 µg budesonide total daily dose groups, respectively, and -27 L/min for the placebo group. A statistically significant dose-response effect for the mean change from baseline over the 12-week study was seen for both morning peak expiratory flow and FEV₁.

Budesonide-treated subjects also demonstrated significant reduction in asthma symptoms and bronchodilator use compared with placebo. There were no clinically significant differences in treatment-related adverse experiences among groups.

Conclusions: Budesonide administered by Turbuhaler exhibited a dose response and was effective at low doses. It was well tolerated and significantly more effective than placebo. (*J Allergy Clin Immunol* 1998;101:457-63.)

Key words: Asthma, budesonide, inhalation, glucocorticosteroids, Turbuhaler

Abbreviations used

ACTH:	Adrenocorticotrophic hormone
BDP:	Beclomethasone dipropionate
FEF _{25-75%} :	Forced mid-expiratory volume
FVC:	Forced vital capacity
GCS:	Glucocorticosteroids
PEF:	Peak expiratory flow
TDD:	Total daily dose

Chronic airway inflammation is a major feature of asthma and contributes to bronchial hyperresponsiveness and airflow obstruction.¹⁻³ Current recommendations include the early use of antiinflammatory medication to control chronic symptomatic asthma, including inhaled glucocorticosteroids (GCS).⁴⁻⁶ However, information on the dose dependency of GCS effects in asthma are lacking.

The inhaled GCS, budesonide, has a topical antiinflammatory action with minimal systemic effects, resulting in a favorable efficacy/side effects ratio.^{7,8} Because of its extensive first-pass hepatic metabolism, the systemic availability of budesonide is low and it is rapidly inactivated to metabolites with low intrinsic glucocorticoid activity (<1% of that of the parent compound).⁹

This study was designed to evaluate the dose-response relation and to determine the clinical efficacy and safety of budesonide relative to placebo when administered by the multidose, dry powder inhaler Turbuhaler (Astra, Sweden) in adult patients with inhaled GCS-dependent chronic asthma. Patients already receiving moderately high doses of inhaled GCS were recruited to assess the improvement in some patients and the potential deterioration in others, thereby increasing the possibility to demonstrate a dose-response pattern. Four total daily doses (TDD) of budesonide (200, 400, 800, and 1600 µg) were evaluated for up to 12 weeks in this randomized, double-blind, placebo-controlled, multicenter study.

METHODS

Subjects

Male and female adult subjects, 18 to 70 years of age, with a diagnosis of asthma as defined by the American Thoracic Society for at least 6 months, were eligible to participate in the

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TABLE I. Baseline demographics and asthma characteristics of study patients

	Placebo	Budesonide (200 µg TDD)	Budesonide (400 µg TDD)	Budesonide (800 µg TDD)	Budesonide (1600 µg TDD)
No. of patients	92	91	93	99	98
Mean age, yrs (range)	43.7 (21-67)	43.2 (21-70)	43.8 (18-69)	44.1 (19-70)	43.4 (19-70)
M/F	46/46	41/50	39/54	48/51	43/55
Mean FEV ₁ (L), (SD)	2.05 (0.59)	2.05 (0.65)	2.06 (0.84)	2.06 (0.59)	1.96 (0.76)
Mean FEV ₁ (% predicted normal) (SD)	65.2 (17.2)	66.0 (16.6)	64.7 (16.4)	66.1 (13.9)	63.1 (16.3)
Mean morning PEF (L/min) (SD)	362 (100)	363 (109)	356 (104)	361 (92)	352 (107)
Mean airway reversibility (%) (SD)	36.2 (20.0)	34.6 (16.6)	36.0 (21.8)	33.7 (15.9)	37.8 (22.1)
Asthma medications					
No. (%) Theophylline	60 (65)	53 (58)	54 (58)	52 (52)	61 (62)
No. (%) Oral GCS	15 (16)	19 (21)	15 (16)	11 (11)	14 (14)
No. (%) BDP (<500 µg/day)	58 (63)	55 (60)	58 (62)	62 (63)	57 (58)
No. (%) BDP (>500 µg/day)	34 (37)	36 (40)	35 (38)	37 (37)	41 (42)

study after demonstration of reversible airway obstruction, as defined by a greater than 15% increase in FEV₁ after inhalation of 180 µg of albuterol by premeasured metered dose inhaler (Proventil, Schering). Moderate to severe asthma was defined as an FEV₁ greater than 40% and less than 75% of predicted normal value at baseline and a history of having been prescribed at least two asthma medications during the previous 6 months. All subjects had to have used inhaled or inhaled and oral GCS for the past 6 months and used six to 20 inhalations (300 to 1000 µg) daily of beclomethasone dipropionate (BDP) 1 month before the screening visit. They were also required to be able to use a peak flowmeter (Mini Wright) and Turbuhaler.

Subjects were excluded if they had a history of carcinoma or significant coexisting disease. Other exclusion criteria included use of injectable GCS and irregular use of oral GCS.

Ethical considerations

Written, signed, informed consent was obtained from all patients before enrollment in the study. The study was approved by each site's institutional review board and performed according to the principles stated in the Declaration of Helsinki.

Study design

The study was conducted as a double-blind, randomized, placebo-controlled, parallel-group, multicenter trial. A 1-week screening period was followed by a 2-week baseline period and a 12-week treatment period. Subjects were stratified on the basis of the daily prestudy dose of 300 to 500 µg and 550 to 1000 µg BDP, respectively. BDP was discontinued at randomization when subjects were assigned to receive one of the four daily doses of budesonide (200, 400, 800, or 1600 µg) or placebo (lactose), each administered in divided doses twice daily by Turbuhaler.

Inhaled albuterol was allowed on an as-needed basis. Previous inhaled GCS were stopped at randomization. Allowable long-term-use medications, provided they were taken at a constant dosage throughout the entire study, included oral and nasal GCS, antihistamines, theophylline, antibiotics, mucolytics, and expectorants. Acute asthmatic exacerbations that required parenteral or oral administration of GCS (or a change in the dose of oral GCS for those patients already taking this medication), subcutaneous epinephrine, nebulized β-adrenergic bronchodilators, parenteral or rectal methylxanthines, or additional oral theophylline resulted in patients being withdrawn from the trial; such subjects were considered treatment failures.

Efficacy assessments

All subjects were required to complete a daily diary card documenting peak expiratory flow (PEF), asthma symptoms, β₂-agonist use, and adverse events. All subjects were trained in the use of a peak flowmeter and the inhalation device. Subjects made seven visits to the study center during the study: at the beginning of the screening period; at the beginning and end of the baseline period; and after 2, 4, 8, and 12 weeks of treatment.

The primary efficacy variables were the mean change from baseline in morning (6:30 to 8:30 AM) FEV₁ and morning PEF. Secondary efficacy variables were the mean changes from baseline in evening PEF, forced vital capacity (FVC), and forced mid-expiratory volume (FEF_{25-75%}); the daily number of bronchodilator inhalations required; and the mean changes in daytime and nighttime asthma severity scores. Asthma severity was measured on a four-point scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). Baseline was defined as the average of values obtained at the clinic visits at the start and the end of the baseline period for spirometric parameters (i.e., FEV₁, FVC, and FEF_{25-75%}) and the average of values recorded daily in the diaries during the 2-week baseline period for PEF, asthma symptoms, and bronchodilator use.

Safety assessments

Preadrenocorticotrophic hormone (ACTH)-stimulated and post-ACTH-stimulated (25 units of Cortrosyn, Organon) plasma cortisol levels were measured in blood samples drawn between 6:30 and 9:30 AM; at baseline; and then at treatment weeks 0, 4, and 12.

All adverse events occurring during the double-blind period and 2 weeks thereafter were recorded (with particular regard to severity and relation to medication) on the patient's case report form in a blinded manner.

Laboratory tests, including hematology, blood chemistry, and urinalysis, and physical examinations, including an ophthalmic examination, were carried out at enrollment and at the end of the study, and an electrocardiogram was obtained at enrollment, at randomization, and at the end of the study.

Statistical analysis

With 75 subjects per treatment group there would be 80% power to detect (two-tailed test, α = 0.05) a treatment group difference of 28 L/min in change from baseline in morning PEF and 0.23 L in FEV₁, assuming a standard deviation of 60 L/min and 0.50 L, respectively. Analysis of variance, with center and

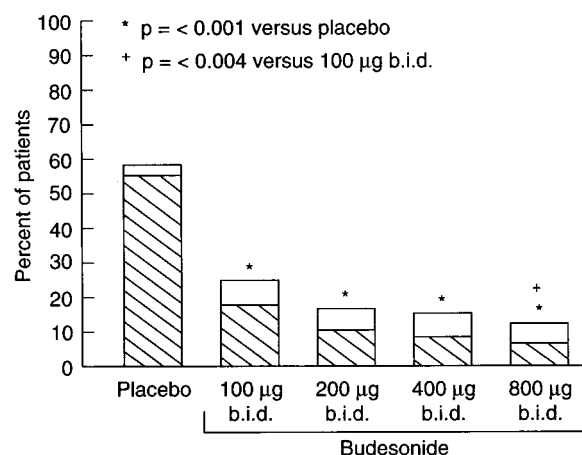


FIG. 1. Discontinuations from study. Total percentage of patients (open bars) discontinuing from study and percentage of patients discontinued because of worsening asthma (closed bars) are shown for placebo- and budesonide-treated groups.

treatment as factors in the model, was used to compare treatment groups for both primary and secondary variables, with change from baseline to the 12-week treatment period. The dose-response effect was assessed by comparing the primary outcome measures of patients in the highest and lowest budesonide dosage groups. The proportion of patients who discontinued the study for any reason was compared among treatment groups with the Cochran-Mantel-Haenszel statistic adjusted for investigator.

RESULTS

Demographics

Four hundred seventy-three subjects received at least one dose of double-blind study medication. The five study groups were similar with regard to demographics, asthma history, baseline pulmonary function tests, medication use, and other baseline characteristics (Table I). The mean duration of dependence on inhaled GCS was 3.3 years for men and 4.6 years for women; the mean daily dose of BDP was 500 µg (range, 150 to 1200 µg). The mean baseline morning PEF and FEV₁ levels were 360 L/min and 2.0 L (65% predicted normal value¹⁰), respectively. More than 90% of patients received β-agonists as concomitant medication for at least the first 3 days of the screening period, more than 50% received theophylline, and approximately 15% received oral steroids.

Study withdrawals

Subjects in this study were required to have moderate to severe asthma for study inclusion. A direct consequence of these subjects' asthma severity was a high study withdrawal rate caused by exacerbation and worsening of asthma: 61% of placebo group, 20% of 200 µg TDD budesonide group, 11% of 400 µg TDD budesonide group, 8% of 800 µg TDD budesonide group, and 7% of 1600 µg TDD budesonide group. The differences between the placebo group and the

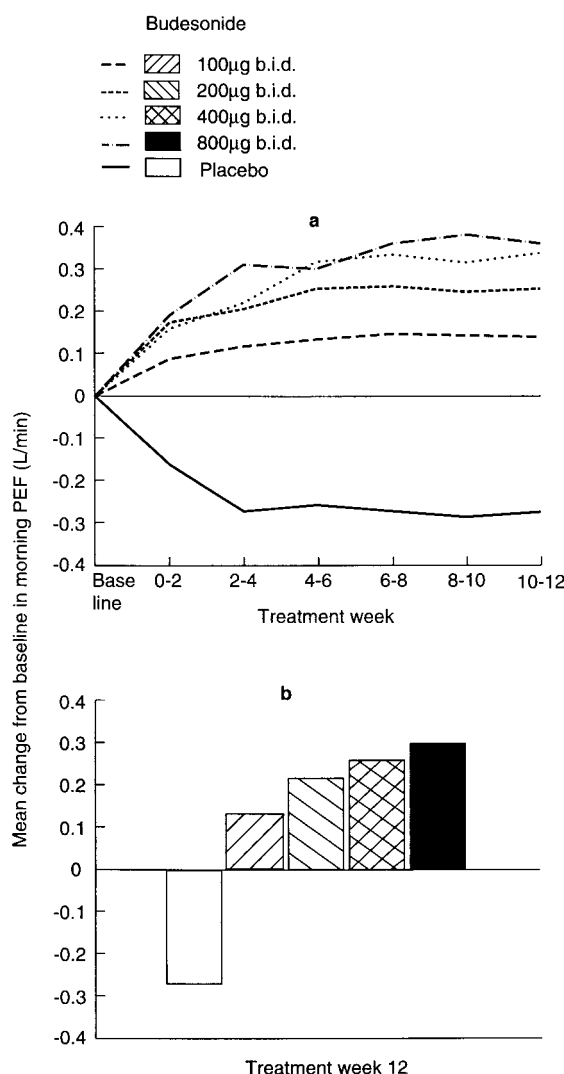


FIG. 2. Mean change from baseline in morning PEF (L/min) for placebo and budesonide-treated groups. **a**, 2-week intervals and **b**, from baseline to week 12.

budesonide groups were statistically significant ($p < 0.001$), as was the difference between the 200 µg TDD budesonide group and the 1600 µg TDD budesonide group ($p < 0.01$), indicating a dose-response relation.

Overall, a significantly lower ($p < 0.001$) percentage of patients in the budesonide groups discontinued therapy (27% in the 200 µg TDD budesonide group, 17% in the 400 µg TDD group, 15% in the 800 µg TDD group, and 12% in the 1600 µg TDD group vs 63% in the placebo group) (Fig. 1). As a result, patients taking budesonide remained in the study for a median of 84 days compared with 35 days for patients in the placebo group ($p < 0.001$, data not shown). A dose response was demonstrated, with significantly fewer ($p = 0.004$) patients discontinuing from the 1600 µg TDD budesonide group than from the 200 µg TDD budesonide group.

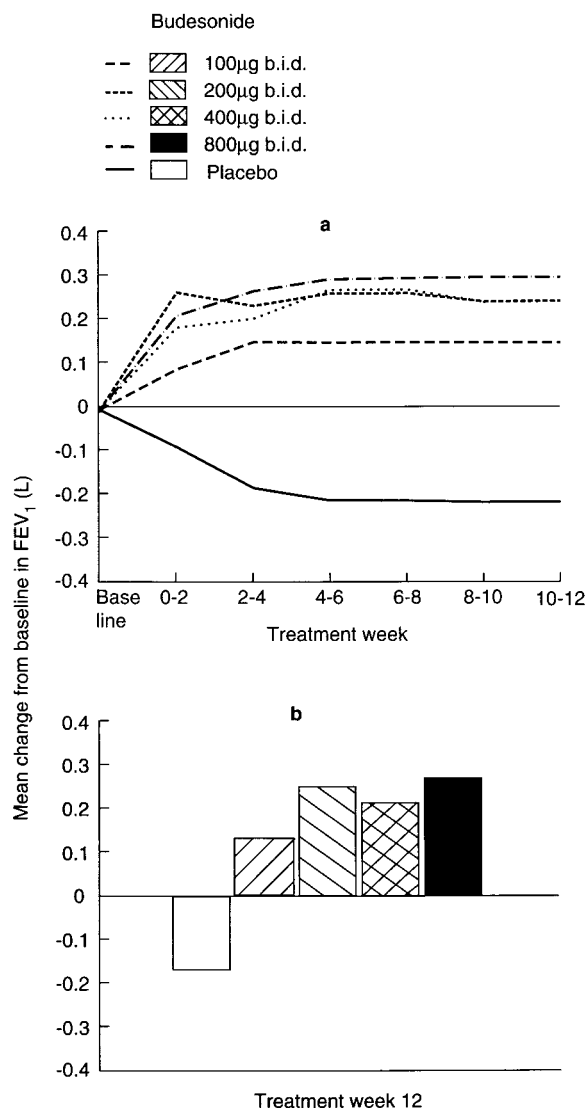


FIG. 3. Mean change from baseline in morning FEV₁ for placebo and budesonide-treated groups. **a**, 2-week intervals and **b**, from baseline to week 12.

Discontinuations because of protocol violations, adverse events, poor compliance, loss to follow-up, and patient prerogative were evenly distributed between the five treatment groups.

Pulmonary function

The mean change from baseline in morning PEF (Fig. 2, *a* and *b*) and FEV₁ (Fig. 3, *a* and *b*) showed statistically significant improvement ($p < 0.001$) in all budesonide treatment groups compared with the placebo group. There was a trend for this improvement to be more pronounced in patients receiving lower prerandomization doses of 300 to 500 µg/day BDP than in those receiving higher prestudy doses of 500 to 1000 µg/day (data not shown).

The onset of action of budesonide was noted within 1

week. The mean change from baseline morning PEF ranged from 9 L/min in the 200 µg TDD group to 19 L/min in the 1600 µg TDD group at weeks 0 to 2. At this point, the mean change in morning PEF in the placebo group was negative: -17 L/min. The therapeutic effects of budesonide were evident by 2 to 4 weeks, reached a maximum after 4 to 6 weeks, and were thereafter maintained throughout the remainder of the double-blind period.

The difference in the effect on both PEF and FEV₁ between the 200 µg TDD and the 1600 µg TDD budesonide groups was significant ($p < 0.01$ for PEF; $p < 0.05$ for FEV₁), indicating dose-related responses.

The results of the analyses of secondary pulmonary function parameters (evening PEF, FVC, and FEV_{25-75%}) were consistent with those observed for FEV₁ and morning PEF (Table II).

Asthma symptoms

Both daytime and evening asthma (Table II) severity scores improved significantly ($p < 0.001$) in all budesonide groups compared with placebo during the double-blind period. There was no statistically significant difference among the four budesonide groups.

Bronchodilator use

The need for concurrent bronchodilator use over the whole 12-week treatment period was reduced in all budesonide-treated groups and, compared with placebo (Table II), was statistically significant ($p < 0.001$). A trend toward a dose-response effect for this variable was observed but did not reach statistical significance ($p = 0.059$).

Safety

Plasma cortisol concentrations. There were no differences in the change in mean basal morning plasma cortisol levels from baseline to week 12 among the different budesonide treatment groups and placebo (Table III). Additionally, the percentage of patients who shifted from a normal basal cortisol value at baseline to a subnormal value after treatment was 8%, 4%, 11%, 4%, and 17% in the 200, 400, 800, and 1600 µg TDD budesonide and placebo groups, respectively. The highest dose of budesonide resulted in a mean change from baseline of postcosyntropin plasma cortisol levels that was statistically significantly different from placebo and the lowest dose of budesonide. However, the difference from placebo was only 10%, and all other doses of budesonide were not statistically different from placebo.

Adverse events. Fifteen patients discontinued the study because of adverse events: seven subjects in the placebo group (all asthma related) and eight subjects in the budesonide groups (three asthma related, two because of viral infections, two because of urticaria, and one because of Graves' disease). Seven patients reported serious adverse events: one exacerbation of asthma (placebo); one chest pain and one status asthmaticus (400 µg TDD budesonide); one bradycardia/hypoten-

TABLE II. Secondary variables, mean change from baseline to treatment (mean 0 to 12 weeks)

	Baseline* (range)	Placebo	Budesonide (200 µg TDD)	Budesonide (400 µg TDD)	Budesonide (800 µg TDD)	Budesonide (1600 µg TDD)
Evening PEF (L/min)	382-392	-23	8†	16†	13†	18†
FVC (L)	2.99-3.13	-0.19	0.11†	0.25†	0.21†	0.24†
FEF _{25-75%} (L)	1.38-1.55	-0.15	0.14†	0.23†	0.26†	0.32†‡
Daytime symptom score	1.53-1.73	0.27	-0.19†	-0.24†	-0.31†	-0.24†
Nighttime symptom score	0.93-1.16	0.43	-0.14†	-0.22†	-0.30†	-0.19†
β-Agonist use (puffs/day)	5.12-6.04	2.28	0.72†	-1.47†	-1.48†	-1.50†

*Mean baseline values, range for the treatment groups.

† $p < 0.001$, significantly different from placebo.

‡ $p < 0.05$, significantly different from 200 µg budesonide TDD.

TABLE III. Mean change from baseline in plasma cortisol levels (nmol/L)

	Placebo	Budesonide (200 µg TDD)	Budesonide (400 µg TDD)	Budesonide (800 µg TDD)	Budesonide (1600 µg TDD)
Morning cortisol levels					
Baseline	342	361	367	356	375
(No. patients)	(92)	(91)	(93)	(98)	(98)
Change to end point	-36	-25	+6	-39	-33
(No. patients)	(64)	(83)	(91)	(94)	(92)
Stimulated cortisol levels					
Baseline	662	673	662	665	693
(No. patients)	(92)	(91)	(93)	(97)	(98)
Change to end point	-8	-3	+6	-17	-75*
(No. patients)	(64)	(83)	(91)	(94)	(93)

*Significantly different from placebo ($p < 0.05$).

sion (800 µg TDD budesonide); and one urticaria, one gastroenteritis, and one syncopal episode (1600 µg TDD budesonide).

The frequency and intensity of reported adverse events were similar in the placebo and the budesonide treatment groups, and there was no clinically relevant difference in adverse event spectrum. The most commonly reported event was respiratory infection. Oral candidiasis occurred in one patient receiving placebo, three receiving 200 µg TDD budesonide, three receiving 400 µg TDD budesonide, seven receiving 800 µg TDD budesonide, and four receiving 1600 µg TDD budesonide, respectively.

Laboratory examinations. General physical examination of patients at the end of the drug treatment period did not reveal any significant alterations, and no clinically relevant effects of budesonide on laboratory measurements, eye examinations, and electrocardiographic findings were observed.

DISCUSSION

This study demonstrates that budesonide administered by Turbuhaler showed superior clinical efficacy to placebo in adult patients with moderate-to-severe, inhaled GCS-dependent asthma at all dose levels evaluated. These results were consistent for all variables measured, including morning PEF, FEV₁, symptom scores, and bronchodilator use. A consistent dose-

response effect was observed when the highest budesonide dose (1600 µg TDD) was compared with the lowest budesonide dose (200 µg TDD) for all lung function parameters measured. All doses, including the lowest dose of budesonide, resulted in increased morning PEF and FEV₁ and decreased asthma symptoms and bronchodilator use compared with the prerandomization baseline period when moderately high doses of BDP were used. It is possible that the patients with more severe symptoms, who required oral steroids before entry into the study, may have had a higher threshold dose at which a response was observed with inhaled budesonide compared with patients who had less severe symptoms that were already reasonably well controlled by inhaled BDP. To address this concern, the dose-response relation for the two primary efficacy end points (FEV₁ and PEF) was evaluated after excluding the patients who were taking oral GCS on entry into the study. All budesonide treatment groups still showed statistically significant improvement compared with the placebo group ($p < 0.001$). With regard to the dose-response relation, the difference in the effect between the 200 µg TDD group and the 1600 µg TDD group remained significant ($p = 0.050$ for PEF and $p = 0.051$ for FEV₁, respectively).

Previous studies in patients with moderate asthma have often failed to show a clear dose-response effect for improvements in lung function with inhaled

GCS.^{11, 12} Other studies investigating subjects with severe asthma have indicated that a dose-response relation does exist for inhaled GCS. For instance, studies have shown that the dose response for inhaled budesonide is log-linear up to at least 1.6 mg daily,¹³⁻¹⁵ and 1.0 mg daily of BDP has been shown to elicit a significant improvement in FEV₁ over 0.4 mg daily.¹⁶

Demonstration of a dose response with inhaled GCS may be dependent on a number of factors, including severity of the disease, prerandomization treatment with GCS, length of treatment period, and the primary variable selected. If patients with more severe asthma are included in a study, the likelihood of demonstrating a dose response increases.¹⁵⁻¹⁸ The implementation of modern guidelines for the management of asthma with increased use of inhaled GCS makes it increasingly difficult to find patients suitable for dose-response studies. In this study patients already receiving inhaled GCS, with compromised lung function and mean FEV₁ of 65% predicted normal, were included. A definite dose response was apparent within 2 weeks of treatment, with little further improvement over the remaining 10 weeks. If short treatment periods are sufficient, it is tempting to consider a crossover design to keep the number of patients required low. However, the risk of carryover effects is well known.¹² If patients with mild-to-moderate persistent asthma are chosen for the study, it may be more difficult to use lung function as a primary variable because low doses of inhaled GCS produce significant improvement in this population and may already be close to the plateau portion of the dose-response curve. In a study in children, Pedersen and Hansen¹⁷ found an exercise challenge to be more sensitive than lung function tests in separating different doses of inhaled budesonide. Challenge with histamine or methacholine has also been shown to be more sensitive than lung function measurements per se in demonstrating a dose response for inhaled GCS.¹⁸ A disadvantage of these pharmacologic agents is that it may take several months to reach a plateau effect.¹⁹ In this study as well as in the studies by Chervinsky et al.²⁰ and Noonan et al.,²¹ an indirect measure, the rate of discontinuations because of loss of asthma control, could also be used to show a dose-response relation for budesonide and fluticasone propionate.

There was good correlation between morning PEF and FEV₁, and relative improvements in these measurements were, as expected, greater than improvements in evening PEF. The trend for a difference in efficacy between patients receiving higher or lower prestudy doses of BDP may be due to increased prestudy compliance in more severe patients and/or the room for improvement in patients already on a high dose of GCS may be too small. A greater increase in morning PEF and in FEV₁ was also noted in patients who did not receive prestudy oral GCS compared with those who did (data not shown).

This study has clear implications for the treatment of moderate-to-severe asthma. Although the study was

limited to 12 weeks, our findings indicate that higher doses of inhaled GCS lead to greater improvement in airflow limitation and control of asthma. It is intuitive that higher doses of inhaled GCS should be of greater benefit. However, this has been debated. The results of our study suggest that greater control of asthma is achieved with higher doses of inhaled GCS.

Clinically significant adrenal suppression was not seen in this study, as demonstrated by the mean basal plasma cortisol measurements and the mean responses to ACTH stimulation. These data confirm the safety of budesonide within the recommended dose range.²² Additionally, the safety margin for inhaled budesonide compares favorably with that of other inhaled GCS.^{23, 24}

Budesonide was well tolerated by the patients in this study, with most adverse events being of mild intensity. However, because of the relatively short duration of study participation by the placebo-treated patients (35 days versus 84 days for patients treated with budesonide), any conclusions on the frequency of adverse events are difficult to draw.

In summary, budesonide delivered by Turbuhaler in a dose range of 200 to 1600 µg daily was significantly more effective than placebo in the treatment of adult patients with moderate-to-severe inhaled glucocorticoid-dependent asthma. Budesonide treatment improved pulmonary function and lowered the discontinuation rate as the result of asthma worsening in a dose-dependent manner and reduced asthma symptoms and the need for β₂-agonist use over the 12-week treatment period. Budesonide delivered by Turbuhaler was well tolerated and effective therapy for this adult population with chronic asthma.

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