

A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function

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A comparison of adrenocortical function before and after treatment with either intranasal triamcinolone acetonide aerosol (ITAA), prednisone, or placebo was done. Sixty-two male subjects with allergic rhinitis were treated for 6 weeks with either ITAA (220 or 440 µg/day), oral prednisone (10 mg/day), or placebo in double-blind, parallel-group fashion. Adrenocortical function was assessed by 6-hour cosyntropin stimulation before and at the end of the treatment period. The placebo-treated and two ITAA-treated groups produced no changes in adrenocortical function with treatment, and the ITAA-treated groups were not different from the placebo-treated group with mean $\pm$ SEM changes in stimulated plasma cortisol (micrograms per deciliter) as follows: placebo, -2.68 ± 1.77 ; ITAA 220 µg, -2.69 ± 1.18 ; ITAA 440 µg, -2.96 ± 1.81 . The prednisone-treated group had a mean reduction in adrenocortical function (mean $\pm$ SEM change in stimulated plasma cortisol of -19.8 ± 1.77 µg/dl) that was significant ($p < 0.0001$) compared with that of the placebo-treated group. The results of this study indicate that 6 weeks of treatment with 220 µg/day or 440 µg/day of ITAA has no effect on adrenocortical function, but prednisone, at a dosage of 10 mg/day for 6 weeks, produces partial adrenocortical suppression. (J ALLERGY CLIN IMMUNOL 1992;89:1151-6.)

Key words: Intranasal triamcinolone acetonide, prednisone, adrenocortical function, allergic rhinitis

The glucocorticoid, TA, has recently been approved for use in the United States as ITAA (Nasacort; Rhone-Poulenc Rorer, Collegeville, Pa.) for the treatment of AR because of its potent antiinflammatory properties. However, exogenous glucocorticoids can be associated with suppression of the HPA axis if the doses are of sufficient magnitude and duration to produce adrenal atrophy.¹⁻³ The resultant adrenocortical insufficiency

Abbreviations used

TA:	Triamcinolone acetonide
ITAA:	Intranasal TA aerosol
AR:	Allergic rhinitis
HPA:	Hypothalamic-pituitary-adrenal
C _{max} :	Maximum concentration

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would make patients vulnerable when they were under physiologic stress, as with trauma or surgery.¹⁻⁴ Even with therapeutic doses of glucocorticoids, this type of adverse effect can occur, having been reported in subjects receiving parenterally injected,^{5, 6} orally inhaled,⁷⁻¹⁰ and oral^{2, 11, 12} glucocorticoids. There have been few studies in the literature of reduced HPA function associated with therapeutic use of intranasal glucocorticoids, but mild reductions in morning plasma cortisol levels have been reported in subjects receiving combined intranasal and orally inhaled beclomethasone dipropionate¹³ for a total daily dose of

1 mg, as well as reductions in morning plasma cortisol and 24-hour urinary 17-ketogenic steroids in subjects receiving 700 μg /day of intranasal flunisolide for only 10 days.¹⁴

ITAA is currently recommended for use at once-daily dosages of 220 or 440 μg /day and has been demonstrated to be efficacious at these dose levels in the treatment of rhinitis.¹⁵ These therapeutic regimens do produce measurable systemic TA exposure as follows: an initial single dose of ITAA, 440 μg , had mean plasma C_{max} of 0.4* and 0.53 ng/ml† and after 6 weeks of continuous daily treatment, produced mean C_{max} and mean steady-state ($C_{\text{ave}(0-24)}$) plasma concentrations of 0.97 and 0.19 ng/ml, respectively.¹⁷ These C_{max} s occurred at 3 to 4 hours after dose, and the half-life of TA appears to be approximately 4 hours when it is delivered intranasally.^{16, 17}

This study was undertaken to determine if 6 weeks of treatment with ITAA at the doses recommended for clinical use would reduce adrenocortical function.

MATERIAL AND METHODS

Subjects

Sixty-four male subjects initially entered the study, but two subjects did not return for follow-up evaluations; therefore, all data reflect results from the 62 remaining subjects. All subjects had at least a 2-year history of AR with positive skin test response to perennial and/or seasonal allergens present in their environment and were symptomatic, requiring treatment. The subjects' ages ranged from 18 to 63 years, with a mean of 32.5 years. None of these subjects had a history of treatment with any glucocorticoid within the previous year. Although approximately 12% of the subjects had concomitant asthma, they were treated with theophylline and inhaled β -agonists only. The subjects were otherwise healthy without conditions or concomitant medications that could have altered glucocorticoid disposition. All subjects gave informed consent before undergoing any study procedures.

Study design

This study was conducted in double-blind, placebo-controlled, and positive-controlled fashion at four study centers in the United States. The protocol and informed consent forms were reviewed and approved by an institutional review board in each case. Subjects were randomly assigned to four groups and received either placebo, ITAA, 220 or 440 μg , or 10 mg of oral prednisone for 6 weeks in parallel fashion. Adrenocortical function testing was conducted before treatment and after the 6-week, double-blind treatment period. With logistics, scheduling, and compliance variations accounted for, the average total exposure was 40 days.

The ITAA, oral placebo, aerosol placebo, and prednisone were supplied by Rorer Pharmaceutical Corp., Ft. Washington, Pa. ITAA was administered by metered-dose inhalers that delivered either 27.5 or 55 μg per actuation; eight actuations were used to achieve both the 220 and 440 μg ITAA doses, maintaining blinding. Subjects received doses once daily, in the morning. No concomitant glucocorticoid preparations were permitted during the treatment period.

Adrenocortical function testing

Adrenocortical function was assessed by response to cosyntropin stimulation conducted as a 6-hour infusion of 250 μg of Cortrosyn (synthetic ACTH, Organon, Inc., West Orange, N.J.) in 500 ml of normal saline. Cosyntropin stimulation is a sensitive and highly reproducible method used to determine the capacity of the adrenal glands to respond to stimulation^{16, 21} and to assess the functional reserve of the adrenal cortex as the end organ of the HPA axis. Test results obtained with cosyntropin stimulation have been demonstrated to correlate highly with results obtained with the insulin-induced hypoglycemia test,^{22, 23} and it is believed to reflect accurately the status of the entire HPA axis.

Blood samples obtained before and at 2, 4, and 6 hours during the infusion were assayed for plasma cortisol by a central laboratory, (SciCor, Inc., Indianapolis, Ind.) with fluorescence polarization immunoassay (TDx, Abbott Laboratories, Irving Texas). This assay method was selected to provide maximal sensitivity at higher ranges of plasma cortisol, with linearity up to 60 $\mu\text{g}/\text{dl}$ and a coefficient of variation of 6.7% at high ranges of plasma or serum cortisol; exogenous steroids are <5% cross-reactive in this assay.* To minimize further potential interference, subjects did not receive medication for more than 24 hours before testing.

Data analyses

Adrenocortical response to stimulation was quantitated as the stimulation end point (sixth hour of stimulation plasma cortisol concentration). The stimulation end point has been demonstrated to be independent of the normal diurnal variation of cortisol.^{20, 23} For analytic purposes, the change from before to after treatment in this value was calculated for each subject. The mean changes were then calculated for each group. The group data were analyzed in two steps: a two-way analysis of variance was used initially to test for treatment effects and interaction of study centers, and then each active-treatment group mean was compared with that of the placebo-treated group by one-sided Student's *t* test.

RESULTS

Pretreatment adrenocortical function

Before treatment, all subjects had normal stimulation responses, with an unequivocal doubling from basal levels to a value >40 $\mu\text{g}/\text{dl}$ by the sixth hour of infusion. Each subject's pretreatment response

*Rhône-Poulenc Rorer Medical Summary WHR5029-115 (data on file).

†Rhône-Poulenc Rorer Medical Summary WHR 5029-119 (data on file).

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clearly exceeded what would be expected from either the rapid cosyntropin test^{17,20} or a prolonged infusion.¹⁷ The pooled results (mean $\pm$ SEM micrograms per deciliter of plasma cortisol) for the 62 subjects were 14.1 ± 0.77 , 36.19 ± 0.77 , 45.88 ± 0.94 , and 50.65 ± 1.42 at the prestimulation and 2-, 4-, and 6-hour time points, respectively. These data reproduced results previously reported in normal volunteers within 6%,¹⁷ and these pretreatment results allowed calculation of internal reference ranges for both group mean and individual subject data. For group means, these reference ranges were derived from the pretreatment means ± 2 SEM (SEMs corrected for the smaller sample size of the treatment groups) before stimulation and at 2, 4, and 6 hours, and were 11.06 to 17.15, 32.46 to 39.92, 41.10 to 50.74, and 45.04 to 56.26, respectively. For individual subject data, the reference ranges were calculated from the pretreatment mean and 2 SD at each time point and were 1.91 to 26.29, 21.27 to 51.11, 26.42 to 65.34, and 31.61 to 69.71. These group mean and individual subject reference ranges represent the approximate 95% confidence limits within which each of the treatment groups or each subject could be expected to reproduce adrenocortical response to stimulation and are included in Figs. 1 and 2.

Treatment effects between groups

At the end of the 6-week treatment period, the prednisone-treated group had a significant reduction in adrenocortical function compared with that of the placebo-treated group, whereas the two ITAA-treated groups did not. These data are presented in Fig. 1 and Table I. The mean plasma cortisol levels of the placebo-treated and both ITAA-treated groups were always within the reference ranges, whereas the prednisone-treated group had mean plasma cortisol below the reference range at each time point, and the differences became more pronounced with ongoing infusion time.

When the stimulation end point (sixth hour of infusion plasma cortisol) data were compared statistically for changes with treatment, the response to stimulation for the prednisone-treated group was significantly reduced ($p < 0.0001$) compared with that of the placebo-treated group. The two ITAA-treated groups were not different from the placebo-treated group. The results of the analyses are included in Table I.

Treatment effects on individual subjects

The posttreatment stimulation-response data for the individual subjects and the calculated reference ranges are presented in Fig. 2. Within the prednisone-treated group, a notable portion (approximately 50%) of the

subjects were below the reference range at the stimulation end point, having had reductions from before treatment that exceeded expected test variability.³⁰ All subjects who had received ITAA reproduced their stimulation response within expected limits and variability, and the placebo-treated group had one subject marginally below the reference range but within expected variability at the sixth hour of stimulation only.

DISCUSSION

The purpose of this study was to assess the effect of two doses of ITAA, 220 and 440 μ g once daily, on adrenocortical function compared with that of inactive and positive controls in a 6-week course of treatment. With these dosing regimens, ITAA has been demonstrated to be an effective treatment for AR,¹⁵ but absorption and some systemic exposure has also been measured with the 440 μ g dose.*† TA, when it is administered as intramuscular injection (calculated daily dose, 1 mg or larger), has been associated with an approximate 18% incidence of adrenocortical suppression.^{5, 6} The probability of adrenocortical suppression is reduced but not eliminated with topical glucocorticoids, and the adverse effects of clinical doses of orally inhaled glucocorticoids on the HPA system have been well addressed in the literature.⁷⁻¹⁰ In other studies, HPA effects with intranasal glucocorticoids do not appear to be prevalent,²⁴⁻²⁶ but at least two studies^{13, 14} have found reductions in adrenocortical function when dose levels larger than levels normally encountered in the clinical setting were used.

ITAA did not induce any changes in adrenocortical function over changes of placebo treatment at either dose studied. Each of these three treatment groups reproduced mean responses to cosyntropin stimulation very closely and were not statistically different. In addition, all subjects who received either ITAA or placebo were within expected ranges after treatment and reproduced pretreatment testing within the limits of expected variability. This is in contrast to the subjects who received prednisone, wherein a reduction in adrenocortical function occurred that was both statistically significant for the group and clinically significant for a notable percentage of the individuals. We therefore conclude that ITAA did not have any detectable effect on adrenocortical function. This finding is very likely related to the doses of ITAA studied. In comparison with the doses used in the studies cited above in which intranasal administration of glucocorticoids produced some measurable HPA effects,

*Rhône-Poulenc Rorer Medical Summary WHR5029-115 (data on file).

†Rhône-Poulenc Rorer Medical Summary WHR 5029-119 (data on file).

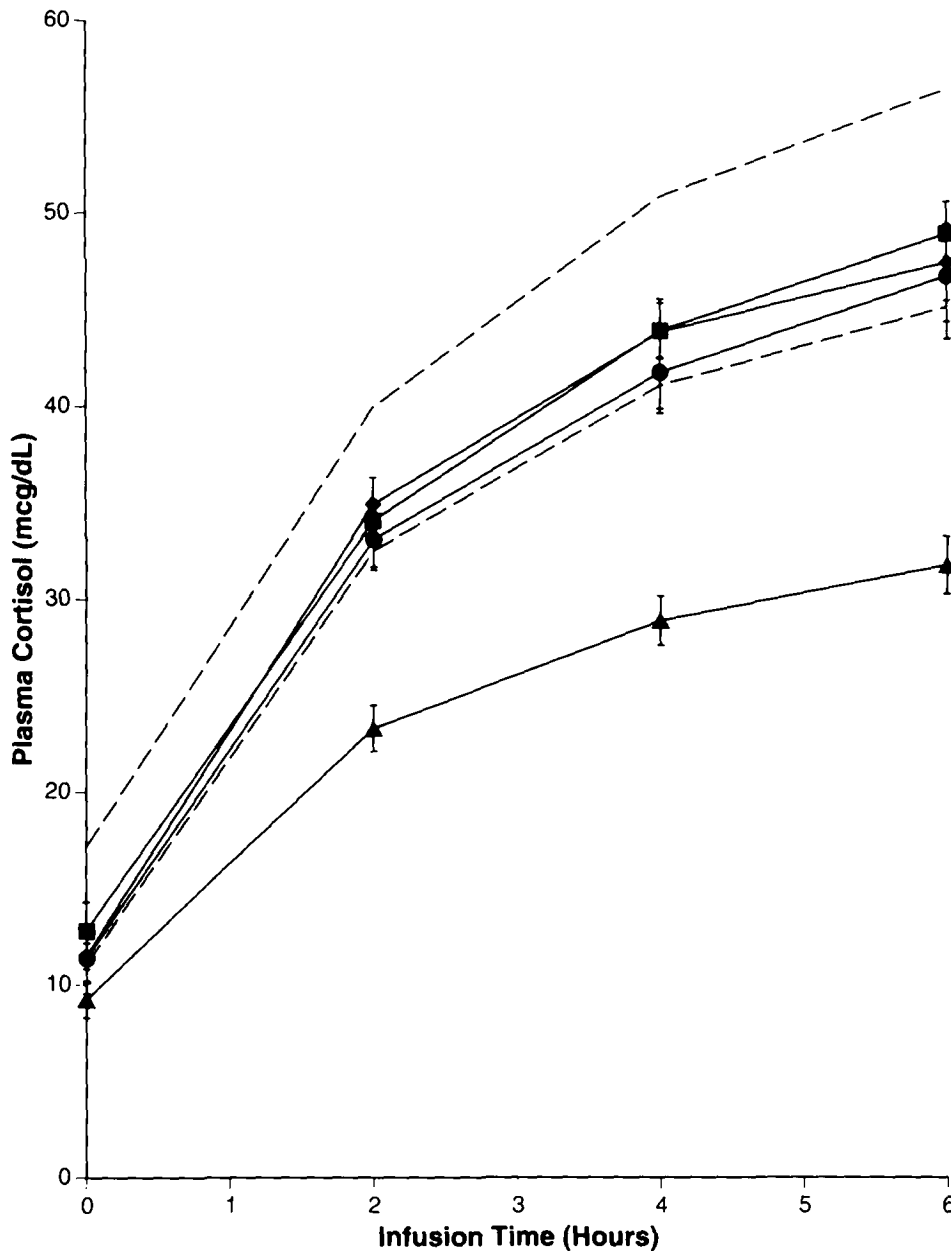


Fig. 1. Group mean plasma cortisol responses to prolonged (6 hour) adrenocortical stimulation with cosyntropin (250 µg). Posttreatment group means $\pm$ SEM: placebo (◆); ITAA, 220 µg (●); ITAA, 440 µg (■); prednisone (▲). Reference range (—) calculated from pretreatment mean $\pm$ 2 SEM of all pooled data of subjects.

even 440 µg of ITAA is fairly low. The findings of this study cannot be extended beyond the doses intended for clinical use, and the risk of HPA effects with ITAA could conceivably increase as doses >440 µg/day were administered.

Whenever a conclusion of no difference between treatments is made, the possibility that the study design or methods were insensitive to detect a real difference must be excluded. The prednisone-treated

group was included in this study as a positive control and was predicted to have a reduction in adrenocortical function.⁴ This prediction did occur, thus validating that the general study design was sufficient to detect differences. With regards to the method of adrenocortical stimulation, the 6-hour infusion that was used can be expected to produce a maximal response of the adrenals to stimulus and thereby minimize the possibility of a false reduction in function.¹⁷ The more

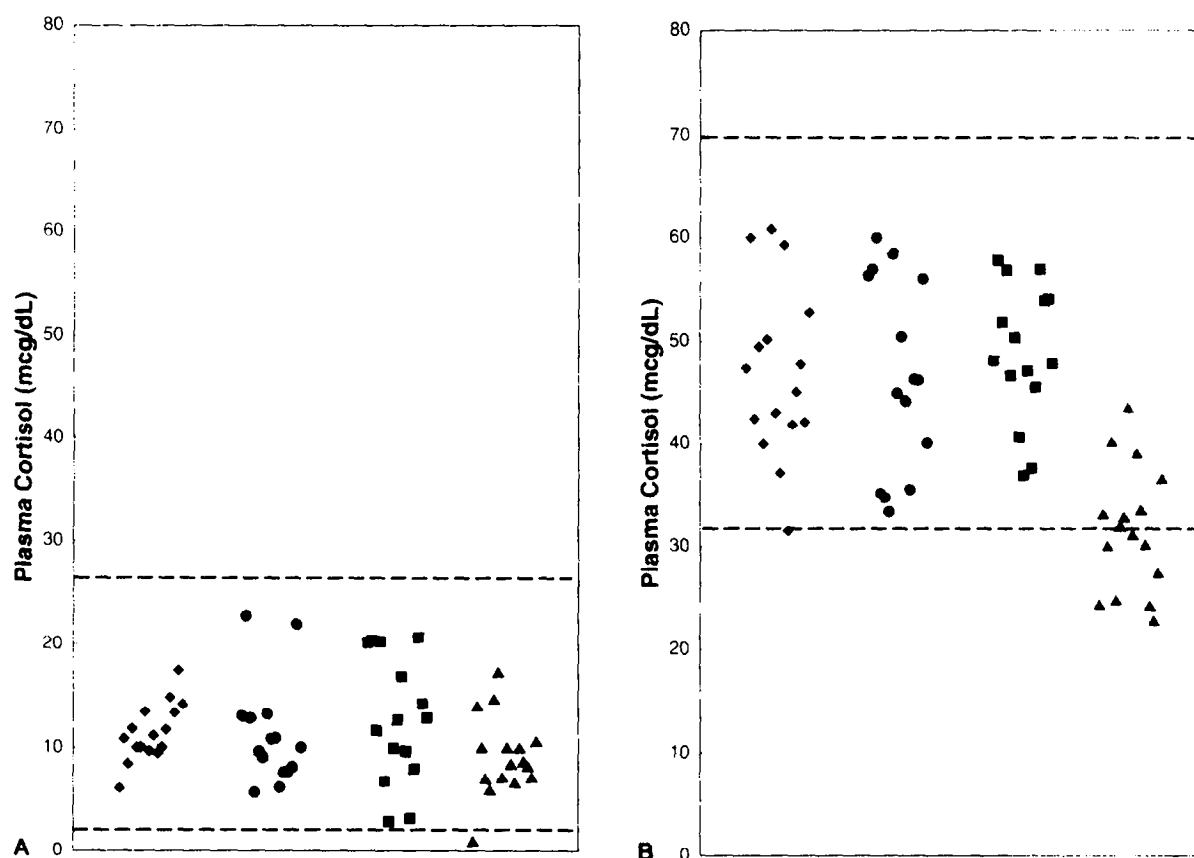


Fig. 2. Individual subject posttreatment responses to prolonged (6 hour) adrenocortical stimulation with cosyntropin (250 µg). **A**, Basal unstimulated plasma cortisol concentrations after 6 weeks of treatment. **B**, End point stimulated plasma cortisol concentrations after 6 weeks of treatment; placebo (◆); ITAA, 220 µg (●) and 440 µg (■); prednisone (▲). Reference range (—) calculated from pretreatment mean $\pm$ 2 SD of pooled data of all subjects.

TABLE I. Adrenocortical function test results (mean [SEM] plasma cortisol, micrograms per deciliter)

Treatment group	N	Treatment phase	Hours of infusion				Change in 6-hour cortisol	p*
			0	2	4	6		
Placebo	16	Before	13.44 (1.51)	36.72 (1.08)	45.76 (1.74)	50.01 (1.86)		
		After	11.46 (0.67)	34.87 (1.38)	43.76 (1.72)	47.33 (1.96)	-2.68 (1.77)	—
ITAA (220 µg)	15	Before	14.33 (0.96)	35.57 (1.34)	44.93 (1.82)	49.33 (1.89)		
		After	11.36 (1.26)	33.04 (1.43)	41.67 (1.87)	46.63 (2.35)	-2.69 (1.18)	0.478
ITAA (440 µg)	15	Before	15.09 (1.62)	36.14 (2.08)	45.27 (2.63)	51.77 (1.71)		
		After	12.78 (1.50)	34.01 (1.01)	43.83 (1.44)	48.81 (1.65)	-2.96 (1.81)	0.435
Prednisone	16	Before	13.63 (1.70)	36.28 (1.44)	47.46 (1.72)	51.49 (1.74)		
		After	9.26 (0.94)	23.29 (1.20)	28.84 (1.27)	31.69 (1.48)	-19.8 (1.77)	0.0001

*Compared with that of placebo; Student's one-sided *t* test.

common rapid synthetic ACTH stimulation test is useful for screening for clinical adrenal insufficiency, but it has been reported to have an approximate 18% to 33% false-positive rate for identifying subjects with

reduced adrenocortical function who were later found to be normal on sustained stimulation,^{5, 6} and unstimulated morning plasma cortisol concentrations were not sensitive enough to detect the effect of prednisone

in this study. Moreover, the 6-hour infusion will make more apparent any relatively small decrement in adrenocortical function, an effect that is demonstrated as the differences between the placebo-treated and prednisone-treated group increasing with ongoing stimulation time.

In conclusion, the results of this study do not preclude the consideration of ITAA as a therapy for AR on the basis of risk of adrenocortical suppression.

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