

The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis

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Background: Suppression of adrenocortical function, a risk associated with oral corticosteroids, is minimized with intranasal corticosteroids. Triamcinolone acetonide (TAA) aqueous nasal spray, at therapeutic doses, has no measurable effect on adrenocortical function in adults with allergic rhinitis.

Objective: This double-blind, placebo-controlled study compared the effect of once-daily TAA aqueous nasal spray (220 or 440 µg) with placebo on adrenocortical function after 6 weeks of treatment in pediatric (children 6 to 12 years of age) patients with allergic rhinitis. The pharmacokinetic profile of TAA was examined after once-daily intranasal administration of TAA aqueous nasal spray 440 µg for 6 weeks.

Methods: Eighty children received TAA aqueous nasal spray 220 µg or 440 µg or placebo for 6 weeks. Adrenocortical function was assessed by analyzing plasma cortisol levels before stimulation (0 hour) and at 30 and 60 minutes after a rapid 1-hour intravenous cosyntropin stimulation test performed before treatment and after 6 weeks of treatment. Samples for pharmacokinetic evaluation were collected from 19 patients at baseline (0 hour) and at 0.5, 1, 1.5, and 6 hours after the final dose of study medication.

Results: After 6 weeks, no significant effects on adrenocortical function were observed at 30 or 60 minutes after cosyntropin stimulation with either dose of TAA aqueous nasal spray. TAA concentrations in plasma showed rapid elimination of the drug, with little or no accumulation.

Conclusions: TAA aqueous nasal spray (220 or 440 µg/day) has no measurable effect on adrenocortical function in pediatric patients with allergic rhinitis. Pharmacokinetic parameters after 440 µg/day of TAA aqueous nasal spray indicate a rapid decline of plasma drug levels, with little or no systemic accumulation of study drug. (*J Allergy Clin Immunol* 1998; 101:157-62.)

Abbreviations used

AE:	Adverse events
PAR:	Perennial allergic rhinitis
SAR:	Seasonal allergic rhinitis
TAA:	Triamcinolone acetonide

Key words: Triamcinolone acetonide, adrenocortical function, corticosteroids, allergic rhinitis, pediatric, hay fever, aqueous nasal spray, clinical trial, pharmacokinetics

Oral corticosteroids have provided patients with relief from the symptoms of perennial and seasonal allergic rhinitis (PAR and SAR).¹⁻⁷ Oral corticosteroids, however, are associated with several adverse events (AEs) such as hypothalamic-pituitary-adrenal suppression,^{5, 8, 9} which is especially problematic with long-term use.^{5, 10} Intranasally administered corticosteroids, on the other hand, show no measurable adrenocortical suppression, even with long-term use.^{1-4, 6, 7, 10-18}

Triamcinolone acetonide (TAA) (Nasacort; Rhône-Poulenc Rorer, Collegeville, Pa.), a once-daily aerosol nasal spray, is effective in adults and children as young as 6 years of age in suppressing the symptoms of PAR and SAR at dosages of 110, 220, and 440 µg/day.^{1, 4, 17, 19-22} In addition to the convenience of once-daily dosing, there are limited AEs with no measurable effect on adrenocortical function.²²⁻²⁴ TAA also is available in an aqueous formulation, TAA aqueous nasal spray. The aqueous formulation maintains the efficacy and safety of the aerosol,²⁵⁻²⁷ follows a once-daily dosing regimen, and sustains its effectiveness with long-term treatment.²⁸ Furthermore, the aqueous formulation offers the property of being thixotropic, that is, the spray becomes a higher viscosity liquid after it is deposited onto the nasal mucosa. This increased viscosity may reduce the drainage of the drug from the nose to the throat.

TAA aqueous nasal spray, in therapeutic dosages (220 and 440 µg/day), does not show any measurable effect on adrenocortical function in adults; both TAA aqueous nasal spray and placebo were comparable in having no measurable effect on adrenocortical function.²⁹ This study evaluated the effect of once-daily, intranasally

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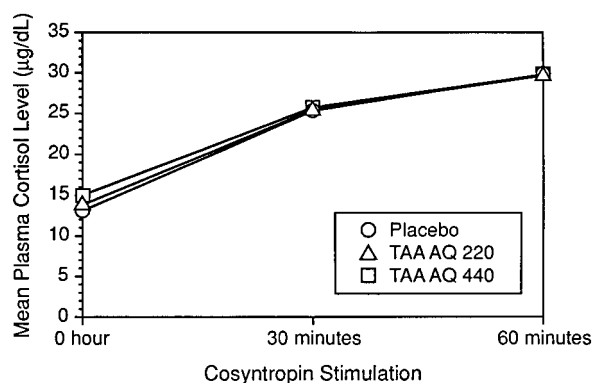


FIG. 1. Pretreatment mean plasma cortisol levels ($\mu\text{g/dL}$) at pre-stimulation (0 hour) and 30 and 60 minutes after cosyntropin stimulation.

administered doses of 220 and 440 $\mu\text{g/day}$ of TAA aqueous nasal spray on adrenocortical function in pediatric patients 6 to 12 years of age. In addition, the pharmacokinetic profile of 440 μg TAA aqueous nasal spray was examined in this population after once-daily intranasal administration for 6 weeks.

METHODS

Patients

Males and premenarcheal females from 6 to 12 years of age with a 1-year history of allergic rhinitis, a positive skin prick test response for perennial or seasonal allergens that were present in the patient's environment throughout the study, and who demonstrated normal adrenocortical function at baseline were enrolled in this study.

Patients were excluded for any clinically relevant deviation from normal medical or laboratory parameters, an intolerance to corticosteroid therapy, any medical condition capable of altering the pharmacokinetics of the drug, acute infectious sinusitis, underlying nasal pathology resulting in occlusion of a nostril, visible evidence of fungal infection of the nose, throat, or mouth, or an initial morning plasma cortisol level outside the range of 5 to 20 $\mu\text{g/dL}$. Patients also were excluded if treated with systemic corticosteroids within 90 days, oral corticosteroids for more than 10 days within the past year, inhaled glucocorticoid therapy within 30 days, or if they participated in any investigational drug study within 60 days or any previous study with TAA aqueous nasal spray. The investigational protocol was approved by an Institutional Review Board at each study site, and written informed consent was obtained from the parent/guardian of each child.

Study design

This was a multicenter (six centers in the United States), randomized, double-blind, placebo-controlled, parallel-group study to determine the effect of TAA aqueous nasal spray on adrenocortical function in pediatric allergic rhinitis patients. Adrenocortical function was assessed by evaluating the response of plasma cortisol to a 1-hour cosyntropin stimulation test, performed before treatment and after 6 weeks of treatment. Patients were administered a once-daily dose of TAA aqueous nasal spray (220 μg or 440 μg) or placebo each morning for 6 weeks. A subgroup of patients who received either TAA aqueous nasal spray, 440 $\mu\text{g/day}$, or placebo also

took part in a pharmacokinetic phase of the study to establish a plasma profile for TAA at that dose level in pediatric patients.

During an initial screening visit, all medical and laboratory procedures were performed, morning plasma cortisol levels were measured, and daily diary cards were distributed to record AEs and concomitant medication use. Adrenocortical function was assessed at a second clinical (baseline) visit by a rapid cosyntropin (Cortrosyn, synthetic ACTH, Organon, Inc., West Orange, N.J.) stimulation test. Patients were randomized to treatment groups at the third visit and given diary cards to record AEs, concomitant medications, and daily dosage of medication. Active drug and placebo were provided in identical bottles to ensure blinding. The correct use of the spray was demonstrated and the patient was instructed to administer two or four sprays in each nostril every morning. Each spray of active drug delivered approximately 55 μg of triamcinolone acetonide to the patient. An interim visit was scheduled 3 weeks after beginning treatment to review diary cards and to dispense medication for the last three weeks of the study. Patients were instructed not to administer study medication on the day of the final visit. Physical examinations were conducted and laboratory tests were performed, including taking samples for week 6 prestimulation (0 hour) plasma cortisol levels and baseline pharmacokinetic (0 hour) samples in selected patients. Cortrosyn was administered, followed immediately by a final dose of study medication. Collection of plasma cortisol samples occurred at 30 and 60 minutes after administration of Cortrosyn and the final dose of study drug. For patients in the pharmacokinetic study, an additional blood sample was collected 30 and 60 minutes after injection/dose, and at 1.5 and 6 hours after injection/dose; this schedule was based on pharmacokinetic data collected in previous studies in adult subjects with and without allergic rhinitis.³⁰ Diary cards were collected and reviewed.

Adrenocortical function testing

An initial morning plasma cortisol level (performed between 7 AM and 9 AM) was obtained during the first visit. Patients with plasma cortisol levels between 5 and 20 $\mu\text{g/dL}$ were considered normal and returned for the second (baseline) visit, which included the rapid (1 hour) cosyntropin stimulation test to measure adrenocortical function at baseline. The cosyntropin stimulation test is an established method of assessing the normality of the cortisol-secreting capacity of the adrenal cortex as the end organ of the hypothalamic-pituitary-adrenal axis, and of determining the capacity of the adrenal glands to respond to stimulation. The shortened procedure used in this study has been shown to detect insufficient adrenal function at 30, 45, and 60 minutes after injection of cosyntropin.³¹⁻³⁴

Plasma cortisol levels were determined before bolus intravenous injection of 0.25 mg Cortrosyn (0 hour) and at 30 and 60 minutes after injection. For randomization into the study, results of the stimulation test were required to show the following: baseline plasma cortisol level between 5 and 20 $\mu\text{g/dL}$; plasma cortisol level greater than 18 $\mu\text{g/dL}$ at 1 hour after cosyntropin stimulation; and an increase of at least 7 $\mu\text{g/dL}$ above baseline cortisol level at 1 hour after cosyntropin stimulation. Those patients demonstrating subnormal or negative function were not entered into the study.

This rapid (1 hour) cosyntropin stimulation test was repeated during the final visit after 6 weeks of treatment. Patients demonstrating subnormal or negative function at the end point were evaluated by a physician for follow-up or further testing.

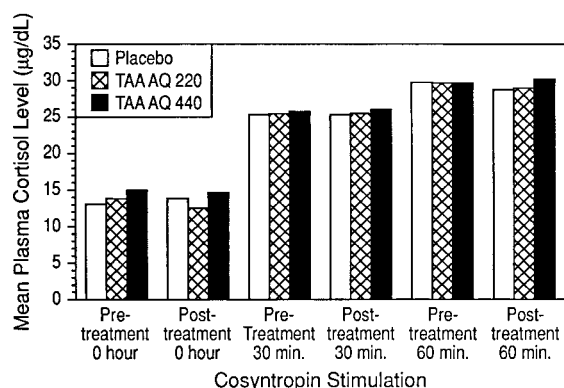


FIG. 2. Pretreatment and posttreatment (6 weeks) mean plasma cortisol levels ($\mu\text{g/dl}$) at prestimulation (0 hour) and 30 and 60 minutes after cosyntropin stimulation.

Data and statistical analyses

The primary parameter to determine the effect of TAA aqueous nasal spray on adrenocortical function was the change in plasma cortisol levels from baseline (pretreatment) to week 6 at 1 hour after cosyntropin stimulation. Secondary parameters included changes in plasma cortisol levels from baseline to week 6 at 30 minutes after cosyntropin stimulation, from baseline to week 6 at precosyntropin stimulation (0 hour), from baseline to week 6 in the difference between 0 hour to 1 hour after cosyntropin stimulation, and from baseline to week 6 in the difference between 0 hour to 30 minutes after cosyntropin stimulation. All parameters were compared between each treatment group and placebo with a one-sided *t* test; statistical significance was set at $\alpha = 0.05$. For the pharmacokinetic portion of the study, an optimal sampling scheme for collection of serial blood samples was determined by using the D-optimal method in ADAPT II software (University of Southern California). Minimal serial blood samples were obtained on the basis of the optimal sample schedule, pharmacodynamic sampling schedule, and the need to minimize the amount of blood obtained from this pediatric population. Plasma samples were analyzed for TAA with a validated radioimmunoassay. Pharmacokinetic parameters were calculated with noncompartmental methods including linear regression analyses.

RESULTS

Eighty pediatric allergic rhinitis (SAR, PAR, or both) patients, 50 males and 30 females, were enrolled in the study. Twenty-eight patients received once-daily TAA aqueous nasal spray 220 μg , 26 received 440 μg , and 26 received placebo. Demographic characteristics were similar for each treatment group; the mean age was 9.5 years, and average height and weight were 140 cm and 37 kg, respectively. Eight-four percent (67 of 80) of the population was Caucasian. Of the 80 patients, 79 completed the study. One patient in the placebo group was discontinued because of a protocol deviation.

Pretreatment adrenocortical function

At pretreatment testing, no apparent differences in plasma cortisol levels were observed among treatment groups either before or after stimulation with cosyntropin (Fig. 1). Mean prestimulation (0 hour) values

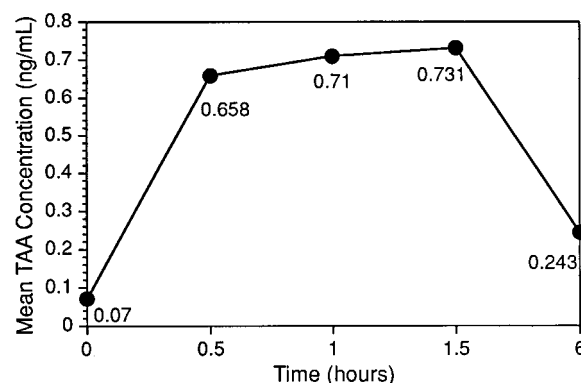


FIG. 3. Mean TAA plasma concentration-time curve.

were 13.82, 14.98, and 13.08 $\mu\text{g/dl}$ for TAA aqueous nasal spray 220 $\mu\text{g/day}$, 440 $\mu\text{g/day}$, and placebo, respectively. At 60 minutes after stimulation, values were 29.68, 29.70, and 29.79 $\mu\text{g/dl}$ for TAA aqueous nasal spray 220 $\mu\text{g/day}$, 440 $\mu\text{g/day}$, and placebo, respectively; these values were within expected ranges.

Posttreatment adrenocortical function

Table I presents mean pretreatment and posttreatment values at precosyntropin stimulation (0 hour) and at 30 and 60 minutes after cosyntropin stimulation for each treatment group. No significant differences, compared with pretreatment, were found in adrenocortical function after 6 weeks of treatment with TAA aqueous nasal spray 220 $\mu\text{g/day}$, 440 $\mu\text{g/day}$, or placebo. Mean plasma cortisol levels after 6 weeks of treatment measured at prestimulation (0 hour) and at 30 and 60 minutes after stimulation were comparable to values measured during pretreatment testing in the three treatment groups (Fig. 2). Mean prestimulation (0 hour) values at week 6 were 12.53, 14.65, and 13.85 $\mu\text{g/dl}$ for TAA aqueous nasal spray 220 $\mu\text{g/day}$, 440 $\mu\text{g/day}$, and placebo, respectively. At 60 minutes after stimulation, values were 28.97, 30.15, and 28.75 $\mu\text{g/dl}$ for TAA aqueous nasal spray 220 $\mu\text{g/day}$, 440 $\mu\text{g/day}$, and placebo, respectively. Internal reference ranges also were established from group pretreatment means ± 2 SEM (standard error of mean); posttreatment cortisol levels at prestimulation (0 hour) and at 60 minutes after stimulation were within these expected ranges.

Effects between treatment groups

As shown in Table I, no significant differences were observed between TAA aqueous nasal spray 220 $\mu\text{g/day}$ and placebo or between TAA aqueous nasal spray 440 $\mu\text{g/day}$ and placebo for pretreatment and posttreatment cortisol values at prestimulation (0 hour) or at 30 and 60 minutes after stimulation. Plasma cortisol levels were consistent among the investigative sites. No differences in cortisol values were found between the placebo group and either of the TAA aqueous nasal spray groups in mean changes from baseline in the difference from 0 to

TABLE I. Mean plasma cortisol levels and mean differences between pretreatment and posttreatment (6 weeks) levels at prestimulation (0 hour) and 30 and 60 minutes after cosyntropin stimulation

Time (pre-stimulation and poststimulation)	Treatment group	Pretreatment mean ($\mu\text{g/dl}$)	Posttreatment mean ($\mu\text{g/dl}$)	Raw mean change from pretreatment	Adjusted mean change from pretreatment (SEM)*	<i>p</i> Value†
0 hr	TAA 220 μg (<i>n</i> =28)	13.82	12.53	-1.29	-1.40 (0.93)	0.0673
	TAA 440 μg (<i>n</i> =26)	14.98	14.65	-0.33	-0.19 (0.96)	0.2645
	Placebo (<i>n</i> =25)	13.08	13.85	0.77	0.67 (0.99)	
30 min	TAA 220 μg (<i>n</i> =28)	25.45	25.47	0.02	0.04 (0.61)	0.6044
	TAA 440 μg (<i>n</i> =26)	25.73	26.01	0.28	0.29 (0.63)	0.7044
	Placebo (<i>n</i> =25)	25.34	25.28	-0.06	-0.19 (0.65)	
60 min	TAA 220 μg (<i>n</i> =28)	29.68	28.97	-0.71	-0.57 (0.70)	0.6421
	TAA 440 μg (<i>n</i> =26)	29.70	30.15	0.45	0.56 (0.72)	0.9247
	Placebo (<i>n</i> =25)	29.79	28.75	-1.04	-0.94 (0.75)	

*1-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 *t* test.

1 hour after stimulation or from 0 to 30 minutes after stimulation.

Pharmacokinetic parameters

Twelve patients from the TAA aqueous nasal spray 440 $\mu\text{g/day}$ group and seven patients from the placebo group were included in the pharmacokinetic study. As expected, no detectable TAA concentrations were found in plasma samples from the seven patients in the placebo group after 6 weeks of treatment. Eight of the 12 (67%) patients in the TAA aqueous nasal spray group had no detectable plasma TAA concentrations at 0 hour (24 hours after previous dose of study medication and immediately before final dose), and two patients had values at the minimal quantifiable limit of the assay. These undetectable or very low plasma TAA concentrations at 0 hour suggest that TAA was eliminated from the plasma before the next daily dose. Two patients had plasma drug concentrations of 0.271 and 0.443 ng/ml at 0 hour, but these TAA levels may be attributed to deviations in dosing. Plasma drug levels at 6 hours after dosing for these two patients (0.105 and 0.296 ng/ml) were approximately 80% lower than levels obtained immediately before the final dose, suggesting that TAA concentrations would decline from the 6-hour time point over the remaining 18-hour interval to plasma concentrations close to or at zero.

Concentration versus time profiles at 0 hour, 0.5, 1, 1.5, and 6 hours after dose were similar for the 12 patients, with some slight interpatient variability. Mean values at 0 hour, 0.5, 1, 1.5, and 6 hours after dose were 0.070, 0.658, 0.710, 0.731, and 0.243 ng/ml, respectively (Fig. 3). Mean values ($\pm$ standard deviation) for maximum drug concentration (C_{max}), time to maximum concentration in hours (T_{max}), and overall extent of exposure over 6 hours (AUC_{0-6}) were also calculated: $C_{\text{max}} = 0.8882 \pm 0.4689$ ng/ml; $T_{\text{max}} = 0.9583 \pm 0.4981$ hr; and $\text{AUC}_{0-6} = 3.0751 \pm 1.6407$ ng $\cdot$ hr/ml. C_{max} and AUC_{0-6} values observed in these pediatric patients were comparable to values determined in adult males after

administration of a single 440 μg dose of TAA aqueous nasal spray (data on file, Rhône-Poulenc Rorer). Results from this study confirm that there is a rapid decline of TAA from plasma, with little to no accumulation of drug administered at the highest dose level of 440 $\mu\text{g/day}$ over a 6-week period.

Safety evaluations

Safety was evaluated for all patients enrolled in the study; no deaths or serious AEs were reported. Fifty-four percent (15 of 28), 42% (11 of 26), and 35% (9 of 26) of patients in the TAA aqueous nasal spray 220 $\mu\text{g/day}$ group, in the 440 $\mu\text{g/day}$ group, and in the placebo group, respectively, reported AEs. Only one AE (epistaxis, 440 $\mu\text{g/day}$ group) was judged by the investigators to be possibly related to study medication; all but two AEs were considered mild or moderate in intensity. The most frequently observed AE was headache, which occurred in 18% of patients receiving TAA aqueous nasal spray 220 $\mu\text{g/day}$, 15% of patients receiving TAA aqueous nasal spray 440 $\mu\text{g/day}$, and 8% of patients receiving placebo. No clinically significant changes in laboratory values or findings on physical examinations were observed for any of the treatment groups.

DISCUSSION

TAA aqueous nasal spray is effective and well tolerated for the short- and long-term treatment of symptoms associated with PAR and SAR, with demonstrated results in both adult and pediatric populations.²⁵⁻²⁸ Koepke et al. found that TAA aqueous nasal spray provided safe and effective relief of PAR symptoms over a 12-month treatment period in adolescent and adult patients (age range, 11 to 59 years).²⁸ In another recent study conducted in children 6 to 11 years of age, TAA aqueous nasal spray (110 and 220 $\mu\text{g/day}$) effectively relieved the symptoms of SAR and was well tolerated.²⁷ Additionally, TAA aqueous nasal spray does not measurably alter adrenocortical function in adults; effects on

adrenocortical function are comparable to placebo.²⁹ The current study was conducted to evaluate the effect of once-daily TAA aqueous nasal spray (220 µg or 440 µg) on adrenocortical function in pediatric patients 6 to 12 years of age. In addition, 19 patients (12 receiving TAA aqueous nasal spray 440 µg/day and 7 receiving placebo) took part in a phase of the study to establish the pharmacokinetic profile of the drug at a higher therapeutic dose than that recommended in a pediatric population.

After 6 weeks of treatment with TAA aqueous nasal spray 220 or 440 µg/day, no significant differences compared with pretreatment were observed in adrenocortical function in the 54 children treated with active drug, nor were any significant differences found in adrenocortical function in patients treated with TAA aqueous nasal spray compared with patients treated with placebo.

Although literature about the use of the 1-hour cosyntropin stimulation test in a pediatric population is scarce, several studies have included patients as young as 13 years of age.^{11, 34} On the basis of data from these studies as well as from studies in adults, baseline cortisol levels, and more importantly cortisol levels at 30 minutes and 60 minutes after stimulation, observed during this study were well within normal ranges,^{11, 23, 31-34} confirming that treatment with TAA aqueous nasal spray (220 µg/day or 440 µg/day) has no measurable effect on adrenocortical function in pediatric patients.

In the pharmacokinetic study, it was demonstrated that there is a rapid decline of TAA in plasma, with peak values occurring approximately 1 hour after the dose. At 24 hours after the dose, 10 of 12 patients had no detectable or minimally detectable levels of TAA present in plasma, with higher TAA concentrations in the remaining two patients attributable to dosing irregularities. This rapid decline of TAA in plasma confirms that there is little or no accumulation of drug during 6 weeks of treatment with a once-daily dose of 440 µg TAA aqueous nasal spray. In addition, since this dose was twice the maximum recommended dose of 220 µg/day, the overall rate and extent of exposure would be expected to be half of the values reported at the higher dose.

This study supports the use of TAA aqueous nasal spray in a pediatric population. Although safety and efficacy have been demonstrated in other studies,²⁵⁻²⁸ findings from the current trial demonstrate that a therapeutic dose (220 µg/day) and a higher dose (440 µg/day) of TAA aqueous nasal spray do not measurably alter adrenocortical function in pediatric patients with allergic rhinitis, and the effect of TAA aqueous nasal spray on adrenocortical function is comparable to the effect of treatment with placebo. In addition, measurement of TAA concentration in plasma over a 6-hour period confirms rapid elimination of the drug with little or no accumulation during long-term (6-week) use in a pediatric population.

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