

Fluticasone propionate powder administered through Diskhaler versus triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma

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Background: Attempts to delineate efficacy and safety differences among inhaled corticosteroids have been difficult because of the lack of well-controlled, comparative studies reported in the medical literature.

Methods: A randomized, double-blind, double-dummy study was conducted in 24 outpatient centers. A total of 291 male and female patients at least 12 years of age with asthma (FEV₁ between 50% and 80% of predicted value), who had previously received maintenance therapy with beclomethasone dipropionate or triamcinolone acetonide, were switched to treatment with fluticasone propionate powder (250 µg twice daily), triamcinolone acetonide aerosol (200 µg four times daily), or placebo for 24 weeks.

Results: Mean increase in FEV₁ from baseline to end point was significantly ($p = 0.009$) greater in patients switched to treatment with fluticasone compared with patients switched to treatment with triamcinolone (0.27 L and 0.07 L, respectively). At end point, mean increase in morning peak expiratory flow from baseline was 21 L/min with fluticasone compared with mean decreases of 6 L/min and 28 L/min with triamcinolone and placebo, respectively ($p < 0.001$ vs triamcinolone and placebo). Supplemental rescue albuterol use decreased by 30% from baseline with fluticasone ($p < 0.05$ vs triamcinolone and placebo) compared with triamcinolone (6%) or placebo (increased by 50%). The percentage of patients withdrawn from the study because they met predefined lack-of-efficacy criteria was higher with placebo (60%) and triamcinolone (27%) than with fluticasone (17%). Incidence

of adverse events and low morning plasma cortisol concentrations were similar across treatment groups except for oral candidiasis ($p = 0.035$, fluticasone vs placebo).

Conclusion: Fluticasone propionate powder twice daily (500 µg/day) was superior in efficacy to triamcinolone acetonide aerosol four times daily (800 µg/day) in patients with persistent asthma. (J Allergy Clin Immunol 1997;100:467-74.)

Key words: Inhaled corticosteroid, asthma, fluticasone propionate, triamcinolone acetonide, randomized controlled trial

Asthma, a chronic inflammatory disorder of the airways characterized by airway hyperresponsiveness and acute airflow limitation, is currently diagnosed in approximately 12 million persons in the United States.^{1,2} There is significant morbidity and mortality associated with asthma. Approximately 5000 deaths are attributed to asthma each year,³ and the costs of asthma exceeded 6.2 billion dollars in 1990.⁴ Results from epidemiologic studies suggest that asthma is underdiagnosed and undertreated in both adults and children.⁵ Pharmacologic therapy for the treatment of asthma includes the use of bronchodilators to relax bronchial smooth muscle and antiinflammatory medications to treat the underlying pathology of the disease. In the past, guidelines for the treatment of asthma have suggested that inhaled corticosteroids may be more appropriately used in patients with moderate to severe asthma.⁶ More recently, the Global Initiative for Asthma guidelines have suggested that "any asthma more severe than mild, intermittent asthma . . . (FEV₁ $\geq$ 80% predicted, intermittent symptoms less than one time per week, nighttime symptoms less than two times per month) . . . is more effectively controlled by treatment to suppress and reverse the inflammation than by treatment only of acute bronchoconstriction and related symptoms."⁷ These guidelines consider inhaled corticosteroids to be the most effective antiinflammatory medications available.⁷

Inhaled corticosteroids that are most frequently used for the treatment of asthma in the United States include beclomethasone dipropionate, triamcinolone acetonide (TAA), flunisolide, and most recently, fluticasone pro-

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Abbreviations used

FP:	Fluticasone propionate
PEF:	Peak expiratory flow
TAA:	Triamcinolone acetonide

pionate (FP). FP is a synthetic, trifluorinated, androstane derivative with high glucocorticoid receptor affinity, rapid receptor association, and slow receptor dissociation, which results in a long corticosteroid-receptor complex half-life.⁸ When swallowed, FP is metabolized to an inactive metabolite, which explains its negligible oral systemic bioavailability.⁹ All of the above-mentioned inhaled corticosteroids have been shown to be effective in the treatment of asthma by lessening the requirements for oral steroids, lowering airway reactivity, reducing the frequency of acute episodes of asthma, and reducing the need for concurrent medications.¹⁰⁻²⁰

However, attempts to delineate differences among these corticosteroids in terms of comparative efficacy and safety profiles have been difficult because of the lack of well-controlled, comparative studies reported in the medical literature. Although most clinicians agree on the characteristics of an ideal inhaled corticosteroid (high topical antiinflammatory effect and low systemic bioavailability), there is much ambivalence regarding the most appropriate clinical model to use in the comparison of relative potencies of inhaled corticosteroids.^{21, 22} Relative potencies have been evaluated on a microgram per microgram basis and by means of topical to systemic potency ratios (through animal models),²³ cutaneous vasoconstriction tests,²⁴ changes in peripheral blood eosinophils and urinary cortisol excretion,²⁵ and dose equivalencies to a reference standard (i.e., oral prednisone).^{26, 27} However, none of these models have been widely accepted as accurate comparative measures of the efficacy and safety of inhaled corticosteroids in the treatment of asthma in human beings.

By means of a double-blind, double-dummy, placebo-controlled clinical model in patients with asthma who had previously been treated with beclomethasone dipropionate or TAA, this study compared the efficacy and safety of FP with that of TAA by using recommended, labeled dosing regimens for the aerosol formulations of both drugs. This study was conducted to complement the results of a similarly designed 24-week clinical trial.²⁸

METHODS**Patient selection**

Patients were nonsmokers, at least 12 years of age, who had asthma (defined in accordance with American Thoracic Society criteria²⁹) and who had required maintenance inhaled corticosteroid therapy for at least 4 weeks preceding the study. All patients had an FEV₁ of 50% to 80% of predicted normal values for age, sex, and height.^{30, 31} Reversibility of airway obstruction was demonstrated by an increase of 15% or greater within 15 minutes after administration of 2 to 4 puffs of

TABLE I. Patient demographics, characteristics, and disposition*

	Placebo	TAA (200 µg QID)	FP (250 µg BID)
No. enrolled	95	101	95
No. (%) completed	26 (27)	56 (55)	63 (66)
No. (%) withdrawn†	69 (73)	45 (45)	32 (34)
Lack of efficacy	57 (60)	27 (27)	16 (17)
Adverse event	8 (8)	5 (5)	4 (4)
Other‡	10 (11)	14 (14)	15 (16)
Mean age in years (range)	37 (12-70)	37 (12-70)	34 (12-74)
Sex, no. (%)			
Male	49 (52)	42 (42)	51 (54)
Female	46 (48)	59 (58)	44 (46)
Ethnic origin, no. (%)			
White	88 (93)	90 (89)	86 (91)
Black	5 (5)	5 (5)	5 (5)
Other	2 (2)	6 (6)	4 (4)
Mean screening % predicted FEV ₁	66	67	68
Screening medication, no. (%)			
BDP	37 (39)	46 (46)	41 (43)
TAA	58 (61)	55 (54)	54 (57)

BDP, Beclomethasone dipropionate; BID, twice daily; QID, four times daily.

*Based on intent-to-treat population.

†Multiple reasons for withdrawal possible.

‡Includes protocol violations and patients who failed to return.

albuterol. Patients had to have at least one documented urgent or emergent care visit or home treatment for asthma within the 12 months before screening.

Patients were excluded for any of the following reasons: pregnancy or lactation; use of methotrexate or gold salts for control of asthma; use of inhaled cromolyn or inhaled nedocromil; use of oral, intranasal, or injectable corticosteroids within 4 weeks of the start of the study; significant concomitant illness; immunotherapy requiring a change in dosage regimen within 12 weeks; or concurrent use of any other prescription or over-the-counter medication that might affect the course of asthma or interact with sympathomimetic amines.

Study design

A double-blind, double-dummy, randomized, placebo-controlled, parallel-group study was conducted at 24 clinical centers throughout the United States. All patients gave written informed consent, and the protocol was approved by an institutional review board for each clinical center.

During screening, patients continued their usual inhaled corticosteroid dosage regimens (open-label beclomethasone dipropionate or TAA aerosols, 8 to 12 actuations daily). In addition, they received placebo FP powder through the Diskhaler twice daily. Previous bronchodilator therapy was replaced with albuterol aerosol, to be used only as needed for relief of acute symptoms; and if already part of their current therapeutic regimen, theophylline was continued at a fixed dosage. At the end of screening, eligible patients were required to meet the following criteria on the basis of the 7-day period immediately preceding the day of random assignment to study group: asthma stability defined as no more than 3 days' use of

TABLE II. Mean change from baseline (SEM) to end point for efficacy variables

Variable	Placebo	TAA (200 µg QID)	FP (250 µg BID)
Morning FEV ₁ (L)			
Baseline	2.25 (0.06)	2.27 (0.06)	2.37 (0.06)
Change	-0.18 (0.06)	0.07 (0.05)*	0.27 (0.05)*†
Morning PEF (L/min)			
Baseline	406 (8)	404 (9)	420 (9)
Change	-28 (4)	-6 (4)*	21 (4)*†
Albuterol use (puffs/day)			
Baseline	3.2 (0.3)	3.3 (0.7)	3.0 (0.3)
Change	1.6 (0.3)	-0.2 (0.7)*	-0.9 (0.3)*†
Rescue-free days (%)			
Baseline	32 (4)	34 (4)	34 (4)
Change	-11 (4)	1 (3)*	14 (4)*†
Night awakenings			
Baseline	0.08 (0.02)	0.10 (0.02)	0.09 (0.02)
Change	0.27 (0.05)	-0.01 (0.03)*	-0.03 (0.03)*
Overall symptom score			
Baseline	1.7 (0.1)	1.8 (0.1)	1.7 (0.1)
Change	0.7 (0.2)	-0.1 (0.1)*	-0.3 (0.1)*
Symptom-free days (%)			
Baseline	25 (3)	23 (3)	33 (4)
Change	-5 (3)	12 (3)*	14 (5)*

BID, Twice daily; QID, four times daily; SEM, standard error of the mean.

* $p < 0.05$ versus placebo.

† $p < 0.05$, FP versus TAA.

more than 12 puffs/day of as-needed albuterol, 4 or fewer mornings when peak expiratory flow (PEF) decreased more than 20% from the previous evening's PEF, and 3 or fewer nights with awakenings caused by asthma requiring inhaled albuterol; FEV₁ between 50% and 80% of predicted values and within $\pm 15\%$ of the screening FEV₁. These criteria were used to ensure that patients' conditions were stable with use of their current medication. In addition, all patients demonstrated adequate compliance (use of $\geq 75\%$ of the placebo powder blisters during screening, ability to withhold antiasthma medications for the required period before visiting the clinic, and completion of diary cards).

Patients who met all entry criteria discontinued their beclomethasone dipropionate or TAA and were randomly assigned to receive one of the following inhaled treatments for 24 weeks: FP through Diskhaler (250 µg twice daily) and placebo through Azmacort Oral Inhaler (2 puffs four times daily), TAA through Azmacort Oral Inhaler (200 µg* [2 puffs] four times daily) and placebo FP through Diskhaler twice daily, or placebo FP through Diskhaler twice daily and placebo through Azmacort Oral Inhaler (2 puffs four times daily). FP was contained in blisters on a Rotadisk (Glaxo Wellcome) and administered through the Diskhaler, a breath-actuated inhalation device. TAA was delivered as an aerosol suspension through Azmacort Oral Inhaler, a metered-dose inhaler with an attached spacer device (Rhone-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, Pa.). The placebo oral inhalers were assembled with identical components to maintain double-blind, double-dummy study conditions. Albuterol aerosol as needed and theophylline (if part of an established fixed dosage regimen) were permitted during the study; however, albuterol had to be withheld for approximately 6 hours and theophylline for 24 to 36 hours before clinic visits.

Patients returned to the clinic on a weekly basis for the first 2 weeks, every 2 weeks for 1 month, and then every 3 weeks for a total of 24 weeks of double-blind treatment. At each clinic visit, diary card information was assessed, and pulmonary function tests were performed to determine whether patients met predetermined asthma instability criteria. Patients were withdrawn from the study because of lack of treatment efficacy if they met any of the following criteria, indicating worsening or unstable asthma: a clinical exacerbation requiring emergency treatment, hospitalization, or asthma medication not allowed by protocol; a 20% decrease from the predose FEV₁ at the randomization visit; a 20% decrease from the mean morning baseline PEF on more than 3 of 7 days immediately preceding a visit; use of more than 12 albuterol puffs per day on more than 3 of 7 days immediately preceding a visit; or more than three nighttime awakenings caused by asthma symptoms that required albuterol aerosol during the week immediately preceding a visit.

Efficacy measures included morning predose FEV₁, probability of remaining in the study over time (i.e., not being withdrawn because of lack of efficacy), patient-measured morning PEF, albuterol aerosol use, number of nighttime awakenings requiring inhaled albuterol, and asthma symptom scores (0 = none, 1 = mild or transient symptoms, 2 = moderate or frequent symptoms, and 3 = continuous symptoms) for wheeze, shortness of breath, and cough.

Safety was assessed by monitoring adverse events and morning plasma cortisol concentrations. Investigators determined whether an adverse event was potentially drug-related (possibly, probably, or almost certainly related to study drug).

Statistical analyses

Analyses were based on data from the intent-to-treat population, comprising all patients exposed to study drug. Statistical testing was performed on end-point data, defined as the final

*Each actuation releases approximately 200 µg of TAA, of which approximately 100 µg is delivered from the unit.

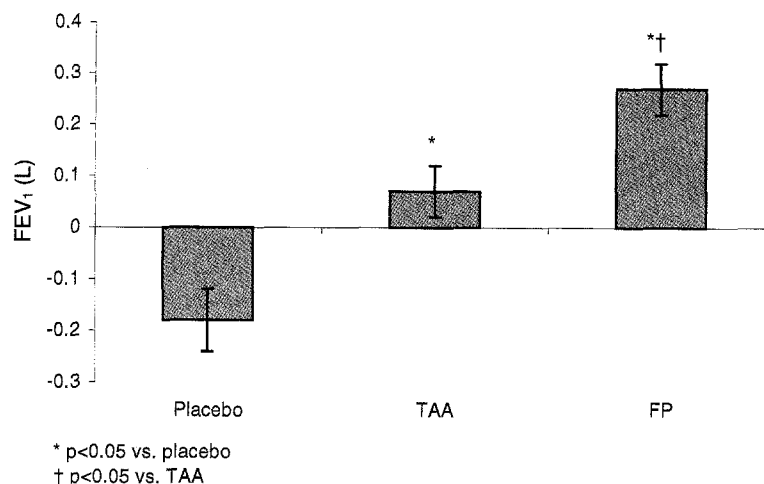


FIG. 1. Mean change from baseline in morning predose FEV₁ at end point (* $p < 0.05$ vs placebo, † $p < 0.05$ FP vs TAA). *BID*, Twice daily; *QID*, four times daily. End-point analysis = final estimable measurement for all patients including those who failed to complete the entire study.

estimable measurement for the patient, regardless of whether the patient completed the study. By-visit analyses were performed only on data from patients remaining in the study at that specific visit.

All statistical tests were two-sided, and treatment differences below the 0.05 level were considered statistically significant. Enrollment of 100 patients per treatment group was estimated to provide a power of 80% in detecting a difference in morning FEV₁ of 0.25 L between treatment groups, assuming a standard deviation of 0.55 L. Assessments of morning predose FEV₁ were tested for treatment differences by using an analysis of covariance F-test. The probability of remaining in the study over time on the basis of asthma instability criteria was plotted by using Kaplan-Meier estimates of survival.³² Log-rank tests of homogeneity were used to compare the resulting survival curves. Analysis of PEF, symptom scores, albuterol use, nighttime awakenings, symptom-free days, and rescue medication-free days were based on 7-day averages within subjects, which were then averaged over treatment groups; and the comparisons of changes from baseline (pretreatment) values between treatment groups were made on the basis of an analysis of covariance with baseline value as covariate. The incidence of adverse events was tabulated by treatment group and analyzed for treatment differences by using Fisher's exact test.

RESULTS

Three hundred seventy-eight patients were screened for participation. A total of 291 patients met the inclusion criteria and were randomly assigned to treatment. Randomization resulted in comparable treatment groups at baseline with respect to patient demographics, pulmonary function, and number of patients receiving either beclomethasone dipropionate or TAA during screening (Table I). Patient demographics, characteristics, and disposition are shown in Table I. The main reason for not completing the study was lack of efficacy according to predefined withdrawal criteria.

Pulmonary function

Table II presents the mean change from baseline to end point for various efficacy measures. At end point, patients in both FP and TAA groups experienced statistically significantly greater improvements in FEV₁ compared with patients in the placebo group ($p \leq 0.001$, Table II). In addition, patients switched to FP experienced significantly ($p < 0.05$) greater improvements in FEV₁ compared with patients treated with TAA by week 4 of treatment and throughout the study (except for week 18), as well as at end point ($p = 0.009$). Patients in the FP and TAA treatment groups had mean increases from baseline to end-point FEV₁ of 0.27 L and 0.07 L, respectively, which represent 11% and 3% improvements from baseline, respectively. In contrast, patients in the placebo group had a mean decrease in FEV₁ of 0.18 L (-8%). Mean changes from baseline in FEV₁ at each visit and at end point are shown in Fig. 1.

Statistically significant ($p < 0.05$) differences in mean change from baseline PEF between the TAA and FP treatment groups were observed by week 1 and maintained throughout the study. Fig. 2 shows the mean change from baseline in morning PEF over the 24-week treatment period. At end point, the mean increase in morning PEF over baseline values in patients who switched to FP was 21 L/min compared with mean decreases of 6 L/min and 28 L/min in the TAA and placebo groups, respectively ($p < 0.001$, FP and TAA vs placebo; Table II).

Probability of remaining in the study

Only 27% of patients in the placebo group remained in the study for the entire 24 weeks compared with 66% and 55% of patients in the FP and TAA groups, respectively. The percentage of patients withdrawn from

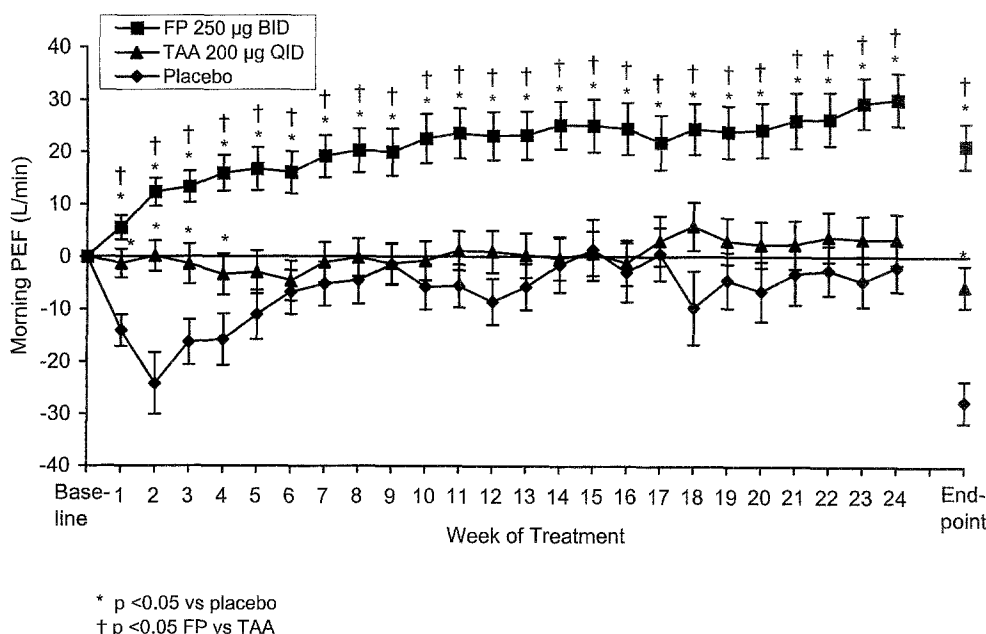


FIG. 2. Mean change from baseline in morning predose PEF (* $p < 0.05$ vs placebo, † $p < 0.05$ FP vs TAA). BID, Twice daily; QID, four times daily. End-point analysis = final estimable measurement for all patients including those who failed to complete the entire study.

the study because they met predefined lack-of-efficacy criteria was much higher in the placebo (60%) and TAA (27%) treatment groups than in the FP treatment group (17%) (Table I). Survival analysis revealed that patients in the FP and TAA treatment groups had a significantly greater probability of remaining in the study over time than patients in the placebo group ($p < 0.001$, Fig. 3). Differences between patients treated with FP and those treated with TAA were not statistically significant ($p = 0.06$).

Albuterol use, nighttime awakenings, and asthma symptoms

Patients treated with FP and TAA had reduced albuterol use by 30% (0.9 puffs/day) and 6% (0.2 puffs/day) at end point, respectively, whereas patients treated with placebo had increased their albuterol use by 50% (1.6 puffs/day, $p < 0.05$, FP vs placebo and TAA; Table II). The percentage of days requiring no backup albuterol use was significantly higher ($p \leq 0.006$) at end point in patients treated with FP compared with patients treated with either placebo or TAA. At end point, the number of nighttime awakenings requiring inhaled albuterol significantly decreased ($p \leq 0.001$ vs placebo) with FP or TAA, whereas nighttime awakenings increased after treatment with placebo (Table II). The two active treatment groups were not significantly different from each other with respect to nighttime awakenings. Overall daily asthma symptom scores increased from baseline to end point in the placebo group but decreased in both FP and TAA treatment groups ($p < 0.001$ vs placebo; Table II). The percentage of symptom-free days also significantly increased from baseline to end point after treat-

ment with both FP and TAA ($p \leq 0.001$) compared with a decrease in symptom-free days after treatment with placebo. There were no significant differences between FP and TAA with respect to symptom scores or symptom-free days.

Safety

FP and TAA were well tolerated throughout the 24 weeks of treatment. No serious drug-related adverse events occurred. Twelve patients (13%) in the placebo group, 14 patients (15%) in the FP group, and eight patients (8%) in the TAA group ($p = 0.174$ vs FP) experienced at least one adverse event that was considered to be potentially related to treatment during the study. The most commonly reported ($\geq 2\%$ in any group) adverse events, considered by the investigator to be potentially related to treatment, are listed in Table III. Most adverse events in patients treated with FP or TAA were pharmacologically predictable events commonly observed with the use of inhaled corticosteroids (e.g., sore throat, oropharyngeal candidiasis, or hoarseness). The only statistically significant difference in incidence of adverse events among treatment groups was with oropharyngeal candidiasis ($p = 0.035$, FP vs placebo). The numbers of patients with postrandomization morning plasma cortisol concentrations less than 5 µg/dl in each treatment group were one (1%), three (3%), and one (1%) in the placebo, TAA, and FP treatment groups, respectively.

DISCUSSION

The results of this 24-week study confirm the results of a similarly designed 24-week study by Gross et al.,²⁸

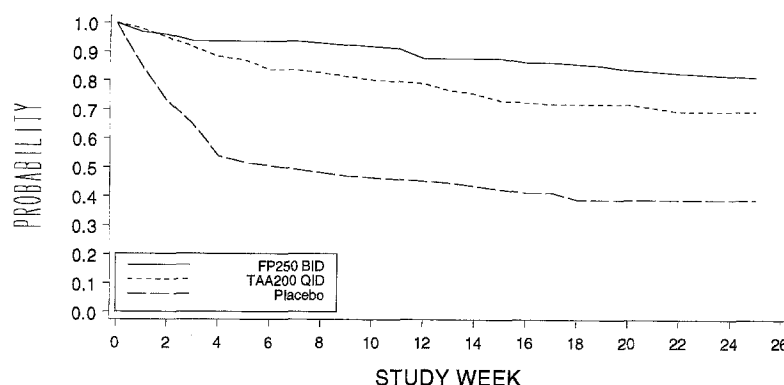


FIG. 3. Probability of remaining in the study according to Kaplan-Meier Survival Curve ($p < 0.001$ vs placebo; $p = 0.06$, FP vs TAA). BID, Twice daily; QID, four times daily.

TABLE III. Frequency (%) of most commonly reported ($\geq 2\%$) drug-related adverse events*

Adverse event	Placebo	TAA (200 μ g QID)	FP (250 μ g BID)
Sore throat	0	1 (1%)	3 (3%)
Oropharyngeal candidiasis	1 (1%)	3 (3%)	8 (8%)†
Candidiasis, unspecified site‡	0	0	2 (2%)
Headache	2 (2%)	0	1 (1%)
Hoarseness	0	0	3 (3%)
Acute bronchitis	2 (2%)	0	0
Chest symptoms	3 (3%)	0	0

*Events considered possibly, probably, or almost certainly related to drug treatment.

† $p = 0.035$ versus placebo.

‡Investigators did not specify location of candidiasis.

which demonstrated the superiority of inhaled FP powder, 500 μ g/day, compared with TAA aerosol, 800 μ g/day, in improvement of pulmonary function and reduction of the need for supplemental rescue medication. In the study by Gross et al.,²⁸ FEV₁ improved by 13% and 1% when patients were switched to FP and TAA, respectively. Likewise, the 11% increase in FEV₁ after switching to FP in this study was significantly higher than that observed with TAA (3%) at end point. Similarly, a small improvement in PEF was observed in both studies with FP, whereas PEF was relatively unchanged after treatment with TAA. In this study patients treated with FP were also able to reduce as-needed albuterol use significantly more (30%) than patients treated with TAA (6%); patients treated with FP in the study by Gross et al.²⁸ had significantly reduced albuterol use by 19% compared with patients treated with TAA who had increased their albuterol use by 19%.

The use of predefined asthma stability criteria in this study provided an additional comparative efficacy measure. These criteria provided a global assessment of patients' asthma stability as determined by deterioration

in FEV₁ or PEF, increased use of as-needed albuterol, or an increase in the number of nighttime awakenings caused by asthma. The ability of these inhaled corticosteroids to maintain asthma control was evaluated by comparing the numbers of patients who dropped out of the study (because of an inability to meet asthma stability criteria) in each treatment group. In this study more patients treated with placebo withdrew because of lack of efficacy (60%) than those treated with either FP (17%) or TAA (27%). In addition, it was also determined, by Kaplan-Meier survival analysis, that patients treated with FP had a greater probability of remaining in the study over time than patients treated with TAA, although this difference was not quite statistically significant ($p = 0.06$). In the study by Gross et al.²⁸, these differences were statistically significant ($p < 0.05$); 65%, 33%, and 17% of patients withdrew from the study because of inability to maintain asthma control after treatment with placebo, TAA, and FP, respectively. These results suggest that FP, 500 μ g/day, maintains asthma stability better than TAA, 800 μ g/day.

It is generally accepted that the onset of action of an inhaled corticosteroid in terms of clinical benefits may take several weeks. In this study FP and TAA showed significant improvements in FEV₁ and PEF compared with placebo by week 1, although TAA was not able to maintain statistical significance, compared with placebo, consistently throughout the study. Other investigators confirmed improvements in pulmonary function by week 1 in two separate 12-week studies, which compared the efficacy of FP, 500 μ g/day,³³ (in patients previously treated with β -agonists alone) or TAA, 800 μ g/day,³⁴ (in patients previously treated with inhaled corticosteroids) with that of placebo. However, in this study improvements in FEV₁ and PEF were significantly greater with FP compared with TAA by week 4 and week 1, respectively. In the study by Gross et al.,²⁸ these differences in FEV₁ and PEF between the two drugs were observed by week 1 and week 4, respectively; these differences were maintained throughout the study.

Both FP, 500 μ g/day, and TAA, 800 μ g/day, were well

tolerated over 24 weeks of treatment. The numbers of patients with low plasma cortisol concentrations were similar across treatment groups. The incidence of adverse events considered to be potentially related to drug therapy was similar to that of placebo, although a slightly higher percentage of patients (8%) treated with FP experienced oropharyngeal candidiasis (a pharmacologically predictable adverse event) compared with 3% of patients treated with TAA. A possible explanation for this difference is that TAA aerosol contains a built-in spacer device, which may have decreased the deposition of drug in the oropharynx. Additionally, mouth-washing techniques were not included in the protocol for this study. The observed increased incidence of oropharyngeal candidiasis may be a reflection of the amount of time patients were exposed to drug. More patients treated with FP remained in the study than patients treated with TAA (66% vs 55%, respectively). In other studies oral candidiasis has been reported in up to 5% of patients with asthma treated with FP powder, 500 μ g/day, for up to 12 weeks.^{33, 35, 36}

Many studies⁷ have shown that inhaled corticosteroids, particularly FP and TAA, are beneficial in the treatment of asthma and are more effective than placebo in improving pulmonary function. However, to understand how one inhaled corticosteroid can be more efficacious than another in the treatment of asthma, as demonstrated in this study, it is necessary to consider the pharmacodynamic and pharmacokinetic profiles of the different drugs within this class of asthma medications. Some of the most important attributes of an inhaled corticosteroid that may translate into differences in efficacy or systemic bioavailability include: lipophilicity, glucocorticoid receptor affinity and association, glucocorticoid receptor half-life, and extent of metabolism in the liver to active or inactive metabolites.³⁷ Some of these parameters have been evaluated for various corticosteroids; however, some data are not yet available.³⁸ Thus the most clinically relevant measures of efficacy to the practitioner in terms of comparing inhaled corticosteroids may be clinical outcome measurements such as improvements in pulmonary function, reduction in rescue medication use, and maintenance of asthma stability.

According to the National Disease and Therapeutic Index from 1987 to 1992, the percentage of physician visits that resulted in the prescription of inhaled corticosteroids for treatment of asthma increased from 7% to 27%, probably reflecting the increased appreciation of the role of inflammation in the pathogenesis of the disease.³⁹ With the increased use and availability of inhaled corticosteroids, further studies must be conducted to delineate more effectively the clinical differences between these agents in the treatment of asthma. This study demonstrates that FP, 500 μ g/day, increased efficacy more than TAA, 800 μ g/day, in patients with asthma who were switched from their previous treatment with either beclomethasone dipropionate or TAA. These results challenge the theory that all inhaled

corticosteroids are equivalent on a microgram basis. Further studies are needed to directly compare FP with other inhaled corticosteroids.

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REFERENCES

1. Asthma—United States, 1982-1992. *MMWR* 1995;43:952-5.
2. Evans R III, Mullaly DI, Wilson RW, Gergen PJ, Rosenberg HM, Grauman JS, et al. National trends in the morbidity and mortality of asthma in the US. *Chest* 1987;91(suppl):65S-74S.
3. Sly RM. Changing asthma mortality. *Ann Allergy* 1994;73:259-68.
4. Weiss KB, Gergen PJ, Hodgson AT. An economic evaluation of asthma in the United States. *N Engl J Med* 1992;326:862-3.
5. Burney PGJ. Current questions in the epidemiology of asthma. In: Holgate ST, Austen KF, Lichtenstein LM, Kay AB, editors. *Asthma: physiology, immunopharmacology, and treatment*. London: Academic Press; 1993. p. 3-25.
6. National Asthma Education Program Expert Panel Report. Executive summary: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Institutes of Health (National Heart, Lung, and Blood Institute); 1991. NIH Publication number 91-3042A.
7. Global Initiative for Asthma. Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Bethesda (MD): National Institutes of Health (National Heart, Lung, and Blood Institute); 1995. NIH Publication number 95-3659.
8. Fuller R, Johnson M, Bye A. Fluticasone propionate: an update on preclinical and clinical experience. *Respir Med* 1995;89(suppl A):3-18.
9. Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;84(suppl A):25-9.
10. Brogden RN, Pinder RM, Sawyer PR, Speight TM, Avery GS. Beclomethasone dipropionate inhaler: a review of its pharmacology, therapeutic value and adverse effects. I. *Asthma. Drugs* 1975;10:166-210.
11. Brogden RN, Heel RC, Speight TM, Avery GS. Beclomethasone dipropionate: a reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. *Drugs* 1984;28:99-126.
12. Williams MH Jr, Kane C, Shim CS. Treatment of asthma with triamcinolone acetonide delivered by aerosol. *Am Rev Respir Dis* 1974;109:538-43.
13. Bernstein IL, Chervinsky P, Falliers CJ. Efficacy and safety of triamcinolone acetonide aerosol in chronic asthma: results of a multicenter, short-term controlled and long-term open study. *Chest* 1982;81:20-6.
14. Meltzer EO, Kemp JP, Orgel HA, Izu AE. Flunisolide aerosol for treatment of severe, chronic asthma in steroid-independent children. *Pediatrics* 1982;69:340-5.
15. Slavin RG, Izu AE, Bernstein IL, Blumenthal MN, Bolin JF, Ovellette JJ, et al. Multicenter study of flunisolide aerosol in adult patients with steroid-dependent asthma. *J Allergy Clin Immunol* 1980;66:379-85.
16. Rafferty P, Tucker LG, Frame MH, Fergusson RJ, Biggs B-A, Crompton GK. Comparison of budesonide and beclomethasone

- dipropionate in patients with severe chronic asthma: assessment of relative prednisolone-sparing effects. *Br J Dis Chest* 1985;79:244-50.
17. Noonan M, Chervinsky P, Busse WW, Weisberg SC, Pinnaas J, deBoisblanc BP, et al. Fluticasone propionate aerosol reduces oral prednisone requirements while it improves control of asthma and quality of life. *Am J Respir Crit Care Med* 1995;152:1467-73.
 18. Crescenzi KL, Wolfe J, Noonan M, Pinnaas J, Kellerman DJ. Standardized methacholine challenge testing to demonstrate bioequivalence of formulations of inhaled corticosteroids [abstract]. *Ann Allergy Asthma Immunol* 1996;74:64.
 19. Sheffer AL, LaForce C, Chervinsky P, Pearlman D, Schaberg A, The Fluticasone Propionate Asthma Study Group. Fluticasone propionate aerosol: efficacy in patients with mild-to-moderate asthma. *J Fam Pract* 1996;42:369-75.
 20. Chervinsky P, van As A, Bronsky EA, Dockhorn R, Noonan M, La Force C, et al. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. *J Allergy Clin Immunol* 1994;94:676-83.
 21. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med* 1995;98:196-208.
 22. Kamada AK. Therapeutic controversies in the treatment of asthma. *Ann Pharmacother* 1994;28:904-14.
 23. Brattsand R, Thalen A, Roempke K, Kallstrom L, Gruvstad E. Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. *Eur J Respir Dis* 1982; 63(suppl 122):62-73.
 24. McKenzie AW, Stoughton RB. Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 1962;86:608-10.
 25. McCubbin MM, Milavetz G, Grandgeorge S, Weinberger M, Ahrens R, Sargent C, et al. A bioassay for topical and systemic effect of three inhaled corticosteroids. *Clin Pharm Ther* 1995;57:455-60.
 26. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson AS. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. *J Allergy Clin Immunol* 1989;84:688-700.
 27. Rosenhall L, Lundqvist G, Adelroth E, Glennow G. Comparison between inhaled and oral corticosteroids in patients with chronic asthma. *Eur J Respir Dis* 1982;63(suppl 122):62-73.
 28. Gross G, Wolfe JD, Noonan MJ, Pinnaas JL, Boltansky H, Nathan RA, et al. Fluticasone propionate 500 µg/day improves asthma more than triamcinolone acetonide 800 µg/day. Presented at the American Thoracic Society, New Orleans, LA, May 11-15, 1996.
 29. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
 30. Polgar G, Promadhat V. Pulmonary function testing in children: techniques and standards. Philadelphia: WB Saunders; 1971.
 31. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659-64.
 32. Lee ET. Statistical methods for survival data analysis. Belmont (CA): Lifetime Learning Publication; 1980.
 33. Wasserman SI, Gross GN, Schoenwetter WF, Munk ZM, Kral KM, Schaberg A, et al. A 12-week dose-ranging study of fluticasone propionate powder in the treatment of asthma. *J Asthma* 1996;33: 265-74.
 34. Grieco MH, Dwek J, Larsen K, Rammohan G. Clinical effect of aerosol triamcinolone acetonide in bronchial asthma. *Arch Intern Med* 1978;138:1337-41.
 35. Lundback B, Alexander M, Day J, Hebert J, Holzer R, Van Uffelen R, et al. Evaluation of fluticasone propionate (500 µg/day) administered either as dry powder via a Diskhaler® inhaler or pressurized inhaler and compared with beclomethasone dipropionate (1000 µg/day) administered by pressurized inhaler. *Respir Med* 1993;87: 609-20.
 36. Pearlman DS, Noonan MJ, Tashkin DP, Goldstein MF, Hamedani AG, Kellerman DJ, et al. Comparative efficacy and safety of twice-daily fluticasone propionate powder versus placebo in the treatment of moderate asthma. *Ann Allergy Asthma Immunol* 1997;78:356-62.
 37. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. *J Allergy Clin Immunol* 1996;97:169-76.
 38. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148:S1-S26.
 39. Terr AI, Bloch DA. Trends in asthma therapy in the United States: 1965-1992. *Ann All Asthma Immunol* 1996;76:273-81.

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