

Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma

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Background: Although inhaled corticosteroids are widely used for the treatment of inflammation in asthma, prospective, long-term, placebo-controlled trials characterizing their systemic safety with chronic use are lacking.

Objective: This study was designed to prospectively evaluate the long-term safety of inhaled fluticasone propionate therapy. **Methods:** Fluticasone propionate powder, 500 µg, or placebo was administered twice daily by means of the Diskhaler for 104 weeks to 64 adults with mild persistent asthma in a randomized, double-blind, parallel-group study. Primary safety variables were measured at baseline and every 6 months thereafter. Although evaluation of efficacy was not an objective of this study, pulmonary function testing was performed at monthly intervals.

Results: Two years of treatment with fluticasone propionate had no significant effects on the skeletal system. No clinically significant changes were observed in ophthalmic parameters (glaucoma and posterior subcapsular cataracts). Mean change from baseline in lumbar spine (L₁ to L₄) bone density at week 104 was not significantly different between fluticasone propionate (-0.006 ± 0.008 g/cm²) and placebo (-0.007 ± 0.010 g/cm²). Markers of bone formation (serum osteocalcin) and resorption (urinary N-telopeptide) did not differ significantly between treatment groups. The effects of fluticasone propionate treatment on the hypothalamic-pituitary-adrenal axis were minimal, with no alterations in morning plasma cortisol concentrations and minor but statistically significant decreases in poststimulation mean peak plasma cortisol concentrations ($P = .021$) and 8-hour plasma cortisol area under the curve

values ($P = .020$) at week 104. Drug-related adverse events were primarily topical effects of inhaled corticosteroids. Pulmonary function improved significantly during 2 years of fluticasone propionate treatment.

Conclusion: Fluticasone propionate powder, 500 µg twice daily for up to 2 years, was efficacious and well tolerated, with no clinically relevant effects on the hypothalamic-pituitary-adrenal axis, bone density, or ophthalmic parameters in adults with mild asthma. (*J Allergy Clin Immunol* 1999;103:1062-8.)

Key words: Asthma, bone mineral density, fluticasone propionate, hypothalamic-pituitary-adrenal axis, inhaled corticosteroids, long-term safety, posterior subcapsular cataract

Airway inflammation is recognized as the major contributor to the pathophysiology of asthma,¹ and there is increasing evidence that it causes airway remodeling and a progressive decline in lung function.^{2,3} Asthma management guidelines⁴ emphasize the importance of early treatment with inhaled corticosteroids because they are the most effective anti-inflammatory agents for daily use on a long-term basis for control of persistent asthma and may also help to prevent lung function decline. Although inhaled corticosteroids are considered to be effective in treating asthma, concerns about their long-term safety remain.

Fluticasone propionate is a highly effective, topically active corticosteroid with negligible oral systemic bioavailability because of poor absorption from the gastrointestinal tract and rapid inactivation during first-pass hepatic metabolism.⁵ Fluticasone propionate demonstrates good binding and retention characteristics in human lung tissue because of its high lipophilicity combined with a high affinity and selectivity for the human glucocorticoid receptor.⁶ These properties may explain why the concentrations of fluticasone propionate in peripheral lung tissue were found to be approximately 100 times greater than those in serum⁷ and could contribute to its high topical anti-inflammatory activity at lower doses. Fluticasone propionate dosages of 100 to 250 µg twice daily have been shown to be effective in improving pulmonary function and maintaining asthma control in the majority of patients with mild-to-moderate asthma,⁸ with dosages of 500 to 1000 µg twice daily

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Abbreviations used

AUC: Area under the curve

HPA: Hypothalamic-pituitary-adrenal

being reserved for patients with severe asthma,⁹ and also to decrease oral corticosteroid use in patients requiring daily or frequent oral corticosteroids.¹⁰

Although fluticasone propionate shows minimal systemic absorption through the oral route, as with all inhaled corticosteroids, absorption occurs from the lungs and may potentially contribute toward systemic effects. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis, an adverse effect commonly associated with systemic corticosteroid therapy, has been observed with high-dose inhaled corticosteroid therapy.¹¹ However, studies examining whether changes observed in this tightly regulated axis can predict long-term safety risks (eg, on bone mineral density) of this class of therapy are limited.

Previous studies examining the potential deleterious effects of inhaled corticosteroids have generally been short term, confounded by the prior use of inhaled and/or oral corticosteroids, or not placebo-controlled.^{12,13} The aim of this study was to prospectively evaluate the long-term clinical effects of inhaled fluticasone propionate therapy. By including tests of HPA-axis function, this trial also allowed for the opportunity to explore relationships between adrenal function tests and effects on bone density. Because fluticasone propionate 500 µg twice daily is at the threshold for causing effects on the HPA-axis, this dose was selected for this trial.

METHODS

Patients

Male (18 to 50 years) and female (18 to 40 years) patients, diagnosed with asthma according to the American Thoracic Society definition,¹⁴ were enrolled in the study if they had a medical history of asthma for at least 6 months before enrollment, an FEV₁ of at least 60% of predicted value, and limited previous corticosteroid therapy (ie, none during the month before the study, ≤4 weeks of cumulative oral therapy, and ≤1 year of cumulative total therapy from any route). Historical medical records were reviewed to verify prior corticosteroid use. Calcium supplements were limited to 500 mg/day or less of elemental calcium.

Patients were excluded if they had life-threatening asthma or other severe chronic disease; a history of glaucoma, posterior subcapsular cataracts, or blindness; abnormal function of the HPA axis (baseline plasma cortisol concentration <5 µg/dL, postcosyntropin stimulation increase <7 µg/dL, and a peak of <18 µg/dL); L₁ to L₄ bone mineral density less than 2 SDs below that of young normal control subjects (males: <1.010 g/cm²; females: <0.960 g/cm²); used methotrexate, gold salts, or any medication that could affect the course of asthma or its treatment, promote cataract formation, or affect bone turnover; or previously participated in a fluticasone propionate Diskhaler (Glaxo Wellcome Inc, Research Triangle Park, NC) study. Postmenopausal, pregnant, or lactating females were also excluded from the study.

Study design

Sixty-four adults with mild, persistent asthma gave informed consent to participate in this randomized, double-blind, parallel-

group, placebo-controlled study (study protocol no. FLTA3017), which was approved by the institutional review boards at 7 clinical sites in the United States. Patients were instructed regarding use of the Diskhaler device, baseline measurements were performed, and patient compliance was assessed in a 2-week, single-blind, placebo lead-in period. Patients were randomly assigned to treatment with 500 µg fluticasone propionate powder or placebo twice daily for 104 weeks, evaluated weekly for the first 4 weeks, and evaluated monthly thereafter. Long-term safety assessments were conducted at weeks 24, 52, 76, and 104 or early termination. A 5% or greater decrease from screening in lumbar spine bone mineral density resulted in withdrawal from the study. Theophylline, long- and short-acting β-adrenergic agonists, cromolyn sodium, or nedocromil were permitted throughout the study, and up to 2 tapering bursts of systemic corticosteroids (prednisone, methylprednisone, or both for ≤10 days) was allowed as needed during a 12-month period. HPA-axis measurements were not performed during the 6-week period after a burst. All patients followed these guidelines. No limits on dosing were defined.

Measurements

Primary safety assessments included measures of HPA-axis function (measured between 7:30 AM and 8:30 AM), bone mineral density, and ophthalmologic status at screening and at 6-month intervals. HPA-axis function was evaluated by performing intravenous infusions of 0.25 mg of the synthetic adrenocorticotrophic hormone cosyntropin (Cortrosyn, Organon Inc, West Orange, NJ) over a 6-hour period and measuring plasma cortisol concentrations at 0, 2, 4, 6, and 8 hours after the start of infusion. Treatment comparisons were based on mean area under the curve (AUC) or cortisol versus time and mean peak cortisol values obtained during the 6-hour infusion. A peak of less than 35 µg/dL was considered an abnormal response as determined by using fluorescence polarization immunoassay methodology.

Bone mineral density was measured by dual energy x-ray absorptiometry of the L₁ to L₄ region of the spine (posterior-anterior evaluation) by using a Lunar DPX bone densitometer (LUNAR Corporation, Madison, Wis). Dual energy x-ray absorptiometry system performance was monitored for consistency by a central laboratory, and all scans were centrally analyzed to ensure consistent and reproducible results.¹⁵ Serum and urine were analyzed for biochemical markers of bone formation (serum osteocalcin) and resorption (urine N-telopeptide). Ophthalmic examination by board-certified ophthalmologists consisted of best corrected visual acuity, pupil response, motility examination, slit lamp corneal and fundus examination, anterior chamber reaction and depth, and intraocular pressure by using applanation tonometry.

Secondary safety assessments included monitoring of adverse events at each visit, clinical laboratory tests (at screening and weeks 24, 52, 76, and 104), physical examinations (at screening and weeks 52 and 104), oropharyngeal examinations (at every visit except weeks 1 and 3), and a 12-lead electrocardiogram (at screening and week 104). Pulmonary function tests (FEV₁) were conducted at each clinic visit.

Statistical analysis

The intent-to-treat population (all patients exposed to study drug) was used for all safety and efficacy analyses. It was estimated that 30 patients per treatment group would provide a power of 80% to detect a difference of 14% in plasma cortisol AUC. A post hoc statistical analysis indicated that 18 patients per treatment group would provide a power of 80% to be able to discern a 3% difference in bone mineral density between treatment groups.

Testing was performed on data combined from all investigators, controlling for investigator effect. Endpoint data (final evaluable

measurement regardless of whether the patient completed the study) were also analyzed. Treatment differences in morning plasma cortisol, AUC, and peak plasma concentrations during the 6-hour cosyntropin infusion, bone mineral density, serum osteocalcin, urine N-telopeptide/creatinine concentration ratio, and FEV₁ values were analyzed by using the ANOVA *F* test.

RESULTS

Study population

Demography and pulmonary function of the 64 randomized patients were similar across treatment groups (Table I). The mean percent predicted FEV₁ for both groups was 91%. Of the 38 (59%) patients who completed the study, 17 (53%) were receiving placebo and 21 (66%) were receiving active medication. One patient was withdrawn because of lack of efficacy, 2 were withdrawn for adverse events, and 9 failed to return. Most of the other withdrawals (14 patients) were due to protocol violations and noncompliance.

Systemic corticosteroid use, study duration, and compliance

During the study, 6 patients in the placebo group and 8 patients in the fluticasone propionate 500 µg twice daily group received prednisone for asthma as permitted by protocol. Mean daily dose and duration of oral prednisone used during the trial was minimal and similar across treatment groups (placebo, 37 mg/day for 8 days; active, 41 mg/day for 8 days).

More patients in the placebo group withdrew from the study, resulting in a shorter mean duration of study drug exposure (placebo, 529 days; active, 592 days). The mean medication compliance rate per month (actual drug blisters used as a percent of prescribed drug) ranged from 90% to 100% in both groups over the 2-year period.

Safety

HPA axis function. One patient in the placebo group had a peak plasma cortisol level of less than 35 µg/dL, and one had morning plasma cortisol concentrations of less than 5 µg/dL. Five fluticasone propionate-treated patients had morning plasma cortisol concentrations of less than 5 µg/dL, but of these only one also had a post-stimulation peak of less than 35 µg/dL on one occasion. During the study, 5 fluticasone propionate-treated patients had peak plasma cortisol concentrations of less than 35 µg/dL at one visit. However, 4 of these patients achieved peak values of greater than 35 µg/dL after all other infusions, whereas one demonstrated a peak plasma cortisol concentration of less than 35 µg/dL at week 104 only.

Mean morning plasma cortisol concentrations showed no statistically significant differences at any time point during the study. In the fluticasone propionate group minor but statistically significant decreases were noted in mean poststimulation 8-hour AUC (area under the cortisol concentration time curve; *P* = .020) and peak plasma cortisol levels (*P* = .021) after adrenal stimulation at week 104 (Table II). Subanalysis of mean morning plas-

TABLE I. Demographics, disposition, and pulmonary function of patients at baseline

	Placebo	FP 500 µg BID
No. of patients	32	32
Sex, M/F (%)	81/19	91/9
Age, y (mean ± SEM)	31.1 ± 1.3	28.0 ± 1.2
Range	18-49	18-41
Height, in (mean ± SEM)	69.2 ± 0.7	69.7 ± 0.5
Range	62-76	65-80
Weight, lbs (mean ± SEM)	187 ± 4.9	177 ± 5.7
Range	126-261	125-238
No. completed	17 (53%)	21 (66%)
No. withdrawn	15 (47%)	11 (34%)
Reasons for withdrawal		
Lack of efficacy	1 (3%)	0
Adverse events	1 (3%)	1 (3%)
Failed to return	7 (22%)	2 (6%)
Other*	6 (19%)	8 (25%)
FEV ₁ , L	3.86 ± 0.17	4.01 ± 0.17
FEV ₁ , % predicted	91 ± 3.0	91 ± 2.9

FP, Fluticasone propionate; BID, twice daily.

*Includes protocol violations and noncompliance with study medication/procedures.

ma cortisol concentrations, 8-hour AUC, and peak values in patients who did not receive oral/intravenous corticosteroid bursts during the study showed no significant differences from the overall population (data not shown).

Bone mineral density. Bone mineral density of the L₁ to L₄ region of the lumbar spine (Table III) was not significantly different between treatment groups at any time point during the study. Percent change in bone mineral density of individual patients at week 104 shows a similar distribution (Fig 1). During the 2-year period, the mean percent decrease from baseline in bone mineral density was 0.54% in the placebo group and 0.43% in the fluticasone propionate-treated group.

Five patients (2 in the placebo and 3 in the active groups) showed a 5% or greater decrease in bone mineral density from screening, and this resulted in the withdrawal of one patient on active treatment at week 52. Subanalysis of lumbar spine bone mineral density in patients who did not receive oral/intravenous corticosteroid bursts during the study showed no significant differences from the overall population (data not shown).

Bone formation and resorption. Mean serum osteocalcin (Fig 2) or urine N-telopeptide/creatinine concentration ratio (Fig 3) did not differ significantly at any time point.

Ophthalmic examination. Posterior subcapsular cataract, glaucoma, or clinically significant changes from the baseline ophthalmic examination were not observed in any patient during the study. One patient in each treatment group had a cortical cataract at screening that remained unchanged during the study, and one placebo patient had a nuclear cataract at 18 months; however, these were not considered clinically significant by the ophthalmologist. Five patients (3 in the placebo and 2 in the active groups) demonstrated intraocular pressures of greater than 21 mm

TABLE II. Mean (SEM) morning plasma cortisol concentrations ($\mu\text{g/dL}$), 8-hour AUC values ($\mu\text{g} \cdot \text{h/dL}$), and peak values ($\mu\text{g/dL}$) over 8 hours

	Placebo				FP 500 μg BID			
	n	AM	AUC	Peak	n	AM	AUC	Peak
Screening	29	13.4 (0.7)	313.1 (9.4)	50.0 (1.6)	32	15.9 (1.1)	343.2 (10.6)	54.8 (1.6)
Week 24	27	12.8 (1.0)	303.1 (12.8)	48.5 (1.9)	29	14.2 (1.2)	307.3 (10.5)	49.8 (1.8)
Week 52	22	13.1 (1.0)	296.6 (13.2)	48.6 (2.1)	25	14.3 (1.3)	291.0 (10.5)	45.2 (1.5)
Week 76	19	13.3 (1.2)	320.0 (14.0)	51.4 (2.1)	22	12.1 (1.4)	307.1 (11.8)	47.6 (1.7)
Week 104	17	13.0 (1.1)	346.5 (9.8)	55.1 (1.6)	20	13.6 (1.3)	311.0* (14.0)	49.4* (2.2)

FP, Fluticasone propionate; BID, twice daily.

* $P \leq .05$ versus placebo.

TABLE III. Lumbar spine bone mineral density (g/cm^2) and mean change from baseline $\pm$ SEM

	n	Placebo	n	FP 500 μg BID
Screening	32	1.251 $\pm$ 0.023	32	1.246 $\pm$ 0.025
Week 24	28	1.255 $\pm$ 0.025	29	1.258 $\pm$ 0.028
Change from baseline		-0.001 $\pm$ 0.005		0.003 $\pm$ 0.007
Week 52	22	1.248 $\pm$ 0.028	25	1.239 $\pm$ 0.032
Change from baseline		-0.001 $\pm$ 0.006		-0.003 $\pm$ 0.009
Week 76	19	1.244 $\pm$ 0.032	22	1.234 $\pm$ 0.034
Change from baseline		-0.002 $\pm$ 0.006		-0.005 $\pm$ 0.009
Week 104	17	1.229 $\pm$ 0.034	21	1.230 $\pm$ 0.035
Change from baseline		-0.007 $\pm$ 0.010		-0.006 $\pm$ 0.008

FP, Fluticasone propionate; BID, twice daily.

Hg during the study. The 2 patients in the fluticasone propionate group had intraocular pressures of 22 mm Hg at screening. Both patients completed all 104 weeks of the study. One of these patients had an intraocular pressure of 22 mm Hg at week 76, whereas the other did not demonstrate an intraocular pressure of greater than 21 mm Hg at any time other than at screening. These were not considered clinically significant by the ophthalmologist because they were not associated with other signs of glaucoma.

Adverse events. Although adverse events were reported by 62 of 64 patients (97%) during the 2-year period, the type of events were typical of this population. Thirteen serious adverse events were reported by 9 patients (5 in the placebo and 4 in the active groups) and included Wolff-Parkinson-White syndrome and chest pain, dyspepsia, and appendicitis in patients treated with fluticasone propionate. These were considered unrelated to the study drug and did not result in withdrawal from the study. Nonserious adverse events considered unrelated to the study drug resulted in 2 withdrawals. Drug-related events in 2 (6%) placebo-treated patients and in 8 (25%) fluticasone propionate-treated patients occurred mostly in the ear, nose, and throat and lower respiratory tract and were predictable inhaled corticosteroid side effects.

Other laboratory and clinical tests. No treatment-related trends were evident in clinical laboratory tests, physical examinations, vital signs, or electrocardiograms.

Efficacy

Mean change from baseline FEV_1 was significantly improved in the fluticasone propionate group compared

with the placebo group at several time points during the study and at endpoint (placebo, -0.17 L; active, 0.04 L; $P = .033$).

DISCUSSION

Few studies have prospectively evaluated the effects of long-term administration of high doses of inhaled corticosteroids on the HPA axis. Prior use of systemic corticosteroids has been a confounding issue in many studies. This trial was designed to evaluate the effect of treatment over 2 years with 1000 μg of fluticasone propionate on adrenal function (at baseline and after stimulation with exogenous adrenocorticotrophic hormone) in patients with minimal prior use of systemic corticosteroids.

The dose of fluticasone propionate used in this trial is greater than that required by most patients with asthma because of the high topical anti-inflammatory activity of fluticasone propionate,¹⁶ and because patients in this study had mild asthma, it probably resulted in greater inhalation and absorption of the drug.¹⁷⁻²⁰ Yet despite this, treatment with 500 μg twice daily fluticasone propionate powder for up to 2 years in adults with persistent asthma was well tolerated in this prospective study, with only minor effects on the HPA axis and no significant effects on the skeletal system. Systemic corticosteroid bursts administered to a few patients did not compromise evaluation of HPA-axis function or bone density.

Treatment with fluticasone propionate for 2 years did not affect mean morning plasma cortisol concentrations. Minor but statistically significant differences were observed in plasma cortisol AUC and peak plasma corti-

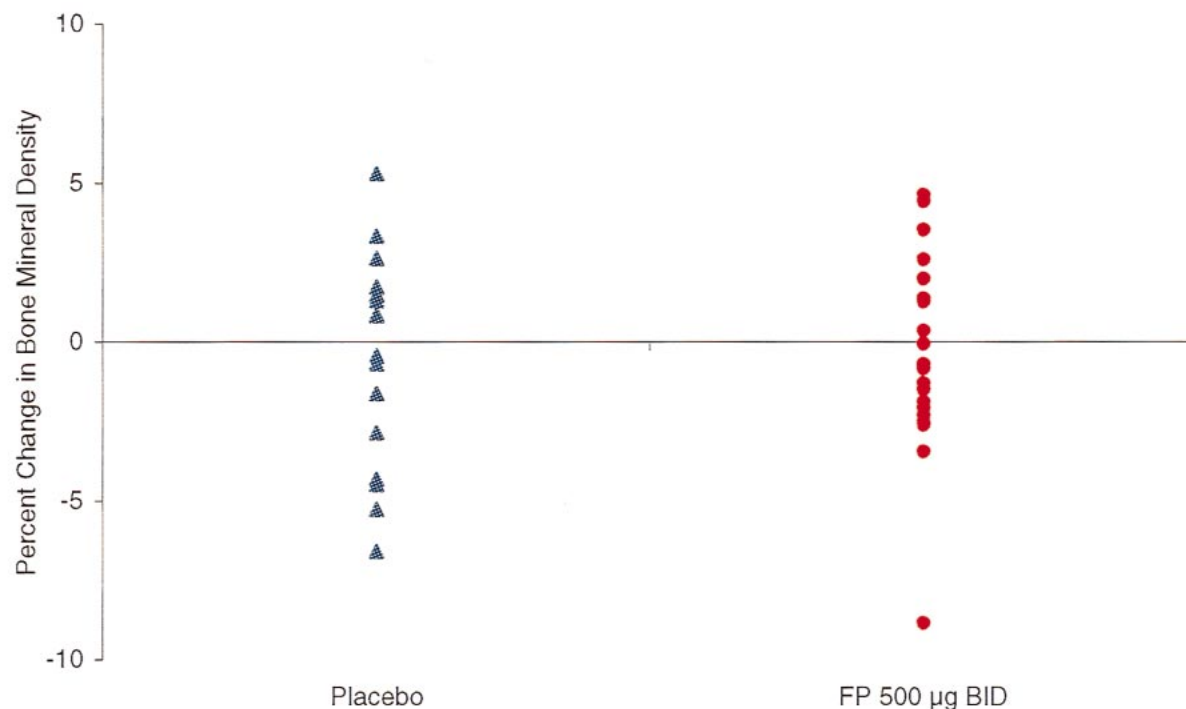


FIG 1. Bone mineral density. Percent change from screening at 2 years is shown. *FP*, Fluticasone propionate; *BID*, twice daily.

sol concentrations after cosyntropin stimulation at the end of 2 years. However, the clinical significance of this is uncertain because the values in the fluticasone propionate group were within the range of placebo values over the 2-year period. The lack of a progressive decline in HPA-axis function with fluticasone propionate treatment provides reassurance that there does not appear to be a cumulative effect of treatment.

Osteoporosis has been estimated to occur in 30% to 50% of patients receiving long-term oral corticosteroid treatment,²¹ with a marked effect on the trabecular bone, including an increased risk of fracture.²² The extent of bone loss appears to be directly correlated with dose and duration of oral corticosteroid therapy. Bone loss ranging from 8% to 18% was reported in patients dosed on alternate days with 17 to 51 mg of prednisone for 1 year.²³ Data suggest an early onset of deterioration, with rapid bone loss occurring predominantly during the first 6 months followed by a slower but continuing decline.²⁴

Serologic and urine markers of bone turnover are also used to assess long-term risks of osteoporosis. Some short-term studies have indicated that inhaled corticosteroids reduce bone formation²⁵ or increase bone resorption.²⁶ However, treatment with at least 800 µg of inhaled budesonide or beclomethasone dipropionate for 2.5 years manifested no detrimental effects on bone formation or resorption when evaluated by 3 conventional and 2 novel parameters of bone metabolism.²⁷ In fact, some short-term changes in serum parameters were reversed over a longer period of time, suggesting that such alterations may not be pertinent indicators of long-term changes in bone turnover.

Many design issues, which confounded previous assessments of the effects of inhaled corticosteroids on bone metabolism, were prospectively avoided in this study. Previous systemic corticosteroid use was limited by enrollment criteria, a low radiation dose technique (dual energy x-ray absorptiometry) was used to measure cortical and trabecular lumbar spine bone mineral density, and long-term changes in indicators of bone formation/resorption were evaluated. To eliminate the confounding effect of menopause on bone loss, the study was limited to premenopausal women, especially because postmenopausal relative to premenopausal women do not appear to be more sensitive to the osteopenic effects of corticosteroids.²⁸⁻³⁰

Results of this rigorously designed, prospective study showed that 2 years of treatment with inhaled fluticasone propionate 500 µg twice daily did not affect biochemical markers of bone formation or resorption. In addition, no significant differences were noted in lumbar spine body bone mineral density, and a similar proportion of patients in the placebo and fluticasone propionate treatment groups experienced a 5% or greater decline in bone density.

A potential limitation of these results is that the study may not have been adequately powered to demonstrate statistically significant differences in bone mineral density between treatment groups. A post hoc statistical analysis indicates that 18 patients would be able to discern a 3% difference in bone mineral density between treatment groups with 80% power. A greater than 3% decrease in bone mineral density was observed in a group of patients

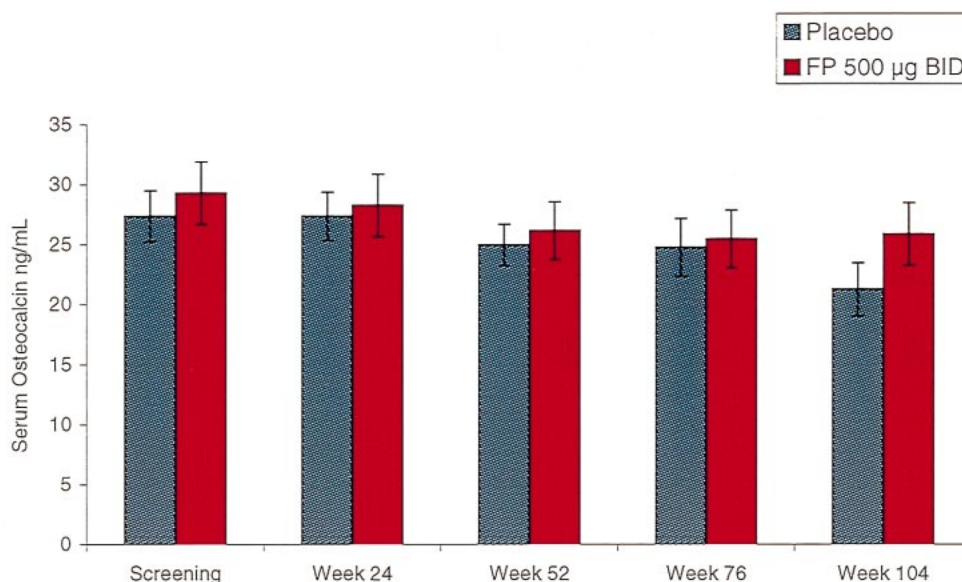


FIG 2. Mean ($\pm$ SEM) serum osteocalcin concentrations. *FP*, Fluticasone propionate; *BID*, twice daily.

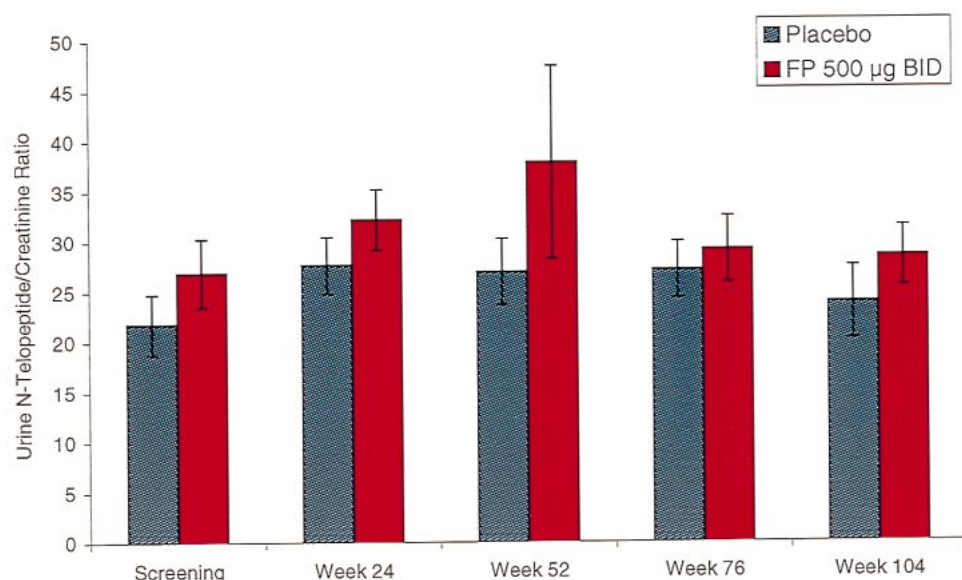


FIG 3. Mean ($\pm$ SEM) urine N-telopeptide/creatinine concentration ratio. *FP*, Fluticasone propionate; *BID*, twice daily.

treated with approximately 10 to 20 mg of prednisone per day for 1 year.²⁹ Additionally, clinically significant decreases of approximately 3% in bone mineral density (bone loss of 2- to 3-fold expected rates) was observed in 19 patients treated with low-dose oral corticosteroids (average daily prednisone dose of 6 mg) over a period of 14 months.³¹

These data suggest that the present trial should have had adequate power to discriminate a substantial treatment effect after 2 years of high-dose fluticasone propionate therapy. The lack of a trend suggestive of a treatment effect, with a mean change in lumbar spine bone mineral

density of -0.43% (active) compared with -0.54% (placebo), at doses primarily reserved for patients with severe asthma, provides reassurance that treatment with fluticasone propionate at doses up to 500 μg twice daily is unlikely to cause clinically meaningful changes in bone density.

Posterior subcapsular cataracts and glaucoma are known complications of chronic oral corticosteroid therapy. The risk of ocular hypertension with inhaled corticosteroids is uncertain; however, a few cases have been reported.³² Few prospective, controlled trials have evaluated the development of posterior subcapsular cataracts associated with inhaled corticosteroid use, and reports of

such an association have been confounded by the prior use of oral corticosteroids¹³ or nonvalidated information obtained by questionnaire in a population-based cross-sectional study.³³ Although the present study lacked the power to detect significant treatment differences in ophthalmic parameters, patients treated for up to 2 years with fluticasone propionate showed no signs of glaucoma, and the absence of posterior subcapsular cataracts is consistent with studies in children³⁴ and adults³⁵ treated with inhaled corticosteroids.

Results of this double-blind, controlled study, which prospectively evaluated the effects of an inhaled corticosteroid over a period of 2 years in asthma patients with minimal prior systemic corticosteroid use, suggest that long-term treatment with fluticasone propionate at 1000 µg/day is not associated with adverse effects on bone density or ophthalmic parameters. Although minor HPA-axis effects consistent with previous reports were observed, these changes were not associated with the development of the side effects commonly associated with systemic corticosteroid administration. Results from this trial support the long-term safety of fluticasone propionate for the chronic treatment of inflammation in asthma.

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