A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma

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Background: Inhaled corticosteroids are recommended for the treatment of persistent asthma. Comparative clinical studies evaluating 2 or more doses of these agents are few.
Objective: We sought to compare the efficacy and safety of 2 doses of fluticasone propionate (88 μg twice daily and 220 μg twice daily) with 2 doses of beclomethasone dipropionate (168 μg twice daily and 336 μg twice daily) in subjects with persistent asthma.
Methods: Three hundred ninety-nine subjects participated in this randomized, double-blind, parallel-group clinical trial. Eligible subjects were using daily inhaled corticosteroids and had an FEV_1 of 45% to 80% of predicted value. Clinic visits, including spirometry, were conducted every 1 to 2 weeks. Subjects recorded symptoms, use of albuterol, and peak expiratory flows on daily diary cards.
Results: Fluticasone propionate treatment resulted in significantly ($P \leq .034$) greater improvements in objective pulmonary function parameters than did beclomethasone dipropionate treatment and significantly greater reductions in daily albuterol use ($P \leq .010$) and asthma symptoms ($P \leq .027$). Both low-dose (88 μg twice daily) and medium-dose (220 μg twice daily) fluticasone propionate significantly increased FEV_1 compared with higher doses of beclomethasone dipropionate ($P = .006$). Low-dose and medium-dose fluticasone propionate improved FEV_1 by 0.31 L (14%) and 0.36 L (15%), respectively, compared with improvements of 0.18 L (8%) and 0.21 L (9%) with low-dose and medium-dose beclomethasone dipropionate. The adverse event profiles were similar for both medications.
Conclusion: Fluticasone propionate provides greater asthma control at roughly half the dose of beclomethasone dipropionate, with a comparable adverse event profile. (J Allergy Clin Immunol 1999;103:796-803.)

Key words: *Fluticasone propionate, beclomethasone dipropionate, asthma, comparative efficacy, inhaled corticosteroid*

Abbreviations used

$FEF_{25-75\%}$:	Forced expiratory flow
FVC:	Forced vital capacity
NIH:	National Institutes of Health
PEF:	Peak expiratory flow

Anti-inflammatory therapy, particularly the use of inhaled corticosteroids, is currently recommended by national guidelines as the mainstay of treatment to improve asthma and normalize pulmonary function.[1] Preliminary studies suggest that early intervention with inhaled corticosteroids may prevent the irreversible airways injury that is characteristic of persistent asthma.[2-6]

Several inhaled corticosteroids have been available for use in the United States since 1974, namely beclomethasone dipropionate, triamcinolone acetonide, and flunisolide. Despite their use for many years, well-controlled clinical comparisons of the efficacy of these agents are few.[7-11] In the first National Institutes of Health (NIH) asthma guidelines[12] published in 1991, no differentiation was noted between these specific compounds because they were assumed to be comparable on a per puff or microgram basis based on available data.[13,14] The more recently published NIH guidelines, however, recognize inherent differences in the pharmacologic properties of these agents. This has led to the establishment of new categories that provide guidance about low, medium, and high dosage levels for each individual inhaled corticosteroid, including the newer, more potent inhaled corticosteroid fluticasone propionate.[1]

The objective of this study was to compare the clinical efficacy of 2 different inhaled corticosteroids, namely fluticasone propionate and beclomethasone dipropionate, in the treatment of moderate-to-severe asthma. Unlike many previous studies in which a single dose of each drug was compared, this study was designed to compare 2 different, commonly prescribed doses of each drug.[1,15] Beclomethasone dipropionate and fluticasone propionate dose ratios of roughly 2:1 were selected for study on the basis of previous research[16-20] and the purported greater potency of fluticasone propionate implied by in vitro data.[21] By using dose classifications from the NIH

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TABLE I. Subject demographics and asthma history

	FP 88μg	FP 220μg	BDP 168μg	BDP 336μg
No. of subjects	99	104	101	95
Mean age, y (±SEM)	38.4 (±1.4)	37.8 (±1.3)	41.5 (±1.5)	39.8 (±1.7)
Range	13-70	13-72	13-83	12-72
Sex, n (%)				
M	46 (46%)	50 (48%)	32 (3%)	39 (41%)
F	53 (54%)	54 (52%)	69 (68%)	56 (59%)
Ethnic origin, n (%)				
White	91 (92%)	99 (95%)	91 (90%)	91 (96%)
Black	6 (6%)	4 (4%)	6 (6%)	3
Other	2 (2%)	1 (<1%)	4 (4%)	1 (1%)
Mean, % predicted FEV_1 (±SEM)	64.7 (±1.0)	65.6 (±1.0)	64.7 (±1.0)	65.7 (±1.1)
Range	45-80	45-79	45-80	45-80
Baseline inhaled corticosteroid, n (%)				
TAA	41 (41%)	36 (35%)	43 (4%)	36 (38%)
BDP	56 (57%)	66 (63%)	56 (55%)	59 (62%)
Flunisolide	2 (2%)	2 (2%)	2 (2%)	0
Concomitant medications, n (%)				
Salmeterol	27 (27%)	27 (26%)	23 (23%)	22 (23%)
Theophylline	20 (20%)	17 (16%)	19 (19%)	14 (15%)

All doses were administered twice daily.
FP, Fluticasone propionate; *BDP,* beclomethasone dipropionate; *TAA,* triamcinolone acetonide.

TABLE II. Subject disposition

	FP 88μg	FP 220μg	BDP 168μg	BDP 336μg	Total
No. of subjects	99	104	101	95	399
No. completing study (%)	72 (73%)	82 (79%)	61 (60%)	73 (72%)	288 (72%)
No. withdrawing from study (%)	27 (27%)	22 (21%)	40 (40%)	22 (23%)	111 (28%)
Reasons for withdrawal, n (%)					
Lack of efficacy	17 (17%)	16 (15%)	26 (26%)	16 (17%)	75 (19%)
Adverse event	3 (3%)	3 (3%)	4 (4%)	2 (2%)	12 (3%)
Other*	7 (7%)	3 (3%)	10 (10%)	4 (4%)	24 (6%)

All doses were administered twice daily.
FP, Fluticasone propionate; *BDP,* beclomethasone dipropionate.
*Includes protocol violations and subjects who failed to return.

Guidelines, 2 low-dose (fluticasone propionate 88 μg twice daily and beclomethasone dipropionate 168 μg twice daily) and 2 medium-dose (fluticasone propionate 220 μg twice daily and beclomethasone dipropionate 336 μg twice daily) regimens were evaluated.

METHODS

Subjects

Three hundred ninety-nine subjects were enrolled in this study. Eligible subjects were nonsmoking males and females aged 12 years or older with an established diagnosis of chronic asthma requiring daily inhaled corticosteroid therapy for at least 6 months before the study. Only subjects using 8 to 12 puffs/day of either beclomethasone dipropionate or triamcinolone acetonide for at least 1 month before the study were eligible for enrollment. In addition, subjects were required to have an FEV_1 between 45% and 80% of predicted normal value at the screening visit and at baseline. Eligible subjects also demonstrated reversible lung function (12% or greater increase in FEV_1 after 2 puffs of albuterol). They were permitted to continue theophylline and/or salmeterol during the study if taken at stable and approved doses and if the morning dose was withheld before all study visits. No other asthma medications were permitted other than albuterol metered-dose inhaler (Ventolin Inhalation Aerosol, Glaxo Wellcome Inc), which was provided for all subjects to use as needed for relief of symptoms. Subjects were not eligible for entry into the study if they had received oral or intravenous corticosteroids, leukotriene modifiers, sodium cromoglycate, or nedocromil sodium for 1 month before the study.

Study design and procedures

This randomized, double-blind, double-dummy, parallel-group clinical trial was conducted at 23 specialty asthma and primary care study centers. The study protocol and the informed consent document were approved by human ethics committees before initiating this study. Subjects meeting all eligibility criteria and providing written informed consent were entered into a 2-week, single-blind, run-in period in which they took beclomethasone dipropionate 168 μg twice daily (4 puffs twice daily; Beclovent Inhalation Aerosol, Glaxo Wellcome Inc) along with placebo in lieu of their previous inhaled corticosteroid. The single-blind, run-in period evaluated the subject's eligibility for the study, assessed compliance with study procedures, and served as the baseline period for comparative purposes.

Baseline FEV_1 measurements were conducted at the end of the single-blind, run-in period. Subject spirometry and diary data were reviewed to determine eligibility to enter the double-blind treatment period. For measurements other than FEV_1, baseline was defined as

TABLE III. Efficacy assessments: Mean change from baseline (±SEM) at endpoint

	FP > BDP† ($P \leq .034$)	FP 88μg (n = 99)	FP 220μg (n = 101)	BDP 168μg (n = 104)	BDP 336μg (n = 95)
FEV_1, L					
Baseline*		2.25 (±0.05)	2.35 (±0.06)	2.18 (±0.06)	2.22 (±0.06)
Change	$P = .006$	0.31 (±0.05)‡	0.36 (±0.05)‡	0.18 (±0.04)‡	0.21 (±0.05)‡
$FEF_{25-75\%}$, L/sec					
Baseline*		1.89 (±0.09)	1.87 (±0.08)	1.75 (±0.08)	1.73 (±0.08)
Change	$P = .015$	0.27 (±0.06)‡	0.41 (±0.07)‡	0.14 (±0.07)‡	0.22 (±0.06)‡
FVC, L					
Baseline*		3.17 (±0.1)	3.31 (±0.09)	3.05 (±0.1)	3.18 (±0.1)
Change	$P = .0034$	0.33 (±0.07)‡	0.39 (±0.06)‡	0.23 (±0.06)‡	0.24 (±0.06)‡
Morning PEF, L/min					
Baseline*		392.3 (±9.3)	403.6 (±9.4)	381.8 (±9.1)	386.1 (±9.3)
Change	$P \leq .001$	15.8 (±5.0)‡	22.8 (±4.2)‡	0.7 (±4.1)	7.2 (±4.2)
Evening PEF, L/min					
Baseline*		419.8 (±9.3)	428.7 (±9.5)	400.0 (±9.5)	397.9 (±9.3)
Change	$P = .06$	7.8 (±4.4)	14.2 (±3.8)‡	2.1 (±4.6)	9.7 (±3.7)‡
Albuterol use, puffs/day					
Baseline*		3.4 (±0.3)	3.2 (±0.3)	3.4 (±0.3)	3.2 (±0.3)
Change	$P = .004$	–0.9 (±0.2)‡	–0.5 (±0.2)‡	0.0 (±0.2)	–0.3 (±0.2)
Percent days with no albuterol use					
Baseline*		26.4 (±3.7)	28.9 (±3.6)	22.7 (±3.4)	27.1 (±3.6)
Change	$P = .010$	15.8 (±3.5)‡	11.0 (±3.3)‡	5.0 (±3.3)	7.7 (±3.3)‡
Night awakenings					
Baseline*		0.19 (±0.02)	0.27 (±0.04)	0.20 (±0.03)	0.22 (±0.03)
Change	$P = .458$	–0.03 (±0.04)	–0.12 (±0.05)‡	–0.03 (±0.04)	–0.07 (±0.04)
Symptom scores (0-3 scale)					
Baseline*		1.21 (±0.06)	1.27 (±0.06)	1.14 (±0.06)	1.20 (±0.07)
Change	$P = .024$	–0.24 (±0.07)‡	–0.26 (±0.06)‡	–0.05 (±0.06)	–0.15 (±0.06)‡
Percent days with no symptoms					
Baseline*		15.6 (±3.0)	16.9 (±3.0)	17.3 (±3.1)	19.6 (±3.2)
Change	$P = .027$	14.0 (±3.2)‡	8.7 (±2.8)‡	4.9 (±3.2)	4.4 (±3.0)

All doses were administered twice daily.
FP, Fluticasone propionate; *BDP,* beclomethasone dipropionate.
*Treatment groups were comparable at baseline ($P \geq .053$).
†Comparison of the combined drug effect of FP versus BDP.
‡Significant improvement from baseline for individual treatments ($P < .05$).

the mean of the 7 days before double-blind treatment. Subjects were randomized without further qualifications if their baseline FEV_1 was between 45% and 65% of their predicted normal value. In addition, subjects with higher pulmonary function, between 65% and 80% of predicted value, were also randomized if they manifested other indicators of asthma instability during the prior week, including using more than 8 puffs/day of supplemental albuterol on any day, averaging 4 or more puffs/day of albuterol, recording peak expiratory flow (PEF) values with morning to evening fluctuations of greater than 20%, or experiencing any nighttime awakening attributed to asthma that required supplemental albuterol. Subjects who experienced an asthma exacerbation or significant decline in pulmonary function during the single-blind, run-in period were not entered into the double-blind treatment period.

Subjects meeting these criteria were randomly assigned to treatment for 12 weeks. These treatments were fluticasone propionate 88 μg twice daily (2 puffs twice daily, 44 μg/puff; Flovent Inhalation Aerosol, Glaxo Wellcome Inc), fluticasone propionate 220 μg twice daily (2 puffs twice daily, 110μg/puff; Flovent Inhalation Aerosol), beclomethasone dipropionate 168 μg twice daily (4 puffs twice daily, 42μg/puff; Inhalation Aerosol), or beclomethasone dipropionate 336 μg twice daily (8 puffs twice daily, 42 μg/puff; Beclovent Inhalation Aerosol). All treatments were administered by means of metered-dose inhalers without a spacer. The identity of the study treatment was concealed from both the subject and the investigator by use of a double-blind, double-dummy system in which the order of the study inhalers was not specified.

The rationale for the dose selection in this study was 2-fold: 1) to evaluate the comparative efficacy of commonly prescribed doses for both fluticasone propionate and beclomethasone dipropionate and 2) to evaluate the efficacy of fluticasone propionate at roughly half the microgram dose of beclomethasone dipropionate. Both doses of fluticasone propionate (88 μg and 220 μg twice daily) are recommended as starting doses for subjects who are being switched to fluticasone propionate from other inhaled corticosteroids; the 220 μg twice daily dose is recommended for subjects with more severe disease or those who have required higher doses of previous inhaled corticosteroids.[15] Beclomethasone dipropionate 168 μg twice daily is a common starting dose for most subjects. The dose of beclomethasone dipropionate 336 μg twice daily is also recommended for subjects with more severe asthma.[15]

Spirometry was performed at the screening visit, at baseline (randomization visit), and at each visit after 1, 2, 4, 6, 8, 10, and 12 weeks of double-blind treatment. In addition, subjects completed

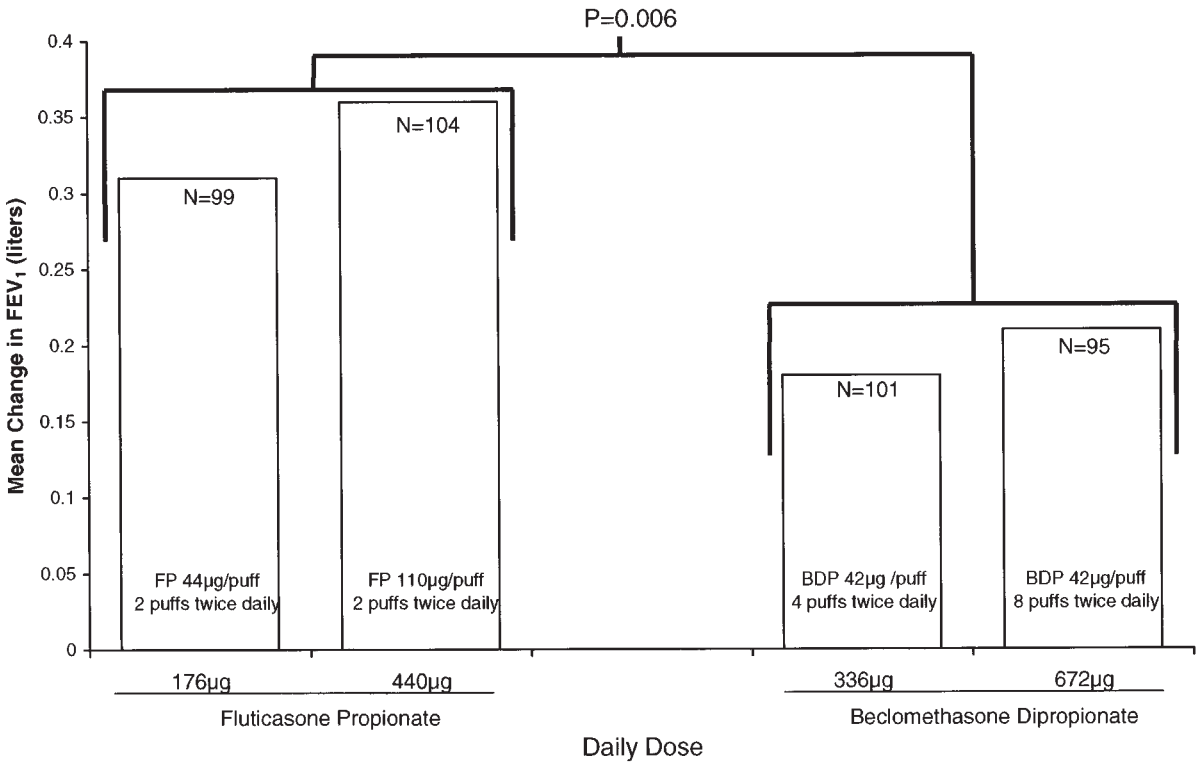

FIG 1. Mean change from baseline at endpoint in morning predose FEV_1. Comparison of drug effect for combined data for fluticasone propionate *(FP)* (0.33 L) versus combined data for beclomethasone dipropionate *(BDP)* (0.20 L). Mean baseline FEV_1 was comparable across treatment groups (range, 2.18 L to 2.25 L; $P = .163$).

diary cards that recorded the use of supplemental albuterol, morning and evening PEF rates, nighttime awakenings caused by asthma, and asthma symptoms on a scale from 0 to 3, with 0 representing no asthma symptoms and 3 representing severe asthma symptoms.

During the double-blind portion of the study, subjects were withdrawn if they manifested evidence of worsening asthma as measured by at least 1 of the following parameters: a reduction in FEV_1 of 20% or more below the baseline; 3 or more days in which the PEF was decreased by 20% or more from the mean baseline; excessive use of supplemental albuterol (>12 puffs per day) on 3 or more days; or 3 or more nights with awakenings caused by asthma requiring treatment with albuterol. For measurements other than FEV_1, baseline was defined as the mean of the 7 days before double-blind treatment.

Comparative safety data was assessed by clinical adverse events, vital signs, oropharyngeal examinations, clinical laboratory tests, and physical examinations.

Statistical analysis

All subjects who received double-blind study drug were included in all efficacy and safety analyses. Statistical tests were 2 sided, with significance levels of .05. Sample size was calculated based on the primary efficacy variable, morning FEV_1. A sample size of 100 subjects per treatment arm was planned on the basis of assumptions from previous studies in which the standard deviation for FEV_1 was 0.55 L. This would provide power at the 80% level to detect a difference in FEV_1 of at least 0.25 L.

The primary objective of this study was to test for differences between fluticasone propionate and beclomethasone dipropionate at doses commonly used to treat patients with persistent asthma. A 2×2 factorial analysis[22] evaluated both drug effects (fluticasone propionate vs beclomethasone dipropionate) and dose effects (low vs medium). Individual treatment group means were pooled to test drug and dose effects once a significant interaction between treatment drug and treatment dose was ruled out.

The 2×2 factorial analysis was conducted for the primary efficacy variable, morning predose FEV_1, and all the other efficacy variables, including forced expiratory flow ($FEF_{25-75\%}$), forced vital capacity (FVC), morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings, and asthma symptoms. Statistical testing was conducted at each visit, at study endpoint, and on weekly means of diary data. Study endpoint was computed by using the last evaluable measurement for each subject, regardless of whether the subject completed the study.

Additionally, comparisons between the individual treatment means were performed for the efficacy and demographic variables by using ANOVA. Duration of subject participation in the study was analyzed by using the Kaplan-Meier product-limit method. Fisher's exact test was used to test for treatment differences in the incidence of adverse events.

RESULTS

Disposition and demographics

There were no statistically significant differences between treatments groups at baseline (Table I). The mean age ranged from 37.8 to 41.5 years. Approximately 50% of the subjects had long-standing asthma, with a duration in excess of 15 years. The mean percent predicted FEV_1 was 64% to 65%. The use of concurrent salmeterol and theophylline were similar across treatment groups.

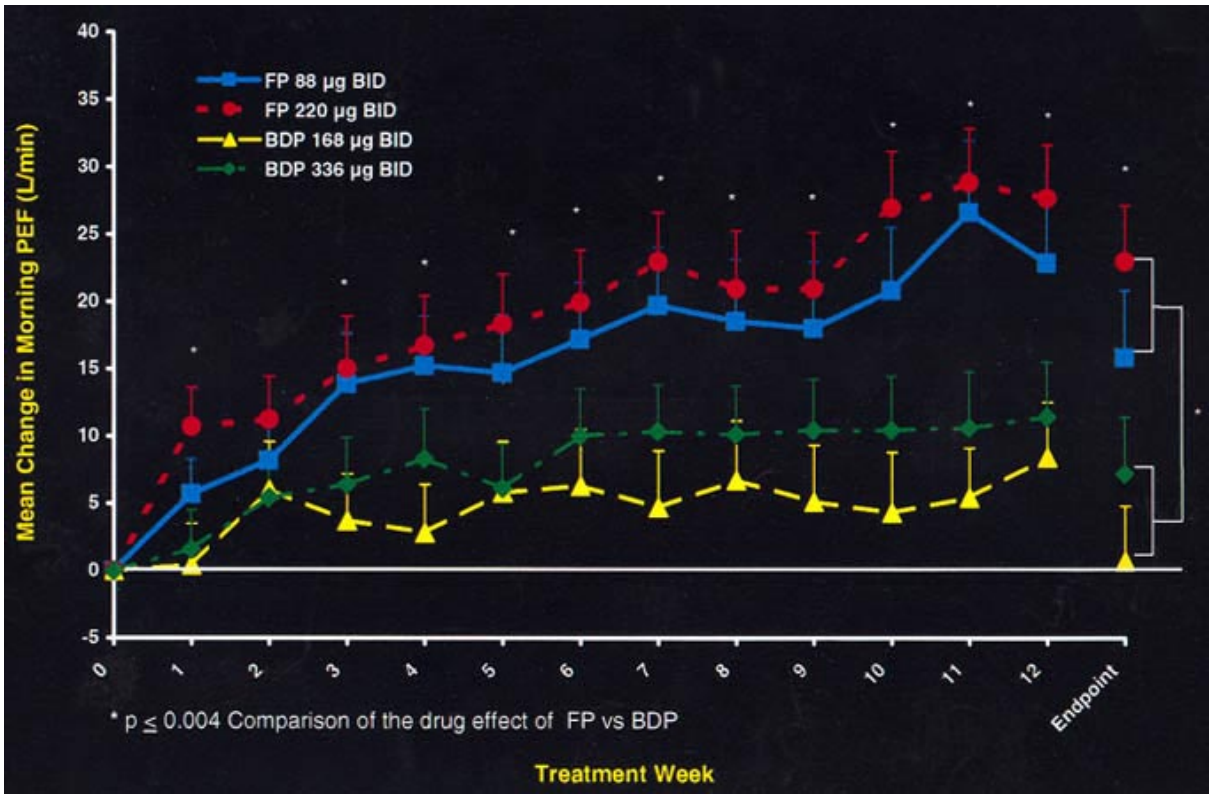

FIG 2. Mean change from baseline in morning PEF. Comparison of drug effect for combined fluticasone propionate *(FP)* data and combined beclomethasone dipropionate *(BDP)* data. Mean baseline morning PEF values were comparable across treatment groups (range, 382 L/min to 404 L/min; $P = .365$).

Withdrawal because of lack of efficacy was similar across the groups (Table II). Withdrawal because of adverse events and other reasons were also similar.

Pulmonary function

The baseline values and change from baseline to endpoint results for all of the efficacy variables are displayed in Table III. The FEV_1 for all treatment groups improved with respect to baseline; however, a significant drug effect was observed in favor of fluticasone propionate compared with beclomethasone dipropionate in the mean change in FEV_1 from baseline at endpoint ($P = .006$, Fig 1). At endpoint, mean FEV_1 values in the low- and medium-dose fluticasone propionate treatment groups improved by 0.31 L (14%) and 0.36 L (15%), respectively, compared with improvements of 0.18 L (8%) and 0.21 L (9%) in the low- and medium-dose beclomethasone dipropionate treatment groups, respectively. Pairwise comparisons showed that low-dose fluticasone propionate caused greater improvement in FEV_1 compared with low-dose beclomethasone dipropionate ($P = .048$) In addition, medium-dose fluticasone propionate caused greater improvement in FEV_1 than medium-dose beclomethasone dipropionate ($P = .034$).

Similar results were observed for both $FEF_{25-75\%}$ and FVC. All treatment groups significantly improved relative to baseline; however, a significant drug effect was observed in favor of fluticasone propionate treatment at endpoint for both parameters ($P \leq .034$, Table III).

The mean change from baseline for morning PEF is displayed in Fig 2. Fluticasone propionate treatment provided significantly greater improvement when compared with beclomethasone dipropionate treatment at endpoint and in all of the other time points except week 2 ($P \leq .004$). The fluticasone propionate treatment groups experienced a significant improvement in morning PEF relative to baseline, but the beclomethasone dipropionate groups did not (Table III). A similar trend was seen in evening PEF, but the improvement observed in response to fluticasone propionate compared with beclomethasone dipropionate did not achieve statistical significance.

Supplemental albuterol use, asthma symptoms, and probability of remaining in the study

Only the fluticasone propionate groups demonstrated a significant reduction in supplemental albuterol use compared with baseline (defined as the mean daily use for the

7 days before double-blind treatment; Table III). When the 2 inhaled corticosteroids were compared, fluticasone propionate provided a significantly greater reduction in albuterol use than did beclomethasone dipropionate (P = .004 at endpoint). Albuterol use declined by 0.9 (26%) and 0.5 (16%) puffs/day in the low and moderate fluticasone propionate treatment groups, respectively, whereas it was unchanged in the beclomethasone dipropionate 168 μg twice daily group and reduced by 0.3 (9%) puffs/day in the beclomethasone dipropionate 336 μg twice daily group.

The percentage of days in which no albuterol was used was significantly higher with fluticasone propionate treatment than with beclomethasone dipropionate treatment (P = .010 at endpoint, Table III). Significant drug effects were observed at endpoint in favor of fluticasone propionate for both asthma symptom scores (P = .024) and in the percentage of days in which no symptoms were recorded (P = .027). There were no significant drug effects noted in the analysis of nighttime awakenings or in the Kaplan-Meier estimates of the probability of remaining in the study over time.

Dose effects

Analyses were conducted on each efficacy variable to evaluate whether the effects seen were related to the dose of inhaled corticosteroid or the actual inhaled corticosteroid received. The pooled effects of low doses (fluticasone propionate 88 μg twice daily and beclomethasone dipropionate 168 μg twice daily) and medium doses (fluticasone propionate 220 μg twice daily and beclomethasone dipropionate 336 μg twice daily) were compared. No significant dose effects were observed for any of the efficacy variables, including pulmonary function assessments, albuterol use, symptom scores, nighttime awakenings, and the probability of remaining in the study over time, indicating that the effects seen were caused by the drug and not the dose. Numeric differences were observed between low and medium doses of each inhaled corticosteroid, but these differences were not statistically significant.

Asthma severity

An analysis was conducted to examine the effects of baseline asthma severity on FEV_1 after treatment. Patients were classified as having mild* (baseline FEV_1 >65% to 80% of predicted value) or moderate/severe asthma (baseline FEV_1 ≥45% to 65% of predicted value). Subjects were distributed in similar numbers between the mild (n = 210) and moderate/severe (n = 189) subject groups for both low and medium doses of fluticasone propionate and beclomethasone dipropionate. The results from this analysis were consistent with those seen in the combined population. Subjects with mild asthma experienced similar increases in FEV_1, with low and medium doses of fluticasone propionate producing a 0.36 L and 0.35 L change, respectively. In more impaired subjects, the medium dose of fluticasone propionate appeared more effective, with a 0.37 L change in FEV_1 compared with a 0.25 L change with the low dose. These trends were consistent for morning PEF, albuterol use, and symptom scores. None of the differences between doses were statistically significant because the study was not powered for this analysis. Regardless of severity, fluticasone propionate was consistently more effective than beclomethasone dipropionate at both the low and medium doses.

*Classifications were based on the original study definitions and may not reflect subject populations as defined in the current National Heart, Lung, and Blood Institute asthma guidelines.

Safety

All treatments were well tolerated in this study. Three subjects receiving each drug were withdrawn because of adverse events that were considered to be possibly related to the use of study medication: headache, insomnia, jitters, and tachycardia (fluticasone propionate 88 μg twice daily); edema and muscle pain (fluticasone propionate 220 μg twice daily); fatigue and light-headedness (fluticasone propionate 220 μg twice daily); rash (beclomethasone dipropionate 168 μg twice daily); hoarseness (beclomethasone dipropionate 168 μg twice daily); and headache (beclomethasone dipropionate 168 μg twice daily).

There were no significant differences across treatment groups in the overall incidence of adverse events potentially related to study treatment (range, 9% to 15%; P = .664) or the most commonly reported of these events: hoarseness (range, 3% to 7%; P = .577), throat irritation (range, 1% to 3%; P = .797), candidiasis (range, 1% to 4%; $P \leq .472$), or headaches (range, 1% to 3%; P = .721). No differences in physical findings or laboratory tests were seen among treatment groups.

DISCUSSION

Comparative efficacy studies of inhaled corticosteroids need to be carefully designed with respect to dose, patient population, and clinical endpoints. It has been suggested that meaningful comparisons of inhaled corticosteroids should be based on low, clinically comparable doses using meaningful endpoints (eg, improved asthma control) in subjects treated for an appropriate period of time.[23] When beclomethasone dipropionate and triamcinolone acetonide were compared as suggested above, there was little evidence to suggest that these agents could be differentiated with respect to clinical efficacy.[24] These study design issues become even more important since the introduction of more potent agents, such as fluticasone propionate, particularly given the differences in the pharmacokinetic and pharmacodynamic properties of inhaled corticosteroids[25] and the significant differences in the recommended dose ranges for these drugs.[1] Studies attempting to compare fluticasone propionate with other inhaled corticosteroids on the basis of equal (and high) microgram doses[26-32] are misleading because they do not compare clinically comparable doses and do not reflect the effects that would be observed at lower, commonly prescribed doses. Furthermore, single-dose studies[27,32] and studies in normal volunteers[26,27,32,33] also fail to sufficiently consider the rele-

vancy of study design and provide little information that can be generalized to subjects with asthma. This study has attempted to examine important clinical endpoints at clinically relevant doses that are common and likely to be prescribed frequently by specialists and primary care providers for subjects with asthma.

This is the first study to compare the efficacy of 2 inhaled corticosteroids at 2 different dosages in subjects with asthma. This clinically relevant, unique design permitted the evaluation of both drug effects (fluticasone propionate vs beclomethasone dipropionate) and dose effects (low vs medium). Fluticasone propionate treatment at approximately one half of the dose provided significantly greater improvements in lung function (FEV_1, $FEF_{25-75\%}$, FVC, and morning PEF) than beclomethasone dipropionate. Additionally, significantly greater reductions in albuterol use and symptoms were observed with fluticasone propionate compared with beclomethasone dipropionate. All treatments were well tolerated, with a comparable adverse event profile.

Although significant differences between drugs (fluticasone propionate vs beclomethasone dipropionate) were observed in this study, no significant differences in dose (low vs medium) were observed. An analysis of the study population on the basis of asthma severity did not reveal a strong dose response, although there were trends that subjects with moderate/severe asthma improved more with the medium dose of fluticasone propionate than with the low dose. Other fluticasone propionate studies that have evaluated this portion of the dose-response curve in similar patient populations have also failed to demonstrate a significant dose response.[34-37] Dose-response relationships have been reported with fluticasone propionate when other endpoints have been evaluated, such as the prednisone reduction capabilities of fluticasone propionate at the high end of the dosing range[38] and with indices of bronchial hyperresponsiveness to methacholine.[39] No dose-response studies have been reported with beclomethasone dipropionate using the low and medium doses in this study.

All subjects were taking beclomethasone dipropionate 168 μg twice daily (low dose) during the run-in period, and therefore the low-dose beclomethasone dipropionate treatment arm served as the control group for this study. Because no increase or change in drug regimen was made on randomization to study treatment in this group, significant changes in asthma control were not expected nor were they consistently observed. Condemi et al[40] and Gross et al[41] observed a similar phenomenon in subjects who received 8 puffs/day of triamcinolone acetonide at baseline and then after randomization in a double-blind trial.

Improvement in asthma control has been previously reported in subjects who were switched from a lower to a higher dose of beclomethasone dipropionate, as they were in this study.[42,43] However, the magnitude of the improvement in these studies was modest in comparison with the improvements that were observed in this and other studies when subjects have been switched from other inhaled corticosteroids to fluticasone propionate.[34-37,40,41]

The results from the current study are consistent with other studies that have evaluated beclomethasone dipropionate and fluticasone propionate in dose ratios of approximately 2:1.[7-11,16,17] In all of these studies, the efficacy of fluticasone propionate has been demonstrated to be at least as good, and sometimes better, than twice the dose of beclomethasone dipropionate, with a comparable safety profile.

The adverse-event profiles of fluticasone propionate and beclomethasone dipropionate were similar. The adverse events that were observed were expected given the study population and the known effects of inhaled corticosteroid therapy. The systemic effects of inhaled corticosteroids were not addressed in this 12-week clinical trial; however, the comparative systemic effects of fluticasone propionate and beclomethasone dipropionate have been evaluated by others.[15,16] In general the doses required to produce systemic effects exceed the doses of fluticasone propionate and beclomethasone dipropionate that are appropriate for the population treated in this study. The risk/benefit ratio of increasing doses of inhaled corticosteroids in subjects with more severe asthma needs to be evaluated with respect to the requirements for good asthma control, safety, and the availability of alternative add-on therapies (eg, long-acting bronchodilators).

In conclusion, fluticasone propionate doses of 88 μg twice daily and 220 μg twice daily are superior to beclomethasone dipropionate doses of 168 μg twice daily and 336 μg twice daily in improving pulmonary function (FEV_1, $FEF_{25-75\%}$, FVC, and morning PEF) and in decreasing asthma symptoms and the need for supplemental albuterol. This improvement in asthma control was achieved conveniently (4 puffs/day vs 8 to 16 puffs/day) and with comparable adverse events.

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