

Effects of fluticasone propionate, triamcinolone acetonide, prednisone, and placebo on the hypothalamic-pituitary-adrenal axis

James T. C. Li, MD,^a Marc F. Goldstein, MD,^b Gary N. Gross, MD,^c Michael J. Noonan, MD,^d Stephen Weisberg, MD,^e Lisa Edwards, PhD,^f Kenneth D. Reed, BS,^f and Paula R. Rogenes, PhD^f Rochester and Minneapolis, Minn, Mt Laurel, NJ, Dallas, Tex, Portland, Ore, and Research Triangle Park, NC

Background: Many clinicians are reluctant to prescribe inhaled corticosteroids because of concerns over potential effects on the hypothalamic-pituitary-adrenal axis.

Objective: The purpose of this study was to compare the adrenal responses to 6-hour cosyntropin infusion after treatment with fluticasone propionate aerosol, triamcinolone acetonide aerosol, prednisone, and placebo for 4 weeks, a sufficient time interval to assess any effects on the adrenal response to stress.

Methods: This double-blind, triple-dummy, randomized, placebo-controlled study was conducted in 128 patients to evaluate adrenal response to 6-hour cosyntropin infusion (a clinically relevant method for evaluating adrenal function) after 28 days of treatment with fluticasone propionate aerosol 88 µg or 220 µg twice daily, triamcinolone acetonide aerosol 200 µg 4 times daily or 400 µg twice daily, prednisone 10 mg once daily, and placebo.

Results: After 28 days of treatment, mean plasma cortisol response to cosyntropin over 12 hours after initiation of the 6-hour infusion was similar among fluticasone, triamcinolone, and placebo groups; cortisol response was significantly ($P < .05$) reduced after treatment with prednisone compared with the other treatment groups. Mean 8-hour area under the plasma cortisol concentration-time curves and peak plasma cortisol concentrations were significantly ($P \leq .003$) lower with prednisone than any other treatment; no significant differences were noted between placebo and either of the fluticasone groups in any assessment. Mean reductions from baseline in area under the plasma cortisol concentration time curves and peak cortisol concentrations were significantly ($P < .05$) greater with triamcinolone 400 µg twice daily compared with placebo.

Conclusion: These results suggest that fluticasone propionate at therapeutic doses has effects on the hypothalamic-pituitary-adrenal axis comparable to that of placebo and has significant-

ly less effect than prednisone as measured by 6-hour cosyntropin infusion after 28 days of treatment. (*J Allergy Clin Immunol* 1999;103:622-8.)

Key words: Fluticasone propionate, triamcinolone acetonide, hypothalamic-pituitary-adrenal axis, inhaled corticosteroids, asthma

Inhaled corticosteroids are the most potent and effective anti-inflammatory medications currently available for the treatment of mild, moderate, and severe persistent asthma.¹ However, some clinicians are reluctant to prescribe inhaled corticosteroids because of concerns over potential systemic side effects, including effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of most concern to clinicians is that during times of stress (eg, surgery, trauma, illness) the adrenal glands may not be able to mount a sufficient cortisol response (Addisonian crisis) in patients who have received long-term treatment with corticosteroids.

The 2 types of tests used to measure HPA axis function are those that evaluate the basal secretion of cortisol from the adrenal gland (morning plasma cortisol concentrations, diurnal variation of cortisol concentrations, 24-hour urinary excretion of cortisol and metabolites) and those that evaluate the integrity of various components of the HPA axis or adrenal reserve (adrenal response after stimulation with cosyntropin, metyrapone, or insulin-induced hypoglycemia). All inhaled corticosteroids at various doses have shown the ability to reduce basal cortisol output.⁷ However, the risk of life-threatening adrenal insufficiency depends on the ability of the HPA axis to respond to stress or illness.^{7,8} Therefore a more clinically relevant and relatively easily performed test for evaluating adrenal function is the measurement of cortisol response to cosyntropin; this may be given as a bolus or as an infusion over 1 hour or 6 hours (or more).⁸ The 6-hour cosyntropin infusion is useful in distinguishing more subtle changes than could be detected by a short test and is the most reliable means of determining adrenal reserve capacity.⁹

Many studies have compared the effect of inhaled fluticasone propionate on the HPA axis with that of other inhaled corticosteroids, but most of these studies measured only basal adrenal function and had other design limitations.¹⁰⁻¹⁶ The current study is the first to compare

From ^athe Mayo Clinic Foundation, Rochester; ^bLarchmont Medical Center II, Mt Laurel; ^cDallas Allergy and Asthma Center, Dallas; ^dAllergy Associates Research Center, Portland; ^eCriterion Group, Minneapolis; and ^fGlaxoWellcome, Inc, Research Triangle Park.

Funded by a grant from GlaxoWellcome Inc.

Received for publication June 9, 1998; revised Nov 16, 1998; accepted for publication Dec 14, 1998.

Reprint requests: James T. C. Li, MD, Mayo Clinic Foundation, 200 1st St SW, Rochester, MN 55905.

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0091-6749/99 \$8.00 + 0 1/1/96647

Abbreviations used

AUC: Area under the plasma cortisol concentration time curves
HPA: Hypothalamic pituitary adrenal
TAA: Triamcinolone acetonide

the adrenal responses to 6-hour cosyntropin infusion after treatment with fluticasone propionate aerosol, triamcinolone acetonide (TAA) aerosol, prednisone, and placebo for 4 weeks, which is a sufficient time interval to assess any effects on the adrenal response to stress. Because recent evidence^{17,18} suggests that fluticasone propionate powder 500 µg/day (250 µg twice daily) is superior in efficacy to TAA aerosol 800 µg/day (200 µg 4 times daily) in patients with asthma, these doses were included to evaluate the HPA axis effects of these inhaled corticosteroids.

METHODS

Patient selection

Patients were nonsmokers between the ages of 18 and 50 years who had asthma (defined in accordance with American Thoracic Society criteria¹⁹) for at least 6 months preceding the study. All patients had an FEV₁ value of 50% or more of predicted normal values for age, sex, and height.^{20,21}

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, inhaled, or injectable corticosteroids within 4 weeks of the start of the study; use of 140 mg or more of prednisone or its equivalent in any dosage form or regimen during the past year; significant concomitant illness; immunotherapy requiring a change in dosage regimen within 12 weeks; reversal of nocturnal sleeping hours; or concurrent use of any other prescription or over-the-counter medication that might affect the course of asthma, interact with sympathomimetic amines, or confound the cortisol assay.

Study design

This was a double-blind, triple-dummy, randomized, placebo-controlled, parallel-group study conducted at 10 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.

The primary measure of safety for this study was HPA axis function. Patients were admitted to the clinic for two 12-hour days to permit cosyntropin stimulation tests conducted at a 6-week interval (1 day 2 weeks before the treatment and 1 day immediately after 4 weeks of treatment). Each cosyntropin infusion stimulation test consisted of an infusion of 0.25 mg cosyntropin (Cortrosyn; Organon Inc, West Orange, NJ) in 500 mL 0.9% NaCl solution over a 6-hour period. Blood samples for plasma cortisol were drawn immediately before the infusion and 1, 2, 4, 6, 8, 10, and 12 hours after the start of the infusion. Patients were required to have a baseline morning prestimulation plasma cortisol concentration of 7 µg/dL or more, a poststimulation increase in plasma cortisol concentration of 7 µg/dL or more to a concentration of 18 µg/dL or more in response to cosyntropin infusion, and a normal morning ACTH plasma concentration (9 to 52 pg/mL) at baseline.

The effects of the study treatment on HPA axis function were assessed with the following measurements for each patient: pre-

stimulation morning plasma cortisol concentrations; area under the plasma-concentration time curve (AUC) for cortisol over the 8-hour time period after the start of the cosyntropin infusion stimulation test; peak plasma cortisol concentrations obtained in the same 8-hour period (8-hour peak); mean plasma cortisol concentrations over 12 hours in response to cosyntropin infusion; and the number and percentage of patients who had an abnormal response to the 6-hour cosyntropin infusion stimulation test.

Secondary measures of safety included physical examinations, clinical laboratory tests, and adverse event assessments. Investigators determined whether or not an adverse event was potentially drug related.

Patients meeting all entry criteria were randomly assigned to receive 1 of the following treatments by way of metered-dose inhaler for 28 days: (1) fluticasone propionate (Flovent Inhalation Aerosol; GlaxoWellcome Inc, Research Triangle Park, NC) 88 µg twice daily, placebo TAA (Azmecort; Rhone-Poulenc Rorer Pharmaceuticals, Inc, Collegeville, Pa)* oral inhaler 2 puffs 4 times daily or 4 puffs twice daily, 1 placebo capsule every morning; (2) fluticasone propionate 220 µg twice daily, placebo Azmacort oral inhaler 2 puffs 4 times daily or 4 puffs twice daily, 1 placebo capsule every morning; (3) TAA 200 µg 4 times daily, placebo Flovent oral inhaler 2 puffs twice daily, 1 placebo capsule every morning; (4) TAA 400 µg twice daily, placebo Flovent oral inhaler 2 puffs twice daily, 1 placebo capsule every morning; (5) prednisone 10 mg capsule every morning, placebo Flovent oral inhaler 2 puffs twice daily, placebo Azmacort oral inhaler 2 puffs 4 times daily or 4 puffs twice daily; or (6) placebo Flovent oral inhaler 2 puffs twice daily, placebo Azmacort oral inhaler 2 puffs 4 times daily or 4 puffs twice daily, 1 placebo capsule every morning. The Azmacort oral inhaler is a metered-dose inhaler with an attached spacer device. A spacer device was not used with the fluticasone propionate metered-dose inhaler. Because the study was triple-dummy, each patient received 2 inhalers and a bottle of overencapsulated prednisone/placebo tablets. To maintain study drug blinding, all patients not assigned to a TAA treatment group were randomly assigned to administer their placebo treatment inhalers on either a twice daily or 4 times daily regimen. Patients were instructed on the proper use of a metered-dose inhaler. Patients were also instructed to mouth-rinse after each dose of study medication.

Assays

Blood samples were sent from each site to a central laboratory (Covance Central Laboratory Services, Inc, Indianapolis, Ind). Plasma cortisol concentrations were determined by the use of HPLC with a reported sensitivity of 0.5 µg/dL. Laboratory personnel were blinded to study drug allocation.

Statistical analyses

Analyses for HPA axis function used the compliance population, comprising all patients who were exposed to the study drug and who had completed both the pretreatment and posttreatment 6-hour infusion tests. All other analyses used the intent-to-treat population, comprising patients who were exposed to the study drug. All statistical tests were 2-sided, with treatment differences at or below the *P* = .05 level considered statistically significant. Enrollment of a minimum of 20 patients per treatment group provided at least 80% power to detect a difference of 14% in AUC of plasma cortisol.

The 8-hour AUC of plasma cortisol, the 8-hour peak plasma cor-

*Each actuation of Azmacort releases 200 µg TAA of which approximately 100 µg are delivered from the unit. Each actuation of Flovent Inhalation Aerosol (1% lecithin formulation) delivers 50 µg or 125 µg of fluticasone propionate from the valve and 44 µg or 110 µg of fluticasone propionate from the actuator, respectively.

TABLE I. Baseline characteristics and patient disposition

	FP 88 Placebo (n = 17)	FP 220 μg bid (n = 22)	TAA 200 μg bid (n = 24)	TAA 400 μg qid (n = 21)	Prednisone μg bid (n = 21)	10 mg qd (n = 23)
Men/women (%)	82/18	68/32	58/42	67/33	76/24	74/26
Age (y)						
Mean	31	30	33	34	29	30
Range	19-41	19-42	18-53	23-47	18-42	19-55
Ethnic origin (%)						
White	16 (94)	21 (95)	21 (88)	18 (86)	19 (90)	19 (83)
Other	1 (6)	1 (5)	3 (13)	3 (15)	2 (10)	4 (17)
Height (in)	69.8	68.8	67.2	69.0	68.7	69.0
Weight (lbs)	192.8	174.6	164.2	193.3	189.5	184.2
FEV ₁ value (% predicted)	89.1	82.5	88.2	87.9	84.3	85.6
Concurrent medications (%)						
Salmeterol	0	0	1 (4)	0	0	1 (4)
Theophylline	2 (12)	0	3 (13)	0	0	0
Cromolyn	0	1 (5)	1 (4)	1 (5)	0	1 (4)
Nedocromil	0	0	1 (4)	0	0	0
No. completed (%)	17 (100)	21 (95)	23 (96)	21 (100)	21 (100)	22 (96)
No. of withdrawals (%)	0	1 (5)	1 (4)	0	0	1 (4)
Adverse event	0	0	1	0	0	0
Lack of efficacy	0	0	0	0	0	0
Other*	0	1	0	0	0	1

FP, Fluticasone propionate; bid, twice daily; qid, 4 times daily; qd, once daily.

*Failure to return or relocation.

tisol, the mean change from baseline, and the percent change from baseline in AUC and peak plasma cortisol were summarized by treatment group. Comparisons across treatment groups for each measure of HPA axis function were based on the overall *F* tests from 2-way ANOVAs in which the model included terms for treatment and investigator. Comparisons between treatment groups were based on contrasts constructed for all pairwise treatment combinations. The number of plasma cortisol abnormalities was tabulated by treatment group, and Cochran-Mantel-Haenszel tests were used to test for overall and pairwise differences adjusted for investigator. The incidence of adverse events was tabulated by treatment group, and treatment differences were tested with Fisher's exact test.

RESULTS

A total of 128 patients were randomly assigned to treatment. Randomization resulted in comparable treatment groups at baseline (no significant differences among treatment groups) with respect to patient demographics and baseline pulmonary function. The demographics and disposition of patients are shown in Table I.

Mean 12-hour response

The mean plasma cortisol response to the 6-hour cosyntropin infusion over 12 hours is shown in Fig 1. Mean cortisol response at baseline was similar among all treatment groups. After 28 days of treatment, mean plasma cortisol concentrations at each time point over 12 hours were significantly ($P < .05$) reduced after treatment with prednisone compared with each of the other treatment groups (except at hour 0 with triamcinolone 400 μg twice daily and at hour 12 with placebo, TAA200, and

TAA400). Mean plasma cortisol concentrations throughout 12 hours were similar among the fluticasone propionate, TAA, and placebo treatment groups.

Morning plasma cortisol concentrations (prestimulation)

Mean morning plasma cortisol concentrations are summarized in Table II. There were no statistically significant differences among the 6 treatment groups in mean morning plasma cortisol concentrations at baseline. However, after 28 days of treatment, there was a statistically significant overall treatment difference in mean morning plasma cortisol concentrations ($P = .007$); pairwise comparisons revealed mean morning plasma cortisol concentrations were significantly lower ($P \leq .045$) in the prednisone group than in any other treatment groups with the exception of the TAA 400 μg twice daily group. There were no significant differences between the placebo treatment group and either of the fluticasone propionate treatment groups. Mean morning plasma cortisol concentrations were significantly ($P = .034$) lower in the TAA 400 μg twice daily treatment group compared with the placebo group. There were no significant pairwise differences between the fluticasone propionate and TAA treatment groups.

8-Hour AUC

Mean 8-hour AUC results are summarized in Table III. There were no statistically significant differences among the 6 treatment groups in mean 8-hour AUC at baseline. Mean change and percent change from baseline in 8-hour AUC revealed significantly ($P < .001$) greater mean

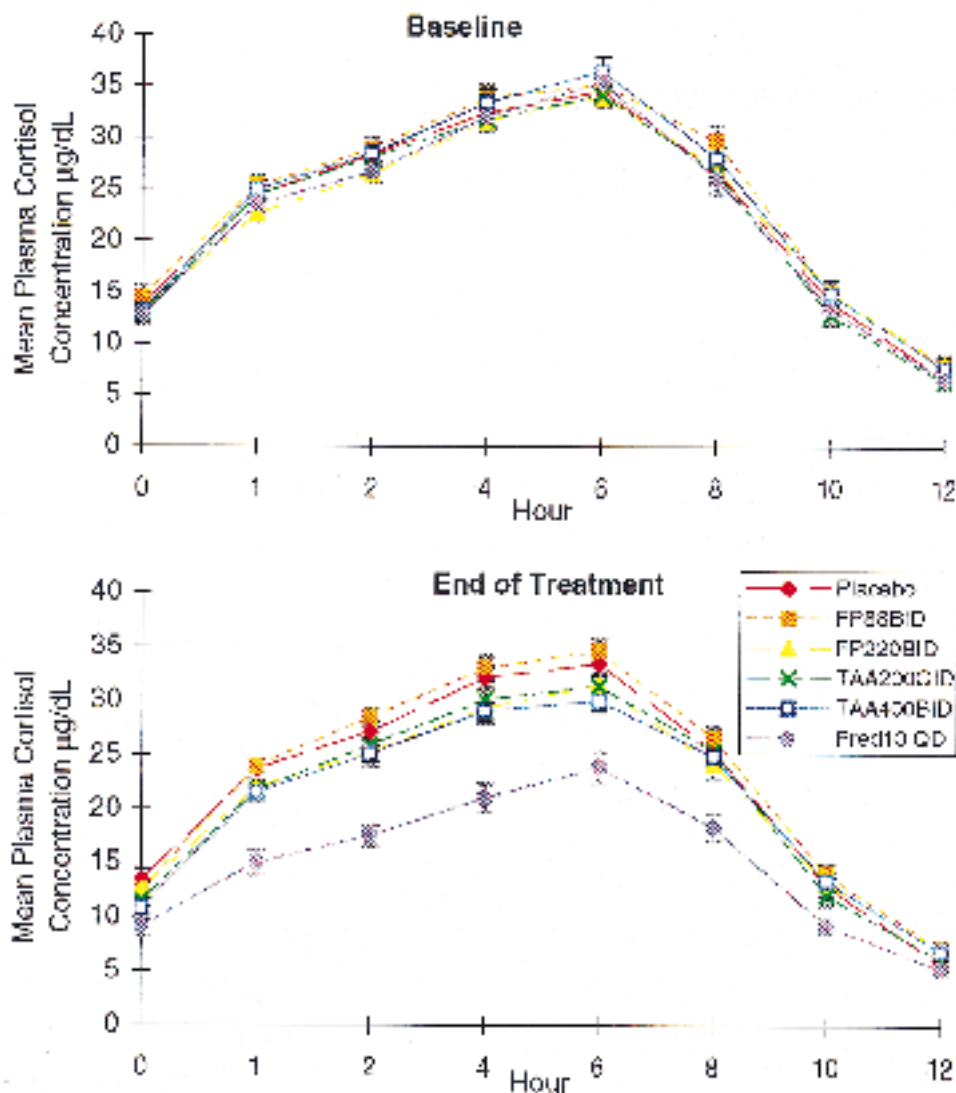


FIG 1. Mean plasma cortisol response over 12 hours ($P < .05$ for all treatment groups at end of treatment versus prednisone, except at hour 0 for TAA400 twice daily and at hour 12 for placebo, TAA200, and TAA400). FP, fluticasone propionate.

decreases in 8-hour AUC in the prednisone treatment group than in any other treatment group; there were no significant differences in mean change and percent change from baseline 8-hour AUC between the placebo group and either of the fluticasone propionate treatment groups. Mean changes and percent changes from baseline in 8-hour AUC were significantly greater in the TAA 400 μ g twice daily treatment group than in the placebo group ($P = .028$ and $P = .022$, respectively) and the fluticasone propionate 88 μ g group ($P = .023$ and $P = .021$, respectively). Individual patient 8-hour AUC data at the end of treatment are presented in Fig 2.

8-Hour peak plasma cortisol concentrations

Mean 8-hour peak plasma cortisol concentrations are shown in Table IV. There were no statistically significant

differences among the 6 treatment groups in mean 8-hour peak plasma cortisol at baseline. Mean change and percent change from baseline revealed significantly greater mean decreases in peak cortisol concentrations in the prednisone treatment group than in any other treatment group ($P \leq .003$); there were no significant differences in mean change and percent change from baseline in peak cortisol concentrations between the placebo and either of the fluticasone propionate treatment groups. Both the mean change and percent change from baseline reductions were significantly greater in the TAA 400 μ g twice daily treatment group compared with the placebo group ($P \leq .027$) and the fluticasone propionate 88 μ g treatment group ($P \leq .013$). Individual patient peak plasma cortisol concentrations at the end of treatment are presented in Fig 2.

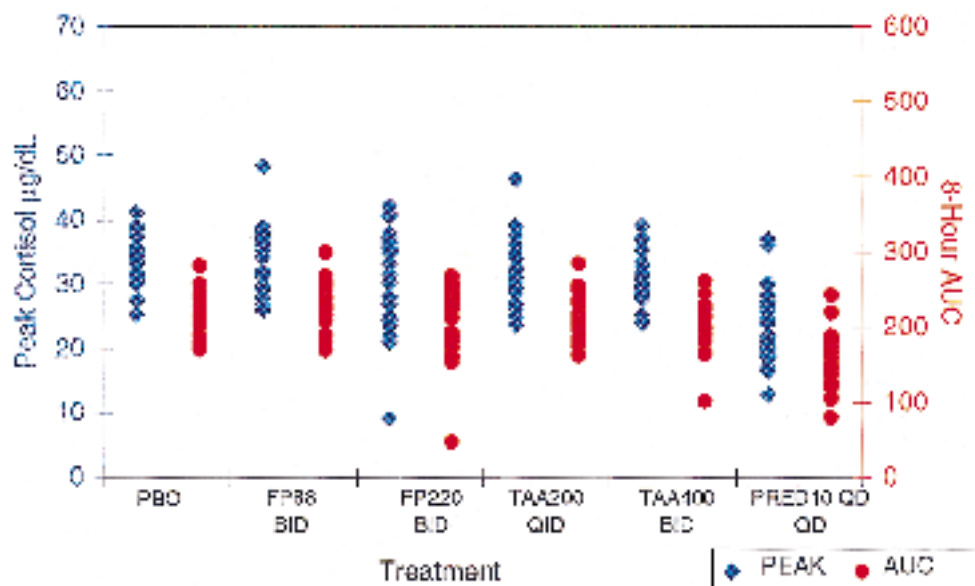


FIG 2. Individual patient 8-hour peak cortisol concentrations and 8-hour AUC at end of 4 weeks. FP, fluticasone propionate.

TABLE II. Mean morning plasma cortisol concentrations, milligrams per deciliters

	Placebo (n = 17)	FP 88 µg bid (n = 21)	FP 220 µg bid (n = 23)	TAA 200 µg qid (n = 21)	TAA 400 µg bid (n = 20)	Prednisone 10 mg qd (n = 21)
Baseline (SEM)	13.8 (1.1)	14.6 (1.1)	13.1 (0.9)	12.8 (0.9)	13.1 (1.0)	12.8 (1.0)
End of treatment (SEM)	13.4 (1.1)	12.5 (0.7)	12.5 (0.8)	11.5 (0.6)	10.8 (0.9)*	9.1 (0.9)*†
Change from baseline (SEM)	-0.4 (1.0)	-2.1 (1.0)	-0.6 (0.7)	-1.3 (0.7)	-2.4 (1.2)	-3.7 (1.4)*‡

FP, Fluticasone propionate; bid, twice daily; qid, 4 times daily; qd, once daily.

* $P \leq .04$ versus placebo.

† $P < .05$ versus FP 88, FP 220, and TAA 200.

‡ $P = .012$ vs FP 220.

TABLE III. Mean 8-hour AUC (µg/dL per hour)

	Placebo (n = 17)	FP 88 µg bid (n = 21)	FP 220 µg bid (n = 23)	TAA 200 µg qid (n = 21)	TAA 400 µg bid (n = 20)	Prednisone 10 mg qd (n = 21)
Baseline (SEM)	232.1 (8.0)	243.7 (8.4)	227.1 (6.5)	230.3 (7.2)	236.7 (10.3)	228.9 (9.6)
Change from baseline (SEM)	-7.0 (7.9)	-8.8 (6.6)	-15.0 (10.6)	-16.7 (6.7)	-33.5 (6.2)*†	-76.3 (9.9)*‡
Percent change from baseline (SEM)	-1.8 (3.4)	-2.6 (2.6)	-5.7 (4.4)	-6.4 (3.0)	-13.0 (2.8)*†	-32.5 (3.5)*‡

FP, Fluticasone propionate; bid, twice daily; qid, 4 times daily; qd, once daily.

* $P \leq .028$ vs placebo.

† $P \leq .023$ vs FP 88.

‡ $P < .001$ vs FP 88, FP 220, TAA 200, TAA 400.

Plasma cortisol abnormalities

The frequencies of plasma cortisol abnormalities that occurred at baseline were similar across treatment groups. The percentage of patients with baseline morning plasma cortisol concentrations of less than 7 µg/dL at the end of treatment was notably greater in the prednisone treatment group (24%) than in the placebo (6%), fluticasone propionate 88 µg (5%), fluticasone propionate 220 µg twice daily (4%), TAA 200 µg 4 times daily (10%),

and TAA 400 µg twice daily (15%) treatment groups, although these differences were not statistically significant. Three patients (14%) in the prednisone treatment group and 1 patient (4%) in the fluticasone propionate 220 µg treatment group had poststimulation cortisol increases less than 7 µg/dL ($P = .04$, overall). Similarly, 3 patients (14%) in the prednisone treatment group and 1 patient (4%) in the fluticasone propionate 220 µg treatment group (the same patient who had a poststimulation cortisol increase below 7 µg/dL) had poststimulation

TABLE IV. Mean 8-hour peak plasma cortisol concentrations ($\mu\text{g/dL}$)

	Placebo (n = 17)	FP 88 $\mu\text{g bid}$ (n = 21)	FP 220 $\mu\text{g bid}$ (n = 23)	TAA 200 $\mu\text{g qid}$ (n = 21)	TAA 400 $\mu\text{g bid}$ (n = 20)	Prednisone 10 mg qd (n = 21)
Baseline (SEM)	35.2 (1.3)	36.4 (1.2)	34.4 (1.1)	34.3 (1.2)	36.7 (1.4)	35.7 (1.6)
Change from baseline (SEM)	-1.6 (1.2)	-1.4 (1.0)	-2.7 (1.7)	-2.7 (1.2)	-6.0 (1.1)*†	-11.7 (1.7)*‡
Percent change from baseline (SEM)	-3.1 (3.5)	-3.1 (2.7)	-6.8 (4.7)	-6.7 (3.3)	-14.9 (3.0)*†	-31.6 (3.7)*‡

FP, Fluticasone propionate; *bid*, twice daily; *qid*, 4 times daily; *qd*, once daily.

* $P \leq .027$ vs placebo.

† $P \leq .013$ vs FP 88.

‡ $P \leq .003$ vs FP 88, FP 220, TAA 200, TAA 400.

peak cortisol concentrations below $18 \mu\text{g/dL}$ ($P = .062$, overall; Fig 2). The patient with the low cortisol response in the fluticasone propionate $220 \mu\text{g}$ group had a low baseline morning plasma cortisol concentration of $3.7 \mu\text{g/dL}$; poststimulation cortisol response was normal at baseline for this patient.

Other safety parameters

No clinically significant differences were observed among treatment groups with respect to abnormal physical examination findings or clinical laboratory test results. There were no statistically significant differences between treatment groups in the number of patients experiencing potentially drug-related adverse events. No serious drug-related adverse events occurred. One patient treated with fluticasone propionate $220 \mu\text{g}$ withdrew from the study because of an adverse event (esophagitis) that was considered by the investigator to be possibly related to study drug treatment. The most commonly reported adverse events considered by the investigator to be potentially related to treatment were throat irritation and headaches. Throat irritation occurred in 3 patients treated with fluticasone propionate $88 \mu\text{g}$, 2 patients treated with fluticasone propionate $220 \mu\text{g}$, and 1 patient in each of the placebo, TAA $200 \mu\text{g}$, and prednisone treatment groups. Headaches occurred in 2 patients treated with fluticasone propionate $88 \mu\text{g}$, 3 patients treated with fluticasone propionate $220 \mu\text{g}$, and 2 patients treated with TAA $400 \mu\text{g}$.

DISCUSSION

The results from this study demonstrate that the effect of fluticasone propionate $176 \mu\text{g/day}$ or $440 \mu\text{g/day}$ and TAA $800 \mu\text{g/day}$ on the HPA axis as measured by cortisol response to 6-hour cosyntropin infusion (mean plasma cortisol 12-hour response, 8-hour AUC, 8-hour peak plasma cortisol concentrations, and morning plasma cortisol concentrations) were comparable to those of placebo after 28 days of treatment in patients with asthma, although significantly lower mean values were noted after treatment with TAA $400 \mu\text{g}$ twice daily compared with placebo in some HPA axis measurements. Prednisone produced significantly greater suppression of HPA axis function than did any of the other treatments, as assessed by peak plasma cortisol concentrations and

AUC during cosyntropin stimulation. Measurements of unstimulated morning plasma cortisol concentrations were significantly lower after treatment with prednisone compared with any of the other treatments except TAA $400 \mu\text{g}$ twice daily. In this study, the inclusion of a prednisone treatment arm, which showed significant effects on the HPA axis, indicated that the 6-hour infusion test was sensitive enough to detect treatment differences between the inhaled corticosteroids.

Streeten et al⁹ and other investigators²²⁻²⁴ have reported that the 6-hour cosyntropin infusion test is more reliable than the short test, presumably because both false-negative and false-positive results have been reported occasionally with the short test. Because the 6-hour test produces a maximal cortisol response, the likelihood of false responses is greatly reduced.

The sensitivity of the 6-hour cosyntropin infusion test is corroborated by the results of other studies. Kellerman et al²⁵ evaluated the adrenal response to the 6-hour cosyntropin infusion test after treatment with fluticasone propionate (administered by way of metered dose inhaler) $220 \mu\text{g}$, $440 \mu\text{g}$, $660 \mu\text{g}$, and $880 \mu\text{g}$ (ex-valve doses) twice daily, prednisone 10 mg once daily, and placebo. All inhaled fluticasone propionate doses had less effect on the HPA axis than did prednisone. The percentage of patients with poststimulation peak plasma cortisol concentrations of less than $18 \mu\text{g/dL}$ in that study were 0%, 0%, 10%, 16%, 12%, and 29% in the placebo, fluticasone propionate $220 \mu\text{g}$, fluticasone propionate $440 \mu\text{g}$, fluticasone propionate $660 \mu\text{g}$, fluticasone propionate $880 \mu\text{g}$, and prednisone treatment groups, respectively; in the current study, percentages of poststimulation abnormalities were 4% (1 patient) in the fluticasone propionate $220 \mu\text{g}$ treatment group and 14% (3 patients) in the prednisone treatment group. The lower dosage regimen of fluticasone propionate $88 \mu\text{g}$ twice daily in this study was not associated with any plasma cortisol abnormalities. Mean 12-hour cortisol responses to 6-hour cosyntropin infusion with fluticasone propionate powder $500 \mu\text{g}$ twice daily and TAA aerosol $500 \mu\text{g}$ twice daily were not significantly different after 4 weeks of treatment in 264 patients with asthma in 2 separate double-blind, placebo-controlled studies. In those studies, 4%, 4%, and 11% of patients treated with TAA $600 \mu\text{g/day}$, flunisolide $1000 \mu\text{g/day}$, and prednisone, respectively, failed to have normal responses to cosyntropin infu-

sion.²⁶ However, the presence of dose or frequency effects on the HPA axis (8-hr AUC and peak after 6-hour cosyntropin infusion) with TAA 800 µg/day in this study (and 1000 µg/day in another study²⁶) but not with fluticasone propionate aerosol 176 µg/day and 440 µg/day in this study (or fluticasone propionate powder 200 µg/day and 1000 µg/day in other studies²⁶) with the 6-hour infusion test suggests that this test is sensitive enough to detect differences between dosage regimens and between inhaled corticosteroids. Finally, long-term data are also consistent with the results from these short-term studies. Ford et al²⁷ evaluated adrenal response to 6-hour cosyntropin infusion in 64 patients with asthma after 2 years of treatment with fluticasone propionate powder 500 µg twice daily. Only 1 patient treated with fluticasone propionate had an abnormal response.

One patient treated with fluticasone propionate 220 µg twice daily had a poststimulation cortisol increase less than 7 µg/dL and peak cortisol less than 18 µg/dL. This patient also had a low morning plasma cortisol concentration at baseline. Although this is likely a spurious result with no clinical significance, one cannot exclude the possibility that some patients may be particularly susceptible to the effects of inhaled corticosteroids, particularly if baseline cortisol is already low. Consequently, it remains appropriate to use the minimum effective dose of inhaled corticosteroid in the treatment of asthma.

Some reports have suggested that fluticasone propionate had a greater effect (up to 4 times as great) on the HPA axis than other inhaled corticosteroids in microgram equivalent (although not necessarily therapeutically equivalent) doses when basal adrenal function was measured (morning plasma cortisol concentrations, AUC, plasma ACTH).¹⁰⁻¹⁶ However, because the bioavailability of these compounds because of absorption through the lung is approximately 20% to 30%, one would expect to see these changes to some degree with all inhaled corticosteroids.^{7,28} In addition, because of limitations in the methods of these studies, including crossover design, small numbers of subjects, use of healthy volunteers, short duration of treatment, and use of therapeutically inequivalent doses, it is difficult to draw any clinically meaningful conclusions from these data.⁷

The clinical significance of abnormal stimulation test results can also be debated.⁷ In a prospective study of 48 oral steroid-dependent patients who underwent elective major surgery, not a single case of acute adrenocortical insufficiency occurred, despite the fact that 28 patients had abnormal intravenous ACTH tests before the operation, and all corticosteroid treatment was withheld from all patients for 36 hours before surgery.^{6,29}

In conclusion, the results of this 4-week study demonstrate that treatment with fluticasone propionate or TAA, when administered at doses most frequently prescribed by clinicians, is comparable to placebo with respect to the effects on the HPA axis as measured by cortisol response to 6-hour cosyntropin infusion in patients with asthma. In contrast, prednisone 10 mg/day was associat-

ed with significant adrenal suppression, indicating a much more favorable safety profile (with respect to systemic effects) with the use of inhaled corticosteroids. When comparing inhaled corticosteroids, it is important to consider both efficacy and safety. Previous work demonstrated that fluticasone propionate 500 µg/day (administered as 250 µg twice daily) was more effective than TAA 800 µg/day (administered as 200 µg 4 times daily) in improving lung function.^{17,18} The present study demonstrates that both of these dosage regimens are equally safe (in terms of their effect on adrenal response to 6-hour cosyntropin infusion), although TAA 800 µg/day administered as 400 µg twice daily may have a slightly more suppressive effect; however, the clinical relevance of this effect is unknown. Finally, this study provides more meaningful results because a clinically relevant test of adrenal reserve capacity was used suggesting that fluticasone propionate, when administered at therapeutic doses of 88 µg and 220 µg twice daily, does not affect HPA axis function in patients with asthma.

We thank the following investigators for their participation in this study: WE Berger, MD, Mission Viejo, Calif; JJ Condemni, MD, Rochester, NY; SL Osur, MD, Albany, NY; DS Pearlman, MD, Aurora, Colo; and JL Pinnas, MD, Tucson, Ariz. We also thank Kim Poinsett-Holmes for her assistance in writing this article.

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