Fluticasone Propionate Aerosol: Efficacy in Patients with Mild to Moderate Asthma

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Background. This double-blind, randomized, parallel-group, placebo-controlled study investigated the efficacy and tolerability of fluticasone propionate aerosol (25, 50, or 100 μg bid for 12 weeks) administered as primary maintenance therapy to patients whose mild to moderate asthma was inadequately controlled by as-needed use of an inhaled beta-agonist.

Results. At all clinic visits, fluticasone propionate compared with placebo was associated with significant ($P<.05$) improvement in pulmonary function indexed by forced expiratory volume in 1 second (FEV_1) as well as fewer night awakenings and less use of rescue albuterol. Values for patient-measured morning peak expiratory flow rates (PEFR) were significantly ($P<.05$) higher and the use of rescue albuterol was significantly ($P<.05$) lower beginning 3 to 5 days after initiation of therapy in the groups treated with fluticasone propionate, compared with the placebo group. Maximal improvement in FEV_1 was achieved during the second week of treatment and maintained throughout the course of therapy. Differences among the three fluticasone propionate dosing groups for these efficacy measures were not statistically significant. The incidence of adverse events was similar across groups.

Conclusions. These data indicate that fluticasone propionate aerosol is an effective and well-tolerated treatment for asthma and significantly improves pulmonary function within days of initiation of treatment in patients whose asthma is inadequately controlled with as-needed beta-agonists.

Key words: Fluticasone propionate; asthma; inhaled corticosteroid; administration inhalation. (*J Fam Pract 1996; 42:369-375*)

The increasing recognition of the importance of inflammation in the pathophysiology of asthma has led to the widespread use of inhaled corticosteroid preparations, which control asthma by means of a topical mechanism of action.[1-4] Flucticasone propionate aerosol,† a corticosteroid preparation for asthma, is one of the most potent corticosteroids developed to date.[5] Administered by a metered-dose inhaler for up to 8 weeks to adults with mild to moderate asthma, fluticasone propionate (25, 100, or 500 μg bid) was significantly more effective than placebo at maintaining asthma control, as measured by pulmonary function test results and symptom scores.[6] Fluticasone propionate (750 μg bid or 100 μg bid) has also been shown to be effective, allowing for a reduction in prednisone dosage for patients with severe oral corticosteroid-dependent asthma.[7] Fluticasone propionate allowed up to 88% of patients to eliminate prednisone use, while pulmonary function as measured by FEV_1 and peak expiratory flow rates (PEFR) improved.

The study reported here was conducted to characterize the efficacy and tolerability of relatively low doses of fluticasone propionate (25, 50, or 100 μg bid) adminis-

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tered as maintenance therapy to adolescents and adults whose asthma was inadequately controlled with as-needed beta-agonists. This population of asthmatics who had not been previously treated with inhaled corticosteroids may be representative of the type of patient who presents to a family physician with a desire to better control asthmatic symptoms. The days to onset of therapeutic efficacy of fluticasone propionate were also examined post hoc using morning PEFR data and records of patients' night awakenings and albuterol use. This study employed predefined criteria for discontinuing patients experiencing worsening asthma. This practice was included in protocols to ensure patient safety but has also afforded a supplemental measure of efficacy.

Methods

Patients

Male and female patients aged 12 years or more were eligible if they gave written informed consent. Inclusion criteria were: a history of asthma requiring daily pharmacotherapy for at least 3 months immediately preceding the study, an unmedicated FEV_1 (forced expiratory volume in 1 second) between 45% and 75% of the value predicted for patient age, sex, and height, and ≥15% increase in FEV_1 within 15 minutes of inhaling albuterol. Women were included in the study if they were practicing acceptable contraception or were surgically sterile or postmenopausal. Pregnant or lactating women were excluded from the study. Other exclusion criteria: patients who had taken long-term oral steroids (daily or every other day use for more than 1 month) or within the past 2 years, or who had used an intranasal, injectable, oral, topical, or inhaled dose of corticosteroids or inhaled cromolyn sodium within 1 month prior to initiation of study. Patients with a history of life-threatening asthma were also excluded.

Procedure

The protocol for this double-blind, randomized, parallel-group study was approved by institutional review boards for the 18 study sites. During the 1-week, single-blind baseline (placebo) period, medical examinations including 12-lead electrocardiograms (ECGs) and standard clinical laboratory tests were performed, and medical histories were obtained. Patients were instructed on the use of peak flow meters and diary cards, on which they recorded (each day throughout the 12-week study) morning and evening PEFR measurements, night awakenings, asthma symptoms (wheeze, shortness of breath, cough), and use of inhaled albuterol. Asthma symptoms were rated on a 4-point scale: 0=none; 1=mild or transient symptoms; 2=moderate or frequent symptoms; 3=continuous symptoms that interfere with activities and sleep. The use of anticholinergic agents, antihistamines (other than terfenadine [Seldane]), beta-blockers, decongestants, digitalis, phenothiazines, polycyclic antidepressants, erythromycin, theophylline, salmeterol, and antitussives was not permitted during the study. Patients could take supplemental inhaled albuterol as needed during the baseline period and throughout the study, and its use was recorded.

After completion of the 1-week baseline period, patients returned to the clinic to begin the 12-week treatment period. To be eligible for treatment, patients had to demonstrate a need for additional asthma medication (besides inhaled albuterol) with either (1) an FEV_1 between 45% and 65% of predicted, or (2) an FEV_1 between 65% and 75% of predicted and at least one of the following events recorded on diary cards within the 7 preceding days; ≥1 day in which >8 puffs of albuterol were used; ≥20% previous evening-to-morning peak flow variability on ≥2 days; total weekly score of ≥7 on any asthma symptom (cough, wheeze, or shortness of breath); or ≥2 nights when the patient awakened due to asthma and used albuterol. Eligible patients were randomly assigned on day 0 to receive orally inhaled fluticasone propionate 25 μg bid (one 25-μg puff of fluticasone propionate and one placebo puff), fluticasone propionate 50 μg bid (one 50-μg puff of fluticasone propionate and one placebo puff), fluticasone propionate 100 μg bid (two 50-μg puffs of fluticasone propionate), or placebo bid (two placebo puffs) for 12 weeks (weeks 1 to 12). The study drug was administered by means of two identical-appearing standard metered-dose inhalers without a spacer. Other than the study drug, inhaled albuterol taken as needed for control of intolerable symptoms was the only asthma drug permitted during the treatment period.

Clinic visits occurred at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12. At each visit, diary cards were reviewed, and medical examinations were performed. Spirometric tests, performed before the morning dose of study drug, included FEV_1, forced expiratory flow 25%–75% of predicted ($FEF_{25\%-75\%}$), and forced vital capacity (FVC). The occurrence of adverse events was recorded at each visit by the clinician, who asked patients if they were having any medical problems. Patients were questioned at each clinic visit by the investigator about compliance with study procedures and use of study medications. Clinical laboratory tests were repeated on weeks 6 and 12, and 12-lead ECGs were obtained on week 12.

To continue the trial, patients needed to satisfy the following asthma stability continuation criteria for the 7 days preceding each clinic visit: (1) no more than 2 days in

which >12 puffs of albuterol were used; (2) no more than 2 nights with awakenings due to asthma requiring albuterol treatment; (3) no more than 2 days when either the morning or the evening PEFR fell ≥20% from mean baseline PEFR; (4) no more than 3 days with a ≥20% variation between the morning PEFR and the previous evening PEFR; and (5) an FEV_1 at least 85% of the best FEV_1 obtained on the first day of study drug treatment. Patients who failed to meet any of these criteria or who experienced a clinical asthma exacerbation were discontinued from the study. The following evaluations were performed on patients discontinuing the study for any reason: pulmonary function tests, vital signs, physical examination, adverse event assessment, and clinical laboratory tests. The last visit during which these evaluations were performed was defined as the study endpoint.

Statistical Methods

Efficacy measures included spirometric results (FEV_1), patient-rated asthma symptoms, number of night awakenings, patient-determined morning and evening PEF, use of inhaled albuterol, and duration of participation in the study. For most efficacy variables, analyses were conducted on endpoint data, as well as data from individual days and/or visits. Endpoint analysis was used because it includes data from the greatest number of patients, since many patients were withdrawn due to lack of efficacy. F tests based on both baseline and change-from-baseline values were performed on FEV_1 and morning and evening PEFR measurements. Also, overall treatment differences were tested using a repeated-measures ANOVA. Change-from-baseline values for patient-rated diary symptom scores, including night awakenings, were tested using the nonparametric van Elteren test. The van Elteren test is a generalization of the Wilcoxon rank sum test that can control for site-to-site differences. A logrank test on Kaplan-Meier estimates of duration of participation was performed. P values ≤.05 were considered statistically significant. A minimum of 75 patients per treatment group provided at least 80% power of detecting a difference in FEV_1 of 0.25 L between any two treatment groups using a two-sided t test with a significance level of .05.

Analysis of the 12-week efficacy data revealed no statistically significant differences among the fluticasone propionate groups. Therefore, data for these three groups were combined for the post hoc statistical analyses of patient-derived daily data (morning and evening PEF, night awakenings, and albuterol use) with respect to the time to onset of therapeutic efficacy of fluticasone propionate.

The primary safety measure was the occurrence of adverse events. The Fisher's exact test was performed on pairs of treatments to detect differences in the number of patients with adverse events. The number of patients with clinically significant changes, as defined by the investigator, in laboratory test values, vital signs, and 12-lead ECGs was tabulated.

Results

Patient Characteristics

Three hundred seven patients were enrolled. Demographic characteristics and pretreatment baseline FEV_1 values (approximately 63% of predicted for each of the groups) were similar among groups (Table 1). All patients receiving a study drug (n=307) were included in the safety analyses. Data from 13 patients were dropped from the efficacy analyses due to factors such as protocol violations and failure to meet entrance criteria; therefore, 294 patients were included in the efficacy population.

Patients in each of the three groups treated with fluticasone propionate were significantly ($P<.05$) less likely to discontinue the study due to worsening asthma than were patients treated with placebo (Figure 1). Differences among the three fluticasone propionate dosing groups were not statistically significant. By the end of the 12-week treatment period, 53% of placebo-treated patients, compared with 37%, 25%, and 33% of patients in the fluticasone propionate 25, 50, and 100 μg bid groups, respectively, had discontinued the study because they failed to meet the predetermined criteria for asthma stability.

Efficacy Data

Spirometry Values

Mean values for FEV_1 did not differ among the groups at baseline. Each of the fluticasone propionate groups compared with the placebo group had greater improvement in FEV_1 at endpoint (0.40 L to 0.51 L in the fluticasone propionate groups compared with 0.14 L in the placebo group; $P<.02$ for each fluticasone propionate group vs placebo; Table 2) and on weeks 1, 2, 3, 4, 6, 8, and 10 ($P<.05$ for each fluticasone propionate group vs placebo with the exception of fluticasone propionate 25 μg bid vs placebo on week 4). Nearly maximal improvement in pulmonary function in the fluticasone propionate groups was achieved by the end of the second week of treatment and was maintained throughout the 12-week treatment period (Figure 2). The percentage of patients who achieved normal lung function (>85% of predicted) at

Table 1. Characteristics of 307 Patients with Asthma Enrolled in Fluticasone Propionate Aerosol vs Placebo Study

Characteristic	Treatment Regimens			
	Placebo	FP 25 μg bid	FP 50 μg bid	FP 100 μg bid
Number enrolled	73	76	79	79
Number (%) completed	29 (40)	47 (62)	48 (61)	52 (66)
Number (%) withdrawn	44 (60)	29 (38)	31 (39)	27 (34)
Reasons for withdrawal*				
Adverse events	0 (0)	0 (0)	2 (3)	3 (4)
Failure to meet stability criteria	39 (53)	28 (37)	20 (25)	26 (33)
Other†	7 (10)	2 (3)	11 (14)	1 (1)
Mean age, y (range)	30 (13–54)	30 (12–69)	30 (12–63)	28 (12–72)
Sex, n (%)				
male	42 (58)	44 (58)	50 (63)	49 (62)
female	31 (42)	32 (42)	29 (37)	30 (38)
Race/ethnic origin, n (%)				
White	57 (78)	67 (88)	69 (87)	68 (86)
Black	9 (12)	6 (8)	4 (5)	8 (10)
Hispanic	6 (8)	3 (4)	3 (4)	2 (3)
Other	1 (1)	0 (0)	3 (4)	1 (1)
Screening FEV_1, L (SE)	2.36 (0.06)	2.43 (0.06)	2.38 (0.07)	2.45 (0.06)
Screening % predicted FEV_1	62	64	62	63

**Patients may have multiple reasons for withdrawal.*
†"Other" includes noncompliance, protocol violation, and failure to meet entrance criteria.
FP denotes fluticasone propionate; bid, twice daily; FEV_1, forced expiratory volume in 1 second; SE, standard error.

endpoint was 10% in the placebo group compared with 23%, 27%, and 28% in the fluticasone propionate 25-, 50-, and 100-μg bid groups, respectively.

Mean values for patient-recorded morning PEFR did not differ among the groups at baseline. Greater mean improvement was observed for morning PEFR in the fluticasone propionate groups (27 L/minute to 45 L/minute) than in the placebo group (12 L/minute) at endpoint ($P<.05$ fluticasone propionate 50 or 100 μg bid vs placebo; Table 2) and on weeks 2, 3, 4, and 5 ($P<.05$ for each fluticasone propionate group vs placebo).

Symptom Scores

Mean patient-rated individual symptom scores did not differ among the four groups at baseline. Change-from-baseline scores for wheeze, but not cough or shortness of breath, were significantly ($P<.05$) improved in the fluticasone propionate 100-μg bid group compared with the placebo group at endpoint (Table 2) and on weeks 2, 3, 4, 5, and 6; in the fluticasone propionate 25-μg bid group compared with the placebo group on weeks 2, 3, 4, 5, and 6; and in the fluticasone propionate 50-μg bid group compared with the placebo group on week 2. Statistically significant differences between groups for reductions in cough and shortness of breath were not observed.

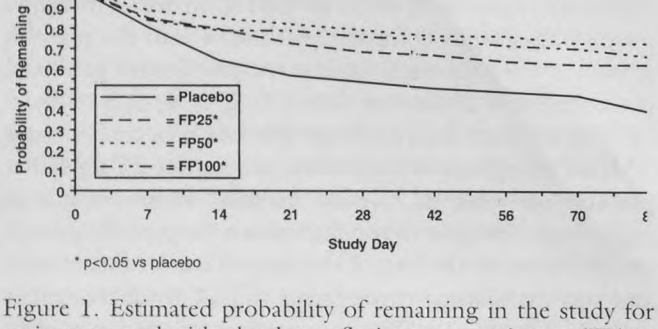

Figure 1. Estimated probability of remaining in the study for patients treated with placebo or fluticasone propionate (FP) in doses of 25 μg, 50 μg, or 100 μg twice daily.

Significantly greater mean reductions in the number of night awakenings were observed in each of the fluticasone propionate groups compared with the placebo group at endpoint ($P<.05$ for each fluticasone propionate group vs placebo; Table 2) and on weeks 1 and 2. Fluticasone propionate 100 μg bid was also significantly ($P<.05$) better than placebo at weeks 3, 5, 6, 7, and 11.

Albuterol Use

Mean albuterol use at baseline was comparable across treatment groups: patients used an average of 3.99 to 4.73 puffs per day. After treatment with fluticasone propionate, there was a significant reduction in albuterol use in the fluticasone propionate groups (1.58 puffs/d to 1.85 puffs/d) compared with placebo (0.28 puffs/d) at endpoint (Table 2).

Onset of Effect

Post hoc analyses revealed that compared with the placebo group, the combined fluticasone propionate groups had higher values for morning PEF on many of the first 14 days of treatment ($P<.05$ among groups on days 3, 5, 6,

Table 2. Mean Change (SE) in Efficacy Variables from Baseline at Endpoint for Patients with Asthma

Variable	Treatment Regimen			
	Placebo	FP 25 μg bid	FP 50 μg bid	FP 100 μg bid
FEV_1 morning predose (L)*	.14 (.06)	.40 (.07)	.51 (.06)	.42 (.07)
Morning PEFR (L/min)†	12 (5)	31 (6)	27 (6)	45 (6)
Evening PEFR (L/min)†	8 (5)	22 (5)	21 (4)	35 (6)
Night awakenings*	.00 (.04)	−.10 (.04)	−.14 (.04)	−.22 (.03)
Wheeze‡	−.19 (.06)	−.29 (.07)	−.37 (.07)	−.56 (.06)
Cough	−.20 (.07)	−.19 (.07)	−.17 (.08)	−.27 (.07)
Shortness of breath	−.20 (.06)	−.34 (.07)	−.36 (.07)	−.39 (.07)
Albuterol use (puffs/day)*	−.28 (.29)	−1.58 (.42)	−1.81 (.34)	−1.85 (.31)

*P<.05 each fluticasone propionate group vs placebo.
†P<.05 fluticasone propionate 50 μg bid and fluticasone propionate 100 μg bid vs placebo.
‡P<.05 fluticasone propionate 100 μg bid vs placebo.
SE denotes standard error; FP, fluticasone propionate; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; bid, twice daily.

7, 9, 11, 12, 13, and 14; Figure 3). In addition, on the majority of the first 14 days of treatment, all patients treated with fluticasone propionate had fewer night awakenings due to asthma ($P<.05$ among groups on days 2, 3, 8, 9, 10, 11, 12 and 13) and used less albuterol ($P<.05$ among groups on days 3, 4, 6, 7, 8, 9, 10, 11, 13, and 14), compared with patients on placebo.

Safety Data

The incidence of physician-assessed potentially drug-related adverse events ranged from 5% in the placebo group to 19% in the group treated with fluticasone propionate 100 μg bid ($P<.05$ placebo vs both fluticasone propionate 50 μg bid and 100 μg bid). The most frequently reported potentially drug-related adverse events were dysphonia (0% incidence in the placebo group; 3% to 6% in the fluticasone propionate groups), cough (3%; 1% to 4%, respectively), and pharyngitis (0%; 1% to 3%, respectively). The frequency of oropharyngeal candidiasis was consistently low: 1% in the placebo group, 0% in the fluticasone propionate 25-μg bid group, 3% in the fluticasone propionate 50-μg bid group, and 5% in the fluticasone propionate 100-μg bid group. There was only one serious adverse event (asthma exacerbation), which occurred on the first day of treatment. No unusual or unexpected drug-related adverse events were reported.

There were no differences among groups in the incidence of clinically significant changes in clinical laboratory test values, vital signs, or 12-lead ECGs.

Discussion

These results show that fluticasone propionate aerosol (25, 50, and 100 μg bid) is effective and well tolerated in patients whose mild to moderate asthma is not adequately controlled with as-needed beta-agonists. Lung function measured by spirometry improved in the fluticasone propionate groups compared with that in the placebo group. Furthermore, fluticasone propionate–treated patients were less likely than placebo-treated patients to be withdrawn from the study because of worsening asthma. Compared with the placebo group, the fluticasone propi-

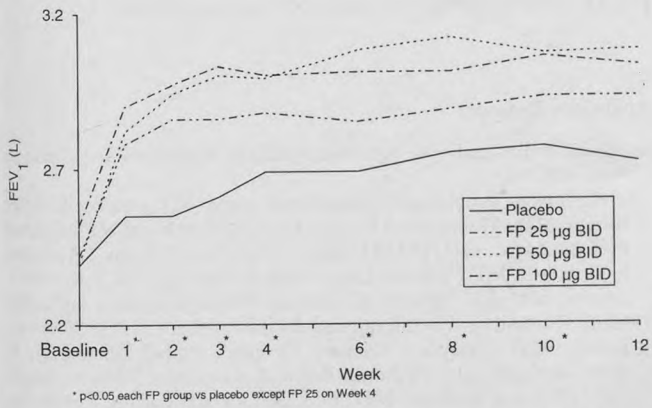

Figure 2. Mean forced expiratory volume in 1 second (FEV_1) values during 12 weeks of treatment with placebo or fluticasone propionate (FP) in doses of 25 μg, 50 μg, or 100 μg twice daily.

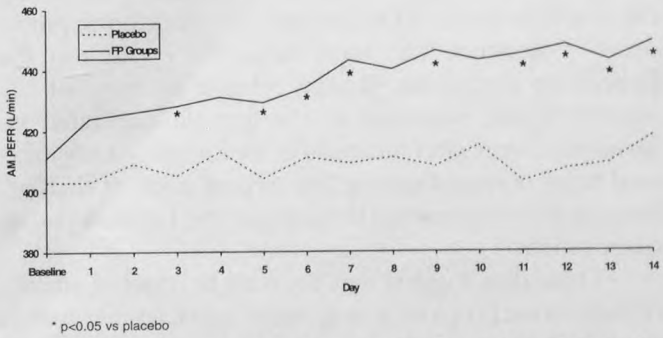

Figure 3. Mean morning peak expiratory flow values during the first 14 days of treatment with placebo or fluticasone propionate (FP) in doses of 25 μg, 50 μg, or 100 μg twice daily.

onate groups also had fewer night awakenings due to asthma and used less albuterol for asthma symptoms.

In this study, there were no consistently statistically significant efficacy differences between doses of fluticasone propionate. Relatively flat relationships between dose and degree of efficacy have also been observed with other inhaled corticosteroids[8,9] and previously with fluticasone propionate in a study employing a wider range of doses of fluticasone propionate (25, 100, and 500 μg bid).[6] In that study, fluticasone propionate 500 μg bid given to patients previously maintained on beclomethasone dipropionate aerosol (8 to 16 actuations per day) was generally associated with better asthma control than lower doses, but differences among dosing groups were only sometimes statistically significant. Although the doses employed in the present study of asthmatics who had not been previously treated with inhaled corticosteroids were considerably lower than 500 μg bid, substantial levels of improvement in pulmonary function (15%) and asthma symptoms were maintained throughout the treatment period in patients receiving fluticasone propionate 25, 50, or 100 μg bid. Whether higher doses of fluticasone propionate are associated with better asthma control in patients with mild to moderate asthma is a subject of continuing study. Between 23% and 28% of patients in this study achieved normal lung function during treatment with fluticasone propionate.

In this study, fluticasone propionate aerosol produced significant improvement in asthma signs and symptoms within days of initiation of therapy. Mean values for morning PEFR were significantly higher in the groups treated with fluticasone propionate compared with placebo beginning on the third day of treatment. Improvements in PEFR compared with placebo at weeks 2 to 5 and at endpoint but not at other times throughout the study is not an unexpected finding, given that the use of stability criteria resulted in a larger percentage of patient withdrawals from the placebo group by the middle of the study. Similarly, significant reductions in wheeze, number of night awakenings, and albuterol use occurred during the first 3 to 5 days of treatment with fluticasone propionate. Consistent with these data, FEV_1 values in the fluticasone propionate groups, relative to those of the placebo group, improved by the first clinician-rated assessment 1 week after initiation of treatment. Nearly maximal relief occurred during the second week of therapy, and relief was maintained throughout the 12-week course of treatment.

These data suggest that the time to onset of efficacy of fluticasone propionate may occur much sooner than is suggested by some characterizations of inhaled corticosteroids, which describe these drugs as taking weeks or months to become effective.[3] The data presented here reflect the rapid onset of efficacy of fluticasone propionate. However, the time to onset of efficacy of fluticasone propionate cannot be compared with that of other inhaled corticosteroids. The time to onset of symptom relief after administration of inhaled corticosteroids other than fluticasone propionate has not been systematically evaluated in controlled clinical studies. In addition, there are no published studies in the medical literature comparing fluticasone propionate aerosol with other inhaled corticosteroid aerosols in patients who had not previously been treated with inhaled corticosteroids. Therefore, the degree to which the results of this study are representative of inhaled corticosteroids as a class remains to be determined.

Like the efficacy data, the tolerability data are consistent with findings of other studies. Few, and only minor adverse events occurred after administration of fluticasone propionate. The most frequently reported adverse events attributed to fluticasone propionate were dysphonia and cough, neither of which led to termination of the study drug in any patient. The frequency of oropharyngeal candidiasis was consistently low.

The effects of fluticasone propionate on adrenal function were not monitored in this study, because of the low dosages of fluticasone propionate employed. The results of another study demonstrate that the doses of fluticasone propionate used in this study had no clinically significant effect on hypothalamic-pituitary-adrenal axis functioning, as measured by plasma cortisol, synthetic ACTH stimulation, and 24-hour urinary free cortisol.[6] Considered together, these data demonstrate that fluticasone propionate is well tolerated.

The high degree of efficacy and tolerability of inhaled corticosteroids has led clinicians to recommend them for the control of inflammation that underlies mild, moderate, and severe asthma.[3,10,11] This study demonstrates that fluticasone propionate is an effective agent for patients poorly controlled on as-needed beta-agonists.

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