

Administration of budesonide once daily by means of Turbuhaler to subjects with stable asthma

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Background: Optimal management of chronic, mild-to-moderate asthma with inhaled steroids may include use of the lowest possible doses, as recommended in guidelines, and a reduction in the frequency of daily administration for greater convenience. Lower doses and once daily treatment with inhaled steroids must be rigorously evaluated in controlled clinical trials.

Objectives: The objective of this study was to assess the efficacy and safety of once daily treatment with budesonide in subjects with stable asthma.

Methods: Once daily budesonide was assessed in 309 adult subjects, including those who were and were not using an inhaled steroid at baseline. The subjects were stratified by inhaled steroid use and randomly assigned to one of 3 treatments: 200 µg budesonide, 400 µg budesonide, or placebo administered by means of Turbuhaler once daily in the morning for 6 weeks. Beyond this point, treatment was continued unchanged for another 12 weeks (maintenance) in those receiving 200 µg budesonide once daily and placebo. In those who received 400 µg budesonide once daily, the dose was reduced to 200 µg once daily at week 6 and held constant for the remaining 12 weeks (400/200 µg group). Primary efficacy endpoints were mean change from baseline in FEV₁ and morning peak expiratory flow.

Results: Once daily budesonide was well tolerated and resulted in significant improvements in all efficacy endpoints, even though baselines were well stabilized. Baseline lung function was elevated with little room for improvement; however, mean increases in FEV₁ during the maintenance period were 0.10 L and 0.11 L in the 200 µg and 400/200 µg groups, respectively, versus a decrease of -0.09 L in the placebo arm ($P < .001$). Results for peak expiratory flow were similar. Significant improvements in secondary endpoints, including symptoms, β -

agonist use, and quality of life, also developed with budesonide 200 and 400 µg once daily.

Conclusion: Inhaled budesonide, in doses as low as 200 µg, may be an appropriate introductory or maintenance dose in subjects with stable, mild-to-moderate asthma. (*J Allergy Clin Immunol* 1999;104:46-52.)

Key words: Asthma, budesonide, inhalation, glucocorticosteroids, Turbuhaler, once daily, quality of life

Asthma is a disease of major public health importance, affecting an estimated 14.6 million patients in the United States and resulting in, or associated with, approximately 500,000 hospitalizations annually.¹ To reduce this impact, the use of inhaled anti-inflammatory agents, including glucocorticosteroids (GCSs), is now recommended in all but the mildest cases.^{1,2} Evidence is accumulating to support the earlier introduction of high doses of inhaled GCSs, with reduction to the lowest possible dose necessary to maintain control of the disease and to minimize the potential for adverse events.³ A pulmonary advisory panel for the US Food and Drug Administration recently reviewed growth issues and corticosteroids in children and adolescents and recommended that manufacturers produce more dose-range data for inhaled steroid products and that physicians titrate to the lowest effective dose when possible (Panel meeting, July 30-31, 1998, Bethesda, Md). Risk of serious side effects in adults, such as cataract formation, glaucoma, and osteoporosis, is most effectively minimized with the smallest daily dose of inhaled steroid sufficient for optimal control.^{4,5}

Compliance with therapy is a major problem in asthma management.⁶ Inhaled products and devices to simplify and improve medication delivery are in development to increase patient compliance.⁷ Budesonide administered by means of Turbuhaler is a novel, multi-dose, dry-powder treatment. Improved lung deposition with budesonide administered by means of Turbuhaler was demonstrated compared with budesonide administered through a pressurized metered-dose inhaler.^{8,9} A significant dose-response improvement in FEV₁ and peak expiratory flow (PEF) was demonstrated for total daily doses of 200, 400, 800, and 1600 µg budesonide administered in divided doses (twice daily) by means of Turbuhaler during a placebo-controlled, 12-week treatment period.¹⁰ Daily doses of budesonide of 200 to 800 µg administered once daily by means of the Turbuhaler resulted in significant improvement in PEF and symp-

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Abbreviations used

GCS: Glucocorticosteroid
PEF: Peak expiratory flow

toms, as well as reduced use of β -agonists, and compared well to regimens where the same total doses were divided and administered twice daily.¹¹⁻¹⁵

The purpose of this study was to investigate the efficacy and safety of budesonide, 200 μ g and 400 μ g once daily, in a large population of subjects with stable, mild-to-moderate asthma. By using a broad spectrum of clinical and functional assessments, the study was designed to determine whether disease stability could be maintained with these relatively low doses of drug administered once daily.

METHODS

Subjects

Adult male and female subjects, 18 to 70 years of age, with a diagnosis of asthma as defined by the American Thoracic Society of at least 6 months' duration, were recruited at 20 centers. All participants had reversible airway obstruction, as demonstrated by an increase in FEV₁ of greater than 15% after the administration of 2 to 4 puffs of albuterol. Subjects who were using inhaled GCSs at study entry (GCS group) were included and consisted of individuals who took inhaled beclomethasone dipropionate at a maximum of 10 inhalations per day for at least 4 weeks before enrollment. The FEV₁ in those using inhaled GCSs had to equal or exceed 80% of predicted value. Those not taking inhaled GCSs at enrollment (non-GCS group) were required to have an FEV₁ between 60% and 90% of predicted value at enrollment. Current smoking, the use of oral or parenteral GCSs within 1 month, or hospitalization for asthma within 2 months before the start of the trial were exclusion criteria. Subjects with other significant concurrent diseases or who had a recent respiratory infection within 6 weeks were also ineligible.

Ethical considerations

The study was reviewed and approved by the human subjects review committee at each center and was conducted according to the principles stated in the Declaration of Helsinki. All subjects provided written informed consent before enrollment in the study.

Study design

A multicenter, randomized, double-blind, placebo-controlled, parallel-group design was used. A study diagram is shown in Fig 1. Randomization was stratified on the basis of inhaled steroid use at baseline. Baseline measurements, including FEV₁ at clinic visits, daily PEF, asthma symptoms, and use of inhaled β -agonist, were obtained during a 2-week baseline period. Subjects in the GCS group continued using inhaled beclomethasone dipropionate (twice daily or 3 times daily) during the 2-week baseline period. This drug was then discontinued at assignment to study treatment.

The subjects, stratified by inhaled steroid use into the GCS and non-GCS groups, were randomized to receive either 200 μ g or 400 μ g of budesonide or placebo (lactose) administered once daily by means of the Turbuhaler in the morning for the initial 6 weeks of the study (initial period). All patients had 1 Turbuhaler and were instructed to take 1 inhalation each morning. The Turbuhalers, all identical in appearance, contained either placebo or budesonide in 1 of 2 dose strengths (ie, 200 μ g or 400 μ g per inhalation). The dou-

ble-blind treatments were then continued for an additional 12 weeks (maintenance period), during which the 400 μ g budesonide dose was reduced to 200 μ g once daily. The treatments for subjects in the placebo and budesonide 200 μ g once daily groups continued unchanged during this maintenance period.

Spirometry measurements and symptoms and safety assessments were made 3 and 6 weeks after randomization in the initial period and at 10, 14, and 18 weeks after randomization during the maintenance phase. Subjects kept a daily record of morning and evening PEF, symptom severity, and use of inhaled albuterol throughout the trial. Quality of life was measured before randomization and after 6 and 18 weeks of treatment. Inhaled albuterol was used as needed throughout the study. Theophylline, oral β -agonists, nasal GCSs, and antihistamines were allowed at constant doses.

Efficacy and safety assessments

Spirometry was performed in the morning at each clinic visit by using a calibrated computerized spirometer. Measurements were conducted in triplicate, and the highest FEV₁ value was reported. Inhaled GCSs and albuterol were withheld before spirometry for at least 8 hours, and methylxanthines were withheld for at least 12 to 24 hours.

PEF was measured at home by using a Mini-Wright peak flowmeter, and the best result of 3 efforts was recorded on the diary card. The subjects were instructed to avoid all asthma medications for at least 4 hours before PEF measurements. Symptom scores were recorded at home according to the following scale: 0, none; 1, mild; 2, moderate; and 3, severe. Health-related quality of life was assessed with the 32-question, self-administered Asthma Quality of Life Questionnaire.¹⁶ Discontinuation from the study for any reason was recorded, including adverse events, noncompliance, and asthma exacerbation or deterioration as judged by the investigator.

Safety was assessed at each clinic visit by standardized questioning to determine the occurrence of adverse events and by measurements of vital signs. All adverse events during the study were recorded. A physical examination and standard clinical chemistry, urinalysis, and hematology analyses were performed at entry and the final visit.

Statistical analyses

The primary efficacy variables were the changes from baseline in FEV₁ and morning PEF. Secondary variables included the changes from baseline in symptom severity scores (day and night), use of rescue albuterol, evening PEF, health-related quality of life, and discontinuation rates from the study.

Baseline diary data (PEF, symptoms, and albuterol use) were the mean of the 2 week prerandomization period. Baseline FEV₁ was the mean of the measurement taken at enrollment (screen) and 2 weeks later at the end of the baseline period (before randomization). Daily diary data during double-blind treatment were summarized as the means for weeks 0 through 6 (initial period) and weeks 6 through 18 (maintenance period). Spirometry data during study treatment were summarized as the mean of weeks 3 and 6 and the mean of weeks 10, 14, and 18 to differentiate potential differences between the periods before and after dose reduction in the 400/200 μ g group.

Comparisons between groups were made by ANOVA for all outcomes except discontinuation rates, which were analyzed by a chi-square test. An analysis with the dichotomous stratification baseline variable of the GCS or non-GCS groups in the ANOVA model was also completed for the primary efficacy variables. Means for efficacy analysis adjusted for center effects are presented. All statistical tests were 2-sided. Results with *P* values of .05 or less were considered statistically significant. Statistical significance of interac-

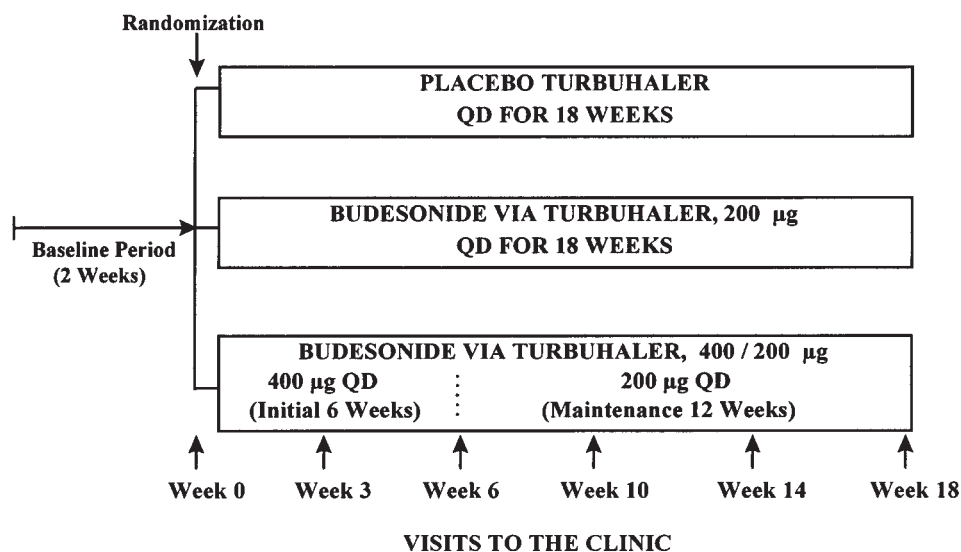


FIG 1. Study design. At week 6, the dose of budesonide was reduced from 400 µg once daily to 200 µg once daily for patients in the 400/200 µg once daily group. *QD*, Once daily.

TABLE I. Patient characteristics

	Placebo (n = 104) [‡]	Budesonide 200 µg (n = 103) [‡]	Budesonide 400/200 µg (n = 102)
Sex (M/F)	44/60	33/70	30/72
Age (y)*	35.5 ± 1.2	38.8 ± 1.3	35.9 ± 1.2
Duration of asthma (y)*	17.2 ± 1.1	18.2 ± 1.3	19.0 ± 1.3
Morning PEF (L/min)*	381 ± 9.9	348 ± 9.9	369 ± 9.4
FEV ₁ (L)*	2.87 ± 0.07	2.50 ± 0.07	2.71 ± 0.07
FEV ₁ (% predicted)*	82.6 ± 1.1	81.2 ± 1.0	81.9 ± 1.3
Reversibility (%)*	24 ± 1.0	22 ± 1.0	23 ± 1.1
Nasal steroid use (%)	20	15	16
Inhaled steroid use (non-GCS/GCS)	57/47	59/44	60/42
Median daily dose of BDP (µg) [†]	336 (84-420)	294 (84-1344)	252 (168-672)

BDP, Beclomethasone dipropionate.

*Values are means ± SEM.

[†]Median total daily dose (range) of beclomethasone dipropionate at enrollment.

[‡]Four patients (2 in each of the placebo and 200 µg once daily groups) had no efficacy data and were excluded from efficacy analyses.

tions was tested at the 0.010 level. The study was powered (90% power, $\alpha = 0.05$) to detect a difference of 0.25 L and 30 L/min in FEV₁ and PEF, respectively, with 85 patients per group. An intent-to-treat analysis is presented in this report, with the last double-blind value carried forward through the remainder of the study to account for missing observations.

Mean scores for the 4 domains of the quality of life questionnaire (activity limitation, asthma symptoms, emotional function, and environmental exposure) and for the overall global score were analyzed. The results of only the global scores are presented in this report. Changes in scores greater than 0.5 units were considered of clinical importance.¹⁷

RESULTS

Subjects

A total of 309 subjects was randomized to study treatment: 104 to the placebo group and 103 and 102 to the budesonide 200 µg and 400/200 µg groups, respectively.

Clinical and demographic characteristics at enrollment (screen) are shown in Table I. Four subjects (2 in each of the placebo and 200 µg budesonide groups) discontinued before any double-blind measurements could be obtained and were not included in efficacy analyses. There were no significant differences among the groups in sex, age, duration of asthma, and pulmonary function (PEF and FEV₁). The percent of subjects who used inhaled beclomethasone (GCS) was 45%, 43%, and 41% in the placebo, 200 µg, and 400/200 µg groups, respectively, and the median daily dose was similar in the 3 groups (Table I). The percent of patients using nasal GCSs was similar across the groups. Mean FEV₁ at baseline ranged between 81% and 83% of predicted value and was consistent with stable asthma. Baseline pulmonary function in the GCS subjects was significantly higher than that in the non-GCS subjects (Table II).

As presented in Table III, 26 subjects in the placebo

TABLE II. Inhaled steroid at enrollment

	Non-GCS (n = 176)	GCS (n = 133)
Age (y)	35.7 ± 0.9	38.1 ± 1.1
Duration of asthma (y)	17.5 ± 0.9	18.9 ± 1.6
Morning PEF (L/min)	351 ± 7.2	386 ± 8.9*
FEV ₁ (L)	2.60 ± 0.05	2.82 ± 0.07†
FEV ₁ (% of predicted value)	76.6 ± 0.7	88.8 ± 0.9‡
Reversibility (%)	26 ± 0.9	20 ± 0.7‡

Values are means ± SEM.

**P* = .0020, †*P* = .0119, ‡*P* ≤ .00005 (GCS vs non-GCS).

group (25%) discontinued the study treatment compared with 15 (15%) in the budesonide 200 µg group and 10 (10%) in the budesonide 400/200 µg group. The majority of withdrawals from the placebo group were GCS subjects and occurred during the initial 6 weeks of treatment or early in the 12-week maintenance period.

Pulmonary function

In the first 6 weeks of treatment the mean FEV₁ in the 200 µg and 400/200 µg budesonide groups increased over baseline by 0.12 and 0.13 L, respectively, compared with a slight decrease of 0.03 L in the placebo group (*P* < .01) (Table IV). These improvements continued during the subsequent maintenance period. The gains in lung function remained constant in the 400/200 µg group after dose reduction at week 6. Improvements in pulmonary function in both budesonide groups were noted at the first visit (3 weeks after the start of treatment) and remained constant thereafter (Fig 2). The largest increase in FEV₁ occurred in the non-GCS subjects (Fig 3). The mean FEV₁ for the GCS subjects who received placebo decreased progressively. Significant improvements also developed in the morning and evening PEF in both budesonide groups (Table IV).

Asthma symptom scores, use of β-agonists, and quality of life

Low mean baseline symptom scores during the day (1.05 to 1.11) and night (0.66 to 0.72) were consistent with stable, controlled asthma (Table IV). Daytime scores improved significantly by 21% to 34% in the 2 budesonide treatment groups during both treatment periods (*P* ≤ .05 or *P* ≤ .001). Evening symptom scores improved in both budesonide groups by 15% to 26% and were also consistently better than those found with placebo. The differences in evening symptom scores between placebo and 200 µg budesonide for the initial 6 weeks and the 400/200 µg budesonide group for maintenance were statistically significant (*P* ≤ .05). The average daily number of inhalations of albuterol during the baseline period varied from 3.6 to 4 per day and decreased significantly in both of the budesonide groups during the study (*P* ≤ .01). Scoring for the Asthma Quality of Life Questionnaire ranges from 1 (maximum impairment) to 7 (no impairment), and fluctuations of 0.5 units or greater are considered clinically meaningful.^{16,17} The mean global score rose in both budesonide groups by 0.6 to 0.8 units

TABLE III. Patient discontinuations

	Placebo (n = 104)	Budesonide 200 µg (n = 103)	Budesonide 400/200 µg (n = 102)
Reason for withdrawal			
Asthma deterioration	11 (11%)	4 (4%)	1 (1%)
Adverse event	8 (8%)	4 (4%)	5 (5%)
Other (eg, noncompliance)	7 (7%)	7 (7%)	4 (4%)
Total	26 (25%)	15 (15%)*	10 (10%)†

**P* = .062, †*P* = .005 vs placebo.

(*P* ≤ .01 or *P* ≤ .001). Negligible changes occurred in the placebo group (Table IV). Statistically significant and clinically superior improvements in scores for all the specific domains of the quality of life questionnaire occurred in both budesonide groups compared with placebo, including activity limitations, symptoms, emotional function, and environmental exposure.

Safety

The incidence of most adverse events was similar in the 3 treatment groups. The most commonly reported and severe adverse events were respiratory infection, headache, and bronchospasm. Bronchospasm was reported in 11% of the placebo patients compared with 4% and 5% of the patients in the 200 µg and 400/200 µg budesonide groups, respectively. The numbers of subjects who discontinued treatment specifically related to adverse events were 8, 4, and 5 subjects in the placebo, 200 µg, and 400/200 µg budesonide groups, respectively. There were no indications of treatment-related effects on vital signs, physical examination, or any laboratory variables for hematology, clinical chemistry, and urinalysis.

DISCUSSION

This study was undertaken to determine whether single daily administration of inhaled budesonide in 200 and 400 µg doses could provide safe and effective treatment in a large population of subjects with stable asthma. Significant improvements in pulmonary function, reduction of symptoms, decreased use of β-agonists, and improvements in health-related quality of life occurred with both doses of budesonide and were maintained throughout the study. The results with the 2 budesonide schedules were similar, indicating that low doses can serve well to maintain remission in this disease.

Our study extends previous studies with once daily budesonide to include spirometry (FEV₁) as a primary efficacy endpoint, assessment of quality of life, and treatment with a dose as low as 200 µg once daily for up to 4.5 months, which is longer than that reported previously.¹¹⁻¹⁴ The results in our study amplify and confirm results from a study in which patients with mild asthma were maintained with budesonide 200 µg once daily for 8 weeks.¹⁵ Subjects in our study included both patients who were using and not using inhaled steroid at baseline and represented a more extensive population than that

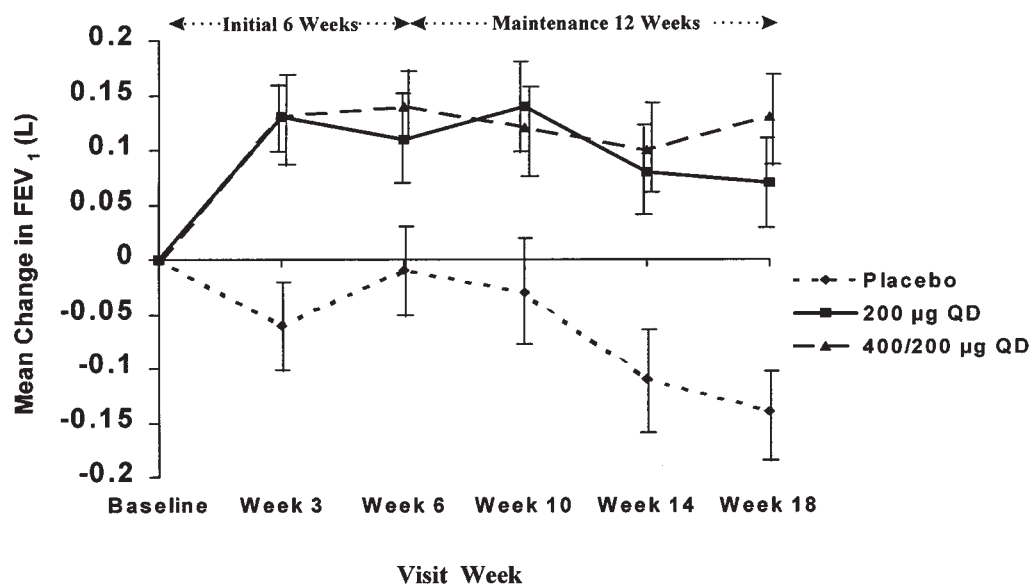


FIG 2. Mean change ($\pm$ SEM) in FEV₁ (L) from baseline at each study visit. QD, Once daily.

TABLE IV. Mean changes from baseline in primary and secondary endpoints

		Placebo (n = 102)	Budesonide 200 µg QD (n = 101)	Budesonide 400/200 µg QD (n = 102)
FEV ₁ (L)	Baseline	2.80	2.52	2.66
	Initial period	-0.03 ($\pm$ 0.04)	0.12 ($\pm$ 0.03) [†]	0.13 ($\pm$ 0.03) [‡]
	Maintenance period	-0.09 ($\pm$ 0.04)	0.10 ($\pm$ 0.04) [‡]	0.11 ($\pm$ 0.04) [‡]
Morning PEF (L/min)	Baseline	381	346	369
	Initial period	0.6 ($\pm$ 3.69)	10.4 ($\pm$ 3.68)	14.4 ($\pm$ 3.67) [†]
	Maintenance period	0.7 ($\pm$ 5.04)	21.0 ($\pm$ 5.02) [†]	22.0 ($\pm$ 5.01) [†]
Evening PEF (L/min)	Baseline	407	374	390
	Initial period	-1.6 ($\pm$ 3.56)	7.5 ($\pm$ 3.54)	10.4 ($\pm$ 3.53) [*]
	Maintenance period	-5.1 ($\pm$ 4.77)	12.2 ($\pm$ 4.75) [†]	19.0 ($\pm$ 4.74) [‡]
Day symptom scores	Baseline	1.05	1.11	1.06
	Initial period	-0.04 ($\pm$ 0.05)	-0.27 ($\pm$ 0.05) [‡]	-0.22 ($\pm$ 0.05) [†]
	Maintenance period	-0.07 ($\pm$ 0.05)	-0.23 ($\pm$ 0.05) [*]	-0.36 ($\pm$ 0.05) [‡]
Evening symptom scores	Baseline	0.72	0.69	0.66
	Initial period	0.02 ($\pm$ 0.05)	-0.15 ($\pm$ 0.05) [*]	-0.10 ($\pm$ 0.05)
	Maintenance period	0.02 ($\pm$ 0.05)	-0.12 ($\pm$ 0.05)	-0.17 ($\pm$ 0.05) [*]
Albuterol (mean daily inhalations)	Baseline	3.58	4.00	3.58
	Initial period	-0.10 ($\pm$ 0.21)	-0.98 ($\pm$ 0.21) [†]	-0.88 ($\pm$ 0.20) [†]
	Maintenance period	-0.22 ($\pm$ 0.24)	-1.11 ($\pm$ 0.24) [†]	-1.09 ($\pm$ 0.24) [†]
Quality of life scores [§]	Baseline	4.89	4.65	4.75
	Initial period	4.90 ($\pm$ 0.09)	5.31 ($\pm$ 0.09) [‡]	5.51 ($\pm$ 0.09) [‡]
	Maintenance period	4.84 ($\pm$ 0.11)	5.26 ($\pm$ 0.10) [†]	5.55 ($\pm$ 0.10) [‡]

Mean values $\pm$ SEM.

^{*} $P \leq .05$, [†] $P \leq .01$, [‡] $P \leq .001$ vs placebo.

[§]Mean quality of life scores, adjusted for both center effects and baseline scores, are shown rather than mean changes.

found in individual previous studies with budesonide administered once daily.

The subjects selected for the study had stable asthma, elevated baseline pulmonary function, and low symptom scores, which are consistent with minimal impairment. The potential to demonstrate improvements in such a group of patients is limited. However, the participants did indeed improve, and their disease was controlled with

doses as low as 200 µg a day. These findings have important clinical applications and lend objective support to treatment guidelines that recommend a reduction in inhaled steroid dose when the disease is controlled.³

The single-dose budesonide regimens had favorable impact on lung function in both the GCS and non-GCS subjects, indicating that any differential effects or patient selection biases were not issues. Slightly greater improve-

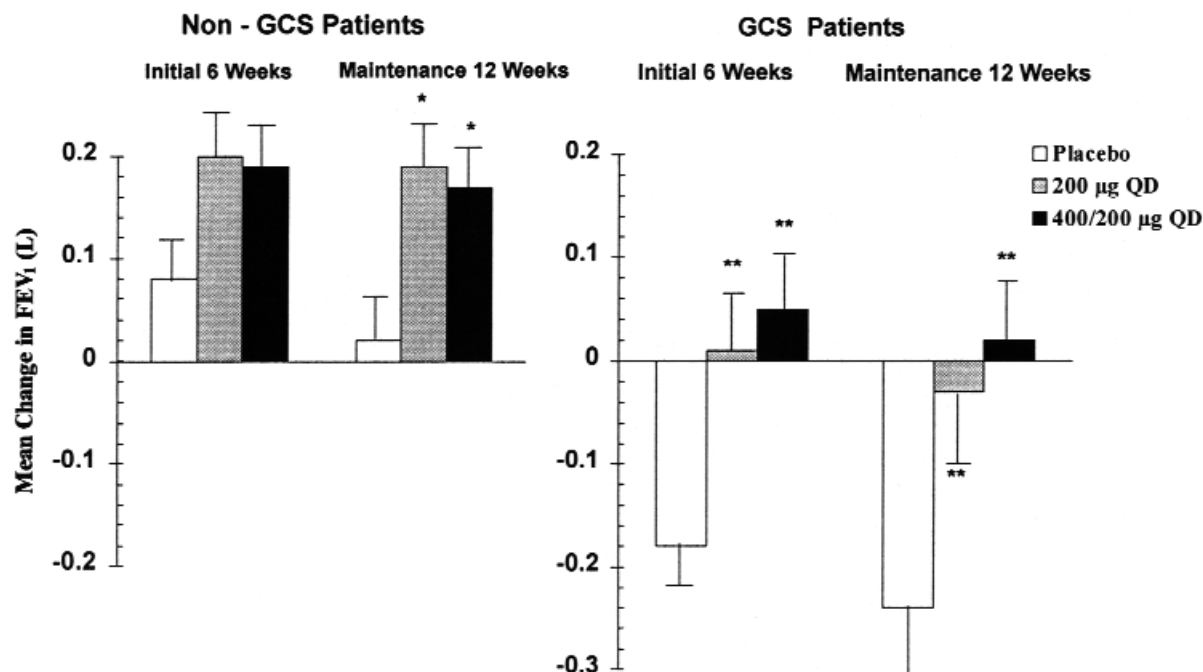


FIG 3. Mean change ($\pm$ SEM) in FEV₁ from baseline in non-GCS and GCS patients. * $P \leq .05$, ** $P \leq .01$ versus placebo. QD, once daily.

ment in lung function in the non-GCS patients was consistent with lower baseline levels as compared with the GCS patients. It is important to note that there was no deterioration in GCS subjects, who were using beclomethasone 2 or 3 times daily before the study and then switched to either 200 µg or 400 µg of budesonide. Those who received placebo, however, did worsen slightly.

In conjunction with the increases in lung function, quality of life also improved in both budesonide treatment groups. Satisfaction with the experimental treatments was not evaluated in this investigation. However, previous studies have demonstrated a clear preference for Turbuhaler and once daily budesonide therapy compared with other treatment regimens and delivery devices.^{13,14,18} This preference may be translated to improved compliance.

Efficacy in the maintenance of asthma control in subjects with mild-to-moderate asthma has been demonstrated in previous studies with other inhaled steroids administered once daily. Subjects well stabilized on flunisolide 500 µg twice daily, as indicated by low symptom scores and elevated pulmonary function, continued with no significant change from baseline when switched to flunisolide 1000 µg once daily administered either in the morning or in the evening for 12 weeks.¹⁹ In another study with a randomized crossover design, patients stabilized with beclomethasone or budesonide at baseline continued with no significant change when switched to beclomethasone at 1000 µg once daily administered either in the afternoon or at night during 1-month treatment periods.²⁰ Subjects in both of these studies were using inhaled steroid twice daily at baseline and were

then switched to once daily treatment, which is similar to the GCS patients in our study. In our study, as in these previous studies with GCS patients, asthma control was maintained with little to no change from baseline when the subjects were switched to once daily inhaled steroid therapy.

A study with a more generalized population of asthmatic subjects who were not using inhaled steroid at baseline was conducted to compare triamcinolone administered at a total daily dose of 800 µg once daily (in the afternoon) with the same dose administered 4 times daily for 4 weeks.²¹ Increases in FEV₁ and PEF and reduction of β -agonist use occurred with both triamcinolone regimens, with no significant differences between the two. The improvements in lung function and β -agonist use in this study were similar to the improvements that occurred in the non-GCS patients in our study.

Study design and endpoints varied in these previous studies; however, the conclusions were consistent: once daily inhaled steroid therapy can maintain asthma control in subjects with mild-to-moderate stable asthma. Unlike many previous studies with other inhaled steroids, a placebo control group was used in our study, demonstrating significant improvements in lung function and symptom scores, even over stable baselines, as compared with placebo. Quality of life, not measured in the previous studies, was also significantly improved with once daily inhaled budesonide, indicating that patient perceptions of disease improvement can be increased with once daily inhaled steroid therapy.

Although budesonide was administered in the morning in our study, increased efficacy with the administra-

tion of inhaled steroid in the afternoon or evening has been suggested.^{20,21} No significant difference was found when once daily administration in the morning was compared directly with once daily administration in the afternoon in previous studies.^{12,19} Recommendation for time of dosing may well be left to the individual physician based on convenience for the patient and the likelihood for increased compliance.

Information on the precise dose of inhaled steroid required to control all aspects of the asthma diathesis is not yet available. For example, the amounts of medication needed to prevent nocturnal awakenings, to prevent visits to the emergency department, or to reduce airway reactivity may be different than the amounts needed to control symptoms or improve lung function. Doses as needed should be used to establish control of symptoms, as defined in guidelines.³ Once control is reached, the dose of inhaled budesonide may be taken once daily.

In our study, as well as in previous studies with once daily inhaled steroid therapy, subjects with stable asthma served as the subject population. In clinical practice periodic increases in the amount and frequency of dosing with inhaled steroids may be expected as the disease process waxes and wanes. Some patients may require continued higher doses or increased frequency of inhaled steroid.^{22,23} However, most patients will eventually return to lower doses with remission. Hence the optimal regimen for once daily inhaled steroid is not yet determined. It is clear from our study that many patients will do well with 200 µg or 400 µg budesonide once daily. These doses were safe and effective in the treatment of subjects with stable asthma compared with placebo. A dose as low as 200 µg once daily may be satisfactory as initial and maintenance inhaled steroid therapy for patients with mild, persistent asthma.

Additional Investigators who participated in this study as members of the Pulmicort Turbuhaler Once Daily Study Group are as follows: Paul Chervinsky, MD, The New England Research Center, Inc (North Dartmouth, Mass); Ben Carasso, MD, Chicago Center for Clinical Research (Chicago, Ill); Joseph D. Diaz, MD, Allergy and Asthma Research Center (San Antonio, Tex); Sidney Friedlaender, MD, Clinical Investigative Site (Gainesville, Fla); David Graft, MD, Park Nicollett Medical Center (Minneapolis, Minn); Frank C. Hampel Jr, MD, Central Texas Health Research (New Braunfels, Tex); William R. Lumry, MD, Allergy and Asthma Research Associates (Dallas, Tex); Scott Osur, MD, Certified Allergy Consultants, PC (Albany, NY); Warren Pleskow, MD (Encinitas, Calif); Paul Ratner, MD, Sylvana Research (San Antonio, Tex); Harry Serfer, DO (Hollywood, Fla); Martin D. Valentine, MD, Maryland Asthma and Allergy Center (Baltimore, Md); and Allan Weinstein, MD (Washington, DC).

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