
Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar

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Background: A nasal spray containing the antiallergy agent olopatadine hydrochloride is being developed for the treatment of seasonal allergic rhinitis (SAR) to mountain cedar.

Objective: To evaluate the safety and efficacy of 2 concentrations of olopatadine nasal spray vs placebo nasal spray in patients with SAR to mountain cedar.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled study. After a 3- to 21-day placebo run-in, 677 patients aged 12 to 81 years were randomized to receive 0.4% or 0.6% olopatadine or placebo, 2 sprays per nostril twice daily for 2 weeks. Patients evaluated morning and evening reflective and instantaneous nasal symptoms (sneezing, stuffy nose, runny nose, and itchy nose, which compose the total nasal symptom score [TNSS]) and ocular symptoms.

Results: Olopatadine spray (0.4% and 0.6%) was statistically significantly superior to placebo for percentage change from baseline in overall reflective and instantaneous TNSSs. Also, 0.6% olopatadine was statistically significantly superior to placebo for reducing the reflective and instantaneous assessments of sneezing, runny nose, itchy nose, stuffy nose, itchy eyes, and watery eyes. Olopatadine spray exhibited a safety profile comparable with that of placebo.

Conclusions: Olopatadine nasal spray (0.4% and 0.6%) provided statistically significant improvements in allergic rhinitis symptoms compared with placebo regarding TNSSs and individual symptoms, including congestion, itchy and runny nose, sneezing, and itchy and watery eyes, in patients with SAR to mountain cedar. Olopatadine nasal spray administered twice daily was safe and well tolerated in adolescents and adults.

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INTRODUCTION

Olopatadine hydrochloride is being developed in a nasal spray formulation for the treatment of seasonal allergic rhinitis (SAR). This disease is an allergen-induced inflammatory response, with an estimated incidence of 10% to 30% in the general population.¹ On exposure to a specific antigen, allergic patients exhibit a hypersensitivity response that may take minutes, or even days, to manifest. Signs and symptoms associated with SAR include sneezing, nasal congestion, rhinorrhea, ocular itching and watering, paranasal pressure, and fatigue.²

Olopatadine is an antiallergy agent that inhibits mast cell mediator release and possesses histamine H₁ receptor antagonist activity.³ An ophthalmic formulation of 0.1% olopatadine solution is approved in the United States and Canada as Patanol and in Europe as Opatanol (both from Alcon Research Ltd, Fort Worth, TX) for the treatment of eye itching and redness due to allergic conjunctivitis. The ocular pharmacology of olopatadine has been extensively reviewed.^{3,4} An oral dosage form, 2.5- and 5-mg tablets, has been approved as Allelock (Kyowa Hakko Co Ltd, Tokyo, Japan) in Japan for the treatment of allergic rhinitis, chronic urticaria, atopic dermatitis, prurigo, pruritus cutaneous, psoriasis vulgaris, and erythema exudativum multiforme.⁵ The pharmacokinetics, pharmacology, and clinical trials of the oral dosage have also been reviewed.⁵ Olopatadine (10 mg/kg by mouth) has also been shown to inhibit the nasal symptoms of allergic rhinitis in sensitized guinea pigs by inhibiting the release of histamine and possibly peptide leukotrienes into the nasal cavity.⁶

This article is the second report of a multicenter clinical trial designed to evaluate the safety and efficacy of 0.4% and 0.6% olopatadine in the form of a nasal spray (443 and 665 µg, respectively, of olopatadine hydrochloride per spray) vs placebo nasal spray in the treatment of patients with SAR. The first reported study on olopatadine nasal spray was

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conducted at 33 sites across the United States that had prevalent fall pollen (predominantly ragweed).⁷ The second multicenter trial on olopatadine nasal spray, reported herein, was conducted in southern Texas between December 9, 2003, and March 3, 2003, where the primary allergen is mountain cedar pollen. Mountain cedar pollen (*Juniperus ashei*) is well recognized for the role it plays as a trigger of several allergic diseases, such as SAR, allergic conjunctivitis, and bronchial asthma.⁸ As such, mountain cedar allergen studies have been conducted with most major allergy products, and the results are similar to those obtained in multicenter trials during the spring and fall allergy seasons. Mountain cedar pollen possesses several characteristics that render it ideally suited for the evaluation of treatments for SAR. The 2 major extractable antigens of mountain cedar pollen that have been isolated, Jun a 1 and Jun a 3, are recognized as being among the most potent of those in the Cupressaceae family of trees. Furthermore, these major allergens are shared among many of the species in this family, leading to a relatively high degree of cross-reactivity.⁹ Mountain cedar pollination is restricted to a relatively short, yet predictable, season beginning in early December and continuing through late January to early February. Although the geographic distribution of mountain cedar trees is limited to regions of central Texas, southern Oklahoma, and northern Mexico, pollen from the tree is widely distributed over several southern states.¹⁰ This allows for relatively precise and predictable allergen exposure.

MATERIALS AND METHODS

Patients

Patients were 12 years or older with a history of SAR for at least the preceding 2 years. All the patients demonstrated allergic sensitivity to a prevalent fall allergen defined by a positive reaction on skin prick testing (a wheal size ≥ 3 mm greater than the diluent) or intradermal testing (a wheal size ≥ 7 mm greater than the diluent). The study protocol was approved by an institutional review board, and an informed consent document was signed by all the patients before participation in the study. Women of childbearing potential were enrolled if they agreed to use an acceptable method of contraception. Patients who had aberrant nasal anatomy, abnormal prestudy laboratory test results, severe congestion, recent sinusitis, or abnormal 12-lead electrocardiographic or other abnormal cardiovascular values were excluded from study participation. Medication washout times were 30 days for systemic, inhaled, and ocular corticosteroids; 14 days for intranasal corticosteroids, leukotriene inhibitors, anticholinergic agents, and systemic antibiotics; 7 days for ocular and nasal antiallergy agents; 3 days for oral antihistamines, non-steroidal anti-inflammatory drugs, and decongestants; and 1 day for nasal and ocular saline. Patients who underwent previous immunotherapy were required to be stable for 30 days before and throughout the trial.

Study Design

This was a 2-week, multicenter (7 sites in Texas), randomized, double-blind, parallel-group, placebo-controlled, 3-armed study of 2 concentrations of olopatadine nasal spray and placebo nasal spray conducted between December 9, 2002, and March 3, 2003. Beginning with the placebo run-in and continuing to study exit, patients recorded in a diary the symptom severity of their itchy nose, runny nose, stuffy nose, sneezing, itchy eyes, and watery eyes using a 4-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe).¹¹ The sum of scores for the 4 nasal symptoms was defined as the total nasal symptom score (TNSS). Patients evaluated their symptoms as experienced at that moment (instantaneous) and in the hours since the last dose of study medication was taken (reflective), in the morning before any other activity and at bedtime.

During the single-blind placebo spray run-in period, patients had to have a minimum reflective TNSS of 36 of a possible 72 points on 3 of the 4 days before randomization into the double-blind treatment phase of the study. Patients were then randomized to receive 1 of 3 treatment regimens: two 100- μ L sprays per nostril twice daily of 0.4% olopatadine (total daily dose of 3.2 mg), 0.6% olopatadine (total daily dose of 4.8 mg), or placebo (vehicle containing no active ingredient) (Alcon Research Ltd). After a week of study treatment, each patient was contacted by telephone to check protocol compliance, medication changes, potential adverse events, and diary completion. Patients returned after 2 weeks of double-blind therapy for an exit visit that included a physical examination, measurement of vital signs, laboratory analyses, and collection of diaries.

Statistical Methods

The primary statistical objective of this study was to demonstrate the statistical superiority of 0.6% and 0.4% olopatadine nasal sprays relative to placebo in the treatment of allergic rhinitis as evidenced by the percentage change from baseline in the TNSS. A Dunnett *t* test was used to compare changes from baseline between the olopatadine treatments and placebo for the primary and each of the secondary variables. This procedure was designed to test multiple treatments against a single control and, therefore, preserved statistical power in the presence of multiplicity.¹²

Primary and secondary conclusions were based on the intent-to-treat data set. A treatment difference of 12.5% in the TNSS change from baseline was assumed, with an approximated SD of 42%. With a projected 240 evaluable patients per group ($N = 720$), this study was predicted to have 90% power to detect a significant treatment difference between the olopatadine nasal sprays and placebo. All statistical tests were 2-sided, with $\alpha = .05$.

Efficacy. The primary efficacy variable was the percentage change from baseline in the reflective TNSS, defined as the average of the morning and bedtime reflective severity scores for the sum of the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing (averaged across all days).

Secondary efficacy variables included percentage change from baseline in the instantaneous TNSS and individual symptoms (ie, runny nose, itchy nose, sneezing, stuffy nose, watery eyes, and itchy eyes). Percentage change from baseline in the instantaneous TNSS was defined as the average of the morning and bedtime instantaneous (how the patient felt at that time) severity scores for the sum of the patients' assessments of symptoms (averaged across all days). All baseline scores were calculated using the appropriate measurements from the 3 highest days of the 4 days before randomization. These 3 days were chosen by calculating the average (mean of the awakening and bedtime assessments) for a given reflective or instantaneous symptom (TNSS or individual symptoms) for each day. To minimize possible bias from early dropouts, efficacy variables were based on an intent-to-treat approach that included all patients with at least 1 postbaseline observation, regardless of the length of therapy. An overall analysis was based on the mean change for each patient using available data and carrying that data forward.

Safety. A total of 910 patients received placebo during a 3- to 21-day run-in period; 233 patients did not qualify for randomization. Of the 677 patients randomized, 2 were excluded from analysis because they enrolled in this study 2 times at different sites. Therefore, 675 patients were randomized and evaluable for the safety analyses: 222 patients (32.9%) received 0.6% olopatadine, 229 (33.9%) received 0.4% olopatadine, and 224 (33.2%) received placebo spray. Safety variables evaluated included extent of exposure, nasal examination (significant anatomic abnormalities, evidence of infection, bleeding, and ulcerations of the mucosa), clinical laboratory (hematology, blood chemistry, and urinalysis), cardiovascular (pulse and systolic and diastolic blood pressure), and physical examination (head/eyes, ears, nose, and throat; neck; cardiovascular; pulmonary; abdomen; skin and extremities; neurologic; and lymph nodes).

RESULTS

Of 910 patients enrolled, 675 met the study criteria, were randomized to treatment, and were evaluable for the safety and intent-to-treat analyses. All the data presented in this article are from the intent-to-treat data set. The 3 treatment

groups were similar in terms of demographic characteristics (Table 1). The average age was 39 years (range, 12–81 years). Of the 675 evaluable patients, 66.4% (n = 448) were female; 64.6% were white, 29.2% were Hispanic, 4.4% were African American, 1.3% were Asian, and 0.4% were of other races.

Primary Efficacy: Reflective TNSS

The 0.4% and 0.6% olopatadine treatments were statistically significantly superior to placebo for the mean change from baseline of the overall reflective TNSS (Table 2). The average percentage reduction in TNSS from baseline was –30.1% for patients who received 0.6% olopatadine, –27.6% for patients who received 0.4% olopatadine, and –18.7% for patients who received placebo.

Secondary Efficacy

Reflective assessments of individual symptoms. The 0.6% olopatadine treatment was statistically significantly superior to placebo in reducing the reflective evaluation of the severity of runny nose, and the 0.4% and 0.6% olopatadine treatments were statistically significantly superior to placebo in reducing the reflective assessments of itchy nose, sneezing, and stuffy nose (Table 2). The 0.4% and 0.6% olopatadine treatments were also statistically significantly superior to placebo in the reflective severity of itchy and watery eyes (Table 2).

TNSS during the 2-week period by day. For each of the 14 days of treatment, 0.4% and 0.6% olopatadine were statistically significantly superior to placebo for percentage change from baseline in reflective TNSS (Fig 1).

Instantaneous evaluation of the overall TNSS and individual symptoms. The 0.4% and 0.6% olopatadine treatments were statistically significantly superior to placebo for percentage change from baseline in overall instantaneous TNSS (Table 3). By instantaneous evaluation, 0.6% olopatadine treatment was statistically significantly superior to placebo for sneezing, runny nose, itchy nose, stuffy nose, and itchy eyes but not for watery eyes (Table 3). The 0.4% olopatadine improvement was slightly less than that noted for 0.6% olopatadine. However, 0.4% olopatadine was superior to placebo for the instantaneous evaluation of all symptoms except runny nose and ocular symptoms (Table 3).

Table 1. Demographic Characteristics by Treatment Group

	0.6% Olopatadine group (n = 222)	0.4% Olopatadine group (n = 229)	Placebo group (n = 224)
Age, y			
Range	12–75	12–81	12–80
Mean ± SD	37.2 ± 14.9	39.1 ± 14.3	40.3 ± 14.9
Sex, F/M, %	64.4/35.6	72.9/27.1	61.6/38.4
Race, No. (%)			
White	140 (63.1)	147 (64.2)	149 (66.5)
Hispanic	58 (26.1)	72 (31.4)	67 (29.9)
African American	16 (7.2)	8 (3.5)	6 (2.7)
Asian	7 (3.2)	1 (0.4)	1 (0.4)
Other race	1 (0.5)	1 (0.4)	1 (0.4)

Table 2. Percentage Change From Baseline in the Reflective Assessments of Symptoms of Seasonal Allergic Rhinitis to Mountain Cedar*

Variable	0.6% Olopatadine group	P value†	0.4% Olopatadine group	P value‡	Placebo group
TNSS	-30.1 ± 27.6	<.001	-27.6 ± 22.4	<.001	-18.7 ± 22.3
Runny nose	-30.0 ± 31.5	<.001	-22.3 ± 32.4	.27	-18.4 ± 24.1
Stuffy nose	-21.7 ± 31.7	.002	-21.3 ± 24.0	.004	-13.2 ± 26.0
Itchy nose	-32.4 ± 32.5	<.001	-30.8 ± 27.5	<.001	-19.4 ± 38.0
Sneezing	-35.7 ± 38.9	<.001	-33.4 ± 37.9	<.001	-18.8 ± 43.4
Itchy eyes	-30.7 ± 53.8	<.001	-25.3 ± 41.9	.008	-12.3 ± 45.7
Watery eyes	-31.9 ± 46.7	.002	-29.9 ± 40.3	.009	-18.0 ± 43.8

Abbreviation: TNSS, total nasal symptom score.

* Data are given as mean ± SD.

† The 0.6% olopatadine group vs the placebo group.

‡ The 0.4% olopatadine group vs the placebo group.

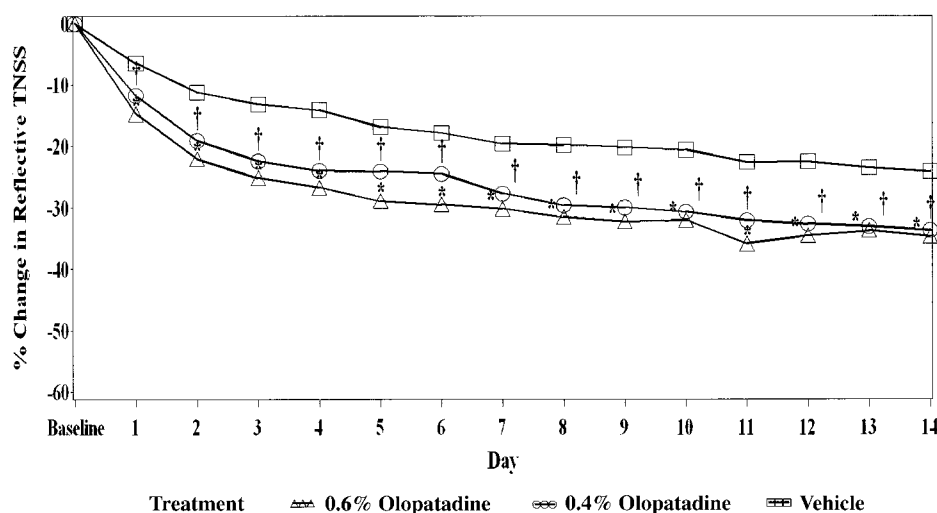


Figure 1. Intent-to-treat analysis of the percentage change in reflective total nasal symptom scores (TNSSs) by day and treatment. Asterisk indicates $P < .05$ for 0.6% olopatadine vs vehicle; dagger, $P < .05$ for 0.4% olopatadine vs vehicle.

Table 3. Percentage Change From Baseline in the Instantaneous Assessments of Symptoms of Seasonal Allergic Rhinitis to Mountain Cedar*

Parameter	0.6% Olopatadine group	P value†	0.4% Olopatadine group	P value‡	Placebo group
TNSS	-26.2 ± 29.6	<.001	-24.3 ± 23.3	.002	-15.8 ± 26.4
Runny nose	-24.6 ± 38.2	.005	-20.2 ± 31.1	.19	-15.4 ± 26.9
Stuffy nose	-17.5 ± 31.9	.004	-17.0 ± 25.2	.005	-7.7 ± 39.2
Itchy nose	-30.2 ± 36.7	<.001	-26.7 ± 34.4	.005	-15.8 ± 43.6
Sneezing	-29.6 ± 45.3	.03	-29.2 ± 60.6	.03	-16.8 ± 57.8
Itchy eyes	-27.6 ± 64.0	.008	-21.8 ± 50.5	.14	-12.9 ± 41.6
Watery eyes	-28.5 ± 54.1	.07	-24.2 ± 51.3	.39	-18.4 ± 46.1

Abbreviation: TNSS, total nasal symptom score.

* Data are given as mean ± SD.

† The 0.6% olopatadine group vs the placebo group.

‡ The 0.4% olopatadine group vs the placebo group.

Safety Results

Adverse events in the overall safety population were nonserious (except for 1 report of syncope not related to 0.6%

olopatadine treatment), were mild to moderate, usually resolved with or without treatment, and generally did not interrupt patient continuation in the study. Eight randomized

Table 4. Summary of 8 Patients Who Discontinued During the Randomized Phase Because of Adverse Events

Patient age, y	Treatment	Adverse event	Outcome of event	Serious	CA
39	0.6% Olopatadine	Epistaxis	Resolved wo/Tx	No	R
58	0.6% Olopatadine	Dizziness	Resolved wo/Tx	No	R
		Headache	Resolved w/Tx	No	R
59	0.6% Olopatadine	Syncope	Resolved wo/Tx	Yes	NR
21	0.6% Olopatadine	Flu syndrome	Resolved w/Tx	No	NR
43	0.6% Olopatadine	Migraine	Resolved w/Tx	No	NR
49	0.6% Olopatadine	Flu syndrome	Resolved w/Tx	No	NR
41	0.4% Olopatadine	Cellulitis	Resolved w/Tx	No	R
		Sinusitis	Resolved w/Tx	No	R
23	Placebo	Sinusitis	Resolved w/Tx	No	NR

Abbreviations: CA, causality assessment; NR, not related; R, related; w/Tx, with treatment; wo/Tx, without treatment.

patients discontinued from the treatment phase of the study owing to adverse events (Table 4). Causality assessments revealed that only 3 of these 8 patients' adverse events were related to therapy. No safety issues were identified and no treatment-related changes were observed in the laboratory test results of hematology, blood chemistry, and urinalysis. The evaluation of cardiovascular variables showed that olopatadine nasal spray (0.4% and 0.6%) administered twice daily was safe and well tolerated. There also were no clinical changes in physical (including nasal) examination findings for any of the treatment arms during this study. The most common related adverse event was bitter taste, and it seemed to be dose related (Table 5). The incidence of somnolence was negligible (0.4% for 0.6% olopatadine, 1.3% for 0.4% olopatadine, and 0.4% for placebo) (Table 5).

DISCUSSION

In this study, treatment with 0.4% and 0.6% olopatadine, 2 sprays per nostril twice daily, provided significant relief from allergy symptoms compared with placebo during the 2-week trial. Use of the TNSS as the primary efficacy variable was appropriate for an allergic rhinitis study with the goal of assessing a medication's overall impact on the rhinitis symptoms (symptom complex) as the best indicator of its therapeutic effect. In this clinical trial, the TNSS was defined as a conglomerate of the 4 major symptoms of allergic rhinitis: sneezing, runny nose, itchy nose, and stuffy nose. The 0.6% olopatadine treatment was statistically significantly greater than placebo use for improving TNSSs and each individual

symptom score. Comparisons of 0.4% olopatadine with placebo also reached statistical significance except for ocular symptoms.

The results of this study compare favorably with those of a previous study by Meltzer et al,⁷ who demonstrated the superiority of 0.6% olopatadine nasal spray to placebo regarding TNSSs and all individual nasal symptoms except for congestion. Meltzer et al also showed that 0.4% olopatadine is superior to placebo regarding TNSSs and all individual nasal symptoms except congestion. Regarding congestion (stuffy nose), both studies demonstrated numerically greater reductions in severity from baseline vs placebo. This difference reached statistical significance in the present study but not in the study by Meltzer et al.⁷ Regarding ocular symptoms, both trials demonstrated numerically greater reductions for both olopatadine concentrations compared with vehicle placebo. The 0.6% olopatadine treatment was statistically significant for the reflective evaluation of itchy eyes in both trials. For watery eyes, 0.6% olopatadine treatment reached statistical significance for instantaneous (but not reflective) evaluation in the study by Meltzer et al⁷ and for reflective (but not instantaneous) evaluation in the present study.

Vehicle nasal spray was used as the placebo. As previously observed,⁷ the placebo spray produced beneficial effects. It reduced symptom scores for every variable (Tables 2 and 3). The placebo nasal spray most likely cleared allergens from nasal passages, thereby reducing the allergen exposure and, consequently, the allergic response.

Table 5. Related Adverse Events by Treatment Group*

Adverse event	0.6% Olopatadine group	0.4% Olopatadine group	Placebo group
Bitter taste	16.1	8.7	0.9
Headache	4.0	1.7	3.1
Epistaxis	2.2	3.5	1.8
Nasal discomfort	1.8	3.1	1.8
Nausea	0.0	1.3	0.9
Pharyngitis	0.9	0.0	0.9
Somnolence	0.4	1.3	0.4

* Data are given as percentages.

Olopatadine nasal spray (0.4% and 0.6%) was well tolerated. The most common related adverse event was bitter taste (Table 5). This effect was often described as a transient bad or bitter taste and was dose related (Table 5): 16.1% incidence for 0.6% olopatadine vs 8.7% for 0.4% olopatadine and 0.9% for placebo. The incidence of bitter taste in this trial was greater than previously observed by Meltzer et al.⁷ Somnolence was not a significant adverse effect of olopatadine nasal spray, 0.4% or 0.6%. In this study, the incidence of somnolence was only 0.4% for 0.6% olopatadine and 1.3% for 0.4% olopatadine vs 0.4% for placebo. This finding agreed with the low results for somnolence observed by Meltzer et al.⁷ This observation is surprising because somnolence (drowsiness) was the most common adverse event reported in the Japanese-approved label for the oral dosage form of olopatadine (Allelock, 2.5- and 5-mg tablets).¹³

In conclusion, olopatadine nasal spray, 2 sprays per nostril twice daily, elicited statistically significant improvements in allergic rhinitis symptoms during the entire 2-week treatment period compared with the placebo nasal spray group based on symptom scores (TNSS) and individual nasal and ocular symptoms. Both 0.4% and 0.6% olopatadine were well tolerated in this study. These data support olopatadine nasal spray as an effective and safe antiallergy agent for the treatment of symptoms of allergic rhinitis.

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