Azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of seasonal allergic rhinitis

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Background: Azelastine rhinitis medications (nasal spray and tablets) have been shown to relieve the symptoms of allergic rhinitis. Nevertheless, many rhinitic subjects suffer from acute exacerbations of symptoms that sometimes require additional treatment.

Objective: To assess the efficacy and safety of azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of symptomatic seasonal allergic rhinitis in subjects who remain symptomatic despite the oral medication.

Methods: A 2-day, randomized, multicenter, double-blind, placebo-controlled, parallel-group study. Two hundred thirty-three subjects with symptomatic allergic rhinitis received azelastine tablets (0.5 mg bid) for a minimum of seven days prior to receiving either azelastine nasal spray (2 sprays per nostril bid) or placebo nasal spray as adjunctive therapy. Efficacy was determined by improvement in rhinitis symptoms that were grouped according to total and major symptom complex severity scores.

Results: Mean percent improvements in the total symptom complex severity scores for azelastine were statistically significant ($P \leq .05$) or showed a trend toward statistical significance ($.05 \leq P < .10$) versus placebo from the second through the first ten hours after the initial dose and for each of the last five hours of the second day, demonstrating a rapid onset of action and sustained efficacy over the 2-day study period. Azelastine was well tolerated, and no subject discontinued therapy with azelastine due to an adverse experience.

Conclusion: Azelastine nasal spray can be effectively administered as adjunctive therapy, in an outdoor environment in which subjects are exposed to pollen and other aeroallergens.

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INTRODUCTION

Allergic rhinitis can be a debilitating disease when acute exacerbations of symptoms over a short period of time are not adequately controlled with routine daily oral medication. During periods of intense pollen exposure, many subjects require supplemental antiallergy therapy to alleviate symptoms before they become severe. Adjunctive therapy can be problematic if the subject is exposed to different classes of drugs, increasing the risk of adverse experiences, especially when the medications are given systemically. In addition, adjunctive therapy with intranasal steroids[1] or cromolyn[2] may take days to weeks to be effective, and prolonged treatment with topical decongestants may result in rebound congestion.

Azelastine, a phthalazinone derivative with a chemical structure unlike other antirhinitis drugs, is a multifunctional antiallergic compound that antagonizes the effects of chemical mediators released during the early-phase and late-phase allergic responses in the upper and lower airways.[3,4] Oral and topical formulations of azelastine have been evaluated in worldwide clinical trials for the treatment of allergic rhinitis. In controlled clinical trials, azelastine administered topically as a 0.1% nasal solution was well tolerated and effectively relieved rhinitis symptoms in subjects with allergic rhinitis.[5–9] The results of the controlled trials with azelastine tablets also demonstrate effective long-lasting relief of symptoms of both seasonal and perennial allergic rhinitis.[10–13]

This 2-day multicenter study was conducted in an outdoor environment (park) during the fall/autumn pollen season to maximize exposure to aeroallergens and standardize as many variables as possible that could influence the outcome of the study. The objective of the study was to assess the efficacy and safety of azelastine nasal spray as adjunctive therapy to oral azelastine in the management of subjects with symptomatic seasonal allergic rhinitis who remain symptomatic despite treatment with 0.5 mg oral azelastine.

METHODS

Subjects

All subjects were 12 years of age and older, had a history and diagnosis of seasonal allergic rhinitis, were symptomatic to allergens prevalent at the time the study was conducted, and required pharmacologic therapy each year for at least the preceding 2 years prior to enrollment in the study. Each subject demonstrated a significant response to one or more of the common prevalent seasonal (grass in San Diego or ragweed in Iowa) allergens as confirmed by a recognized epicutaneous

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scratch or prick test within the past year.

Subjects with histories of asthma were enrolled if no chronic antiasthma medication had been taken within the past 24 months. Subjects with a history of exercise-induced asthma could be enrolled if only inhaled β agonists were used to treat their asthma. Females were postmenopausal, were documented as surgically incapable of conception or, if of childbearing potential, agreed not to become pregnant during the study.

Subjects with a clinically significant nasal anatomical deformity (ie, septal defects, polyps), an episode of acute sinusitis within 30 days of study entry, or subjects starting or changing an immunotherapy regimen during the course of the study were excluded from participation. Additionally, subjects were excluded for any abnormal prestudy laboratory test value or physical examination measurement that was considered to be clinically significant by the investigator and limiting to the conduct of the study.

Prior to the screening visit, subjects were not permitted to use intranasal or ophthalmic steroids for 14 days or systemic steroids for 30 days; intranasal or ophthalmic cromolyn, monoamine oxidase inhibitors, reserpine, or β blockers for 14 days; decongestants for 48 hours; or astemizole for 60 days.

All subjects or their parents or guardians signed informed consent statements, and the study protocol was approved by institutional review boards.

Study Design

This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study conducted in parks on two consecutive days during the fall/autumn grass season in California and ragweed season in Iowa. Subjects received azelastine tablets (0.5 mg bid) for a minimum of seven days prior to the double-blind treatment period. Aeroallergen data, obtained using a volumetric sampler, were recorded by the principal investigator during all evaluations conducted in the park.

Table 1. Symptom Scoring Scale for the Individual Rhinitis Symptoms

Symptom	Scoring Scale
Runny nose, left side Runny nose, right side Sniffles Itchy nose, left side Itchy nose, right side Watery eyes Itchy eyes and ears Itchy throat Cough Postnasal drip Dry nose	0 = None 1 = A little, mild 2 = Moderate 3 = Quite a bit 4 = Severe 5 = Very severe
Nose blows Sneezes	0–5 = Actual number 6 = 6 through 9 7 = 10 through 15 8 = Greater than 15
Stuffiness	0 = Clear, fully open 1 = Slight block 2 = Stuffy 3 = Very stuffy 4 = Blocked

On the morning of the first study day, all subjects were instructed to take one tablet of azelastine at home at 7 AM. Subjects arrived at the park before 8 AM and recorded their baseline symptom severity in diaries at 8 AM, 9 AM, and 10 AM prior to treatment. Subjects qualified for randomization to study treatment if the sum of the three hourly prestudy evaluations for the combined symptom-rated scores for nose blows, sneezes, itchy nose left side, itchy nose right side, runny nose left side, runny nose right side, dry nose, sniffles, postnasal drip, watery eyes, itchy eyes and ears, itchy throat, and cough was 12 or more (based on the scoring scale described in Table 1).

Qualified subjects were randomized to receive either azelastine nasal spray (2 sprays each nostril bid) or placebo (saline) nasal spray (2 sprays each nostril bid) as adjunctive therapy to their low-dose azelastine tablet regimen. The total daily dose of azelastine administered (in 2 sprays per nostril twice a day) was 1.10 mg. Subjects took the first dose of study medication at 10 AM (Fig 1).

After the initial dose of study medication, symptom scoring diary cards were completed by each subject for the next six hours (11 AM to 4 PM) while in the park. Subjects were allowed to leave the park after recording symptoms on the 4 PM diary card. They continued to complete the symptom scoring diary cards at 6 PM, 8 PM, and 10 PM at home. At 7 PM, each subject took the second dose of oral azelastine and, at 10 PM, subjects took their second intranasal dose of study medication immediately after completing the diary card for that hour.

On the second day, each subject took the first dose of oral azelastine at 7 AM at home and returned to the park between 7:30 AM and 8 AM, where they resumed rating their symptoms hourly on the symptom scoring diary cards. Following the 10 AM evaluation, subjects took the third and final intranasal dose of study medication and continued to rate symptoms on their diary cards until 4 PM. Subjects received a follow-up physical examination and laboratory evaluation within seven days of the second study day.

Response Measurements

The primary efficacy variables were the total and major symptom complex

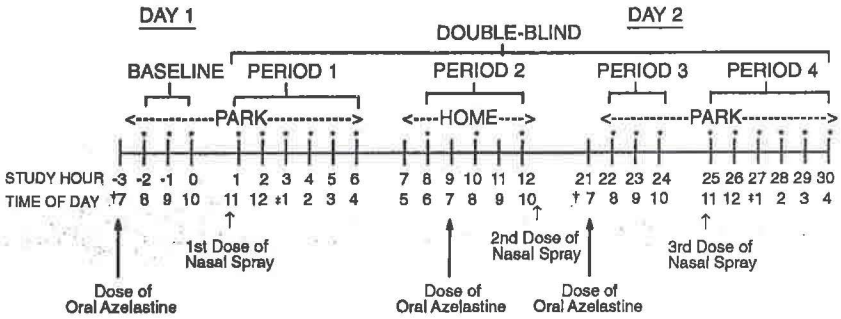

Figure 1. Schematic design of the study. * = symptom scoring, †AM, and ‡PM.

severity scores. Scores for eight rhinitis symptoms (runny nose left side, runny nose right side, sniffles, itchy nose left side, itchy nose right side, sneezes, nose blows, and watery eyes) were summed to form the major symptom complex severity score and scores for five additional rhinitis symptoms (postnasal drip, cough, dry nose, itchy throat, and itchy eyes and ears) were summed with the major symptom complex severity score to form the total symptom complex severity score (Table 1). The secondary efficacy variables were the total symptom complex severity score with the additional symptom of stuffiness, the individual rhinitis symptom scores, and subject global evaluations. Safety evaluations consisted of vital sign measurements, physical examination findings, clinical laboratory test values, and adverse experience reports.

For the purpose of the efficacy analyses, the 2-day, double-blind, treatment period was divided into five separate periods including baseline (Fig 1). The total duration of the double-blind period was 30 hours. The baseline period is the average of the three hours prior to the first intranasal dose taken at the park. Period 1 is the average of the first six hours (11 AM to 4 PM) after the first intranasal dose. Period 2 is the average of the three hourly evaluations at 6 PM, 8 PM, and 10 PM, 8 to 12 hours after the first intranasal dose and prior to receiving the second intranasal dose. Period 3, the following morning, is the average of the three hourly evaluations at 8 AM, 9 AM, and 10 AM just prior to the third dose of study medication (at 10 AM). Period 4 is the average of the six hours (11 AM to 4 PM) following the third dose of study medication. All periods, except period 2, were conducted in a park.

Statistical Methods

Pretreatment baseline comparability of the treatment groups for each efficacy variable was determined by a two-way analysis of variance (ANOVA) model, incorporating terms for treatment, center, and their respective interaction.

The treatment effect at each evaluation period and at each of the 18 specified assessment points was analyzed for each of the efficacy variables. In addition, an overall intent-to-treat analysis, based on averages of all available subject-response data during treatment at each evaluation period, and an endpoint analysis, based on each subject's last observation period during double-blind treatment, were performed. For each of the evaluation periods, the symptom complex severity scores were calculated based on the sum of the hourly severity scores. Improvements in the total and major symptom complex severity scores were analyzed in terms of percent change from baseline, and the individual symptoms were analyzed in terms of absolute change from baseline.

The improvements in the total symptom complex, major symptom complex, and individual rhinitis symptom scores during double-blind treatment were evaluated by an analysis of covariance (ANCOVA) model, incorporating terms for treatment and center, with the baseline value as the covariate. Treatment differences for the global evaluation were analyzed by the Cochran-Mantel-Haenszel test (adjusting for investigator effect).

The proportions of subjects with the most frequently reported adverse experiences across the treatment groups were analyzed by chi-square tests. The changes from baseline to the end of treatment for each clinical laboratory test and the mean change from baseline for vital sign measurements and body weight were analyzed by the two-factor ANOVA model, incorporating

Table 2. Demographic and Baseline Characteristics

Treatment (Azelastine, 0.5 mg PLUS)	Azelastine Nasal Spray N = 116	Placebo Nasal Spray N = 117
Age, yr		
Mean	27.4	30.5
Range	12–73	12–64
Sex, %		
Male	53	54
Female	47	46
Race, %		
White	91	89
Other	9	11
Weight, lb		
Mean	157.9	163.4
Range	92–272	91–259
Mean baseline scores		
Total symptom complex	16.9	18.2
Major symptom complex	10.7	11.2

terms for treatment, center, and center-by-treatment interaction. The level of significance for all statistical tests was set at .05. All treatment comparisons utilized two-sided tests. A clinically significant improvement was defined as a mean improvement with azelastine nasal spray that was at least 50% greater than that observed with placebo nasal spray.

RESULTS

Two hundred thirty-three subjects were randomized to the double-blind phase of the study, and 228 completed the study. Treatment groups were similar at baseline with regard to demographic characteristics and the total and major symptom complex severity scores (Table 2). Of the five subjects who did not complete the study, two in the placebo group developed intercurrent illness, one in each group failed to return to the park on the second day, and one in the azelastine group failed to take the medicine in the evening of the first study day. All 233 subjects were included in the intent-to-treat analyses.

Pollen counts, temperature, and humidity were typical for the fall allergen season during the 2-day study at each site.

Primary Efficacy Variables

In this study, the azelastine group had improvements in the total symptom complex severity score that were superior to those for the placebo group at every evaluation period (Fig 2). At periods 1 and 4, the mean percent improvements for the azelastine group were clinically and statistically significant ($P \leq .041$) versus placebo. In addition, the results of the endpoint analyses showed statistically significant ($P = .043$) mean percent improvement for the azelastine group when compared with the placebo group. The difference in the overall mean percent improvement in the total symptom complex severity score and the total symptom complex severity score including the additional symptom of stuffiness showed a trend toward statistical significance ($P = .061$) in favor of azelastine.

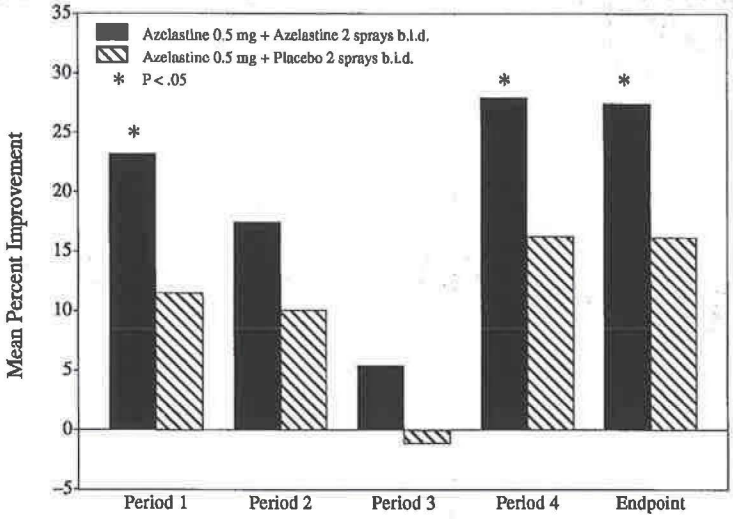

Figure 2. The mean percent improvement from baseline in the total symptom complex severity scores at each period and at endpoint.

The mean percent improvements in the total symptom complex severity scores for each treatment group at the 18 specified hourly evaluations during the double-blind treatment period are shown in Figure 3. At hours 2 through 6 and hours 27 and 30, the differences in the improvement between the azelastine group and the placebo group were statistically significant ($P \leq .05$) in favor of azelastine and showed a trend toward statistical significance ($P \leq .10$) at hours 8, 10, 24, 26, 28, and 29. The azelastine group had clinically significant mean percent improvements in the total symptom complex severity scores at hours 2 through 10 and hours 23 through 30.

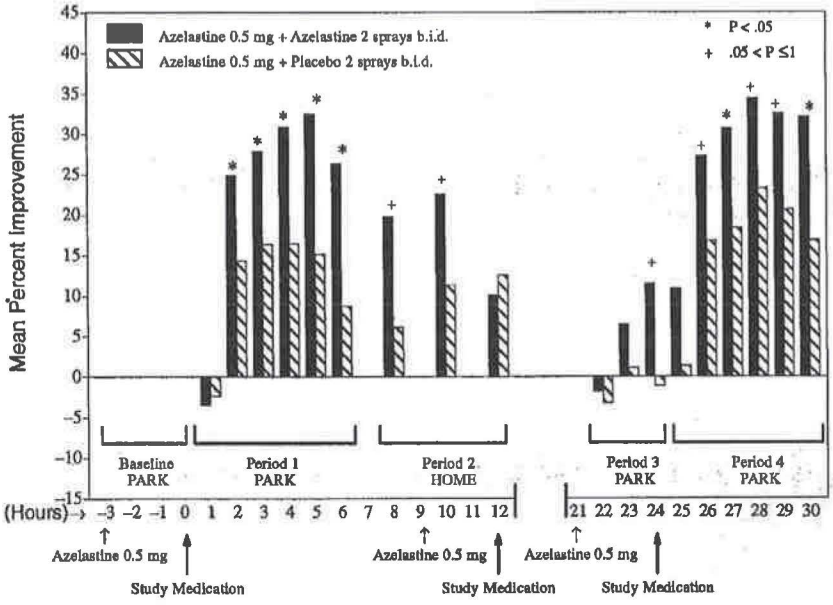

Figure 3. The mean percent improvement from baseline in the total symptom complex severity scores at each hour during the double-blind treatment period.

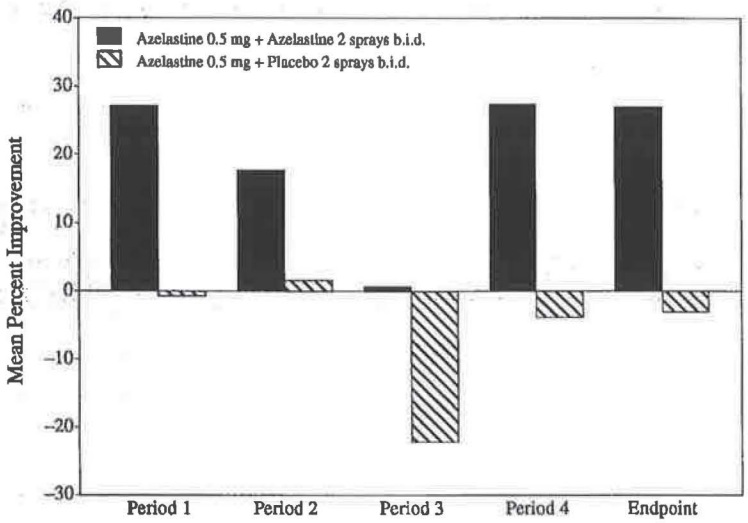

Figure 4. The mean percent improvement from baseline in the major symptom complex severity scores at each period and at endpoint.

For the major symptom complex severity score, the mean percent improvements for the azelastine group were clinically significant compared with those for the placebo group at each period (Fig 4). At periods 1 and 4, the azelastine group had the highest mean percent improvements (27.1% and 27.4%, respectively) compared with those for the placebo group (−0.7% and −3.9%, respectively). In addition, at each of the specified hourly evaluations during the 30-hour, double-blind, treatment period, the azelastine group had mean percent improvements in the major symptom complex severity score that were greater than the improvements for the placebo group. These differences from placebo showed a trend toward statistical significance ($P \leq .095$) at hours 3, 4, 5, 27, and 30 and were clinically significant at each hour, except hour 12.

Secondary Efficacy Variables

The overall improvements for the individual rhinitis symptoms of nose blows, sneezes, sniffles, postnasal drip, itchy eyes and ears, itchy nose, and runny nose for the azelastine group were superior to those for the placebo group. For sniffles and itchy eyes and ears, the differences from placebo were statistically significant ($P < .05$) and showed a trend toward statistical significance ($P = .07$) for postnasal drip. The subject global evaluations of the overall drug effect showed that 64% of the subjects in the azelastine group rated their response as improved versus 59% in the placebo group.

Table 3. Number and Percentage of Patients Who Reported Adverse Experiences During the Double-Blind Phase of the Study (.5% Incidence in Any Treatment Group)

Adverse Experience	Number (%) of Patients	
	Azelastine Nasal Spray	Placebo Nasal Spray
Headache	18 (15.5)	19 (16.2)
Taste perversion	15 (12.9)	1 (0.9)*
Nasal burning	8 (6.9)	2 (1.7)*
Somnolence	6 (5.2)	3 (2.6)

* $P < .05$: placebo versus azelastine groups.

Safety

The most frequently reported adverse experiences during the double-blind phase of the study are presented in Table 3. Subjects in the azelastine group reported taste perversion and nasal burning significantly more frequently than those in the placebo group. For the majority of the subjects, the altered taste sensation was due to the bitter taste of the medication itself and was of very short duration. The episodes of nasal burning were mild and transient, were related to the use of the nasal spray, and began immediately after administration. In addition, they did not affect the ability of the subject to complete the study. No subject in the azelastine group discontinued therapy due to an adverse experience. There were no clinically meaningful mean changes in laboratory test values, vital sign measurements, or physical examination findings associated with the use of azelastine.

DISCUSSION

Adjunctive therapy with different classes of drugs is often used in the management of allergic rhinitis, when routine medication does not satisfactorily control symptoms. In this study, adjunctive therapy with azelastine 2 sprays twice a day demonstrated clinically significant improvements in the severity of rhinitis symptoms during each treatment period and statistically significant improvements during the periods immediately following administration of azelastine nasal spray (periods 1 and 4). Because both treatment groups received a dose of azelastine tablets during the second and third periods, the lack of statistical significance versus placebo at these evaluation points may have been due to the timing that the treatment groups received the oral medication. Although not statistically significant at periods 2 and 3, subjects treated with adjunctive azelastine nasal spray experienced greater improvements in their rhinitis symptoms than subjects treated with placebo.

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