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Original article

Comparison of the effects of desloratadine 5-mg daily and placebo on nasal airflow and seasonal allergic rhinitis symptoms induced by grass pollen exposure

Background: Nasal congestion is a chronic symptom of seasonal allergic rhinitis (SAR) that is often difficult to treat with antihistamines. Desloratadine, a new, potent, H_1-receptor antagonist has been shown to decrease nasal congestion in clinical trials and to maintain nasal airflow in response to grass pollen exposure. We compared the effects of desloratadine 5 mg and placebo on nasal airflow, nasal secretion weights and SAR symptoms, including nasal congestion, in patients exposed to grass pollen in an environmental exposure unit.
Methods: Forty-six grass pollen allergic SAR patients received desloratadine or placebo for 7 days, followed by a 10-day washout, and then crossed over to the other treatment for 7 days. A 6-h allergen exposure was performed at the end of each treatment period.
Results: Desloratadine was significantly superior to placebo in maintaining nasal airflow ($P \leq 0.014$) and lessening the increase in nasal secretion weights ($P < 0.001$) throughout allergen exposure. SAR symptom scores, including nasal congestion, were significantly less with desloratadine than placebo ($P \leq 0.001$). Desloratadine was well tolerated.
Conclusions: This study confirms that, compared with placebo, desloratadine can maintain nasal airflow and reduce nasal secretion weights and the severity of SAR symptoms, including nasal congestion, in SAR patients exposed to grass pollen allergen.

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In seasonal allergic rhinitis (SAR), the initial response by mast cells to allergen involves the release of preformed and rapidly generated mediators, primarily histamine and eicosanoids, which are responsible for acute symptoms, such as sneezing, rhinorrhea and nasal itch. Chronic allergic inflammation of the nasal mucosa develops subsequently, with cellular infiltration and vascular mucosal engorgement producing nasal obstruction (1). The pathogenesis of nasal obstruction is complex and many allergic mediators are involved, including eicosanoids (2, 3), histamine (4), neuropeptides (5), and cytokines, such as interleukin-4 (IL-4) (6). Nasally inhaled corticosteroids are an effective treatment for allergic symptoms in SAR (7) and down-regulate the allergic inflammatory response at the molecular level (8). The efficacy of nasal topical corticosteroids depends on regular use, and a period of at least 1–2 days is required before symptoms improve and maximum efficacy is usually noted after 1–2 weeks (9). Existing antihistamines provide rapid and effective control of early phase symptoms via histamine blockade, but have a lesser impact on nasal congestion (10). Sympathomimetic α-agonists are effective for short-term control of nasal congestion by reducing nasal mucosal vascular engorgement, but long-term treatment is not recommended due to the occurrence of adverse events and rebound hypersecretion/congestion upon discontinuation of oral and topical sympathomimetics, respectively (10, 11).

Desloratadine is a new, nonsedating antihistamine, which exhibits potent histamine H_1 receptor binding compared with other compounds (12), and has demonstrated efficacy and safety in the treatment of SAR (13), perennial allergic rhinitis (14) and chronic idiopathic urticaria (15). In clinical trials in SAR, desloratadine has been shown to improve nasal congestion during the allergy season (16), and we reported recently that desloratadine maintained nasal airflow and reduced nasal congestion following grass pollen exposure in the Vienna Challenge Chamber (VCC), a controlled, experimental

Abbreviations: AUC, area under the curve; IL, interleukin; SAR, seasonal allergic rhinitis; TNNSS, total nonnasal symptom score; TNSS, total nasal symptom score; TSS, total symptom score; VCC, Vienna Challenge Chamber.

allergen exposure unit (17). We report here the results of a second, identically designed study, which was performed in a different group of grass pollen sensitive SAR patients.

Materials and methods

Patients

Forty-seven adults, with a history of SAR for ≥2 years and were responders to antihistamine treatment were enrolled in the study. The study was performed outside of the grass pollen allergy season. Patients had to demonstrate sensitivity to grass pollen (*Dactylis glomerata*) at screening or during the previous year by a positive skin prick test and a positive RAST (class ≥2). Exclusion criteria were pregnancy/lactation, asthma that required medical therapy, chronic diseases that could impact the study outcome (renal, hepatic, cardiac, infectious or others), known sensitivity to study medication, and respiratory infection within 30 days of commencement of the study. Women had to use a medically acceptable hormonal or barrier form of contraception for the duration of the study. Washout periods were required for the following drugs: corticosteroids [depot (90 days), systemic (30 days), dermatological (14 days)], cromones (14 days), sympathomimetics (1–3 days), other antihistamines [astemizole (90 days), nasal or oral (10 days), short-acting oral (12 h to 2 days), ocular (3 days)], leukotriene inhibitors (10 days), systemic antibiotics for respiratory infection (14 days), anticholinergics (7 days), tetracyclic antidepressants (14 days), ophthalmic NSAIDs (3 days), immunotherapy (1 day), herbal remedies (3 days), and nasal or ophthalmic wash solutions (12 h). Patients could also be excluded if physical examination revealed abnormalities that could impact the patient's health or the study outcome.

The Ethics Committee of the University of Vienna approved the study, which was performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participating patients during the screening period.

A screening assessment (see below) was performed during the 2 weeks before the start of the study. Eligible patients were randomized in a double-blind fashion to receive either desloratadine 5 mg (Schering-Plough, Dardilly, France) or identical placebo once daily in the morning for 7 days. Following the initial 7 days of treatment (Phase I), patients underwent a 10-day washout period, and then crossed over to the other treatment for 7 days (Phase II). Patients, therefore, received study medication in one of two treatment sequences: Sequence I: desloratadine (7 days), washout (10 days), placebo (7 days); Sequence II: placebo (7 days), washout (10 days), desloratadine (7 days).

Allergen exposure procedure

The VCC is a specially designed sealed room in which a precisely defined concentration of allergen can be administered to subjects (in groups of up to 14) and maintained over a period of hours. Air temperature (24°C) and humidity (30%) were closely regulated, and the grass pollen concentration was maintained at a mean density of 1500 ± 120 *D. glomerata* grains/m^3 and was measured at 5-min intervals with a modified Burkard pollen trap. At screening, patients underwent a 2-h VCC grass pollen allergen exposure, while during the study a 6-h VCC exposure was performed on day 7 of each treatment period.

Nasal airflow was measured by active anterior rhinomanometry immediately before ('baseline') and every 30 min during allergen exposure in the VCC. After clearing nasal secretions, patients wore a tight-fitting facemask, and with the mouth closed, patients breathed through one nostril, while a sensor in the other nostril captured data on pre- and postnasal pressures via airflow and pressure transducers. The system (Rhinotest MP441, J. Ganzer KG, Germany) was connected to a personal computer and the transduced signals of transnasal airflow and pressure were amplified, digitized and saved for statistical analysis in a Centronics database. Nasal airflow was reported as the sum of recorded airflow through right and left nostrils in milliliter per second at a pressure difference of 150 Pa across the nasal passages. Two full rhinomanometry systems were employed to insure that nasal airflow data could be recorded for groups of 14 patients within a 10-min period. Five or more airflow measurements were recorded for each patient at each time point before and during exposure, and the mean was recorded when reproducible values were obtained.

Nasal secretions were collected every 30 min using sealed, preweighed packets of paper tissues. Patients recorded the current severity of SAR symptoms via computer terminals immediately before grass pollen exposure ('baseline') and every 15 min during exposure. Nasal SAR symptoms assessed were nasal congestion, rhinorrhea, sneezing, and nasal itching. Nonnasal SAR symptoms evaluated were eye itching, eye tearing, eye redness, and itching of ears/palate. A four-point scale was used to score the severity of each symptom (0 = no symptoms to 3 = severe/intolerable symptoms). Individual SAR symptom scores were used to calculate three composite symptom scores: total nasal symptom score (TNSS) = the sum of all four nasal symptom scores; total nonnasal symptom score (TNNSS) = the sum of all four nonnasal symptom scores; and total symptom score (TSS) = the sum of TNSS and TNNSS.

At the screening visit, a 2-h VCC grass pollen allergen exposure was performed. Subjects had to have mild/no nasal congestion symptom severity (i.e. score ≤ 1) before entering the VCC. To be eligible, the nasal congestion symptom severity had to increase to at least moderate (i.e. score ≥2) by the end of the 2-h allergen exposure, and patients' nasal airflow, measured by active anterior rhinomanometry, had to fall by ≥30% by the end of the 2-h screening allergen exposure.

Adverse events

Vital signs (blood pressure, heart rate, temperature) were recorded at baseline, and at each of visit to the VCC. Patients were questioned daily about the onset and severity of all adverse events during the treatment periods, and all reported adverse events were recorded and classified according to a standard grading system of severity and relationship to study medications.

Statistical methods

The main efficacy parameter was the mean area under the time curve (AUC) for nasal airflow. Other efficacy parameters included nasal secretion weights, individual and composite SAR symptom severity scores (nasal congestion, rhinorrhea, sneezing, TNSS, TNNSS and TSS), which were assessed as AUC and as mean change from baseline values. AUC values were derived for the periods, 0–2 h, 2–6 h and 0–6 h, and *P*-values were calculated for differences between treatments. The efficacy parameters were analyzed with analysis of variance (ANOVA) for baseline and AUC analyses. For change from baseline at each time-point, the analysis of covariance (ANCOVA) model with baseline as a covariate was used. Both statistical models were for a crossover design with factors of drug, subject within sequence, sequence and phase. The comparisons were two-sided, $\alpha = 0.05$ level of significance. For adverse

events, the incidence, severity and relationship to treatment were calculated for each treatment group. Adverse events that involved ≥5% of the study population were analyzed for difference in incidence rates between treatments using McNemar's test ($\alpha = 0.05$).

Results

Of the 47 patients who met the eligibility criteria and were randomized to receive treatment, three withdrew early for personal reasons unrelated to the study, while one patient was lost to follow-up without receiving any study medication. The safety population comprised 46 patients, while the intent-to-treat population contained 43 patients. Demographic data were similar for both treatment sequences (Table 1).

Nasal airflow

During grass pollen exposure, both the placebo and desloratadine groups experienced decreases in nasal airflow, but the decrease in nasal airflow was less in patients treated with desloratadine. The AUC for nasal airflow was greater with desloratadine, during the early (0–2 h, $P = 0.005$) and late stages (2–6 h, $P = 0.014$) of pollen exposure, and over the entire exposure period (0–6 h, $P = 0.006$) (Table 2).

Nasal secretion weights

Significantly lower nasal secretion weights in response to allergen exposure were recorded during desloratadine treatment than during placebo treatment. The effect of desloratadine on the AUC for nasal secretion weights was noted during the first 2 h ($P < 0.001$), and lasted for the 6-h duration of grass pollen exposure ($P < 0.001$) (Table 2). During desloratadine treatment, the mean increase from baseline values for nasal secretion weights was consistently significantly lower than placebo ($P < 0.001$) (data not shown).

Table 1. Demographic data for study population

Demography	All subjects ($n = 43$)
Age (years)	
Mean (SD)	24.4 (3.1)
Range	19–34
Gender	
Male, *N* (%)	18 (42%)
Female, *N* (%)	25 (58%)
Height (cm)	
Mean (SD)	173.0 (8.6)
Range	157–192
Weight (kg)	
Mean (SD)	66.6 (11.4)
Range	46–93
Duration of SAR (years)	
Mean (SD)	12.4 (6.4)
Range	2–27
Race	
Caucasian, *N* (%)	43 (100%)

Symptom scores

Grass pollen exposure caused an increase in all symptom scores in all patients. During desloratadine treatment, however, the mean AUC for nasal congestion severity was significantly lower than when on placebo dosing during both the first 2 h and the entire 6 h of grass pollen exposure ($P \leq 0.001$, Table 2). There was a lesser increase from baseline in nasal congestion with desloratadine compared with placebo from the first assessment after 15 min, through to the end of exposure at 6 h ($P \leq 0.033$) (Fig. 1).

Mean AUC at 0–2 h, 2–6 h and 0–6 h for TNSS was significantly lower with desloratadine compared with

Table 2. Area under the curve (AUC) results at 0–2 h, 2–6 h and 0–6 h for the objective and subjective efficacy criteria in patients who received desloratadine 5 mg or placebo daily for 7 days (SD = standard deviation)

Efficacy parameter	Time (h)	Desloratadine	Placebo	*P*-value
Nasal airflow (ml/s)				
AUC (SD)	0–2	1838.7 (540.2)	1617.0 (499)	0.005
	2–6	3110.3 (990.19)	2243.9 (1113.8)	0.014
	0–6	4949.0 (1456.6)	4360.9 (1556.7)	0.006
Nasal secretion weights (g)				
AUC (SD)	0–2	0.5 (0.7)	1.6 (1.3)	<0.001
	2–6	1.3 (1.6)	3.7 (2.7)	<0.001
	0–6	1.8 (2.3)	5.3 (3.9)	<0.001
Nasal congestion				
AUC (SD)	0–2	2.1 (1.3)	3.0 (1.2)	<0.001
	2–6	5.8 (3.0)	8.0 (3.0)	<0.001
	0–6	8.0 (4.1)	11.0 (4.1)	<0.001
Sneezing				
AUC (SD)	0–2	1.0 (1.2)	2.4 (1.6)	<0.001
	2–6	2.7 (2.7)	5.9 (3.5)	<0.001
	0–6	3.7 (3.8)	8.3 (5.0)	<0.001
Rhinorrhea				
AUC (SD)	0–2	1.7 (1.2)	2.7 (1.4)	<0.001
	2–6	4.4 (3.0)	6.8 (3.2)	<0.001
	0–6	6.1 (4.0)	9.5 (4.5)	<0.001
Total nasal symptoms				
AUC (SD)	0–2	6.1 (4.2)	10.5 (5.1)	<0.001
	2–6	16.1 (10.2)	27.3 (11.2)	<0.001
	0–6	22.1 (14.0)	37.8 (15.9)	<0.001
Total nonnasal symptoms				
AUC (SD)	0–2	1.8 (2.8)	3.1 (3.6)	0.005
	2–6	4.9 (7.7)	9.5 (10.9)	0.002
	0–6	6.7 (10.2)	12.6 (14.2)	<0.001
Total symptoms				
AUC (SD)	0–2	7.8 (6.2)	13.7 (7.4)	<0.001
	2–6	21.0 (15.6)	36.8 (18.0)	<0.001
	0–6	28.8 (21.1)	50.5 (24.9)	<0.001

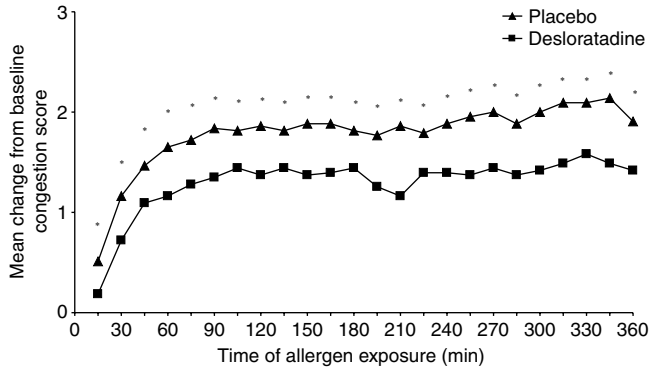

Figure 1. Change from baseline in nasal congestion symptom severity during grass pollen allergen exposure in patients treated with either desloratadine 5 mg or placebo once daily for 7 days. $^*P \leq 0.033$.

placebo ($P < 0.001$), and, as with nasal congestion, the increase from baseline in TNSS was less with desloratadine than with placebo and lasted for the duration of pollen exposure ($P < 0.001$). The mean AUC for symptom severities from 0–2 h, 2–6 h and 0–6 h for rhinorrhea, sneezing, TNNSS and TSS were all significantly lower with desloratadine compared with placebo ($P \leq 0.005$) (Table 2). Increases from baseline symptom scores for all parameters were consistently significantly less with desloratadine than with placebo (data not shown).

Safety analysis

No clinically significant change in vital signs and no serious adverse event occurred during the study. Five subjects in each treatment sequence reported adverse events (P = not significant). The most frequent treatment-related adverse events during placebo treatment were dry mouth ($n = 1$), headache ($n = 2$), nausea ($n = 1$) and somnolence ($n = 1$). During desloratadine treatment, the most frequent treatment-related adverse events were headache ($n = 1$), nausea ($n = 1$) and somnolence ($n = 3$). No subject withdrew from the trial due to an adverse event.

Discussion

This double-blind, placebo-controlled, crossover study showed that, compared with placebo, desloratadine treatment was associated with greater nasal airflow and less nasal congestion due to grass pollen exposure in patients with SAR. These results confirm the effect of desloratadine on nasal airflow, symptomatic nasal congestion and other SAR symptoms that we noted in a study performed under identical experimental conditions (17). Taken together, the results demonstrate the reproducibility of assessments made in the VCC, which is an increasingly important factor for experimental allergen exposure models (18). Many second-generation antihistamines provide good efficacy in terms of controlling SAR symptoms such as rhinorrhea and sneezing (10). However, they are considered poorly effective against nasal congestion in SAR, and clinical trials of antihistamines often exclude nasal congestion when reporting composite SAR symptom scores (19–21).

The reason why desloratadine demonstrated benefits in terms of subjective and objective measures of nasal congestion may be a function of its potent H_1-receptor antagonism allied with inhibition of allergic inflammatory mediators. It is now accepted that the allergic inflammatory response in SAR is a complex network of local and systemic immune interactions (22). Classical mediators, such as histamine interact with cells, cytokines, chemokines and adhesion molecules to cause cellular infiltration and chronic nasal mucosal inflammation (1). *In vitro* studies of desloratadine have shown that it can inhibit many of the key mediators involved in the allergic inflammatory response (23). Apart from its potent H_1-receptor blocking effects, desloratadine inhibits the release of mediators implicated in nasal congestion, such as prostaglandin D2, leukotriene C4, and IL-4 (24–26). Although these *in vitro* data are interesting, their significance results remains to be determined in humans.

In conclusion, the present study confirms the beneficial impact of desloratadine on nasal airflow and nasal congestion previously reported in the VCC. These benefits were accompanied by lower nasal secretion weights and lower SAR symptom scores compared with placebo in response to allergen exposure.

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