

Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen-induced allergic rhinitis in an allergen-exposure unit

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Background: Unlike many antihistamines, desloratadine can reduce nasal congestion in patients with seasonal allergic rhinitis (SAR).

Objective: We compared the effects of 5 mg of desloratadine and placebo on nasal airflow and SAR symptoms, including nasal congestion, in response to grass pollen in an allergen-exposure unit.

Methods: In a randomized, double-blind, placebo-controlled, crossover trial, 47 subjects with histories of SAR received desloratadine or placebo every morning for 7 days and, after a 10-day washout period, were crossed over to the other treatment arm for 7 days. Subjects underwent a 6-hour allergen exposure on day 7 of each treatment period. Nasal airflow and nasal secretion weights were measured before and every 30 minutes during allergen exposure; SAR symptoms (including nasal congestion) were scored before exposure and every 15 minutes thereafter.

Results: Nasal obstruction, as measured by nasal airflow, was less severe with desloratadine than with placebo ($P < .02$). Individual and combined SAR symptom severity scores, including nasal congestion and sneezing, were significantly lower with desloratadine than with placebo (all $P \leq .003$). Within 30 minutes of allergen exposure, less severely decreased nasal airflow ($P < .02$), less nasal secretions ($P < .001$), and less severe symptoms, including nasal congestion ($P < .002$), rhinorrhea, and sneezing, occurred with desloratadine compared with placebo, and this continued throughout (0-6 hours) allergen exposure. Desloratadine was well tolerated, with an adverse event profile similar to that of placebo.

Conclusion: In subjects with allergen-induced SAR symptoms, desloratadine significantly reduced the severity of nasal obstruction and accompanying complaints of nasal congestion and other SAR symptoms compared with the effects of placebo. (J Allergy Clin Immunol 2002;109:956-61.)

Key words: Desloratadine, antihistamine, nasal obstruction, seasonal allergic rhinitis, allergen exposure, rhinomanometry

Abbreviations used

AUC: Area under the curve
SAR: Seasonal allergic rhinitis
TNNSS: Total nonnasal symptom score
TNSS: Total nasal symptom score
TSS: Total symptom score

Second-generation antihistamines are an effective treatment for seasonal allergic rhinitis (SAR) symptoms, including, sneezing, nasal itching, and rhinorrhea.¹ These drugs, however, have a lesser effect on the complaint of nasal congestion. Nasal corticosteroids or α -adrenergic decongestants may be required to relieve nasal obstruction more effectively. Topical nasal decongestants (eg, oxymetazoline) are rapid acting but are indicated for short-term use only. Oral α -adrenergic agents (eg, pseudoephedrine) are effective decongestants; however, unwelcome side effects and their contraindication in certain medical conditions can limit their usefulness.²

In allergic rhinitis nasal obstruction occurs as a result of an allergic inflammatory response of the nasal mucosa,³ in which allergen exposure triggers a complex cascade of mediators and activated cells. This produces engorgement of sinusoidal capacitance vessels, decreased size of nasal airway passages, and increased serous and mucinous secretions. Leukotrienes⁴ and histamine, through H_1 and possibly H_2 receptors,⁵ are among the mediators that cause vascular engorgement. Sympathomimetics reduce nasal obstruction by increasing arteriolar and venous tone within mucosa capacitance vessels through α_1 and α_2 adrenoreceptors.⁶ Nasally inhaled corticosteroids relieve symptoms of SAR, including nasal congestion, by means of their anti-inflammatory actions.

Desloratadine, a new, potent,⁷ nonsedating H_1 receptor antagonist, has demonstrated significant relief of all symptoms of SAR,⁸ including nasal stuffiness and congestion, in clinical trials.⁹ If the latter effect is due to decreased nasal mucosa engorgement, it should be accompanied by measurable objective changes, such as increased nasal airflow. Hence we performed a randomized, double-blind, placebo-controlled, crossover trial of the effects of 5 mg of desloratadine or placebo daily for 7 days on nasal airflow, nasal secretion weights, and

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SAR symptoms, including nasal congestion, in response to grass pollen in an allergen-exposure unit, the Vienna Challenge Chamber.^{10,11}

METHODS

Subjects

The study subjects were 19 to 45 years of age, with a history of SAR for at least 2 years. All subjects demonstrated sensitivity to grass pollen (*Dactylis glomerata*), as determined by means of a positive skin prick test response (wheal diameter ≥ 3 mm larger than that produced by the negative control) and a positive RAST result of class 2 or greater at screening or during the previous 12 months. For skin prick testing, saline was the negative control, and 0.1% histamine was the positive control. Subjects were excluded if they met any of the following criteria: pregnancy or lactation; use of an investigational drug or antiallergy antibody within 30 and 90 days, respectively; hepatic or renal impairment; respiratory infection within 30 days; and allergy or hypersensitivity to the study medication. Any subject with an abnormal physical examination result was excluded if the investigator judged that this could affect the subject's safety or study conduct. Certain medications required the following washout periods before enrollment: corticosteroids (depot, 90 days; systemic, 30 days; dermatologic, 14 days); cromones (14 days); antihistamines (astemizole, 90 days; nasal and long-acting oral, 10 days; short-acting oral, 12-48 hours; ocular, 3 days); leukotriene inhibitors (10 days); decongestants (1-3 days); herbal remedies (3 days); systemic antibiotics (14 days); anticholinergics (7 days); tetracyclic antidepressants (14 days); ophthalmic non-steroidal anti-inflammatory drugs (3 days); immunotherapy (24 hours); and nasal-ophthalmic wash solutions (12 hours).

The study was conducted outside of the grass pollen allergy period. The study protocol was reviewed and approved by the ethics committee of the University of Vienna and was performed in accordance with the Declaration of Helsinki. All subjects provided written informed consent and demonstrated that they understood and could adhere to the planned study design.

Study design

During a 2-week screening period (day -14 to day -1), each subject underwent a 2-hour continuous grass pollen allergen exposure to ensure they would have an adequate, measurable nasal allergic response. During this exposure, nasal congestion symptoms and nasal airflow were measured. At entry to the exposure unit, eligible subjects had to have no or mild nasal congestion (score ≤ 1), which had to increase to at least moderate congestion (score ≥ 2). Nasal airflow, measured with active anterior rhinomanometry, had to decrease by at least 30% by the end of the 2-hour allergen exposure.

Eligible subjects were randomized to receive a 5-mg desloratadine tablet or identical placebo each morning for 7 days (days 1-7: phase I) at the study site, followed by a 10-day washout period (days 8-17), after which subjects crossed over to the other treatment arm for 7 days (days 18-24: phase II). Study medications were administered in 2 treatment sequences: (1) desloratadine for 7 days and then placebo for 7 days (sequence I) and (2) placebo for 7 days and then desloratadine for 7 days (sequence II). Study drugs were provided by Schering-Plough.

The Vienna challenge unit is a sealed room in which a defined concentration of allergen can be maintained over a period of hours. Subjects (in groups of 14) were separated from supervising staff by means of a Perspex screen and communicated through an intercom. Ambient air was kept at a steady temperature (24°C) and humidity (30%), and these conditions were monitored every 5 seconds. A dispersal system was used to maintain a uniform grass pollen concentration throughout the chamber (average pollen density, 1500 $\pm$

120 *Dactylis glomerata* pollen grains/m³), which was monitored every 5 minutes with a modified Burkard pollen trap. On day 7 of each treatment period, subjects underwent a 6-hour continuous allergen exposure with periodic nasal airflow measurements, nasal secretion collections, and scorings of nasal and nonnasal SAR symptom severity.

Nasal airflow was measured by means of active anterior rhinomanometry immediately before (baseline) and every 30 minutes during the screening (2-hour) and treatment (6-hour) allergen exposures. After clearing nasal secretions, subjects wore an airtight face mask, kept their mouths closed, and breathed through one nostril to measure the nasal airflow, while a sensor in the other nostril measured the difference in prenasal and postnasal (choanal) pressures. Nasal airflow (in milliliters per second) was the sum of recorded airflow through the right and left nostrils at a pressure difference of 150 Pa across the nasal passages. The computerized system (Rhinotest MP441, J. Ganzer KG) amplified and digitized transnasal airflow and pressure signals. At least 5 measurements were taken for each report, and if results were reproducible, the mean values were recorded, printed, and stored with a Centronics database. Two complete rhinomanometry systems were used simultaneously to guarantee that a full cycle of measurements for up to 14 subjects was recorded within 15 minutes. Computerization and staff training ensured that each subject assessment took a maximum of 2 minutes to complete and report.

Nasal secretions were collected with sealed, preweighed packets of absorbent paper tissues. Subjects cleared nasal secretions at baseline and whenever necessary (at least every 30 minutes) during allergen exposure. Secretion weights were calculated for every 30-minute period.

Nasal and nonnasal SAR symptom severity scores were self-assessed immediately before (baseline) and every 15 minutes during allergen exposure. Nasal symptoms were nasal congestion, rhinorrhea, sneezing, and nasal itching. The nonnasal symptoms were eye itching, eye tearing, eye redness, and itching of ears-palate. The immediate severity of each symptom was scored as follows: 0, none (no signs-symptoms); 1, mild (signs-symptoms clearly present, minimal awareness, easily tolerated); 2, moderate (definite awareness of signs-symptoms, bothersome but tolerable); and 3, severe (signs-symptoms hard to tolerate, interfered with planned activities during allergen exposure). Nasal congestion, rhinorrhea, and sneezing were also evaluated separately. Composite symptom scores were calculated as follows: total nasal symptom score (TNSS) was defined as the sum of all 4 nasal symptom scores; total nonnasal symptom score (TNNSS) was defined as the sum of all 4 nonnasal symptom scores; and total symptom score (TSS) was defined as the sum of TNSS and TNNSS.

Vital signs (blood pressure, heart rate, and temperature) were recorded at the screening visit (day -14 to day -1), on the first day of each treatment phase, and before allergen exposures. Subjects were questioned about the occurrence, onset, and severity of all adverse events during the study, and all adverse events were classified according to severity and relationship to study medication.

Statistical methods

The efficacy parameters were nasal airflow, nasal secretion weights, individual SAR symptom severity scores (nasal congestion, rhinorrhea, sneezing, and nonnasal symptoms), and composite SAR symptom scores (TNSS, TNNSS, and TSS). All parameters were assessed as follows: (1) the mean area under the curve (AUC) at 0 to 2 hours, 2 to 6 hours, and 0 to 6 hours during allergen exposure; (2) the mean observed, or actual, values measured at each time point; and (3) the mean changes of observed values at 2 and 6 hours from the baseline values immediately before allergen exposure.

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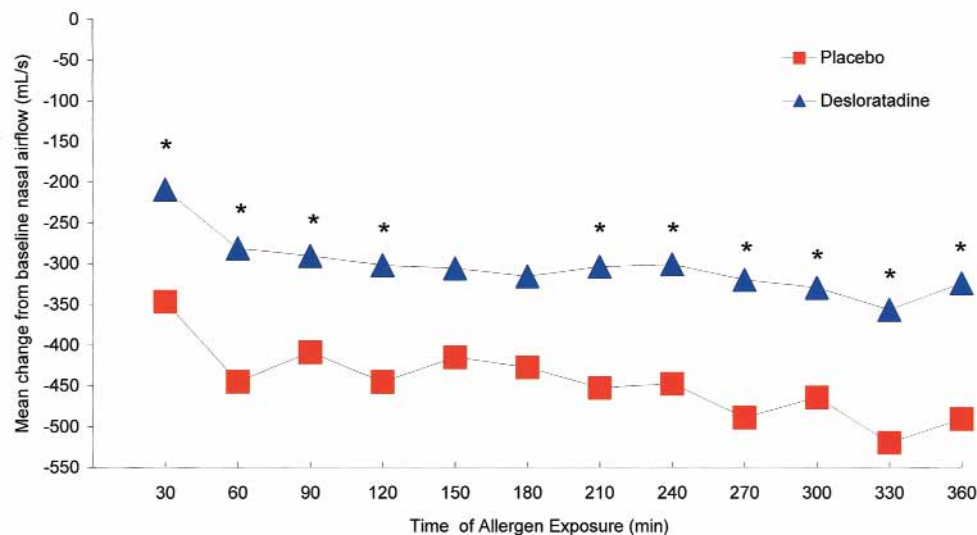


FIG 1. Mean change from baseline nasal airflow (in milliliters per second) in response to allergen exposure after treatment with 5 mg of desloratadine or placebo every morning. *P* values refer to comparison between desloratadine and placebo (**P* < .02).

All efficacy parameters were assessed by using an ANOVA model for a crossover design with factors of study drug, subject nested within sequence, sequence, and phase. Data were analyzed specifically according to sequence and phase to assess for period and carryover effects. For the observed and change-from-baseline values, time and time-by-treatment interactions were assessed also. *P* values were calculated for the differences between values after desloratadine and placebo dosing, and comparisons were 2-sided with an α level of significance of .05. The incidence, severity, and relationship to drug treatment of adverse events were calculated. Adverse events that involved at least 5% of the study population were analyzed for difference in incidence rates between treatments by using the McNemar test (α = .05 level of significance).

RESULTS

Demographics and baseline parameters

Forty-seven eligible subjects who were randomized to receive either desloratadine or placebo did not differ in terms of demographic data according to treatment sequence (Table I). The safety and intent-to-treat populations consisted of 47 and 46 subjects, respectively. One subject from treatment sequence I withdrew for personal reasons before any postdose efficacy data were collected. One patient from treatment sequence II withdrew because of an adverse event at day 13 and only had efficacy data for placebo treatment.

Baseline values before each 6-hour allergen exposure for nasal airflow, nasal secretion weights, nasal congestion, and other individual SAR symptom severity scores and TNNSSs were similar for the 2 treatment groups. The observed values at baseline for the composite parameters TNNSS and TSS were significantly higher in the placebo group compared with those in the desloratadine group (*P* = .032 and *P* = .019, respectively). Analysis of these and all other data according to sequence and phase demonstrated that neither a sequence nor a carryover effect occurred during this study.

Nasal airflow and nasal secretion weights

Allergen exposure caused decreases in nasal airflow during both desloratadine and placebo dosing. The decrease in mean nasal airflow AUC was significantly less with desloratadine dosing than with placebo both early (0-2 hours, *P* = .017) and throughout (0-6 hours, *P* = .002) the allergen exposure (Table II). Observed nasal airflow was significantly greater with desloratadine than with placebo (Table II), whereas the mean decrease from baseline in nasal airflow was significantly less with desloratadine than with placebo (Fig 1). Compared with placebo, desloratadine dosing was associated with significantly lesser nasal secretion weights over time (AUC, Table II), mean observed weights at each time point (Table II), and increase from baseline values (data not shown; *P* < .001 for all parameters).

SAR symptom severity scores

Mean nasal congestion symptom severity scores over time (AUC) were significantly less with desloratadine dosing than with placebo (Table II). The difference between the AUCs for desloratadine and placebo during the first 2 hours of exposure (*P* < .001) endured for the entire 6-hour exposure period (*P* < .001). Both the observed values (Table II) and mean change from baseline in nasal congestion symptom severity scores were significantly lower with desloratadine than with placebo (Fig 2).

The AUCs, observed values, and change from baseline values for all individual and composite nasal and non-nasal SAR symptom severity scores were also significantly less during desloratadine treatment compared with those during placebo treatment (Table II).

Safety

No serious adverse event occurred during the study,

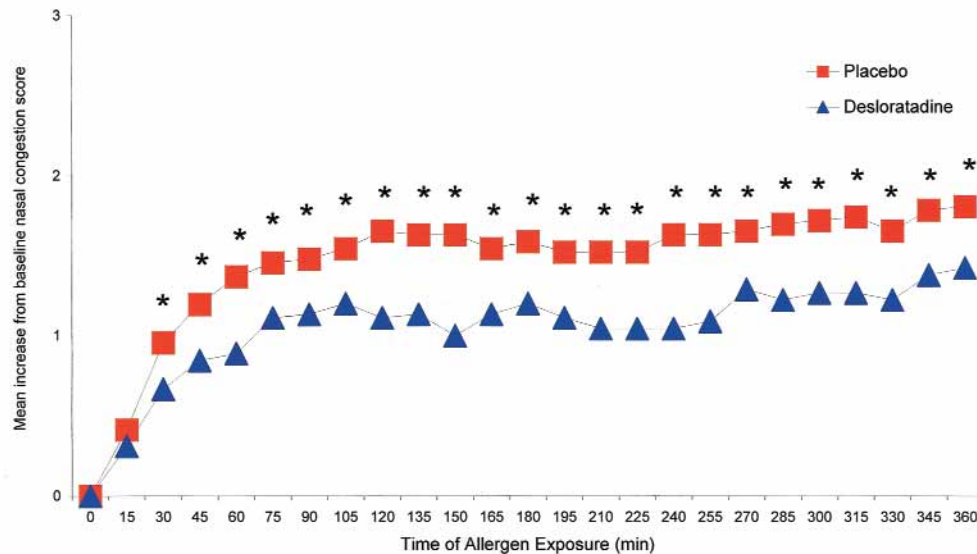


FIG 2. Mean increase from baseline in nasal congestion symptom severity score in response to allergen exposure after treatment with 5 mg of desloratadine or placebo every morning. *P* values refer to comparison between desloratadine and placebo (**P* < .03).

TABLE I. Patient demographics (intent-to-treat population)

	Sequence I*	Sequence II†	Total
Age (y)			
Mean ± SD	25.0 ± 3.7	24.9 ± 3.2	25.0 ± 3.4
Range	19-31	19-31	19-31
Sex			
Male, n (%)	8 (36)	14 (58)	22 (48)
Female, n (%)	14 (64)	10 (42)	24 (52)
Race			
White, n (%)	21 (96)	24 (100)	45 (98)
Black, n (%)	1 (5)	0 (0)	1 (2)
Height (cm)			
Mean ± SD	172.0 ± 9.1	175.1 ± 10.2	173.6 ± 9.7
Range	161-188	160-196	160-196
Weight (kg)			
Mean ± SD	66.8 ± 17.0	69.5 ± 10.8	68.2 ± 14.0
Range	49-109	48-92	48-109
Duration of SAR (y)			
Mean ± SD	11.0 ± 5.3	13.2 ± 4.7	12.1 ± 5.1
Range	2-19	4-21	2-21

*Sequence I (n = 22): 5 mg of desloratadine (7 days), washout period (10 days), placebo (7 days).

†Sequence II (n = 24): placebo (7 days), washout period (10 days), 5 mg of desloratadine (7 days).

and there was no difference in adverse event rates between desloratadine (2/47 [4%]) and placebo (3/47 [6%]) treatments. The reported adverse events were viral infection (placebo, n = 2), migraine (desloratadine, n = 1; placebo, n = 1), somnolence (desloratadine, n = 1), dysmenorrhea (placebo, n = 1), and coughing (placebo, n = 1). One subject discontinued the study during placebo treatment because of moderately severe viral infection and coughing, neither of which was treatment related. Moderate, probably treatment-related somnolence in one subject receiving desloratadine did not require discontinuation from the study.

DISCUSSION

Second-generation antihistamines are effective for the symptomatic treatment of SAR. In particular, rapid durable control of sneezing, nasal itching, rhinorrhea, and nonnasal symptoms can be achieved with once-daily oral medications.^{12,13} These symptoms are caused primarily by the release of preformed and rapidly generated mediators associated with allergic effector cells.³ The use of second-generation antihistamines as monotherapy in SAR may be restricted by poor relief of nasal obstruction. Placebo-controlled clinical studies of desloratadine in patients with

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TABLE II. Summary of objective and subjective efficacy parameters

Parameter	Time	Desloratadine	Placebo	P value
Nasal airflow (mL/s)				
AUC (SD)	0-2 h	1755.0 (548.7)	1623.0 (556.5)	.017
	2-6 h	3081.4 (1202.3)	2748.9 (969.1)	.002
	0-6 h	4836.3 (1705.3)	4372.0 (1491.3)	.002
Observed value* (SD)	Baseline	1095.2 (332.4)	1153.9 (303.8)	NS
	2 h	792.7 (318.2)	708.4 (286.4)	.021
	6 h	770.3 (336.1)	663.2 (296.7)	.004
Nasal secretion weights (g)				
AUC (SD)	0-2 h	0.5 (0.9)	1.4 (1.7)	<.001
	2-6 h	1.3 (2.3)	3.3 (3.2)	<.001
	0-6 h	1.9 (3.1)	4.7 (4.7)	<.001
Observed value (SD)	Baseline	0.0 (0.0)	0.0 (0.0)	NA
	2 h	0.73 (1.7)	1.85 (1.8)	<.001
	6 h	0.94 (1.9)	1.97 (1.9)	<.001
Symptom severity scores				
Nasal congestion				
AUC (SD)	0-2 h	2.0 (1.2)	2.8 (1.2)	<.001
	2-6 h	5.2 (2.6)	7.5 (2.3)	<.001
	0-6 h	7.1 (3.7)	10.3 (3.2)	<.001
Observed value (SD)	Baseline	0.1 (0.3)	0.2 (0.4)	NS
	2 h	1.2 (0.8)	1.9 (0.8)	<.001
	6 h	1.6 (0.8)	2.0 (0.7)	<.001
Sneezing				
AUC (SD)	0-2 h	1.2 (1.0)	2.4 (1.3)	<.001
	2-6 h	3.3 (2.5)	6.4 (2.8)	<.001
	0-6 h	4.4 (3.3)	8.8 (3.8)	<.001
Observed value (SD)	Baseline	0.0 (0.0)	0.1 (0.3)	NS
	2 h	0.8 (0.7)	1.6 (0.8)	<.001
	6 h	0.8 (0.8)	1.7 (0.9)	<.001
Rhinorrhea				
AUC (SD)	0-2 h	1.5 (1.1)	2.8 (1.4)	<.001
	2-6 h	3.9 (2.4)	7.1 (2.6)	<.001
	0-6 h	5.4 (3.4)	9.9 (3.7)	<.001
Observed value (SD)	Baseline	0.0 (0.2)	0.2 (0.4)	NS
	2 h	1.0 (0.8)	1.8 (0.9)	<.001
	6 h	1.1 (0.8)	1.8 (0.8)	<.001
TNSS				
AUC (SD)	0-2 h	6.1 (3.6)	10.6 (4.3)	<.001
	2-6 h	16.4 (8.8)	27.5 (8.7)	<.001
	0-6 h	22.5 (12.0)	38.1 (12.4)	<.001
Observed value (SD)	Baseline	0.2 (0.4)	0.5 (1.1)	.032
	2 h	4.0 (2.4)	6.9 (2.8)	<.001
	6 h	4.4 (2.6)	7.3 (2.8)	<.001
TNNS				
AUC (SD)	0-2 h	2.0 (2.3)	4.0 (3.3)	<.001
	2-6 h	6.0 (6.2)	10.8 (8.6)	<.001
	0-6 h	8.0 (8.2)	14.8 (11.3)	<.001
Observed value (SD)	Baseline	0.1 (0.4)	0.3 (0.8)	NS
	2 h	1.5 (1.8)	2.5 (2.1)	.003
	6 h	1.7 (2.0)	3.0 (2.5)	<.001
TSS				
AUC (SD)	0-2 h	8.1 (4.9)	14.6 (6.6)	<.001
	2-6 h	22.4 (13.0)	38.3 (14.6)	<.001
	0-6 h	30.4 (17.3)	52.9 (20.3)	<.001
Observed value (SD)	Baseline	0.3 (0.6)	0.8 (1.6)	.019
	2 h	5.7 (3.5)	9.3 (4.2)	<.001
	6 h	6.1 (4.1)	10.4 (4.3)	<.001

AUC and observed values in response to allergen exposure on day 7 of treatment with 5 mg of desloratadine or placebo are shown.

NS, Not significant; NA, parameter could not be tested.

*Observed values: actual measurement at time point.

SAR have shown, however, significant improvements in patient-assessed complaints of nasal congestion.⁹

Like second-generation antihistamines, nasal topical corticosteroids are first-line therapy for patients with SAR.¹⁴ A meta-analysis and individual comparative trials between the 2 drug classes have shown that intranasal corticosteroids are at least as effective as antihistamines in controlling nasal and nonnasal symptoms of SAR.¹⁵ Corticosteroids are particularly effective in relieving symptomatic nasal congestion. Despite their efficacy in clinical trials in SAR, studies of nasal corticosteroids with controlled allergen challenge models or rhinomanometric measurements are relatively sparse. Schmidt et al¹⁶ compared intranasal ciclesonide with placebo in a crossover trial similar to our study, although they performed rhinomanometry 5 and 30 minutes after direct allergen insufflation, which is in contrast to our repetitive measurements during continuous allergen exposure. Although nasal congestion symptoms improved by day 2, nasal airflow was not improved until day 5. Pipkorn¹⁷ reported that intranasal budesonide for 1 week reduced nasal obstruction significantly after a single allergen challenge; other groups, however, found no advantage of intranasal corticosteroids over placebo in terms of nasal airflow in response to ragweed insufflation¹⁸ or nasal airway resistance during the pollen season.¹⁹ Neither intranasal corticosteroid nor combined antihistamine-leukotriene receptor antagonist treatment of patients with SAR was superior to placebo in terms of posterior rhinomanometry or acoustic rhinometry.²⁰

Although we and other groups²¹ have performed comparative efficacy and onset-of-action studies with antihistamines in allergen-exposure units, few studies have measured the effect of antihistamines on nasal obstruction assessed by nasal airflow. We showed that 2 days of treatment with cetirizine or fexofenadine produced significantly less nasal congestion symptoms than placebo; nasal airflow, however, was not improved significantly.²² In another study²³ we found that cetirizine-pseudoephedrine treatment produced a lesser decrease in nasal airflow and an increase in nasal congestion symptoms than that seen with placebo, although it is not possible to separate the effect on nasal congestion of the sympathomimetic from that of the antihistamine in this study.

The main findings of the present study, namely that desloratadine treatment was associated with less restricted nasal airflow, less complaints of nasal congestion, and less severe symptomatology in response to grass pollen exposure, suggest that relief of nasal obstruction in SAR can be achieved by treatment with this new antihistamine. Preclinical in vitro and in vivo animal studies have shown desloratadine to have potent H₁ receptor-blocking and receptor-binding activities and to inhibit components of the allergic inflammatory cascade.²⁴ Whether and how these actions might affect nasal mucosa inflammation and nasal obstruction remains to be determined.

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