

Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis

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Background: Fluticasone propionate is a glucocorticoid with negligible oral bioavailability and very low intranasal bioavailability that is used as an intranasal spray for the treatment of rhinitis.

Objective: The purpose of this study was to evaluate the hypothalamic-pituitary-adrenal (HPA)-axis effects of fluticasone propionate aqueous nasal spray (FP ANS) compared with oral prednisone and placebo by using a 6-hour cosyntropin infusion test.

Methods: In a 4-week, randomized, double-blind, double-dummy, placebo-controlled parallel-group study, 105 adult patients with allergic rhinitis were randomly assigned to receive FP ANS 200 µg once daily, FP ANS 400 µg twice daily, oral prednisone 7.5 mg once daily, oral prednisone 15 mg once daily, or placebo. HPA-axis function was assessed at the screening visit and after 4 weeks of treatment by measuring morning plasma cortisol concentrations and poststimulation concentrations of plasma and urinary cortisol.

Results: There was no evidence of altered HPA-axis response to cosyntropin by the end of treatment with FP ANS 200 µg once daily or FP ANS 400 µg twice daily when compared with placebo. In contrast, 4 weeks of treatment with oral prednisone 7.5 or 15 mg once daily was associated with significant ($p < 0.05$ vs placebo) reduction in HPA-axis function, as evidenced by lower plasma cortisol concentrations (area under the plasma concentration-time curve and peak concentrations) after cosyntropin stimulation and reduced mean 24-hour urinary cortisol excretion. FP ANS 400 µg twice daily and both prednisone regimens were associated with a significant ($p < 0.05$ vs placebo) reduction in mean morning plasma cortisol concentrations.

Conclusion: These results indicate that a 4-week course of FP ANS at four times the recommended dose does not suppress adrenal function in response to a 6-hour cosyntropin stimulation test. (*J Allergy Clin Immunol* 1998;102:191-7.)

Key words: Cosyntropin, fluticasone propionate, intranasal

Fluticasone propionate is a potent glucocorticosteroid with negligible oral bioavailability because of its first-pass metabolism to an inactive carboxylic acid derivative.¹ Administered intranasally to patients at the recommended dose of 200 µg once daily, fluticasone propionate aqueous nasal spray (FP ANS) (Flonase; Glaxo Wellcome Inc., Research Triangle Park, N.C.) is effective in relieving the symptoms of allergic rhinitis.^{2,3} No significant effects on the hypothalamic-pituitary-adrenal (HPA) axis were noted with FP ANS in these or other trials in which the spray was administered at up to eight times the recommended dose.^{4,5} However, only resting morning plasma cortisol concentrations, plasma cortisol response to an intravenous bolus of cosyntropin (short adrenocorticotrophic hormone test), and 24-hour urine steroid excretion were monitored.

Assessment of adrenal response to a 6-hour infusion of cosyntropin (long adrenocorticotrophic hormone test) can provide more complete information about adrenal reserve and HPA-axis integrity than resting morning plasma cortisol concentrations or a short cosyntropin test in which a bolus injection of cosyntropin is administered.⁶ The 6-hour cosyntropin test is also less complex and costly than either the metyrapone or insulin stress test and better tolerated. Although the 6-hour cosyntropin test has been used routinely for decades to distinguish primary from secondary adrenal insufficiency,⁷ it has been only recently that this sensitive measure has been used to distinguish the relative systemic effects of intranasal or inhaled corticosteroid therapies.

This study was designed to extend the safety evaluation of FP ANS by comparing its effects on the HPA axis with those of oral prednisone by using the 6-hour cosyntropin test. The other objective was to confirm the utility of the 6-hour cosyntropin test as a sensitive measure in detecting drug or dose differences in systemically available corticosteroids under standardized conditions. Prednisone has suppressive effects on the cortisol response to the 6-hour cosyntropin test, which appear to be related to both dose and duration of therapy⁸; therefore two doses of prednisone were chosen as active comparators. Patients were evaluated before and after 4 weeks of treatment with FP ANS (at the recommended dose and at

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TABLE I. Patient characteristics

	Placebo	FP ANS 200 µg QD	FP ANS 400 µg BID	Prednisone 7.5 mg QD	Prednisone 15 mg QD
No. of patients	21	20	23	20	21
Age (yrs)					
Mean	29.7	31.6	34.1	35.1	30.7
Range	18-52	18-56	18-64	19-65	18-52
Sex					
M (%)	18 (86)	18 (90)	17 (74)	16 (80)	17 (81)
F (%)	3 (14)	2 (10)	6 (26)	4 (20)	4 (19)
Weight (lbs)					
Mean	165.3	177.9	165.6	167.7	178.3
Range	115-230	120-240	124-216	118-221	138-218
Ethnic origin					
White (%)	19 (90)	20 (100)	17 (74)	18 (90)	18 (86)
Black (%)	1 (5)	0 (0)	5 (22)	1 (5)	3 (14)
Other (%)	1 (5)	0 (0)	1 (4)	1 (5)	0 (0)

QD, Once daily; BID, twice daily.

TABLE II. Pretreatment cortisol measurements (mean ± SD)

Parameter	Placebo (n = 19)	FP ANS 200 µg QD (n = 20)	FP ANS 400 µg BID (n = 22)	Prednisone 7.5 mg QD (n = 20)	Prednisone 15 mg QD (n = 21)	p Value
Unstimulated						
AM plasma cortisol (µg/dl)	11.4 ± 5.0	11.7 ± 4.6	11.9 ± 4.8	11.1 ± 4.2	11.8 ± 4.0	0.975
24-hour urine cortisol (µg)	27 ± 11	29 ± 17	30 ± 20*	28 ± 10	28 ± 11	0.975
Stimulated						
Peak plasma cortisol (µg/dl)	30.8 ± 6.9	29.4 ± 4.9	31.8 ± 5.4	29.4 ± 4.1	29.0 ± 4.8	0.381
8-hour AUC (µg/dl)	199 ± 39	195 ± 30	212 ± 35	195 ± 27	192 ± 29	0.263

QD, Once daily; BID, twice daily.

*Mean was calculated after removal of one outlier value (a value of 1293 µg).

Abbreviations used

AUC:	Area under the curve
FP ANS:	Fluticasone propionate aqueous nasal spray
HPA:	Hypothalamic-pituitary-adrenal
HPLC:	High-performance liquid chromatography

a dose four times greater than recommended), oral prednisone (7.5 mg daily or 15 mg daily), or placebo.

METHODS**Patients**

One hundred five male and female outpatients (mean age, 32.2 years; range, 18 to 65 years) with seasonal or perennial allergic rhinitis were enrolled at four study centers. The female patients (n = 19) were surgically sterile, used an intrauterine device, or were at least 1 year postmenopausal. Five patients (5%) discontinued the study before completing treatment, including one withdrawn for an adverse event (placebo treatment). There were no significant differences in demographic characteristics among treatment groups.

Patients were required to have a morning plasma cortisol concentration of 5 µg/dl or greater and an increase in plasma cortisol concentration of 7 µg/dl or greater in response to a 6-hour intravenous infusion of cosyntropin at screening. In addition, patients

were ineligible if they had any conditions known to cause an abnormal response to exogenous glucocorticoids, to be adversely affected by prednisone use, or to affect assessments of HPA-axis function. Such conditions included depression, reversal of normal nocturnal sleeping hours, deviation of greater than 25% from ideal body weight, hypothyroidism, or alcoholism.

Medications excluded during the study period because of possible effects on baseline or stimulated cortisol production or because of contraindication during prednisone therapy included gonadal steroids, anticonvulsants, rifampin, sympathomimetics, methylphenidate, meprobamate, benzodiazepines, tricyclic antidepressants, coumarin, potassium-depleting diuretics, or live virus vaccines. Prior or concurrent use of systemic corticosteroids (3 months before screening) or intranasal/inhaled corticosteroids (2 months before screening) was also excluded.

The study was approved by an institutional review board for each center, and written informed consent was obtained from all patients.

Study design

This randomized, double-blind, double-dummy, placebo-controlled study was conducted at four centers in the United States between February and July 1992. At the first screening visit (Study Day -15), subjects underwent assessment of rhinitis symptoms, physical examination, measurement of vital signs, clinical laboratory tests, and skin tests for allergens, and they also provided a medical history. The second clinic visit (Study Day -15 to -13) was a 3-day inpatient stay with the primary objective of determining the patient's baseline HPA-axis function in a controlled setting by mea-

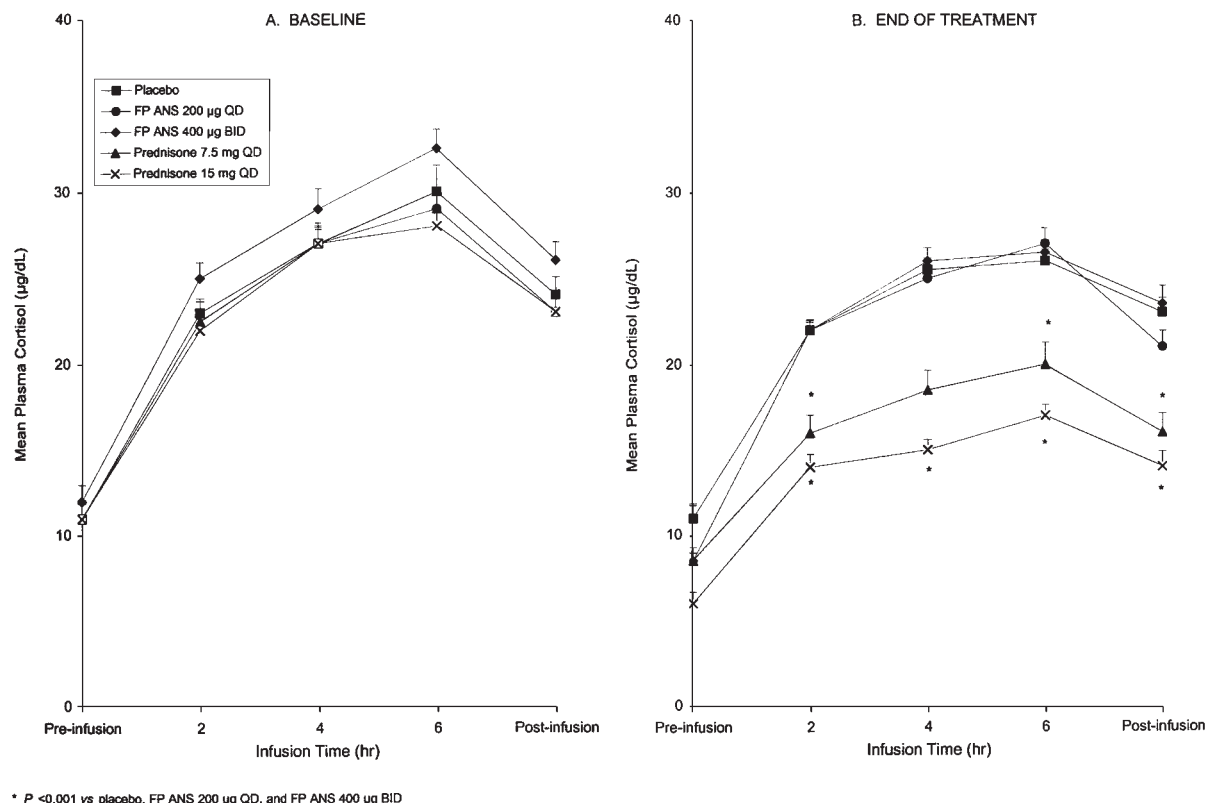


FIG. 1. Response of mean plasma cortisol concentrations to 6-hour intravenous infusion of cosyntropin 250 µg at screening (A) and after 4 weeks of treatment (B). QD, Once daily; BID, twice daily.

During the following: morning (8 AM) plasma cortisol concentrations, the response of plasma cortisol concentrations to a 6-hour (8 AM to 2 PM) intravenous infusion of 250 µg cosyntropin (Cortrosyn; Organon, Inc., West Orange, N.J.), and 24-hour (7 AM until 7 AM next day) urinary-free cortisol excretion under unstimulated and cosyntropin-stimulated conditions. For the infusion, cosyntropin was dissolved in 500 ml of 0.9% sodium chloride. Blood samples for plasma cortisol were taken immediately before the start of the cosyntropin infusion and every 2 hours until 4 PM. Plasma cortisol response to the cosyntropin infusion was expressed as the area under the plasma cortisol concentration-time curve (AUC) and peak plasma cortisol concentrations. Because of their influence on circadian cortisol secretion, meals and light-dark cycles were standardized during the inpatient stay.

On Study Day 1 of the treatment period, at least 2 weeks after the screening cosyntropin test, qualifying patients were randomly assigned to one of the following five treatment groups for 4 weeks: FP ANS 200 µg once daily (50 µg/spray), FP ANS 400 µg twice daily (100 µg/spray), oral prednisone 7.5 mg once daily, oral prednisone 15 mg once daily, or placebo. For double-blinding purposes, tablets containing 2.5 mg of prednisone (Deltasone; The Upjohn Co., Kalamazoo, Mich.) were encapsulated, and bioequivalence of encapsulated and nonencapsulated prednisone was confirmed before study initiation. Each patient took both a morning and evening nasal spray (active or placebo) and two capsules in the morning (active or placebo).

At the end of the treatment period (Study Days 28 to 30), there was a second 3-day inpatient stay to repeat the 24-hour urine collections, 6-hour cosyntropin infusion test, a physical examination, and clinical laboratory tests. Morning and evening doses of study drug were administered on the day before, but not the day of, the 6-

hour cosyntropin infusion test. Patients also had a 1-week posttreatment clinic visit (Study Day 36) for follow-up assessments.

Assays

Blood and urine samples were shipped from each site to a central laboratory (Mayo Medical Laboratories, Rochester, Minn.). Plasma and urinary-free cortisol concentrations were determined by using high-performance liquid chromatography (HPLC) with a reported sensitivity of 1 µg/dl and an interassay variability (coefficient of variation) of approximately 10%.

Statistical analysis

Differences between treatment groups in mean age and weight, mean plasma cortisol response (AUC), peak plasma cortisol concentration, and urinary steroid concentration were determined by analysis of variance F test. A minimum of 20 patients per treatment group was determined to provide an 80% or greater power of detecting a difference in AUC of 6 µg/dl·h, assuming a standard deviation of 5.4, by using a *t* test with a significance level of 0.05. Fisher's exact test was used to detect differences in the incidence of adverse events and the incidence of abnormalities in plasma cortisol. All testing was two-sided with statistical significance defined as *p* values less than 0.05. Outlier values (values that deviated very greatly from the mean) for urinary cortisol concentrations of several samples were identified and excluded before statistical analysis.

RESULTS

HPA-axis effects

The demographic characteristics of the patients in each treatment group were similar (Table I). At baseline,

TABLE III. Post treatment cortisol measurements (mean $\pm$ SD)

Parameter	Placebo (n = 19)	FP ANS 200 μ g QD (n = 20)	FP ANS 400 μ g BID (n = 22)	Prednisone 7.5 mg QD (n = 20)	Prednisone 15 mg QD (n = 21)	p Value
Unstimulated						
AM plasma cortisol (μ g/dl)	11.0 $\pm$ 3.3	10.4 $\pm$ 3.9	8.8 $\pm$ 2.2*	8.7 $\pm$ 3.5*	6.1 $\pm$ 3.1†	<0.001
24-hour urine cortisol (μ g)	25 $\pm$ 15	25 $\pm$ 15	27 $\pm$ 15‡	12 $\pm$ 7§	7 $\pm$ 7§	<0.001
Stimulated						
Peak plasma cortisol (μ g/dl)	28.3 $\pm$ 3.1	28.8 $\pm$ 3.9	28.7 $\pm$ 3.8	20.7 $\pm$ 5.4§	18.0 $\pm$ 3.4†	<0.001
8-hour AUC (μ g/dl)	188 $\pm$ 19	187 $\pm$ 25	187 $\pm$ 21	138 $\pm$ 36§	117 $\pm$ 22†	<0.001

QD, Once daily; BID, twice daily.

* $p < 0.05$ vs placebo.† $p < 0.05$ vs placebo, FP ANS 200 μ g once daily, FP ANS 400 μ g twice daily, and prednisone 7.5 mg once daily.‡Mean was calculated after removal of one outlier value (a value of 898 μ g).§ $p < 0.05$ vs placebo, FP ANS 200 μ g once daily, and FP ANS 400 μ g twice daily.

before start of study treatment, there were no significant differences between treatment groups in morning plasma cortisol levels or response to the 6-hour cosyntropin test (Table II, Fig. 1, A). Cosyntropin infusion stimulated a similar rise in plasma cortisol in all treatment groups.

At the posttreatment visit, the mean plasma cortisol response to cosyntropin (peak and AUC) was significantly reduced in groups treated with either dose of prednisone compared with placebo or compared with either dose of FP ANS ($p < 0.05$; Table III, Fig. 1, B). Fifteen milligrams of prednisone suppressed plasma cortisol response to a greater extent than 7.5 mg of prednisone ($p < 0.05$; 39% vs 29% reductions in 8-hour cortisol AUC from pretreatment levels, respectively). FP ANS did not affect the peak or AUC of the plasma cortisol response to cosyntropin compared with placebo. Mean morning plasma cortisol concentrations (before cosyntropin infusion) on the day after the last dose of study medication were unaffected by treatment with FP ANS 200 μ g once daily but were significantly reduced in patients treated with FP ANS 400 μ g twice daily or either dose of prednisone compared with placebo (Table III).

Treatment with prednisone 7.5 or 15 mg once daily significantly reduced mean urinary-free cortisol excretion on the days before and during cosyntropin stimulation by 56% to 57% and 72% to 75% from pretreatment levels, respectively, a significant reduction compared with placebo or either dose of FP ANS ($p < 0.05$; Table III).

Abnormalities in plasma cortisol parameters (reduced more than 2 standard deviations below the mean of the placebo group) after 4 weeks of treatment were observed in significant numbers of patients receiving either dose of prednisone and in no more than 5% to 10% of patients receiving either dose of FP ANS or placebo (Table IV). One half (50%) of the patients treated with prednisone 7.5 mg daily and 95% of patients treated with prednisone 15 mg daily demonstrated an abnormal 8-hour plasma cortisol level or AUC in response to cosyntropin infusion ($p < 0.05$ compared with placebo and either FP ANS dose). Morning cortisol concentrations were abnormally low in a significant percentage of the high-dose, but not the low-dose, prednisone group.

Adverse events

No serious adverse events occurred during the study. There were no statistically significant differences among groups in the incidence of all or potentially drug-related adverse events. No alterations in vital signs, physical examination, or laboratory values were noted in any treatment group.

DISCUSSION

The results of this study confirm that 4 weeks of treatment with FP ANS at the recommended dose of 200 μ g once daily and at four times the recommended dose does not affect the HPA-axis response to stimulation, in this case by the very sensitive 6-hour cosyntropin test. These findings corroborate those of earlier clinical trials in patients with rhinitis that showed FP ANS at doses as high as eight times the recommended dose to have no significant effect on HPA-axis function, as evaluated by plasma cortisol response to a short cosyntropin test^{2,4,5} or 24-hour urinary excretion of free cortisol.^{4,5}

Unlike placebo and FP ANS 200 μ g once daily, FP ANS 400 μ g twice daily significantly reduced morning plasma cortisol concentrations. These results are in conflict with previous reports demonstrating normal mean morning plasma cortisol levels after repeated treatment with FP ANS 400 μ g twice daily ($n = 106$) or 800 μ g twice daily ($n = 24$) in patients^{4,5} or FP ANS 2 mg twice daily ($n = 20$) in volunteers.¹ Although it is unclear why our findings differ from those of the other studies with respect to this parameter, part of the reason may be due to differences in study design. The study by Meltzer et al.⁵ evaluated the same high-dose regimen of FP ANS as was assessed in our study but did so over a shorter time period (2 weeks), thus exposing patients to less corticosteroid. The study by Harding¹ was also conducted over a shorter time period (1 week) than our study. Van As et al.,⁴ who evaluated FP ANS at twice the higher dose used in our study (800 μ g twice daily) over an identical time period, used stricter study entry criteria with respect to the most recent time patients could have used systemic corticosteroids (12 months

TABLE IV. Incidence of abnormalities in morning plasma cortisol concentrations and response to 6-hour cosyntropin infusion after 4 weeks of treatment

Parameter	Placebo	FP ANS 200 µg QD	FP ANS 400 µg BID	Prednisone 7.5 mg QD	Prednisone 15 mg QD
Patients with abnormal morning plasma cortisol levels*	0/19	0/20	0/22	1/20 (5%)	6/21 (29%)†
Patients with abnormal peak response to cosyntropin*	0/19	2/20 (10%)	1/22 (5%)	8/18 (44%)†	19/21 (90%)‡
Patients with abnormal AUC in response to cosyntropin*	0/18	1/20 (5%)	0/21	9/18 (50%)†	19/20 (95%)‡

QD, Once daily; BID, twice daily.

*Defined as 2 SD below the mean of the placebo group.

† $p < 0.05$ vs placebo, FP ANS 200 µg once daily, and FP ANS 400 µg twice daily.‡ $p < 0.05$ vs placebo, FP ANS 200 µg once daily, FP ANS 400 µg twice daily, and prednisone 7.5 mg once daily.

vs 3 months) or intranasal or inhaled corticosteroids (3 months vs 2 months). However, there is no reason to suspect that the patients in our study had any residual HPA-axis suppression from earlier corticosteroid use because they all showed a normal plasma cortisol response to a 6-hour intravenous infusion of cosyntropin at screening.

Although the posttreatment reduction in mean morning plasma cortisol concentration in patients treated with FP ANS 400 µg twice daily (20%) was similar in magnitude to that observed in patients treated with prednisone 7.5 mg once daily (21%), the clinical importance of this is questionable in view of the other HPA-axis findings of our study. First, none of the patients treated with FP ANS 400 µg twice daily had a posttreatment mean morning plasma cortisol concentration more than two standard deviations below the mean of the placebo group (Table IV). Second, unlike systemically absorbed oral prednisone 7.5 and 15 mg once daily in the current study, FP ANS 400 µg twice daily had no effect on plasma cortisol response (peak and AUC) to cosyntropin. In view of this and the results of the earlier studies involving cosyntropin stimulation tests, treatment with FP ANS 400 µg twice daily would be unlikely to produce a clinically significant effect on HPA-axis function. These results point out the lack of reliability of morning cortisol assessments when used alone to evaluate HPA-axis integrity, particularly when higher-than-recommended dosages of exogenous corticosteroids are administered in the evening.

This study demonstrated the sensitivity of the 6-hour cosyntropin test in determining dose differences in the systemic effects of corticosteroid therapy. Daily treatment for 4 weeks with prednisone 15 mg had a significantly greater suppressive effect on HPA-axis function than treatment with prednisone 7.5 mg. Both peak cortisol levels and AUC, as well as the incidence of abnormalities in cortisol response, were affected more by the higher prednisone dose. The ability to detect these differences in prednisone dose lends credibility to the use of this test to detect small but significant effects on HPA-axis function by intranasal or inhaled corticosteroids.

Unlike unstimulated plasma cortisol monitoring, the accuracy of the 6-hour cosyntropin test in the assessment of HPA-axis integrity is not limited by the episodic nature of cortisol release.⁹ Test results from cosyntropin stimulation tests have been shown to correlate well with results obtained with the insulin-induced hypoglycemia test, which is very accurate but too complex and costly to be a useful screening tool.^{10,11} The 6-hour cosyntropin test is more reliable than the short cosyntropin test as a screening tool for HPA-axis integrity. Although inaccuracies with the short test are uncommon,^{12,13} both false-negative¹⁴ and false-positive¹⁵ results have been reported occasionally. The 6-hour cosyntropin infusion test can be expected to produce a maximal response of the adrenals to stimulation and should thereby minimize the possibility of either a false-positive or false-negative alteration in HPA-axis function.⁶ Another test of HPA-axis integrity that has proved more accurate than the short cosyntropin test is the low-dose cosyntropin test, which involves intravenous injection of 0.2 µg/kg cosyntropin per evaluation.^{16,17} However, to date, the accuracy of the low-dose cosyntropin test has not been compared with that of the 6-hour cosyntropin test.

Although acceptable responses to a short cosyntropin test are standardized (peak of 18 µg/dl and change of 7 µg/dl), there is less unanimity concerning the 6-hour cosyntropin test. Streeten et al.⁶ report a study wherein all 24 volunteers achieved a peak of greater than 37 µg/dl, whereas others report a normal response to be 25 µg/dl¹⁸ or 30 µg/dl.¹⁹ In the current study HPLC was used for assay of plasma and urinary cortisol to avoid possible cross-reactivity of prednisone or FP ANS with the antibodies in immunoassays. HPLC is considered highly accurate for cortisol measurement because there is no interference from drugs and medications, nor does it detect prednisone, prednisolone, cortisone, dexamethasone, or other common natural or synthetic steroids, as can occur with radioimmunoassay.¹⁸

Plasma cortisol results reported by Mayo Medical Laboratories from samples assayed by HPLC correlate

well with radioimmunoassay ($r = 0.992$) but are substantially lower (slope = 1.156, intercept = 0.709) (Nai-Siang Jiang, Mayo Medical Laboratories, personal communication, November 27, 1991). For this reason, a normal response was arbitrarily set in this study on the basis of deviations from results achieved by our placebo patients. Patients with morning preinfusion cortisol concentrations or response to cosyntropin infusion (peak and AUC) two standard deviations or more below the placebo group were considered abnormal.

After 4 weeks of treatment with either dose of prednisone, 50% and 95% of patients treated with 7.5 and 15 mg of prednisone, respectively, failed to achieve a normal AUC response to cosyntropin infusion, a clear dose-related difference. Prednisone treatment for various inflammatory diseases has been reported to reduce adrenocortical function in a dose- and duration-dependent manner.^{8,20-22} However, the majority of these reports have been under relatively uncontrolled conditions and used tests of HPA-axis function that were less sensitive than the 6-hour cosyntropin test. In contrast, this study used strict inclusion/exclusion criteria. Because of reported effects on adrenal function, we excluded patients with conditions that would affect either normal adrenal function, response to prednisone, or response to cosyntropin stimulation, including any who were elderly,^{23,24} outside standard body weight limits,²⁴ or using any estrogenic compounds that could elevate cortisol binding globulin and, hence, total plasma cortisol.²⁵ Our study included only patients who had normal baseline HPA-axis function and no recent history of systemic corticosteroid treatment or use of any confounding treatments during the study period. The inpatient setting was used to control for effects of meals and sleep-wake cycles and to insure accurate collection of 24-hour urine samples. The study was also designed to eliminate the confounding effect on adrenal function tests of acute, rather than chronic, dosing with corticosteroids by eliminating the use of study medication on the day of post-treatment testing.

The abnormalities in adrenal function observed with prednisone treatment in this study are similar to those previously reported.^{26,27} Using the 6-hour cosyntropin test, Feiss et al.²⁶ found that mean plasma cortisol concentrations at 6 hours were significantly reduced by 38% after 6 weeks of treatment with prednisone 10 mg daily. Using the same test, Howland et al.²⁷ found that 6 weeks of treatment with prednisone 10 mg daily resulted in a 28% decrease in prestimulation plasma cortisol concentrations and a 43% decrease in poststimulation cortisol concentrations. Our study differed from the others in that it evaluated two dosing regimens of prednisone, thus allowing an assessment of the effect of dose on HPA-axis suppression. Dose-related differences in the two regimens of prednisone on plasma cortisol concentrations were evident in this study, with 8-hour cortisol AUC reductions of 29% and 39% after 4 weeks of treatment with prednisone 7.5 and 15 mg daily, respectively. These results were supported by the more pronounced effect of

the higher dose on mean urinary cortisol excretion, although there were no statistical differences between the two prednisone doses.

Two factors may explain the lack of clinically important effects of FP ANS on the HPA axis. First, fluticasone propionate itself was synthesized from the androstane 17 β -carbothioates to combine maximal anti-inflammatory activity with minimal HPA inhibitory potency.²⁸ This allowed the activity of the corticosteroid to be primarily local. Second, the oral bioavailability of fluticasone propionate is negligible because oral doses are rapidly converted to an inactive 17-carboxylic acid derivative by virtually complete first-pass metabolism.^{1,29} Thus any drug absorbed from the gastrointestinal tract after swallowing the intranasal preparation will be metabolized, giving rise to undetectable plasma concentrations and no systemic effects. It has been estimated that 2% or less of an intranasal dose of fluticasone propionate is absorbed into the systemic circulation, an amount too small to measure.^{1,29}

In conclusion, these results provide confirmation that the 6-hour cosyntropin stimulation test is a sensitive assay for distinguishing dose-related effects of prednisone on the HPA axis. This test also rules out clinically significant HPA-axis effects of FP ANS at up to four times the recommended dose. In view of the latter finding and the fact that many patients use FP ANS only seasonally, routine monitoring of plasma cortisol concentrations in patients receiving recommended doses of FP ANS as monotherapy appears unnecessary.

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