

A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis

William C. Howland III, MD,^a Robert Dockhorn, MD,^b
Sherwin Gillman, MD,^c Gary N. Gross, MD,^d Darcy Hille, MS,^e
Brandon Simpson,^f John A. Furst,^f Gary Feiss, MS,^f and
Joseph A. Smith, MD^f Austin, Texas, Lenexa, Kan., Orange, Calif., Dallas,
Texas, Paris, France, and Collegeville, Pa.

Background: One of the risks associated with the use of oral corticosteroids is suppression of adrenocortical function. Triamcinolone acetonide (TAA) aqueous nasal spray administered once daily (110 µg and 220 µg) has been shown to reduce allergic rhinitis symptoms.

Objective: This multicenter, placebo-controlled, double-blind study determined the effects of TAA aqueous nasal spray, placebo, and oral prednisone on adrenocortical function in patients with allergic rhinitis.

Methods: Sixty-four patients received TAA aqueous nasal spray (220 µg or 440 µg), oral prednisone (10 mg), or placebo once daily for 6 weeks. Adrenocortical function was assessed after cosyntropin stimulation for 6 hours before treatment and after 6 weeks of treatment.

Results: There was no statistically significant effect on adrenocortical function in patients who received either dose of TAA aqueous nasal spray compared with placebo. In contrast, prednisone produced statistically significant ($p < 0.001$) reductions in adrenocortical function compared with placebo; reductions occurred in both the mean 6-hour plasma cortisol levels and mean change in 6-hour plasma cortisol levels from pretreatment.

Conclusion: This study demonstrated that, unlike oral prednisone, TAA aqueous nasal spray, in therapeutic doses, did not alter adrenocortical function and was comparable to treatment with placebo in its absence of measurable effects on adrenocortical function. (*J Allergy Clin Immunol* 1996;98:32-8.)

Key words: Triamcinolone acetonide, adrenocortical function, adrenal gland hypofunction, corticosteroids, allergic rhinitis, hay fever, aqueous nasal spray, prednisone, clinical trial

Before the development and use of intranasal corticosteroids, the treatment of perennial and seasonal allergic rhinitis with oral corticosteroids was hampered by the relative risk of systemic adverse events, despite the obvious amelioration of

Abbreviations used

17-OHCS: 17-Hydroxycorticosteroid
TAA: Triamcinolone acetonide

From Healthquest Research: ^aAustin, Texas; ^bLenexa, Kan.; ^cOrange, Calif.; ^dDallas, Texas; ^eRhône-Poulenc Rorer, Paris, France; and ^fRhône-Poulenc Rorer, Collegeville, Pa.

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Reprint requests: William Howland, MD, Healthquest Research, Therapy & Research Institute, Inc., 3807 Spicewood Springs Rd., Suite 250, Austin, TX 78759.

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symptoms with use of drugs from this pharmacologic class.^{1,2} One of the risks associated with the use of oral corticosteroids is suppression of adrenocortical function,¹⁻³ which can result in a variety of responses including acute adrenal insufficiency.^{2,3} Limited adrenocortical suppression may occur with single doses of oral corticosteroids; however, clinically significant suppression is more likely with long-term administration.^{3,4} This risk of

suppression with extended use is of particular concern for patients with chronic diseases, such as seasonal and perennial allergic rhinitis, although the benefit of regular use of oral corticosteroids is well established.^{3, 5-10} Thus the risk of adrenocortical suppression and its associated morbidity must be considered relative to the obvious symptomatic relief experienced by the patient receiving oral corticosteroids regularly.

In the past few years, many corticosteroids have become available as inhaled formulations, both bronchial and nasal, for the treatment of asthma and allergic rhinitis, respectively.^{7, 10, 11} With the advent of nasal inhaled corticosteroids, clinicians have been able to treat patients with allergic rhinitis effectively with decreased concern about systemic side effects and long-term adrenocortical suppression.^{7, 10, 12, 13} Although intranasal dexamethasone was shown to have significant adrenocortical suppressive effects,¹⁴ new intranasal synthetic corticosteroids have not resulted in measurable adrenocortical suppression after either short- or long-term use.^{5-9, 13, 15-19}

One currently available intranasal corticosteroid, triamcinolone acetonide (TAA) aerosol, has been shown to be effective in suppressing the symptoms of perennial and seasonal allergic rhinitis when administered once daily at doses of 110 μ g, 220 μ g, and 440 μ g.^{5, 8, 19-21} It offers the advantage of once-daily dosing with limited adverse effects and no measurable effects on adrenocortical function.^{21, 22} TAA aqueous nasal spray is a new formulation of the drug, which has also been shown to be effective in managing the symptoms of seasonal and perennial allergic rhinitis at doses of 110 μ g/day and 220 μ g/day.^{23, 24} In addition, TAA aqueous nasal spray was safe and maintained its effectiveness over a 1-year period in patients with perennial allergic rhinitis.²⁵ This study was designed to compare the effect of TAA aqueous nasal spray on adrenocortical function with that of placebo and oral prednisone in male patients with allergic rhinitis.

METHODS

Patients

Sixty-four male patients with allergic rhinitis were enrolled in this study. Eligible patients were men, 18 to 65 years of age, with a minimum 2-year history of allergic rhinitis and a positive skin prick test response to seasonal or perennial allergens. Exclusion criteria included an initial morning plasma cortisol level (performed between 7:00 and 9:00 AM) less than 5 μ g/dl or greater than 18 μ g/dl, oral corticosteroid therapy within 90 days

of initial study visit, more than 10 days of oral corticosteroid therapy within the past year, inhaled (bronchial or nasal) corticosteroid therapy within 42 days of initial visit, nasal candidiasis, acute or chronic sinusitis, significant nasal polyposis or other gross anatomic nasal deformity that could impair breathing. Patients were allowed to use medications required to manage acute or chronic illness with the exception of any type of corticosteroid or any other medication that could interfere with the assessment of adrenocortical function. The study protocol was approved by the Institutional Review Board at each of the four U.S. study sites, and each participating patient signed an informed consent form.

Study design

This multicenter study used a double-blind, placebo-controlled design. Patients were randomized to receive once daily either 220 μ g or 440 μ g of TAA aqueous nasal spray, 10 mg of oral prednisone as capsules, or placebo for 42 consecutive days (6 weeks). Oral prednisone was included as a positive control. Each patient was initially screened to establish a diagnosis of allergic rhinitis by means of a positive skin prick test response to seasonal or perennial allergens present in the patient's environment. Adrenocortical function was assessed before treatment and after completion of the 6-week, double-blind study phase. A complete physical examination and laboratory tests (hematology, serum chemistry, and urinalysis) were performed at the initial visit and on completion of the study. Safety was evaluated by monitoring the frequency and severity of adverse effects of the study treatments as recorded by each patient on diary cards. Side effects were assessed by site investigators at patient interviews performed at the end of weeks 3 and 6 of the study.

Patients were supplied with bottles containing TAA aqueous nasal spray or identical placebo spray. In addition, patients received 10 mg of oral prednisone as capsules or identical placebo capsules. Each patient received enough study medication for 3 weeks, after which time the patient returned for an interim interview and then received enough medication to complete the study. TAA aqueous nasal spray, placebo spray, prednisone 10 mg capsules, and placebo capsules were supplied by Rhône-Poulenc Rorer Pharmaceuticals, Inc. (Collegeville, Pa.). Compliance was documented by evaluation of the patients' diary cards.

Adrenocortical function testing

Adrenocortical function was evaluated over a 3-day baseline period before initiation of the study by using the cosyntropin stimulation test. The cosyntropin stimulation test was conducted as a 6-hour intravenous infusion of Cortrosyn, 250 μ g (synthetic adrenocorticotrophic hormone; Organon, Inc., West Orange, N.J.), diluted in 500 ml of 0.9% sodium chloride intravenous solution. The cosyntropin stimulation test has been shown to rapidly

TABLE I. Demographic characteristics of the patient population

Treatment	n	% Caucasian	Mean age (yr) (range)	Mean height (cm) (range)	Mean weight (kg) (range)
Placebo	16	88	32 (22-44)	179 (168-187)	87 (70-119)
TAA aqueous (220 µg/day)	16	88	29 (19-38)	183 (170-196)	88 (69-159)
TAA aqueous (440 µg/day)	16	75	29 (22-40)	181 (175-188)	89 (68-122)
Prednisone (10 mg/day)	16	81	33 (19-50)	178 (164-188)	83 (65-108)
Total	64	83	31 (19-50)	180 (164-196)	87 (65-159)

and accurately reflect the functional status of the adrenal glands, especially in response to stimulation.²⁶⁻²⁸

An initial morning plasma cortisol level (performed between 7:00 and 9:00 AM) and a 24-hour urine collection for determination of urinary 17-hydroxycorticosteroid (17-OHCS), urinary free cortisol, and urinary creatinine levels were obtained. The next day, a 6-hour cosyntropin stimulation test was performed, which included a second 24-hour urine collection to determine the effects of the stimulation test. The urine collection and cosyntropin stimulation test were repeated at the conclusion of the 6-week treatment period. All samples were assayed for plasma cortisol, as described previously,²² by fluorescence polarization immunoassay at a central laboratory (Corning SciCor, Inc., Indianapolis, Ind.).

Data and statistical analyses

Primary analyses were performed for each TAA aqueous nasal spray dose and prednisone compared with placebo. The primary variables were the proportion of patients with clinical adrenocortical suppression and the mean plasma cortisol levels at the end of the study. Clinically significant adrenocortical suppression was defined as plasma cortisol levels that were below the normal range at the end of the sixth hour of cosyntropin stimulation. The normal plasma cortisol range was based on results of previous studies^{22, 29} and was calculated from the pretreatment means $\pm$ 2 SDs of the pooled data from all patients. The lower limit reference ranges at the sixth-hour time point reported in previous studies were 31.61 µg/dl²² and 39.91 µg/dl.²⁹ Secondary analyses were conducted on the mean changes from pretreatment to posttreatment in sixth-hour plasma cortisol levels, 24-hour urinary 17-OHCS, and 24-hour urinary free cortisol.

Statistical analysis was performed on continuous variables by using a one-sided trend test on the mean response. The means and standard errors used in the analysis were obtained from a two-way analysis of variance with treatment and investigator as primary effects and no interaction term. Both TAA aqueous nasal spray groups, as well as the prednisone group, were separately compared with the placebo group in this analysis. All

tests were conducted with one-sided statistical significance set at $\alpha = 0.05$.

RESULTS

Sixty-four male patients with allergic rhinitis were enrolled in this study. All patients experienced allergy symptom relief, regardless of treatment regimen. One patient (placebo group) did not complete the study because of a protocol violation on day 5 of the study. However, safety data from this patient were included in the appropriate analyses. The demographic characteristics of the patient groups were comparable with regard to race, age, height, and weight (Table I). The number of days patients received treatment ranged from 5 to 50; the average numbers of days treated were 38.3, 41.1, 41.4, and 41.4 for patients who received placebo, TAA aqueous nasal spray (220 µg/day), TAA aqueous nasal spray (440 µg/day), and prednisone, respectively.

Pretreatment adrenocortical function

Table II shows the results of the baseline adrenocortical function testing. For the purposes of this study, the normal plasma cortisol reference range was consistent with results of previous studies by Feiss et al.²² and Streeten et al.²⁹ and was calculated to be between 34.89 µg/dl and 69.17 µg/dl. Therefore plasma cortisol levels within this range after a 6-hour cosyntropin stimulation were considered normal and indicated normal adrenocortical function. The pretreatment results indicated that all treatment groups were comparable with regard to mean plasma cortisol levels both before and after cosyntropin stimulation before initiation of study medication.

Treatment effects between groups

Overall, no patient in the study exhibited clinical symptoms related to adrenocortical suppression

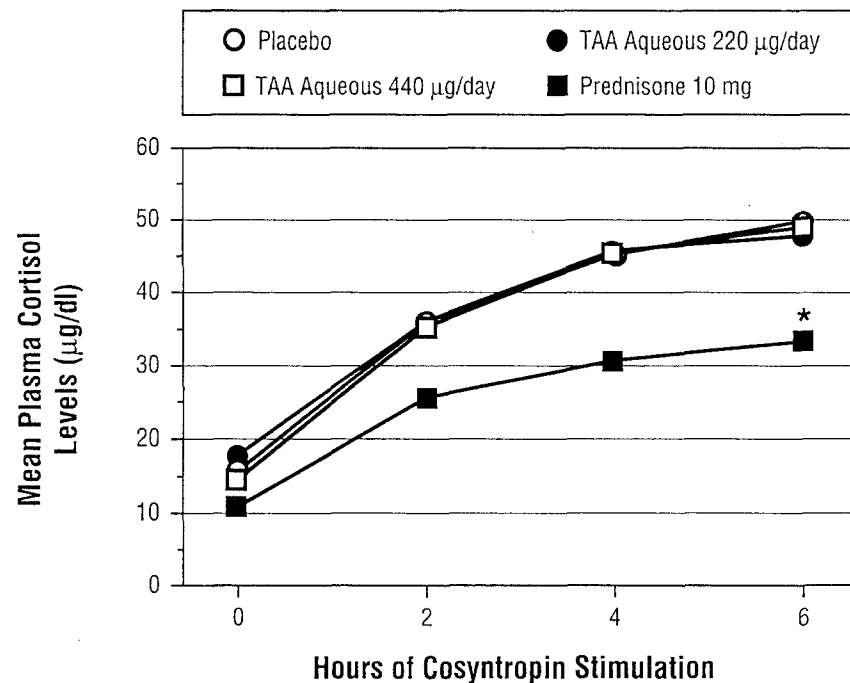


FIG. 1. Week 6 mean plasma cortisol responses to 6-hour adrenocortical stimulation test with cosyntropin. Asterisk indicates significantly different from placebo at $p < 0.001$.

TABLE II. Mean differences ($\pm$ SD) in plasma cortisol production from pretreatment to posttreatment

Treatment	n	Treatment phase	Adrenocortical function results				Mean (SEM) 6-hour plasma cortisol levels (μ g/dl) posttreatment analysis	
			Mean (SD) plasma cortisol levels (μ g/dl) hours of cosyntropin stimulation				Adjusted mean (SEM)*	p Value†
			0	2	4	6		
Placebo	16	Pretreatment	16.81 (3.80)	38.31 (5.29)	48.44 (6.16)	52.56 (7.30)	49.81 (1.92)	—
		Posttreatment	15.69 (3.38)	36.00 (5.69)	45.19 (8.16)	49.81 (8.12)		
TAA aqueous (220 μ g/day)	16	Pretreatment	15.94 (5.42)	37.25 (6.64)	46.19 (6.20)	47.63 (11.28)	47.81 (1.92)	0.232
		Posttreatment	17.81 (5.42)	36.06 (7.85)	45.75 (9.52)	47.81 (8.68)		
TAA aqueous (440 μ g/day)	16	Pretreatment	16.13 (5.86)	38.44 (5.03)	48.88 (5.00)	53.56 (8.10)	49.00 (1.92)	0.383
		Posttreatment	14.56 (4.43)	35.25 (4.49)	45.50 (5.13)	49.00 (7.02)		
Prednisone (10 mg/day)	16	Pretreatment	15.19 (5.54)	39.13 (4.49)	49.56 (4.08)	54.38 (5.74)	33.38 (1.92)	<0.001‡
		Posttreatment	10.88 (4.62)	25.56 (5.27)	30.75 (6.41)	33.38 (7.74)		

*Six-hour plasma cortisol level means were adjusted for imbalances among investigative sites.

†p values indicate difference between treatment group and placebo according to one-sided trend test.

‡Significantly different from placebo.

before or after treatment with study medication. After treatment at week 6 of the study, analyses of data from the 6-hour cosyntropin stimulation test revealed no statistically significant effect on adrenocortical function in patients treated with either

dose of TAA aqueous nasal spray compared with placebo (Table II, Figs. 1 and 2). In contrast, oral prednisone did significantly ($p < 0.001$) reduce adrenocortical function compared with placebo. These reductions in adrenocortical function were

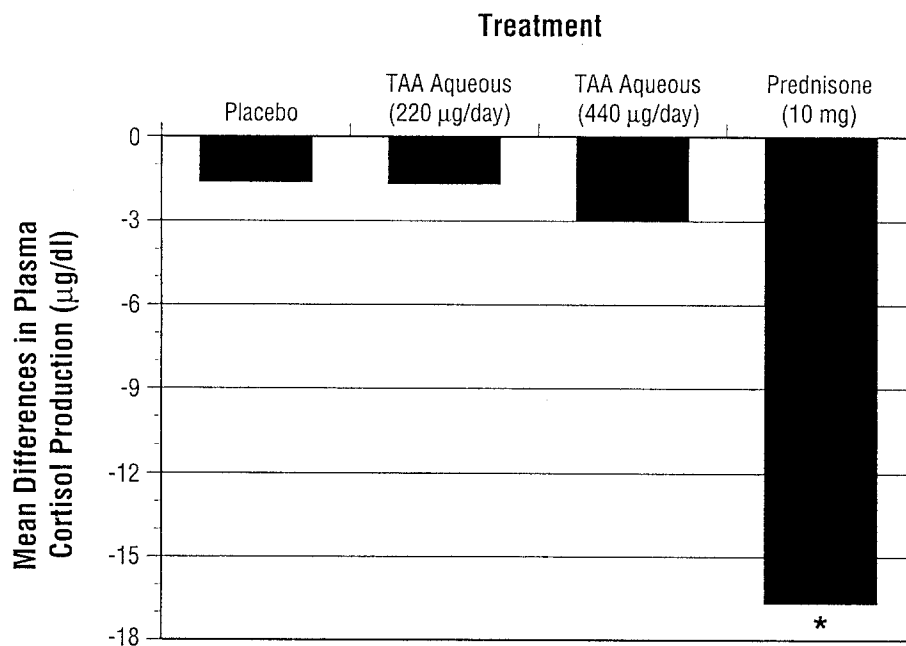


FIG. 2. Mean differences in plasma cortisol production from pretreatment to posttreatment after a 6-hour cosyntropin stimulation test. Asterisk indicates significantly different from placebo at $p < 0.001$.

TABLE III. Pretreatment to posttreatment mean differences ($\pm$ SEM) in urinary free cortisol and urinary 17-OHCS levels

Treatment	Urinary free cortisol ($\mu\text{g}/24 \text{ hr}$)		Urinary 17-OHCS ($\text{mg}/24 \text{ hr}$)	
	Difference adjusted mean (SEM)*	p Value†	Difference adjusted mean (SEM)*	p Value†
Placebo	289.04 (105.61)	—	1.16 (1.80)	—
TAA aqueous (220 $\mu\text{g}/\text{day}$)	128.05 (113.48)	>0.5	0.26 (1.61)	>0.5
TAA aqueous (440 $\mu\text{g}/\text{day}$)	128.10 (105.63)	>0.5	0.97 (1.61)	>0.5
Prednisone (10 mg/day)	-379.48 (105.63)	$<0.001\ddagger$	-7.16 (1.73)	$<0.001\ddagger$

*Mean was derived by subtracting the prestimulation values from the poststimulation values. Difference from pre- to posttreatment (week 6) minus results based on the actual individual values; mean differences were adjusted for imbalances among investigative sites.

†p values indicate difference between treatment group and placebo according to one-sided trend test.

‡Significantly different from placebo.

noted in both the mean 6-hour plasma cortisol levels ($p < 0.001$, Table II, Fig. 1) and mean differences in 6-hour plasma cortisol production from pretreatment to posttreatment ($p < 0.001$, Fig. 2). The effect of prednisone treatment on adrenocortical activity was demonstrated as a blunting of adrenocortical activity as shown in Figs. 1 and 2. Prednisone treatment, based on pretreatment to posttreatment mean plasma cortisol levels, resulted in an approximate 28% decrease in pre-stimulation values and a 43% decrease in the mean

change in 6-hour stimulated cortisol production after 42 days of treatment.

The changes in urinary free cortisol and urinary 17-OHCS by treatment groups are presented in Table III. In both cases the levels were adjusted for creatinine clearance. The results of these analyses indicated that treatment with TAA aqueous nasal spray had no statistically significant effect on either mean urinary free cortisol or 17-OHCS levels during the course of the study. In contrast, prednisone treatment significantly ($p \leq 0.001$) reduced

both urinary free cortisol and 17-OHCS when compared with pretreatment means.

Safety evaluations

Clinical safety was evaluated in all patients enrolled in this study. The incidence of adverse events was comparable among all four treatment groups, and none were considered severe. The most frequently observed adverse event was headache, which occurred in 25.0% of patients who received placebo, 6.3% of patients who received 220 µg of TAA aqueous nasal spray, 12.5% of patients who received 440 µg of TAA aqueous nasal spray, and 37.5% of those who received prednisone. There were no deaths, serious adverse clinical events, or clinically significant changes in physical examination results during the study. No clinically significant laboratory abnormalities related to study medication were observed.

DISCUSSION

This study evaluated the effects of once-daily administration of TAA aqueous nasal spray (220 µg and 440 µg) for 6 weeks on adrenocortical function; these doses have previously been shown to be efficacious and safe with the aerosol formulation of TAA.^{6, 19-21} Recent studies have shown TAA aqueous nasal spray to be effective for the symptomatic treatment of seasonal and perennial allergic rhinitis at doses of 110 µg/day and 220 µg/day.^{23, 24} In this study intranasal TAA aqueous nasal spray (220 µg/day or 440 µg/day) did not alter adrenocortical function, whereas oral prednisone, 10 mg/day, significantly ($p < 0.001$) suppressed adrenocortical function compared with placebo. In response to cosyntropin stimulation, each of the TAA aqueous nasal spray treatment groups had results very similar to and not statistically different from baseline responses. In comparison, patients who received oral prednisone, 10 mg/day, demonstrated a statistically significant ($p < 0.001$) depression of adrenocortical function in response to cosyntropin stimulation after the 6-week treatment period when compared with baseline responses. These results support the conclusion that TAA aqueous nasal spray has no measurable effects on adrenocortical function when administered in doses of 220 µg and 440 µg daily for up to 6 weeks.

Intranasal administration of newer corticosteroids is not associated with measurable effects on adrenocortical suppression when used in either aerosol^{5, 7-9, 19} or aqueous formulations compared with oral corticosteroids.^{6, 13, 15} One study with

intranasal dexamethasone demonstrated greater than expected adrenocortical suppression with therapeutic doses.¹⁴ Michels et al.¹⁴ reported that almost two thirds of patients with allergic rhinitis treated with therapeutic doses of intranasal dexamethasone for 2 weeks had mild-to-moderate adrenocortical suppression. In contrast, TAA aerosol nasal spray has not resulted in any measurable effects on adrenocortical function when used in doses similar to those evaluated in this study.^{5, 8, 19, 22}

Because no difference in adrenocortical function was found between patients who received TAA aqueous nasal spray or placebo, one could consider whether a different study design might permit detection of potential differences between these groups. However, this study was designed to address such concerns by including prednisone, a corticosteroid known to demonstrably reduce adrenocortical function, as a positive control arm.^{3, 30} The results in this study with prednisone validated the study design.

In conclusion, the results of this study demonstrated that, unlike oral prednisone, intranasal administration of therapeutic doses of TAA aqueous nasal spray did not alter adrenocortical function and was comparable to treatment with placebo in its absence of measurable effects on adrenocortical function.

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