

Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma

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Background: Recent emphasis on the control of airway inflammation in asthma highlights the need for safe and effective antiinflammatory agents. Fluticasone propionate is one of the most potent antiinflammatory corticosteroids developed to date.

Objective: This study assessed the safety and efficacy of fluticasone propionate aerosol in the treatment of mild to moderate asthma.

Methods: Fluticasone propionate aerosol (25, 100, or 500 µg twice daily) or placebo was given for as long as 8 weeks to adults with mild to moderate asthma in a randomized, double-blind, parallel-group study. Patients were removed from the study if they showed predefined signs of worsening asthma.

Results: Sixty-three percent of placebo-treated patients and 23%, 13%, and 4% of patients treated with fluticasone propionate 25, 100, and 500 µg twice daily, respectively, were removed from the study. Mean forced expiratory volume in 1 second, forced vital capacity, and forced expiratory flow at midexpiratory phase at weekly visits throughout the study demonstrated that fluticasone propionate was more efficacious than placebo in maintaining asthma control. Measurements of peak expiratory flow and symptom scores significantly improved and nighttime awakenings and albuterol use to treat symptoms significantly declined in fluticasone propionate-treated groups relative to the placebo-treated group. Differences among fluticasone propionate groups for these variables were not statistically significant. Incidence and severity of adverse events were similar across groups. Fluticasone propionate did not affect morning or stimulated plasma cortisol concentrations, although slight, transient reductions in urinary free cortisol and urinary 17-hydroxy steroids occurred in the group receiving 500 µg fluticasone propionate twice daily.

Conclusion: These data indicate that fluticasone propionate provides safe and effective treatment for mild to moderate asthma. (*J ALLERGY CLIN IMMUNOL* 1994;94:676-83.)

Key words: Asthma, fluticasone propionate, inhaled corticosteroid

Recent therapeutic emphasis on the control of airway inflammation in asthma highlights the need for safe and effective antiinflammatory agents.^{1, 2} Topical corticosteroid preparations that

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Abbreviations used

FEF_{25%-75%}: Forced expiratory flow at midexpiratory phase
FEV₁: Forced expiratory volume in 1 second
FVC: Forced vital capacity
PFT: Pulmonary function tests

deliver drug directly to the lungs control asthma with a low risk of serious side effects.³ The trifluorinated glucocorticoid fluticasone propionate is one of the most potent antiinflammatory corticosteroids developed to date. Its vasoconstrictor potency in the McKenzie test is twice that of

beclomethasone dipropionate and more than nine times that of triamcinolone acetonide.⁴ Highly lipophilic, fluticasone propionate undergoes extensive first-pass metabolism and has virtually no bioavailability following oral administration, a characteristic that limits corticosteroid systemic effects.⁵

Fluticasone propionate aerosol (1 mg daily for 6 weeks⁶ or 1.5 mg daily for 1 year⁷) has been shown to be at least as effective as beclomethasone dipropionate aerosol (1.5 mg or 2 mg daily) for the control of severe asthma in adults. In another study,⁸ fluticasone propionate aerosol at a dose of 200 µg daily was as effective as beclomethasone dipropionate aerosol at a dose of 400 µg daily in children with mild to moderate asthma. Fluticasone propionate aerosol did not adversely affect measures of hypothalamic-pituitary-adrenal function (such as plasma cortisol concentrations) in any of these studies.

This study was designed to evaluate the safety and efficacy of fluticasone propionate (25 µg twice daily, 100 µg twice daily, or 500 µg twice daily) administered by metered-dose inhaler to adults with mild to moderate asthma. The three dosage regimens were selected to reflect the minimal effective dose (25 µg twice daily), the dose comparable to 400 µg beclomethasone dipropionate (100 µg twice daily), and a dose 20 times the minimal effective dose (500 µg twice daily). Because of concerns regarding the safety of assigning patients who had stable asthma while taking inhaled corticosteroids to a placebo regimen, "early escape criteria" for significant worsening of asthma were defined. Patients were released from the study if these criteria for worsening asthma were met. Further, the failure to meet criteria for worsening asthma provided an efficacy measure reflecting asthma stability. In statistical analysis of measurements of pulmonary function and asthma symptoms, data from the last evaluable visit were used for patients discontinuing the study; data from the final visit during treatment were used for patients completing the study.

METHODS

Subjects

Three hundred thirty-one men and women 18 years of age or older with mild to moderate asthma⁹ participated in the study. Patients had been maintained on a regimen of beclomethasone dipropionate aerosol (8 to 16 actuations/day) for at least 1 month before the study and had received daily β-sympathomimetic bronchodilator

or daily theophylline for at least 2 weeks before the study. Patients were required to have an unmedicated forced expiratory volume in 1 second (FEV₁) between 60% and 90% of the predicted value for their age, sex, and height.

Design and procedures

This randomized, double-blind, parallel-group study was approved by institutional review boards for each of the 24 research centers. During the 2-week screening phase, baseline asthma symptoms and patient compliance with a regimen of fixed daily doses of beclomethasone dipropionate were established. Theophylline and inhaled albuterol were permitted. At the end of the screening period, patients eligible for treatment completed baseline 12-hour serial pulmonary function tests (PFTs), and physicians rated the effectiveness of beclomethasone dipropionate in controlling asthma on a 4-point scale from 0 (ineffective) to 3 (very effective).

After patients completed the baseline serial PFTs, they were randomly assigned to receive fluticasone propionate aerosol (25 µg twice daily, 100 µg twice daily, or 500 µg twice daily) or placebo in place of beclomethasone dipropionate for the 8-week treatment phase (weeks 1 to 8). Albuterol was withheld for at least 6 hours and theophylline was withheld for at least 24 hours before weekly evaluations on weeks 1 to 8. FEV₁, forced vital capacity (FVC), and forced expiratory flow at midexpiratory phase (FEF_{25%-75%}) were measured weekly before morning administration of the study drug. Physicians rated the effectiveness of the study drug in controlling asthma at weeks 4 and 8 and 1 week after treatment according to the 4-point scale described previously.

The patient recorded asthma-related symptoms and the use of albuterol twice daily on a diary card. Asthma-related wheezing, shortness of breath, and coughing were rated on a 4-point scale from 0 (none) to 3 (intolerable). In addition, patients completed 12-hour serial PFTs at weeks 4 and 8.

Adverse events were recorded weekly on weeks 1 to 8 by the investigator who rated the severity of the event and the perceived relationship of the event to the study drug. Standard hematologic and urinary tests were conducted at screening and weeks 1, 3, 5, and 8. Morning plasma cortisol concentrations (screening and weeks 4 and 8); 24-hour urinary free cortisol, 17-hydroxy steroid, and 17-ketogenic steroid concentrations (screening, weeks 4 and 8, and after treatment if abnor-

TABLE I. Demographic and dispositional characteristics of patients in the efficacy testing population

	Placebo	FP 25	FP 100	FP 500
<i>N</i>	80	78	80	79
Sex (%)				
Male	48	49	59	43
Female	53	51	41	57
Mean age (yr)	41	35	36	40
FEV ₁ at screening				
FEV ₁ value (L)	2.53	2.66	2.75	2.56
% predicted	71	72	72	73
% taking theophylline	60	42	54	56

FP 25, Fluticasone propionate 25 µg twice daily; FP 100, fluticasone propionate 100 µg twice daily; FP 500, fluticasone propionate 500 µg twice daily.

mal at week 8); and results of the synthetic corticotropin stimulation test (screening and week 8) were monitored.

Blood samples for determination of plasma cortisol concentrations were collected before the morning dose of drug and, on synthetic corticotropin test days, 30 to 60 minutes after administration of synthetic corticotropin (given intramuscularly or intravenously after the predose blood sample according to package insert directions). A normal response to synthetic corticotropin stimulation was defined as a plasma cortisol concentration of at least 18 µg/dl and an increase from baseline of at least 7 µg/dl. Twenty-four-hour urine specimens were collected for the 24 hours before the designated sampling days for determination of free cortisol, 17-hydroxy steroid, and 17-ketogenic steroid concentrations.

Vital signs were monitored and ophthalmologic, oropharyngeal, and physical examinations were performed periodically throughout the study. Twelve-lead electrocardiograms were obtained at screening and both before and after dosing on week 8.

Patients were released from the study if they met any of the predetermined criteria for clinical deterioration:

- A clinical exacerbation—intolerable symptoms or need for additional asthma medications.
- A decrease in the morning predose FEV₁ of at least 20% of baseline or to not more than 50% of predicted.
- A 20% decrease (mean weekly value) in either morning or evening peak expiratory flow on 4 of 7 days before a visit, as compared with the mean value for the week immediately preceding assignment to treatment.
- One nighttime awakening requiring the use of

albuterol on 4 or more nights, or 2 or more nights with two awakenings, during the 7 nights immediately preceding a visit.

- Albuterol use of more than 12 actuations per day on more than 3 of 7 days immediately preceding a visit.

The following evaluations were carried out on patients leaving the study for any reason: vital signs, physical examination, clinical laboratory tests, a 12-lead electrocardiogram, PFTs, adverse event assessment, review of diary card, physician-rated global assessment, and morning plasma cortisol measurement. The last visit during which these evaluations were performed was defined as the study end point.

Statistics

Efficacy analyses were conducted with data from the last evaluable visit for patients leaving the study (end point analysis); data from the final visit during treatment were used for patients completing the study. For most efficacy variables, data from individual visits were also analyzed. *F* tests based on both baseline and change from baseline values were performed on FEV₁, FVC, and FEF_{25%-75%}, as well as on peak expiratory flow measurements. Physician-rated global assessments of efficacy were tested with the Cochran-Mantel-Haenszel test. Patient-rated diary symptom scores (based on 7-day averages) were tested with the nonparametric van Elteren test. A log-rank test was performed on Kaplan-Meier estimates of duration of participation.

For the hypothalamic-pituitary-adrenal axis evaluations, a sign-rank test was performed within each treatment group to detect significant changes from screening values. A Wilcoxon sign-rank test was performed to detect between-treat-

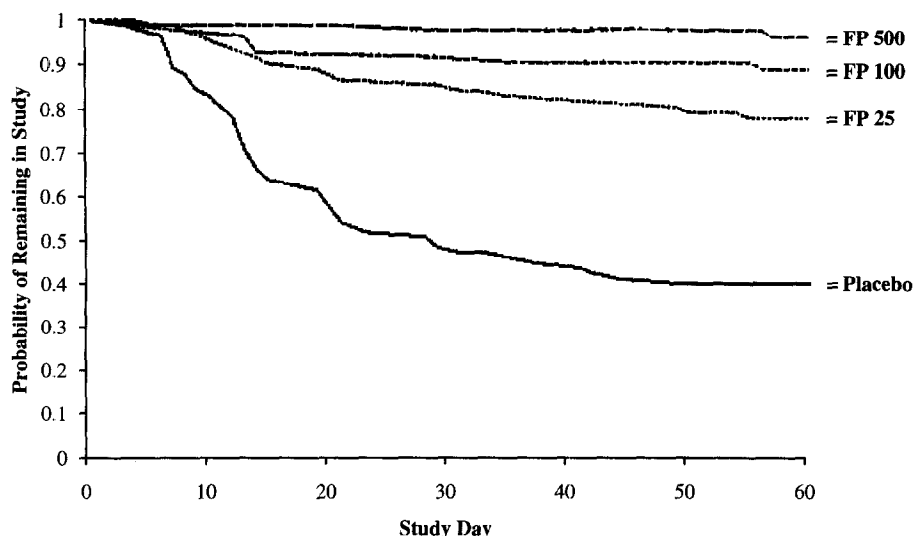


FIG. 1. Estimated probability of remaining in the study for patients treated with placebo, fluticasone propionate at 25 μg twice daily (FP 25), fluticasone propionate at 100 μg twice daily (FP 100), or fluticasone propionate at 500 μg twice daily (FP 500). For each experimental group versus placebo, $p \leq 0.001$.

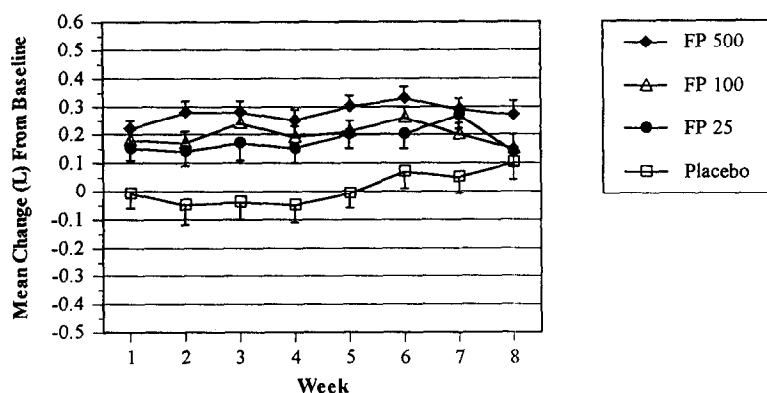


FIG. 2. Mean change in FEV₁ from baseline in patients with mild to moderate asthma treated for 8 weeks with placebo, fluticasone propionate at 25 μg twice daily (FP 25), fluticasone propionate at 100 μg twice daily (FP 100), or fluticasone propionate at 500 μg twice daily (FP 500). Among groups for weeks 1, 2, 3, 4, 5, and 7, $p < 0.05$.

ment differences. Vital signs were analyzed with analysis of variance.

RESULTS

Patient population

Mean ages of patients in the four treatment groups ranged from 35 to 41 years (Table I). Percentage of patients in each treatment group who used theophylline during the treatment phase of the study ranged from 42% to 60% (Table I). All patients receiving the study drug ($n = 331$) were included in safety analyses, and 317 patients were included in efficacy analyses.

Fourteen of the 331 patients were excluded from efficacy analyses because they did not meet entrance criteria or failed to comply with the therapeutic regimen.

Efficacy data

Duration of participation. Patients in the three groups treated with fluticasone propionate had significantly ($p = 0.001$) greater probability of remaining in the study than did patients treated with placebo (Fig. 1). Sixty-three percent of patients treated with placebo, compared with 23%, 13%, and 4% of patients treated with fluticasone

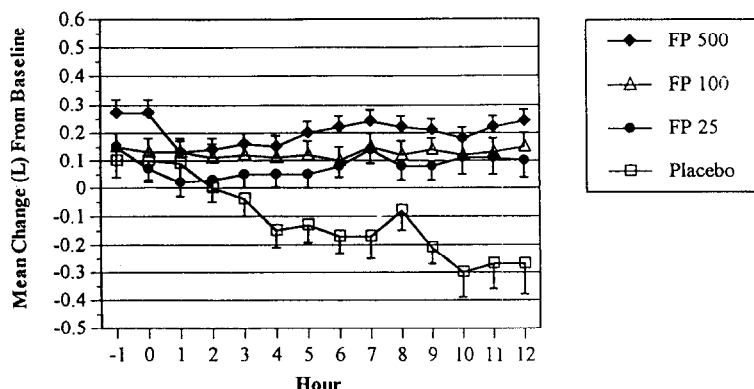


FIG. 3. Mean change in FEV₁ from baseline (screening period) during 12-hour serial PFTs conducted at week 8 in patients with mild to moderate asthma treated with placebo, fluticasone propionate at 25 μ g twice daily (FP 25), fluticasone propionate at 100 μ g twice daily (FP 100), or fluticasone propionate at 500 μ g twice daily (FP 500). Among groups for hours 0, 4, 5, 6, 7, 8, 9, 10, 11, and 12, $p < 0.05$.

TABLE II. Mean change ($\pm$ standard deviation) from baseline at end point for efficacy variables

Variable	Placebo	FP 25	FP 100	FP 500
FEV ₁ AM predose (L)	-0.26 ± 0.51	$0.09 \pm 0.53^*$	$0.14 \pm 0.46^*$	$0.26 \pm 0.41^*$
FVC AM predose (L)	-0.31 ± 0.66	$-0.02 \pm 0.59^*$	$0.08 \pm 0.56^*$	$0.21 \pm 0.45^*$
FEF _{25%-75%} AM predose (L/sec)	-0.16 ± 0.72	$0.22 \pm 0.73^*$	$0.30 \pm 0.78^*$	$0.40 \pm 0.73^*$
AM PEFR (L/min)	-19 ± 37	$11 \pm 40^{*\dagger}$	$15 \pm 38^{*\dagger}$	$39 \pm 56^*$
PM PEFR (L/min)	-23 ± 30	$7 \pm 38^*$	$12 \pm 37^*$	$25 \pm 49^*$
Total symptom score	0.10 ± 0.50	$-0.14 \pm 0.39^*$	$-0.21 \pm 0.39^*$	$-0.22 \pm 0.32^*$
Albuterol use (puffs/day)	0.20 ± 1.97	$-0.63 \pm 1.55^*$	$-0.65 \pm 1.57^*$	$-0.76 \pm 1.33^*$
Night awakenings	0.14 ± 0.38	$0.02 \pm 0.43^*$	$-0.03 \pm 0.25^*$	$-0.08 \pm 0.18^*$

FP 25, Fluticasone propionate 25 μ g twice daily; FP 100, fluticasone propionate 100 μ g twice daily; FP 500, fluticasone propionate 500 μ g twice daily; PEFR, peak expiratory flow rate.

* $p < 0.01$ versus placebo.

$\dagger p < 0.05$ versus FP 500.

propionate 25 μ g twice daily, 100 μ g twice daily, and 500 μ g twice daily, respectively, did not complete 8 weeks of treatment because they experienced clinical deterioration.

Spirometric data. PFT results at baseline did not differ among the groups. Fluticasone propionate was more effective than placebo throughout the study in maintaining pulmonary function ($p < 0.05$ among groups on weeks 1, 2, 3, 4, 5, and 7; Fig. 2). Each of the fluticasone propionate groups had significantly ($p < 0.001$) greater improvement in morning FEV₁, FEF_{25%-75%}, and FVC than did the placebo group at end point (Table II).

Twelve-hour serial PFT measurements at weeks 4 and 8 also demonstrated the superiority of fluticasone propionate compared with placebo ($p < 0.05$ on hours 0, 4, 5, 6, 7, 8, 9, 10, 11, and 12; Fig. 3). Baseline PFT results were similar for all treatment groups. FEV₁, FVC, and FEF_{25%-75%} decreased

during both 12-hour assessment periods at week 4 and week 8 in the placebo group and were maintained at a relatively constant level in the fluticasone propionate groups. All fluticasone propionate treatments were significantly ($p < 0.05$) better than placebo in maintaining pulmonary function at most time points during the two 12-hour assessment periods.

Physician-rated global assessment. Physicians' ratings of beclomethasone dipropionate's efficacy at baseline did not differ among treatment groups. Significantly fewer patients treated with fluticasone propionate compared with placebo, however, were rated as having ineffective treatment ($p < 0.001$ at 4 weeks and at 8 weeks), and more were rated as having effective or very effective treatment. Sixty-two percent of placebo-treated patients, compared with 17%, 9%, and 4% of patients treated with fluticasone propi-

TABLE III. Patients with adverse events considered by the institutional investigator to be drug-related

Adverse event	Placebo (n = 83)		FP 25 (n = 82)		FP 100 (n = 81)		FP 500 (n = 85)	
	No.	%	No.	%	No.	%	No.	%
Candidiasis	0	0	1	1	1	1	6	7
Hoarseness	0	0	1	1	1	1	9	11
Cough	7	8	1	1	3	4	2	2

Adverse events occurring in at least three patients in a group are reported. FP 25, Fluticasone propionate 25 µg twice daily; FP 100, fluticasone propionate 100 µg twice daily; FP 500, fluticasone propionate 500 µg twice daily.

TABLE IV. Mean change from baseline and number of patients with abnormal results to indexes of hypothalamic-pituitary-adrenal axis functioning at week 8

Index	Placebo		FP 25		FP 100		FP 500	
	Mean change	No. abnormal	Mean change	No. abnormal	Mean change	No. abnormal	Mean change	No. abnormal
AM plasma cortisol (mcg/dl)*	-0.8	5	0.0	1	0.2	1	0.4	4
Urinary free cortisol (mg/day)*	-3.1	6	6.6	5	-5.7	7	-4.1	21
17-hydroxy steroids (mg/day)*†	-0.78	5	0.54	9	-0.65	12	-1.08	18
Corticotropin stimulation test‡	13.83	8	14.06	5	12.51	7	12.08	13

FP 25, Fluticasone propionate 25 µg twice daily; FP 100, fluticasone propionate 100 µg twice daily; FP 500, fluticasone propionate 500 µg twice daily.

*Change from baseline values computed as difference between week 8 and screen.

† $p < 0.05$ among groups.

‡Change from baseline in plasma cortisol is difference between baseline before stimulation with corticotropin and 60 minutes after stimulation.

onate at 25 µg, 100 µg, and 500 µg twice daily, respectively, were rated as having ineffective treatment. Only 17% of placebo-treated patients were rated as having effective or very effective treatment. In contrast, 55%, 73%, and 85% of patients treated with fluticasone propionate at 25 µg, 100 µg, and 500 µg twice daily, respectively, were rated as having effective or very effective treatment.

Patient-recorded data. Fluticasone propionate, compared with placebo, significantly ($p < 0.001$) improved both combined and individual symptom scores (wheeze, cough, shortness of breath, number of nighttime awakenings) at end point ($p < 0.001$ each fluticasone propionate group vs placebo; Table II). Patients treated with fluticasone propionate (25 µg twice daily, 100 µg twice daily, or 500 µg twice daily) used significantly less albuterol for relief of symptoms than did patients treated with placebo ($p < 0.001$ for total, daytime, and nighttime albuterol use). Both morning and evening peak expiratory flows were also significantly improved compared with placebo

($p < 0.001$) in each of the three groups treated with fluticasone propionate (Table II).

Safety data

Adverse events. Overall frequency of adverse events did not differ among groups. The most frequently reported potentially drug-related adverse events were hoarseness, candidiasis, and cough (Table III).

Hypothalamic-pituitary-adrenal axis evaluations. Few patients in any treatment group had abnormal values for measures of hypothalamic-pituitary-adrenal axis function on week 8 (Table IV). No significant differences among treatment groups were observed in morning plasma cortisol change from baseline (Table IV). A small but statistically significant between-treatment difference was observed in urinary free cortisol levels at week 4 but not at week 8. A significant between-treatment difference in change in urinary 17-hydroxy steroid level from screening level was observed at weeks 4 and 8. In this case, changes from baseline were similar in patients treated with

placebo and patients administered higher (100 μ g twice daily and 500 μ g twice daily) doses of fluticasone propionate. No significant between-treatment differences were observed for 17-ketogenic steroid levels at weeks 4 and 8.

There were no significant differences among treatments in the increase in plasma cortisol after injection of synthetic corticotropin (Table IV). At visit 8, mean baseline plasma cortisol levels ranged from 15.59 μ g/dl in patients treated with fluticasone propionate at 100 μ g twice daily to 17.19 μ g/dl in patients treated with fluticasone propionate at 25 μ g twice daily. After corticotropin stimulation, mean plasma cortisol levels ranged from 27.98 μ g/dl in patients in the fluticasone propionate 100 μ g twice daily group to 30.31 μ g/dl in patients in the fluticasone propionate 25 μ g twice daily group.

Other laboratory and clinical tests. No between-group differences were observed for other laboratory evaluations, physical examinations, vital signs, or body weight. There were also no clinically significant changes in electrocardiograms.

DISCUSSION

Results of this 8-week, dose-ranging study indicate that fluticasone propionate aerosol is effective and well tolerated in patients with mild to moderate asthma. Fluticasone propionate was superior to placebo both on spirometric tests and on physicians' and patients' subjective assessments of efficacy. The patients treated with fluticasone propionate required less albuterol for relief of asthma than did the patients treated with placebo. Statistically significant differences in efficacy were not noted among the fluticasone propionate groups, but the dose of fluticasone propionate was often directly related to the degree of efficacy.

An additional measure of efficacy was the probability of completing the study. Patients treated with fluticasone propionate were significantly less likely than placebo-treated patients to meet criteria for clinical deterioration and were therefore more likely to complete the study. Probability of completing the study was directly related to dose, but the differences among fluticasone propionate groups did not achieve statistical significance. The fact that a similar pattern of results also occurred with spirometric and subjective efficacy variables reflects the suitability of probability of completion as an efficacy measure. The practice of removing patients with clinical deterioration, which both ensures patient safety and affords additional ways

of assessing efficacy, could be further explored in future asthma studies.

Nearly two thirds of placebo-treated patients compared with 23%, 13%, and 4% of patients treated with fluticasone propionate at 25 μ g twice daily, 100 μ g twice daily, and 500 μ g twice daily, respectively, discontinued the study because of clinical deterioration. Because a disproportionately high number of placebo-treated patients relative to fluticasone propionate-treated patients were removed from the study, results of PFTs with the remaining placebo-treated patients (who possibly had more stable lung functioning than placebo-treated patients who left the study) improved (Fig. 2). These findings demonstrate the appropriateness and utility of this study's emphasis on end point data, rather than efficacy data from the last week of drug treatment.

The lack of a strong, statistically significant relationship between dosage of fluticasone propionate and degree of efficacy was not unexpected. Similarly flat dose-response relationships have been observed with other inhaled corticosteroids,^{3, 10, 11} although increases in efficacy corresponding to increases in dose have been found in patients responding poorly to initial low doses¹² and in patients with severe asthma.¹³ In this study, the degree of efficacy was generally directly related to dose; however, the between-treatment differences were only rarely statistically significant (e.g., morning peak expiratory flow rate). The lack of a statistically significant relationship between degree of efficacy and dose could be attributable to a number of factors, including the severity of patients' asthma (mean FEV₁ of 72%), variability in inhaler technique and dose delivered, and the heterogeneity of patients with asthma. Studies to validate a useful clinical model for detecting dose-response relationships are ongoing.

All doses of fluticasone propionate aerosol were well tolerated. Fluticasone propionate aerosol administered for 8 weeks was shown in this study not to affect or to affect only minimally a number of hypothalamic-pituitary-adrenal axis measurements, including morning plasma cortisol concentrations, urinary free cortisol concentrations, 17-hydroxy steroid concentrations, 17-ketogenic steroid concentrations, and plasma cortisol response to synthetic corticotropin. These data provide a more comprehensive description of the hypothalamic-pituitary-adrenal axis effects of an inhaled corticosteroid than many other studies in which only plasma cortisol concentrations were

used as a measure.^{3, 13, 14} The findings of this study complement the results of studies in which plasma cortisol concentrations were shown to be unaffected by fluticasone propionate aerosol.⁶⁻⁸

Candidiasis and hoarseness were the most frequently reported adverse events attributed to fluticasone propionate. Both occurred at a frequency of only 1% in the groups treated with 25 µg and 100 µg fluticasone propionate twice daily and at frequencies of 7% (candidiasis) and 11% (hoarseness) in the fluticasone propionate 500 µg twice daily group. These results compare favorably with those obtained with other inhaled corticosteroids.¹⁵

Ultimately, the superiority of a new topical corticosteroid for the treatment of asthma is dependent on the demonstration of efficacy and minimal systemic toxicity. The clear demonstrations of efficacy in this placebo-controlled trial, combined with a low incidence of side effects and minimal effects on the hypothalamic-pituitary-adrenal axis, indicate that fluticasone propionate aerosol is a safe and effective inhaled corticosteroid for the treatment of mild to moderate asthma.

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