
Effect of desloratadine therapy on symptom scores and measures of nasal patency in seasonal allergic rhinitis: results of a single-center, placebo-controlled trial

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Background: Desloratadine reduces symptoms and maintains nasal airflow in patients with seasonal allergic rhinitis (SAR) during experimental allergen exposure.

Objective: To compare the effects of desloratadine and placebo on symptom scores, quality of life (QOL), and nasal airway patency in patients with SAR during the allergy season.

Methods: Adults with symptomatic SAR were randomized in a double-blind manner to receive desloratadine, 5 mg, or placebo for 14 days. Patient-rated SAR symptoms were recorded twice daily (morning and evening). On days 1 and 15, SAR symptoms were scored jointly (investigator and patient), nasal airflow was measured using 4-phase rhinomanometry, and QOL and the overall condition of SAR were rated. Overall treatment response was scored on day 15. Adverse events were recorded.

Results: At day 15, total symptom ($P = .03$) and total nasal symptom ($P = .02$) scores and patient morning-rated individual nasal symptom scores (except nasal stuffiness) ($P \leq .04$) decreased significantly from baseline with desloratadine vs placebo. Flow in the descending expiratory nasal airflow phase was significantly greater ($P = .046$) and the percentage increase in total inspiratory nasal airway resistance was less ($P = .03$) in the desloratadine group vs the placebo group. The overall condition of SAR was less severe ($P = .045$), the therapeutic response was greater ($P = .004$), and the nasal symptom domain of the QOL score was significantly better ($P = .03$) in the desloratadine group. Adverse event rates were similar in both groups.

Conclusion: Desloratadine treatment for 14 days improved nasal airflow and resistance as well as symptom and QOL scores in patients with symptomatic SAR during the allergy season.

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INTRODUCTION

Antihistamines are a usual first-line treatment for patients with symptomatic seasonal allergic rhinitis (SAR).¹ These compounds exhibit good efficacy against early-phase symptoms, such as sneezing, watery rhinorrhea, and nasal pruritus, but less efficacy against nasal congestion.² Desloratadine is a potent,³ H₁-receptor-selective,⁴ second-generation antihistamine that is effective in the treatment of (1) rhinitis due to seasonal⁵ and perennial⁶ allergens and (2) chronic idiopathic urticaria.⁷ In SAR clinical trials,^{8–10} desloratadine has been shown to decrease nasal congestion symptom scores. In environmental exposure unit studies^{11,12} using grass pollen allergens, a beneficial effect of desloratadine on SAR symp-

toms and nasal airflow has been demonstrated reproducibly using anterior rhinomanometry.

Traditional rhinomanometry may provide an incomplete picture of the nasal breathing cycle because it simplifies the breathing cycle into discrete linear sets of points. The pressure-flow relationship in the nasal breathing cycle consists of 4 distinct phases that can be mapped accurately using 4-phase rhinomanometry,¹³ an anterior, active, uninasal technique that has been shown to be effective and objective in evaluating nasal patency in patients with SAR.¹⁴ This single-center, randomized, placebo-controlled trial was designed to study the effects of desloratadine, 5 mg once daily, on symptoms, quality of life, and nasal airflow in patients with SAR during the allergy season.

METHODS

Patient Population

This was a randomized, double-blind, placebo-controlled, single-center, parallel-group study of desloratadine, 5 mg, vs placebo daily for 14 days in adults aged 18 to 60 years with SAR. Eligible patients attended 3 study visits: screening (days –14 to –5, visit 1), baseline/randomization (start of treatment) (day 1, visit 2), and end of treatment (EOT) (day 15, visit 3). To be eligible, patients had to have a history of

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mild-to-moderate SAR for at least 2 years. At screening or within the previous 12 months, patients had to have a positive skin test reaction to a seasonal allergen (including seasonal molds) that was prevalent during the study.

Eligible patients also had to be free of other significant diseases that could interfere with the study. Specifically, patients with unstable asthma, nasal polyps or nasal anatomic malformations, or a history of clinically significant sinusitis or chronic purulent postnasal drip were excluded. Patients with incipient or active sinusitis or a respiratory tract infection within 2 weeks of screening were ineligible for the study. Suitable washout periods had to be observed for concomitant medications, including other antihistamines, local or systemic corticosteroids, cromolyn, decongestants, leukotriene inhibitors, and inhibitors of cytochrome P450 3A4. The use of oral or long-acting inhaled sympathomimetic bronchodilators was not permitted for the duration of the study. Patients with stable intermittent asthma were permitted to use inhaled albuterol as required. The use of any investigational product within 30 days of study enrollment was prohibited. Patients were ineligible if they had a previous history of an idiosyncratic drug reaction to antihistamines or a history of multiple drug reactions. Pregnant or nursing women were excluded, and patients of childbearing potential had to use an acceptable form of hormonal or barrier contraception or be surgically sterilized and had to have a negative pregnancy test result.

Patients had to have a combined nasal symptom severity score of 6 or greater, a nasal congestion score of 2 or greater, and a total symptom score (TSS) combining the total nasal symptom score (TNSS) and the total nonnasal symptoms score (TNNSS) of 11 or greater for at least 3 of the preceding 5 morning scores up to and including the baseline visit (visit 2). The study was approved by the Sterling Institutional Review Board, Atlanta, GA, and it was conducted according to the Declaration of Helsinki. All the patients provided informed written consent.

Efficacy Measures

Symptom scores. Nasal and nonnasal reflective symptom severity scores were rated by the patients twice daily (morning and evening) and were recorded in a study diary. Joint patient and investigator assessments of symptom severity in the previous 24 hours were performed at all the scheduled study visits. Nasal signs and symptoms included nasal discharge (anterior or posterior), stuffiness (congestion), sneezing, and nasal itching. Nonnasal signs and symptoms included eye tearing or watering, eye itching or burning, eye redness, and itching of ears, throat, and palate.

Individual signs and symptoms were rated for severity on the following 4-point scale: 0 indicates none (no signs or symptoms evident); 1, mild (signs and symptoms present but minimal awareness and easily tolerated); 2, moderate (signs and symptoms definitely present and bothersome but tolerable); and 3, severe (signs and symptoms hard to tolerate and may cause interference with activities of daily living or

sleeping). The TNSS, TNNSS, and TSS were the sums of the individual symptom scores.

The overall condition of SAR at the time of the visit and representative of the period since the last visit was evaluated together by the investigator and the patient at baseline (visit 2) and at the EOT (visit 3). The previously mentioned 4-point scale was used to rate the overall condition of SAR.

The overall response to treatment was evaluated by the investigator and the patient at the EOT. The following 5-point scale was used to rate the therapeutic response: 0 indicates complete relief (no symptoms present); 1, marked relief (symptoms vastly improved and, although present, scarcely troublesome); 2, moderate relief (symptoms present and perhaps troublesome but noticeably improved); 3, slight relief (symptoms present and only minimal improvement obtained); 4, no relief (symptoms unchanged); and 5, worse (symptoms worsened since baseline).

Rhinoconjunctivitis Quality of Life Questionnaire. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), developed by Juniper et al,¹⁵ was administered at baseline and at the EOT in both study groups.

Four-phase rhinomanometry. The FPR-2 unit (RhinoLab, Rendsburg, Germany) was used for this study. Four-phase rhinomanometry,¹³ also known as high-resolution rhinomanometry, differs from traditional rhinomanometry in that airflow and differential air pressure data are sampled separately as time-dependent functions and then averaged by using a spline interpolation. The averaged data are plotted into a cartesian system, and the generated curve has the general shape of a double loop instead of a simple curved line (Fig 1). Four distinct phases of the nasal breathing cycle can be

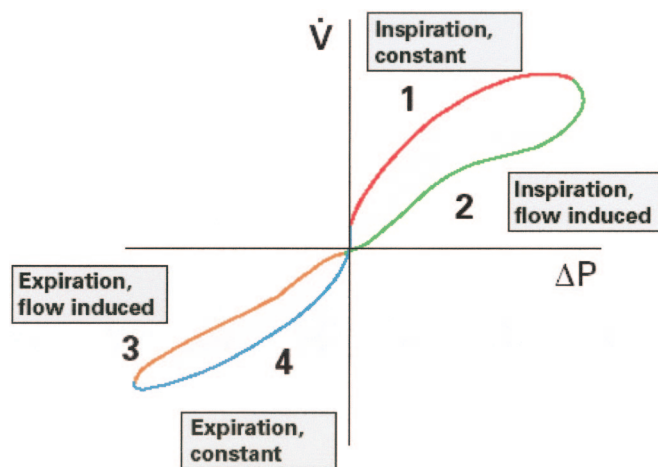


Figure 1. Hysteresis loops demonstrating the 4 phases of the breathing cycle as measured using 4-phase rhinomanometry. Airflow and differential air pressure data are sampled separately and averaged; these data are then plotted into a cartesian system, and 4 distinct phases of the nasal breathing cycle can be observed and analyzed. Nasal airflow (V) was measured at an inspiratory pressure of -150 Pa and an expiratory pressure of $+150$ Pa in accelerating (flow-induced) phases 1 and 3, respectively. ΔP indicates change in airway pressure.

observed and analyzed. For the present study, nasal airflow was measured at baseline and at the EOT at an inspiratory pressure of -150 Pa and an expiratory pressure of $+150$ Pa, in accelerating phases 1 and 3, respectively.

Nasal airflow was measured according to the manufacturer's instructions. The test maneuver was repeated 5 consecutive times for each nostril; the highest and lowest inspiratory and expiratory flow values were discarded, and the remaining 3 values were used for analysis. Total inspiratory and expiratory nasal airway resistance (T_{NAR}) was calculated after measuring the left (L_{NAR}) and right (R_{NAR}) resistances using the following formula:

$$T_{\text{NAR}} = (R_{\text{NAR}} \times L_{\text{NAR}}) / (R_{\text{NAR}} + L_{\text{NAR}})$$

Safety Assessments

Patients underwent physical examinations at visits 1 and 3 and had vital signs recorded at all the study visits. Any adverse event that occurred during the study was recorded and rated according to severity and relationship to study treatment. The difference between treatments in the incidence of adverse events reported by 2% or more of the patients in any treatment group was analyzed using the Fisher exact test.

Statistical Analysis

Sample sizes of 110 in each treatment group were calculated to provide 80% power to detect a difference of 0.75 U between treatment groups for the primary end point of determining the efficacy of desloratadine vs placebo using joint clinician and patient evaluation of symptom severity scores at baseline (day 1) and at the EOT (day 15) by evaluating the mean change from baseline in TNSSs at day 15. Other efficacy evaluations included rhinomanometric airflow and nasal resistance scores, RQLQ scores, the overall condition of SAR, the overall therapeutic response to treatment, and the changes from baseline in TSSs, TNNSSs, and individual symptom scores. Data for TSSs, TNSSs, TNNSSs, and rhinomanometry were analyzed using an analysis of covariance model, with baseline as a covariable. The overall condition of SAR and the overall therapeutic response to treatment were analyzed using the Cochran-Mantel-Haenszel test, whereas RQLQ data were analyzed using the unpaired *t* test.

RESULTS

Demographics

The baseline demographic and disease characteristics of the 2 groups were similar (Table 1). Of the 220 patients randomized to the study (111 in the placebo group and 109 in the desloratadine group), 219 received at least 1 dose of study medication (safety population). One patient had no postbaseline efficacy assessments; therefore, the intent-to-treat population consisted of 218 patients. Four patients in each group in the overall randomized population discontinued the study because of protocol noncompliance (3 in the placebo group), ineligibility (1 in each group), adverse events (2 in the desloratadine group), and personal reasons (1 in the desloratadine group).

Table 1. Demographic and Disease Characteristics of the Study Population

Characteristic	Placebo (n = 110)	Desloratadine (n = 108)	P value
Sex, No. (%)			.48*
M	48 (43.6)	42 (38.9)	
F	62 (56.4)	66 (61.1)	
Age, y			
Mean (SD)	32.0 (10.2)	32.3 (10.0)	.81†
Median	31.5	31.0	
Range	18.0–58.0	18.0–58.0	
Race, No. (%)			.92*
White	72 (65.5)	66 (61.1)	
Black	10 (9.1)	14 (13.0)	
Hispanic	21 (19.1)	21 (19.4)	
Asian	5 (4.5)	5 (4.6)	
Other	2 (1.8)	2 (1.9)	
Height, cm			.56†
Mean (SD)	169.9 (10.2)	169.2 (8.9)	
Median	170.2	167.6	
Range	147.3–195.6	147.3–190.5	
Weight, kg			.37†
Mean (SD)	76.7 (16.8)	78.9 (19.7)	
Median	75.7	75.5	
Range	47.6–127.5	47.6–135.2	
Duration of seasonal allergic rhinitis, y			
Mean (SD)	19.5 (9.8)	21.0 (11.2)	NA
Median	19.0	20.0	
Range	4.0–50.0	2.7–54.0	
Concomitant perennial allergic rhinitis, No. (%)			NA
No	3 (2.7)	3 (2.8)	
Yes	107 (97.3)	105 (97.2)	

Abbreviation: NA, not applicable.

* By χ^2 test.

† By 1-way analysis of variance.

Symptom Scores: Joint Evaluation

At the EOT, patients in the desloratadine group showed a significantly greater decrease from baseline in joint patient- and investigator-rated TNSSs compared with the placebo group (-2.7 U vs -1.9 U; $P = .02$). Similarly, patients in the desloratadine group experienced a greater decrease from baseline than placebo-treated patients in jointly rated TSSs at the EOT (-5.2 U vs -3.8 U; $P = .03$) (Fig 2). Jointly evaluated individual symptom scores revealed a significantly greater decrease from baseline in sneezing in the desloratadine group vs the placebo group (-0.9 U vs -0.6 U; $P = .03$).

Symptom Scores: Patient Diary Data

Evaluation after week 1 of treatment showed that patients receiving desloratadine experienced significantly greater mean changes from baseline in TNSSs in the morning ($P = .005$) and evening ($P = .01$) compared with the placebo group. Across the 2 weeks of treatment, the decrease in TNSSs was significantly greater with desloratadine use than with placebo use in the morning ($P = .03$). Evening-rated

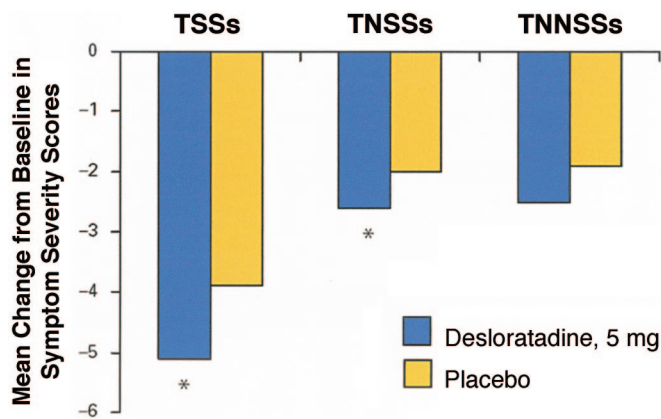


Figure 2. Mean change from baseline to the end of treatment (14 days) in joint patient- and investigator-assessed total symptom scores (TSSs), total nasal symptom scores (TNSSs), and total nonnasal symptom scores (TNNSSs) in patients treated with desloratadine, 5 mg, vs placebo daily for 14 days. Asterisk indicates $P < .05$ for desloratadine vs placebo.

TNNSSs at week 1 showed a significantly greater decrease in the desloratadine group vs the placebo group (-2.2 U vs -1.6 U; $P = .03$).

The mean changes from baseline in morning-evaluated individual nasal and nonnasal symptom scores demonstrated significantly greater decreases favoring desloratadine therapy in the severity ratings for nasal discharge, nasal itching, and sneezing (Fig 3) and for itching ears, throat, and palate (data not shown). Among the evening-rated individual symptoms, significantly greater decreases from baseline were seen with desloratadine use compared with placebo use for nasal discharge (week 1 and weeks 1 and 2 combined), sneezing (week 1), eye redness (week 1), and itching ears, throat, and palate (week 1 and weeks 1 and 2 combined).

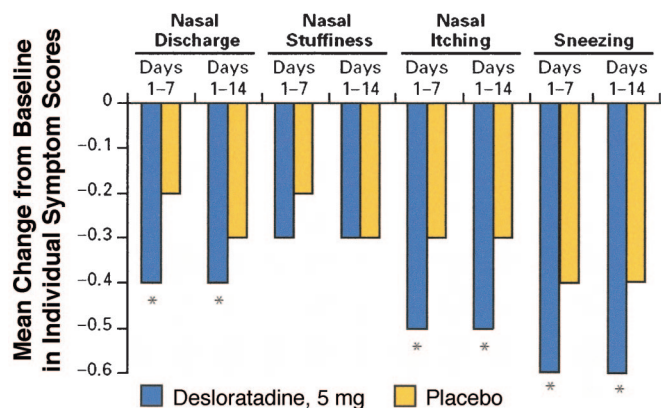


Figure 3. Mean change from baseline to the end of week 1 (day 7) and to the end of treatment (day 15) in individual morning-rated nasal seasonal allergic rhinitis symptom scores in patients treated with desloratadine, 5 mg, vs placebo daily for 14 days. Asterisk indicates $P < .05$ for desloratadine vs placebo.

Overall Condition of SAR and Response to Treatment

The improvement from baseline in the overall condition of SAR was significantly greater with desloratadine vs placebo treatment ($P = .045$); 57.4% of patients treated with desloratadine had 1-point or greater improvement compared with 40.9% of patients receiving placebo. The therapeutic response at the EOT was significantly better with desloratadine use than with placebo use ($P = .004$). At the EOT, 44% of patients receiving desloratadine reported moderate or better relief vs 28% of the placebo group.

Quality of Life

All the domains of the RQLQ demonstrated decreases in mean scores for both groups during treatment. Patients in the desloratadine group had a significant decrease in the nasal symptom domain compared with the placebo group ($P = .03$); significant intergroup differences were not seen in other RQLQ domains.

Four-Phase Rhinomanometry

Expiratory airflow at a pressure difference of +150 Pa was significantly greater for the desloratadine group compared with the placebo group ($P = .046$) (Fig 4). The nasal airflow rate during the ascending inspiratory phase increased in the desloratadine group (mean change from baseline, 20 cm^3/s) and decreased in the placebo group (mean change from baseline, -9 cm^3/s) ($P = .16$). At the EOT, the placebo group

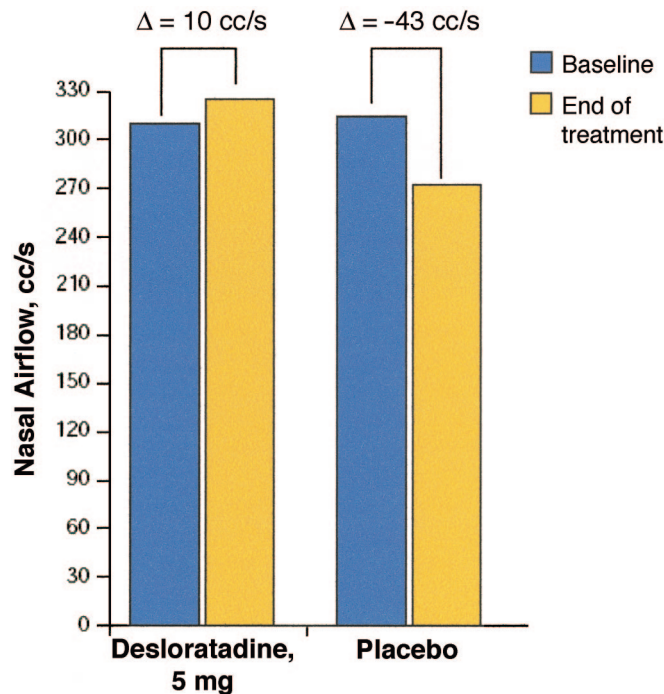


Figure 4. Expiratory airflow at baseline and at the end of treatment (day 15) with desloratadine and placebo measured using 4-phase rhinomanometry ($P = .046$ for desloratadine vs placebo). Nasal airflow was measured at a pressure difference of +150 Pa.

had a significantly greater increase from baseline compared with the desloratadine group in total inspiratory nasal airway resistance measured at a pressure difference of -150 Pa (15.1% vs 0.5% ; $P = .03$).

Safety

The study treatments were well tolerated. Most adverse events were mild or moderate in severity, and the most common adverse event was headache, which was reported by 8 patients (7.3%) in the desloratadine group and 10 (9.1%) in the placebo group. The rates of treatment-related adverse events were similar in the desloratadine and placebo groups (15 and 9 patients; $P = .20$). Two patients in the desloratadine group discontinued the study because of adverse events (1 with hives and 1 with middle ear infection and inflammation), and the investigator rated these as mild and unlikely to be treatment related.

DISCUSSION

This large, single-center study demonstrates the beneficial effects of desloratadine, compared with placebo, on subjective and objective measures of SAR. Significant improvements in nasal and nonnasal SAR symptoms were seen with desloratadine use, and these improvements were accompanied by increases in nasal airflow and concomitant decreases in nasal airway resistance. Quality-of-life measures also improved during the 2 weeks of desloratadine treatment, although in this study significant benefits over placebo use were limited to the nasal symptom domain.

Improvement in nasal airflow as measured by means of active anterior rhinomanometry has been noted previously in patients with SAR receiving desloratadine. Horak et al^{11,12} demonstrated reproducibly in an environmental allergen exposure unit that 7 days' treatment with desloratadine led to a significantly smaller decrease in nasal airflow compared with placebo in response to allergen exposure. Allergen-induced SAR symptoms, including subjectively rated nasal congestion, were also lower after desloratadine treatment than with placebo in both of these studies. Other previous clinical trials⁸⁻¹⁰ of desloratadine have demonstrated some effects on nasal congestion symptoms; however, a beneficial impact on nasal airflow and patency has not been reported during clinical treatment until now.

Subjective feelings of decreased nasal blockage do not always correlate with objective measurements of increased nasal airflow using rhinomanometry.¹⁶ The sensation of congestion in the nose is determined in part by the relative cooling effects of varying volumes of air passing across the nasal mucosa. This sensation of decreased congestion can be mimicked by the nasal inhalation of menthol vapor, which is associated with decreased subjective nasal congestion but no significant improvement in nasal airflow.¹⁷ Various research groups have studied the relationship between subjective nasal congestion and objective nasal airflow, with differing results. Hirschberg and Rezek¹⁸ reported a significant correlation between subjective and objective measurements of nasal pa-

tency in a large population, but this correlation disappeared when patients with or without actual obstruction as measured using active anterior rhinomanometry were evaluated separately. Nasal endoscopic uncinectomy improved nasal congestion symptom ratings in one study,¹⁹ and this occurred against a background of unchanged nasal resistance using rhinomanometry. The existence of a positive correlation between subjective and objective measures may be a function of the type of nasal challenge, as one study²⁰ found a significant correlation between congestion symptom scores and rhinomanometry after histamine challenge in 103 patients with allergic or nonallergic rhinitis. Clarke et al²¹ found that topical application of the mucosal vasoconstrictor xylometazoline produced a significant linear correlation between rhinomanometric and symptomatic measures of nasal obstruction. It is clear that the relationship between objective and subjective measures of nasal obstruction is complex. Both measures may not always be in concordance, but together they provide a more complete evaluation of nasal mucosal activity in response to challenges and subsequent treatment effects.

Vogt and coworkers^{13,14} demonstrated that errors can be introduced in the measurement of nasal airway resistance if the nasal airflow is derived from a single best-fit line through the pressure-flow points; this error can be as large as 30% to 100% using traditional rhinomanometric methods. Use of the expiratory phase, instead of the inspiratory phase, for evaluating changes in nasal airway resistance is also of importance. During inspiration, the nasal valve—the point of greatest resistance to airflow—exerts its maximum effect. The effect can vary, depending on the inspiratory effort generated from breath to breath. With forcible inspiration, the nasal valve collapses and limits the inspiratory flow. Arguably, it is desirable to eliminate the effect of the nasal valve when measuring the effectiveness of antihistamines to reduce mucosal inflammatory changes. In conclusion, this placebo-controlled study demonstrates that the symptomatic improvements seen with desloratadine treatment in patients with SAR in the clinical setting during the allergy season were accompanied by beneficial effects on nasal airflow and nasal airway resistance.

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