

Comparison of triamcinolone acetonide nasal inhaler with astemizole in the treatment of ragweed-induced allergic rhinitis

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Background: Few clinical trials have directly compared the efficacy of antihistamines with topical nasal corticosteroids.

Objective: The study was performed to compare the efficacy and safety of triamcinolone acetonide nasal spray at a dose of 110 µg in each nostril once daily with 10 mg of oral astemizole once daily for the treatment of seasonal allergic rhinitis.

Methods: A multicenter, double-blind, parallel-group study was conducted in 239 patients who were randomized to receive either triamcinolone acetonide or astemizole. A 5-day, drug-free, lead-in period was followed by 4 weeks of double-blind treatment. One hundred four patients treated with triamcinolone acetonide and 105 patients treated with astemizole could be evaluated.

Results: Overall, triamcinolone acetonide was more effective than astemizole in reducing total nasal symptoms, nasal stuffiness, nasal itching, and sneezing ($p \leq 0.01$). Triamcinolone acetonide was superior to astemizole at weeks 1, 2, and 3 in reduction of the total nasal symptom score ($p \leq 0.0401$) and in reduction of nasal stuffiness ($p \leq 0.05$). Improvements in individual nasal symptoms (itching, postnasal drip, runny nose, and sneezing) were greater for triamcinolone acetonide at week 2 ($p \leq 0.01$). Ocular symptoms improved from baseline in both groups. When pollen counts were correlated to mean nasal rhinitis scores, the triamcinolone acetonide group showed continued improvement from week 1 to week 2 in nasal symptoms when pollen counts were at their highest. During the same period, patients treated with astemizole failed to show improvement from week 1 to week 2. This study demonstrated that once daily administration of triamcinolone acetonide was more effective than astemizole for controlling nasal symptoms of seasonal allergic rhinitis, especially during the peak pollination period. (*J ALLERGY CLIN IMMUNOL* 1996;97:749-55.)

Key words: Triamcinolone acetonide, astemizole, allergic rhinitis, antihistamine, nasal corticosteroid

Both nasal topical corticosteroids and antihistamines are effective in the treatment of seasonal and perennial allergic rhinitis. With the develop-

ment of nonsedating antihistamines, the latter drugs have been increasingly used as first-line agents for treatment of seasonal allergic rhinitis.¹ Previous studies in which intranasal beclomethasone dipropionate was compared with the nonsedating antihistamine terfenadine or astemizole have demonstrated either equal² or superior³⁻⁵ efficacy, often favoring beclomethasone. Other studies have demonstrated that antihistamines combined with intranasal steroids offered no greater benefit for control of rhinitis symptoms than intranasal steroids used alone.^{5,6}

The pharmacologic profile of either class of

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Supported by Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pa.

Received for publication Feb. 1, 1995; revised May 18, 1995; accepted for publication May 22, 1995.

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0091-6749/96 \$5.00 + 0 1/1/66382

drugs requires regular and continuous use for maximal benefit,^{7,8} thus making patient compliance especially important. It has also been shown that patient compliance is inversely related to the recommended frequency of dosing, making once daily dosing preferred to multiple daily dosing.⁹

Previous studies have shown that the nasal topical steroid, triamcinolone acetonide, is effective in the treatment of seasonal and perennial allergic rhinitis when administered on a once-daily dosing schedule. Astemizole, a nonsedating antihistamine, has also been shown to be effective in the treatment of seasonal allergic rhinitis when administered once daily.¹ However, few clinical trials have directly compared antihistamines and intranasal steroids, which are known to be effective when administered on a once-daily basis. Therefore this study was designed to compare the efficacy and safety of once daily intranasal triamcinolone acetonide, 220 µg/day, with once daily astemizole, 10 mg/day, in the treatment of seasonal allergic rhinitis.

METHODS

Patients

Two hundred thirty-nine patients with a diagnosis of seasonal allergic rhinitis during the ragweed pollinating season were enrolled in the study; 120 patients were randomized to receive triamcinolone acetonide, and 119 patients were randomized to receive astemizole. The mean age of all patients was 35.7 years; 111 patients were male (46%) and 128 were female (54%).

To be included in this study, patients had to have a history of at least 2 consecutive years of nasal symptoms during the ragweed pollinating season and a positive skin prick test response to a commercial ragweed allergen extract. Patients were required to have a combined rhinitis symptom score of 24 points or greater for 4 of the 5 days during the baseline period, according to a 4-point symptom scale for the six symptoms evaluated: 0 = none, symptoms absent; 1 = mild, symptoms present but not annoying; 2 = moderate, symptoms present and annoying; and 3 = severe, symptoms interfere with daily activities or sleep.

Women who were pregnant, lactating, or of childbearing potential and not practicing an approved method of birth control (e.g., oral contraceptive, spermicide and barrier methods) were excluded from the study. Exclusion criteria included: recent use of systemic steroids, topical corticosteroids, or intranasal cromolyn; clinically significant medical disease; active sinusitis; rhinitis medicamentosa; and underlying nasal disease resulting in nasal obstruction caused by conditions such as nasal polyposis or nasal septal deviation. Patients who had initiated allergen immunotherapy within 1 month of the study were excluded. All participants signed an informed

consent statement, which had been approved by an institutional review board for each investigational site.

Study design

This multicenter study was conducted at nine sites. Prospective subjects were evaluated for eligibility on visit 1 during a 4-week screening period. After recording nasal and eye symptoms during a 5-day, drug-free, baseline lead-in period, qualified patients were randomized on visit 2 to receive either intranasal triamcinolone acetonide (220 µg) once daily, given as 2 sprays (55 µg/spray) in each nostril, or oral astemizole (10 mg) once daily. A double-dummy design was used: patients treated with triamcinolone acetonide received a placebo oral medication and patients treated with astemizole received a placebo nasal inhaler. During the 4-week active treatment period, patients were evaluated at week 2 (visit 3) and at week 4 (final visit) of treatment. Procedures conducted during these visits included: issuance and collection of patient diary forms (only collection at week 4); physician global evaluations and nasal examinations; and documentation of adverse experiences. Clinical laboratory tests (complete blood count, blood chemistry, and urinalysis) were performed at the screening and final visits. A 12-lead electrocardiogram was done at the screening visit and at the final visit.

Statistical analysis

Efficacy analyses were carried out on the patient population that could be evaluated, and safety analyses were carried out on the entire treated patient population. The primary efficacy end points were the mean scores for each individual rhinitis symptom (nasal stuffiness, rhinorrhea, postnasal drip, sneezing, nasal itch, and ocular symptoms) and the mean total nasal score. Secondary efficacy variables included an assessment of the physician's global evaluations of effectiveness, the assessment of onset of action, treatment failure rates, and the analysis of efficacy relative to pollen counts. The overall analysis included data from the last evaluation for each patient.

The mean total nasal symptom score was determined by summing the daily scores for each individual nasal symptom and then determining the mean. The mean change from baseline improvement was used as the primary tool to evaluate efficacy. The poolability of the rhinitis symptom data for each center was assessed by fitting a two-way analysis of variance model (including center, treatment, and center-by-treatment interaction effects) to the overall total and individual nasal score data. The significance of the treatment-by-center interaction was determined with a two-sided test at a conservative significance level of 15%.

Overall and weekly mean changes from baseline in total nasal score, individual nasal scores, and ocular symptom scores were analyzed with analysis of variance models, including center and treatment effects. Physician global evaluations were analyzed by a Wilcoxon sum of ranks procedure, stratified by center. Similar analyses

were carried out for the by-visit and overall analyses. All efficacy comparisons of the treatment groups used a 0.05 level of significance.

Descriptive statistics were used to summarize incidence rates of all demographic parameters, adverse events, adverse events considered related to the study medication, and abnormal laboratory values. Two-sided Student's *t* tests were used to compare the treatments with respect to mean changes from baseline in clinical laboratory parameters.

The impact of pollen count on the treatment comparisons was determined by the daily mean changes from baseline. Means for pollen counts were calculated for each center. For each study center, "relative day" was calculated relative to the first day the first patient began receiving study medication. Only days with diary data were included in these mean analyses. Because of the high degree of variability among centers in pollen counts, the data were normalized within each center by using a Z score, which was calculated for each relative day as follows:

$$Z = \frac{\text{Value of pollen count} - \text{Mean}}{\text{Standard deviation}}$$

All Z scores of the same relative day were calculated and averaged and presented graphically, with mean changes in total nasal symptom scores relative to the pollen count. The mean total rhinitis symptom score was calculated on each of the first 7 days of therapy for both treatment groups in order to assess onset of action.

RESULTS

Patient disposition

Of the 120 patients in the triamcinolone acetonide group, 106 (88%) completed the study. Five were withdrawn because of protocol deviations, four discontinued treatment because of adverse clinical experiences, three experienced treatment failures, one was lost to follow up, and one discontinued treatment for unspecified reasons. Of the 119 patients in the astemizole group, 109 (92%) completed the study, three were withdrawn because of protocol deviations, four were withdrawn because of adverse clinical experiences, two experienced treatment failures, and one was lost to follow up. The triamcinolone acetonide and astemizole groups had comparable numbers of patients who could be evaluated (104 and 105 patients, respectively) for efficacy analyses.

Efficacy

Overall percent improvements in individual nasal symptoms from baseline mean are shown in Table I. Values ranged from 43% to 56% improvement in the triamcinolone acetonide group and

TABLE I. Overall summary of mean changes from baseline in nasal and ocular symptoms

Symptom parameter	Triamcinolone acetonide (n = 104)	Astemizole (n = 105)
Total nasal score		
Baseline	9.102	9.074
Mean change (SD)	-4.548 (2.65)*	-3.359 (2.81)
% Change	50	37
Itchy nose		
Baseline	1.848	1.752
Mean change (SD)	-1.000 (0.70)†	-0.742 (0.81)
% Change	54	42
Stuffy nose		
Baseline	1.928	2.002
Mean change (SD)	-0.836 (0.68)*	-0.532 (0.66)
% Change	43	27
Postnasal drip		
Baseline	1.726	1.630
Mean change (SD)	-0.773 (0.66)	-0.578 (0.67)
% Change	45	35
Runny nose		
Baseline	1.726	1.789
Mean change (SD)	-0.888 (0.69)	-0.699 (0.68)
% Change	51	39
Sneezing		
Baseline	1.877	1.903
Mean change (SD)	-1.044 (0.62)†	-0.805 (0.68)
% Change	56	42
Ocular symptoms		
Baseline	1.842	1.823
Mean change (SD)	-0.818 (0.72)	-0.805 (0.76)
% Change	44	44

**p* ≤ 0.01.

†*p* ≤ 0.05.

from 27% to 42% in the astemizole group. There were statistically significant (*p* ≤ 0.0183) differences between treatment groups, favoring triamcinolone acetonide in overall mean scores for total nasal symptoms, nasal itching, nasal stuffiness, and sneezing. There were no significant differences between the two treatment groups in overall scores for postnasal drip and runny nose. The overall percent reductions in ocular symptoms were identical (44%) for the two treatments.

Mean changes in weekly symptom scores from baseline were compared between the two treatment groups. As shown in Fig. 1, there were significantly greater improvements in the triamcinolone acetonide group than in the astemizole group for the following symptoms: nasal stuffiness at weeks 1, 2, and 3; sneezing at weeks 2 and 3; and nasal itch, postnasal drip, and runny nose at

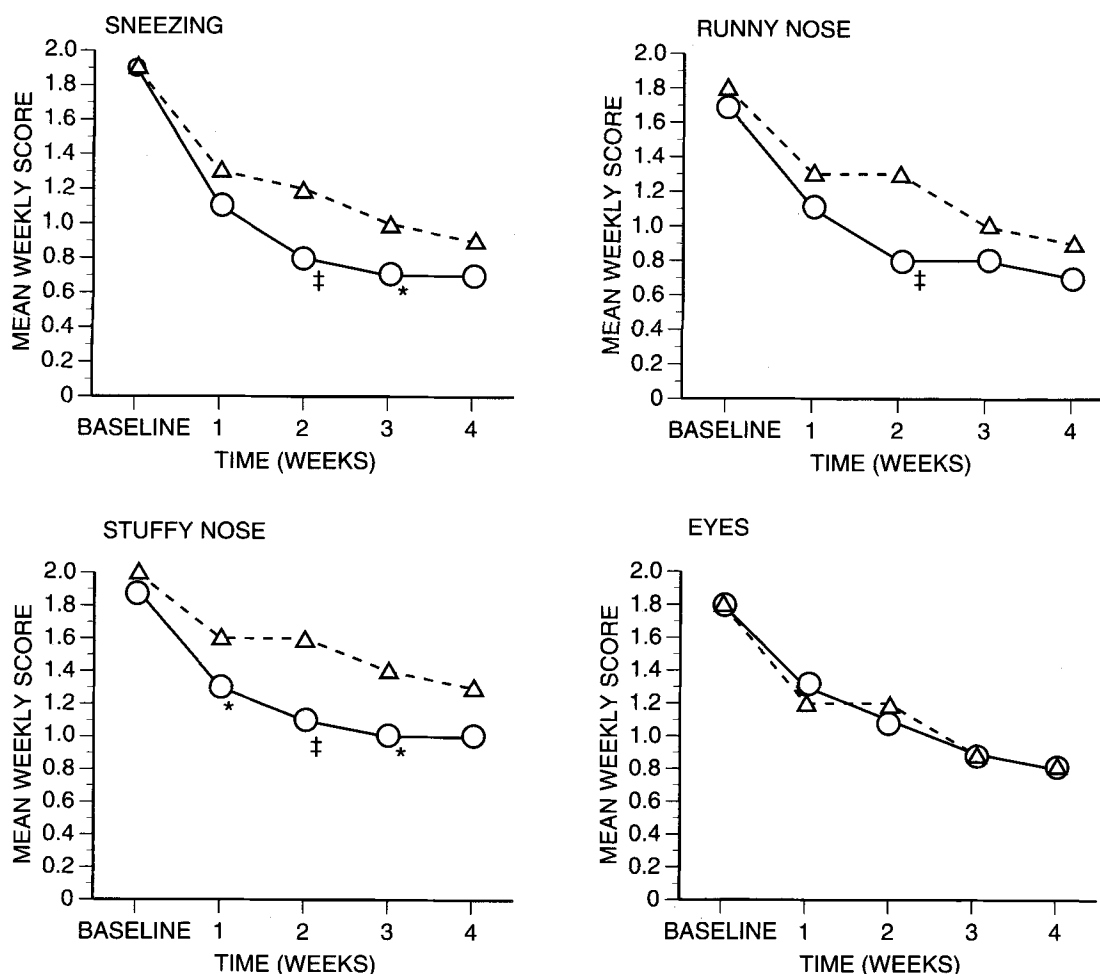


FIG. 1. Mean weekly nose and eye symptom scores throughout the ragweed pollen season in triamcinolone acetonide-treated (circles) versus astemizole-treated groups (triangles). Statistically significant differences: * $p \leq 0.05$, $^{\dagger}p \leq 0.01$, and $^{\ddagger}p \leq 0.001$.

week 2. The most significant differences between triamcinolone acetonide and astemizole groups in all nasal symptoms were apparent at week 2, when there were significant ($p \leq 0.0018$) differences between groups in every nasal symptom. It was noteworthy that there was improvement from baseline in ocular symptoms for both astemizole and triamcinolone acetonide groups, but there were no significant differences between the two groups.

Analysis of physician global evaluations showed that 77.3% (92 of 119 patients) of the triamcinolone acetonide group had moderate to complete relief compared with 62.7% (74 of 118 patients) of the astemizole group ($p \leq 0.001$; Wilcoxon rank sum test).

Although patients in both treatment groups experienced relief of nasal symptoms by day 1, patients treated with triamcinolone acetonide

achieved a significantly greater ($p \leq 0.05$) reduction in mean symptom scores from baseline by week 1 in total nasal score and nasal stuffiness than patients treated with astemizole by week 1.

As shown in Fig. 2, pollen counts were at their highest levels during week 2 of the study. Patients treated with triamcinolone acetonide had a greater decrease from baseline in the mean total nasal score, regardless of pollen counts, than patients treated with astemizole. During week 2, patients in the triamcinolone acetonide group maintained improvement in rhinitis symptoms, whereas patients receiving astemizole appeared to show reduced effectiveness during the peak pollen counts (expressed as mean Z scores).

Safety

The most frequently occurring adverse events in the triamcinolone acetonide and astemizole

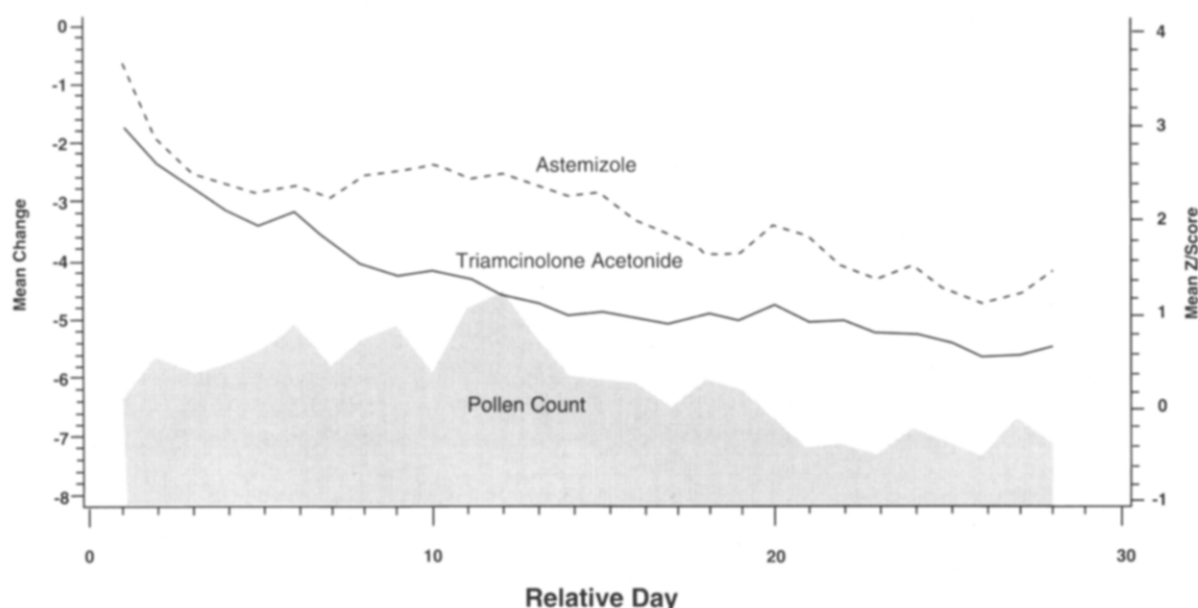


FIG. 2. Mean change in total nasal score for triamcinolone acetonide and for astemizole versus pollen count, expressed as Z score (see Methods).

groups, respectively, were headache (38% and 37%) and pharyngitis (7% and 9%). The only major difference between treatment groups was in weight gain; 11% of the patients in the astemizole group gained weight compared with 2% of the patients in the triamcinolone acetonide group.

Four patients treated with triamcinolone acetonide and four patients treated with astemizole discontinued treatment because of adverse events related to upper respiratory infections. In the astemizole group, one patient discontinued treatment because of nasal congestion, postnasal drip, and pharyngitis; and one patient discontinued treatment because of conjunctivitis.

There were no clinically significant changes in results of physical examinations in either treatment group, except for weight. There was a mean weight increase of 2.2 pounds over 4 weeks in the astemizole group compared with an increase of 0.66 pounds in the triamcinolone acetonide group. Two patients treated with astemizole had prolonged corrected QT intervals; electrocardiograms revealed normal sinus rhythm, and no cardiac symptoms were reported. There were no clinically significant changes in laboratory parameters in either treatment group.

DISCUSSION

Antihistamines and nasal topical steroids are widely used in the treatment of seasonal allergic rhinoconjunctivitis. Both classes of agents have

been demonstrated to be more effective than placebo in the treatment of seasonal allergic rhinitis.^{10, 11} It is generally acknowledged that H₁ antihistaminic agents modify histamine-mediated symptoms, including nasal and ocular itching, rhinorrhea, lacrimation, and conjunctival erythema.¹¹ It has been recognized that antihistamines are clearly less effective than nasal steroids in relieving nasal obstruction.^{5, 12, 13} The latter observations are supported by previous studies of seasonal allergic rhinitis, showing that antihistamines are effective if initiated early in the pollen season but that their efficacy rapidly declines thereafter, presumably because of the inability of these agents to control nasal congestive symptoms.^{5, 7} This observation was confirmed by data in this study showing that triamcinolone acetonide was significantly better than astemizole in reducing nasal obstructive symptoms during 3 of 4 weeks of active treatment.

The primary aim of this investigation was to determine the relative efficacy of a nasal topical steroid (triamcinolone acetonide) given once daily compared with a comparable dose of antihistamine (astemizole) in the treatment of seasonal allergic rhinitis. We found that triamcinolone acetonide produced significantly greater overall improvement in total nasal symptoms and in individual nasal symptoms of itching, stuffiness, and sneezing. At week 1, statistically significant differences favoring triamcinolone acetonide over astemizole were noted in total nasal score and nasal stuffiness. By week 2,

significant differences were noted for total nasal scores and all individual nasal symptoms, which corresponded to the peak in ragweed pollen counts. Subsequently, differences between the two treatment arms declined by weeks 3 and 4; significant improvement favoring triamcinolone acetonide was noted for three nasal symptoms at week 3 and for only two nasal symptoms at week 4. The latter trend may have been attributable to spontaneous improvement in both treatment groups, resulting from an overall decline in allergen exposure. This experience suggests that direct comparisons of efficacy between two active treatments are most valid during periods of peak allergen exposure.

The onset of action for both treatments was evident as early as day 1 of treatment, and by week 1, triamcinolone acetonide was significantly better than astemizole in relieving nasal itching and stuffiness. Because of the rapid onset of action and superior performance of the intranasal steroid used in this study, concurrent administration of an antihistamine may not be necessary for control of nasal symptoms of seasonal allergic rhinitis. It should be emphasized that the results of this study, which showed greater efficacy of triamcinolone acetonide compared with astemizole, may or may not be directly applicable to other agents in either drug class.

Clinicians often prescribe antihistamines because of their ameliorative effects on eye symptoms associated with allergic rhinoconjunctivitis. For this reason, it was surprising that ocular symptoms improved equally in both treatment groups and that astemizole was not superior to triamcinolone acetonide. In similar studies in which astemizole or loratadine was compared with nasal beclomethasone, ocular itching was significantly reduced in the groups treated with antihistamines.^{2,12} In one of the latter trials, decreases in eye symptoms from pretreatment baseline were observed in the group treated with intranasal steroid, albeit significantly less than those observed with antihistamine treatment.¹² Inclusion of a placebo group in this study may have helped to further elucidate the clinical significance of the decreases in ocular symptoms observed in both treatment groups.

Our study design did not permit evaluation of possible additive effects of antihistamines and nasal steroids in controlling allergic nasal or ocular symptoms. However, Juniper et al.⁵ found no significant advantage in combined treatment with beclomethasone and astemizole over therapy with

beclomethasone alone in modifying nasal symptoms of seasonal allergic rhinitis. This study did not compare the effects of either active treatment with those of placebo. Because both astemizole and triamcinolone acetonide have been shown to be more effective than placebo in controlling nasal symptoms, the inclusion of a placebo arm in this study was not essential.¹⁴⁻¹⁶

In conclusion, this study demonstrated that once daily dosing with triamcinolone acetonide was safe and far more effective than oral administration of astemizole in reducing nasal symptoms of seasonal allergic rhinitis, particularly during peak levels of exposure to ragweed allergens.

We would like to acknowledge the invaluable contribution of our late colleague and co-investigator in this study, Steven R. Findlay, MD, Austin, Texas.

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