

Increased Nasal Airflow With Budesonide Compared With Desloratadine During the Allergy Season

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Objective: To compare the effects of desloratadine, an H₁-blocking antihistamine, and budesonide, an intranasal corticosteroid, on nasal peak inspiratory flow (NPIF) in patients with seasonal allergic rhinitis.

Design: We performed a randomized, double-blind, double-dummy, parallel study comparing oral desloratadine, 5 mg/d (n=31), and budesonide, 32 µg/d per nostril (n=30), for 2 weeks during the spring allergy season.

Main Outcome Measures: Subjects recorded NPIF and nasal symptoms twice daily. Baseline measurements were obtained before initiation of treatment. The Rhinoconjunctivitis Quality of Life Questionnaire was completed at baseline and after treatment.

Results: Desloratadine and budesonide caused a significant increase in NPIF compared with baseline on the evening of the first dose ($P<.01$). Budesonide, however, led to a significantly greater increase in NPIF than

did desloratadine when the change from baseline was compared for the entire treatment period (median, 475 vs 150 L/min; $P=.01$). Both treatments resulted in clinically significant reductions of the individual domains and overall scores on the Rhinoconjunctivitis Quality of Life Questionnaire ($P<.01$). There was a significant reduction in total symptom scores ($P\leq.01$) compared with baseline during all treatment days in both treatment groups, with no statistically significant differences between treatments (median, -60.0 vs -59.5; $P=.67$).

Conclusions: Both treatments led to significant improvements in NPIF, but the improvement was greater with the intranasal corticosteroid. Both treatments improved quality of life and reduced symptoms. The difference between the objective and subjective outcomes probably reflects the small sample size, the low pollen counts for the season, and the greater variability in subjective compared with objective measures.

Arch Otolaryngol Head Neck Surg. 2005;131:223-228

ALLERGIC RHINITIS CAUSES significant morbidity for nearly 50 million Americans. The sneezing runny and stuffy nose are accompanied by adverse effects on the patients' quality of life.^{1,2} At present, multiple treatment options exist, but nonsedating antihistamines are the most frequently prescribed treatment for seasonal allergic rhinitis.² Most antihistamines have not been especially effective in treating the symptom of obstructed airflow.³ The usual strategy for dealing with this underperformance has been to combine antihistamine and decongestant therapy.

Several clinical studies have demonstrated the efficacy of desloratadine, a nonsedating antihistamine, in treating nasal stuffiness.⁴⁻⁶ Studies of different doses of desloratadine, from 5 to 20 mg, all produced significant changes from baseline symptoms, which lasted 24 hours.⁷ Horak et al⁸ have also shown in a continuous pollen exposure model that

patients receiving desloratadine had significantly smaller decreases in airflow compared with those receiving placebo. In other seasonal studies, nasal peak inspiratory flow (NPIF) improved significantly in patients receiving desloratadine.^{9,10} Other studies have shown beneficial effects of fexofenadine hydrochloride, another nonsedating antihistamine, on nasal airflow and NPIF.^{10,11}

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The improvement in airflow with desloratadine may be related to its antihistamine or anti-inflammatory properties. Desloratadine has been successful in reducing inflammation and the symptom of nasal airflow obstruction in allergic rhinitis compared with placebo.¹² Desloratadine has also been shown to inhibit histamine and leukotriene release, adhesion molecule transcription, and chemotaxis of effector immune cells.¹³⁻¹⁶ It has even more potent ef-

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Financial Disclosure: None.

fects on the production of cytokines such as interleukin 4 and interleukin 13 than on the release of histamine and leukotriene.¹⁷ All of these anti-inflammatory effects may affect the symptoms of nasal airflow obstruction.

Intranasal corticosteroids have been the treatment option of choice for most cases of allergic rhinitis involving nasal airflow obstruction.^{18,19} A meta-analysis comparing the effects of intranasal corticosteroids and oral antihistamines showed that the corticosteroids produced greater improvement in most symptoms, including nasal blockage.^{18,19}

Although desloratadine has produced greater improvement in the symptom of nasal airflow obstruction when compared with placebo, no study to date has compared this antihistamine with an intranasal corticosteroid.²⁰ We chose to compare the effects of an intranasal corticosteroid, budesonide, and desloratadine in a seasonal study using NPIF as the primary outcome. The rationale for this study was to compare the objective effects of desloratadine and the intranasal corticosteroid on airflow so that clinicians can become aware of the relative magnitude of the decongestant effects of these 2 agents.

Because of its proven efficacy in improving quality of life²¹ and relieving nasal symptoms, especially congestion, and its potent anti-inflammatory properties, we chose budesonide as the intranasal corticosteroid. Day et al²² showed that budesonide nasal spray was more effective than placebo in a pollen challenge unit, and Pedersen et al²³ showed in a seasonal study that budesonide was significantly better than placebo in treating several nasal symptoms, including runny nose, sneezing, and blocked nose. In addition, its onset of action in treating allergic symptoms, including a blocked nose, was within 7 to 12 hours after initiation of treatment.²²

METHODS

SUBJECTS

We recruited patients aged 18 to 45 years who had a clinical history of sensitivity to tree or grass pollens. The patients underwent skin testing for sensitivity to tree or grass allergens. A positive skin test result and symptoms during the spring season for the past 2 years were required for patients to be eligible for enrollment in the study. Subjects were excluded from the study if they had used systemic corticosteroids in the previous 30 days, oral antihistamines or decongestants in the past 7 days, and topical antihistamines or decongestants in the past 24 hours. We also excluded individuals who were using long-term antiasthma medications or who had received immunotherapy in the previous 2 years. Women were excluded if they were pregnant or nursing a child. All women were given a urine pregnancy test, and only those with negative results were allowed to enroll. The only medications allowed during this study were acetaminophen, birth control pills, medroxyprogesterone acetate (Depo-Provera), or as-needed bronchodilators. The Institutional Review Board of the University of Chicago, Chicago, Ill, approved the study, and all patients gave consent before enrolling.

STUDY DESIGN

We performed a 2-week, randomized, double-blind, double-dummy, parallel clinical trial comparing the effects of desloratadine

(Clarinet; Schering Corp, Kenilworth, NJ) and budesonide (Rhinocort Aqua; AxtaZeneca, Westborough, Mass) on symptoms, quality of life, and NPIF during the spring allergy season in Chicago. Subjects needed to be symptomatic owing to their allergies to be enrolled in the study. Once enrolled, the patients received their study medications. If not symptomatic, the patients waited until they were symptomatic and then returned to begin the trial. Before starting medications, they filled out the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), which evaluated their quality of life during the preceding week.²⁴

The randomization was assigned by a code in blocks of 4, with each patient receiving a pill and a spray labeled by a third party. Those in the budesonide treatment arm received the active spray and the placebo pill, and those in the desloratadine treatment arm received the active pill and the placebo spray. The active pill was 5-mg desloratadine, and the active spray (per nostril) was 32- μ g budesonide. The placebo pills and sprays appeared identical to their active counterparts.

The patients also received a symptom diary card and an NPIF meter with their medication. They recorded their symptoms twice daily, in the morning and evening, during their 2-week enrollment period. The patients also recorded their NPIF twice daily. In the diary, they recorded their medication use throughout the study. They were to take the medication once a day, after refraining from using medication for an initial 2-day period to record baseline symptoms. We recorded pollen counts throughout the study.

After 2 weeks of taking their medication, the patients returned with their symptom diary card, flowmeter, and medication bottles and filled out another RQLQ.

We calculated the number of subjects for this study on the basis of findings of a previous study from our group comparing the combinations of fexofenadine and pseudoephedrine hydrochloride and of loratadine and montelukast sodium.²⁵ We chose the difference in peak nasal flow from baseline as the primary variable because it is the most relevant objective variable addressing our hypothesis. Assuming $P < .05$, a difference of 20 mL in flow, and a population standard deviation of 0.6, having 30 patients in each group will have 80% power to detect a difference.

OUTCOME MEASURES

Rhinoconjunctivitis Quality of Life Questionnaire

The RQLQ included 7 domains of symptoms, which included activity, sleep, and non-nose/eye, practical, nasal, eye, and emotional problems. There were several questions in each domain, and the patients rated their symptoms on a scale from 0 to 6, with 6 being the worst quality of life. An overall quality-of-life score was calculated by averaging the 7 individual domains.²⁴

Peak Flow

An In-Check peak and inspiratory flowmeter (Ferraris Medical, Inc, Louisville, Colo) was used for measuring the patients' NPIF in liters per minute.⁸ The patients were told to make 3 measurements and record the best one at each recording time.

Symptom Diary

The symptom scores were recorded on a scale of 0 to 3, with 0 being no symptoms and 3 being severe. The symptoms included sneezing, runny nose, stuffy nose, and itchy eyes/nose. Each recording of symptoms reflected on the hours since the last recording. For the morning recordings, the patients re-

Table 1. Subject Characteristics

Variable	Treatment Group	
	Budesonide (n = 30)	Desloratadine (n = 31)
Sex, No. (%) men	16 (53)	12 (39)
Race, No. (%) white	24 (83)	17 (55)
Skin test result, mean±SD diameter of wheal, mm	9.82 ± 1.90	9.32 ± 2.17
Age, mean ± SD, y	25.6 ± 5.97	26.4 ± 7.41

corded their symptoms and peak flow measurements before taking the medication for the day.

Baseline measurements were established when the patients were symptomatic. These were the recordings during the first 2 days of the study, starting from the first day's evening measurement. Because this evening measurement reflected the 12 hours before the recording, the first day of baseline included this evening recording and the next day's morning recording. The second baseline day then included the second day's evening recording and the third day's morning recording. Following that morning recording, the patients began taking their medication and recording their symptoms in the diaries and their NPIF. The next recording, in the evening, was the first one for the first day of active treatment. The patients continued recording the symptoms and NPIF twice a day for a total of 12 days.

STATISTICAL ANALYSIS

The statistical analysis was performed on the following 3 variables: peak nasal flow values, the RQLQ responses, and the symptom scores. The RQLQ data were assessed by parametric statistics, as they were normally distributed. For each domain and the overall quality-of-life score, the differences between the first (baseline) and final visits within each treatment arm were compared and analyzed by use of a paired *t* test. The change was also compared between the treatment arms by use of a nonpaired *t* test. The differences between the 2 treatment arms, in terms of the baseline and final scores for each, were also analyzed by use of a nonpaired *t* test.

For the NPIF and symptom scores, nonparametric statistics were used. Daily measurements were the sum of the evening and morning recordings. The 4 symptoms were also summed for each day, creating a total daily symptom measurement. The Wilcoxon signed rank test was used to analyze the change from baseline for each day of treatment within each treatment group. The Mann-Whitney test was used for comparing these changes in symptoms and NPIF between treatment arms.

RESULTS

One hundred two volunteers underwent assessment for sensitivity to tree or grass allergy; 61 met the entrance criteria and were randomly assigned to the treatment groups. Thirty-one were assigned to the desloratadine group, and 30 were assigned to the budesonide group. The demographic data did not show any significant differences between the groups (**Table 1**).

All of these subjects completed the study and were included in the data analysis. The study period began on March 17, 2003, when the first volunteer underwent skin testing. Enrollment began on April 22, 2003, and pro-

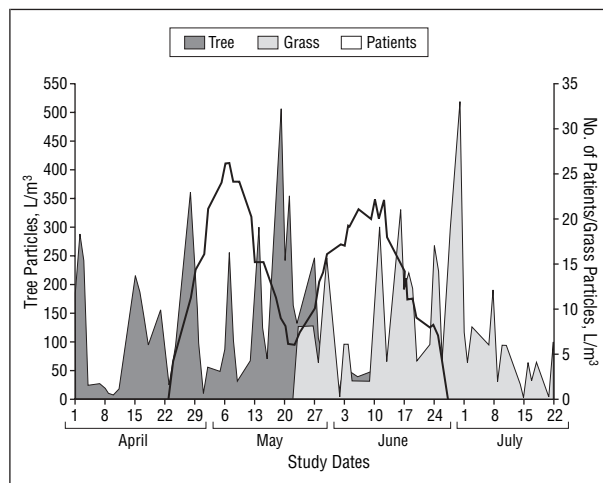


Figure 1. Pollen count and subject enrollment. Study dates are for 2003.

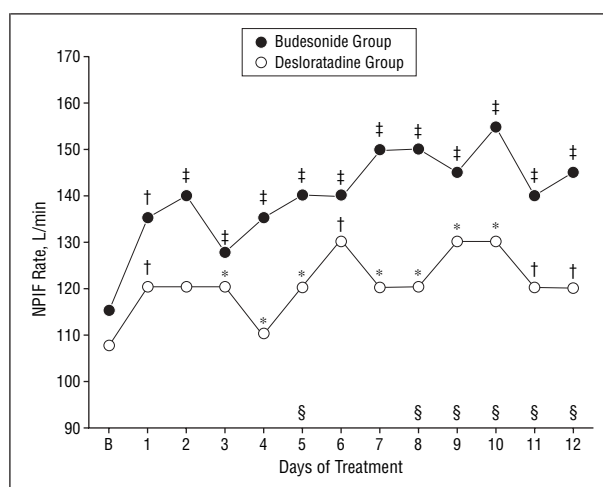


Figure 2. Evening nasal peak inspiratory flow (NPIF). The baseline (B) is the average of the measurements of the 2 pretreatment days. Asterisk indicates $P < .05$, dagger, $P < .01$, and double dagger, $P < .001$ vs respective baselines within treatment arms; section mark, $P < .05$ comparing the 2 drug treatments.

ceeded until 2 weeks before the conclusion of the study on June 26, 2003, on the return of the last volunteer's materials. Tree and grass pollen counts were recorded throughout the study (**Figure 1**).

The primary outcome variable was the NPIF. For the baseline measurements, there was no significant difference between baseline days 1 and 2; therefore, the 2 recordings were averaged ($P \geq .05$). The morning NPIFs from the desloratadine group showed a significant increase from baseline on days 8, 10, and 12, whereas the budesonide group had significant improvements starting on day 1, going through day 12 ($P \leq .05$). The morning NPIF comparison between the treatment groups showed significant differences on days 2, 3, 4, 6, 7, 9, 10, and 11. For the evening NPIFs, the desloratadine group showed significant increases on every day except day 2, and the budesonide group was improved on all the days ($P \leq .05$) (**Figure 2**). The evening NPIF comparison between the 2 groups showed significant differences on day 5 and days 8 through 12, with budesonide showing more improvement than deslorata-

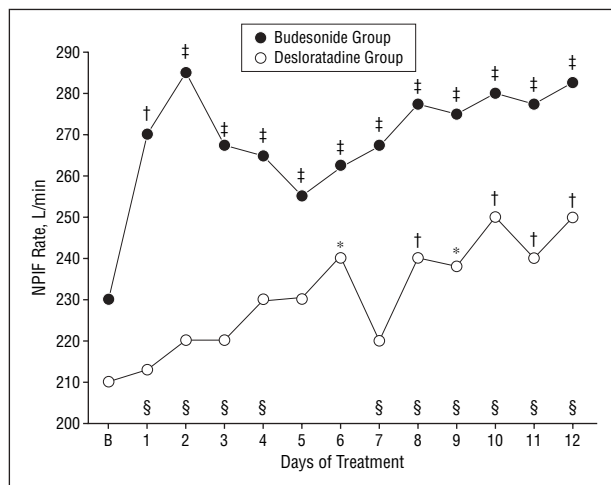


Figure 3. Total nasal peak inspiratory flow (NPIF). Total NPIF represents the sum of the morning and evening measurements of NPIF. Symbols are described in the legend to Figure 2.

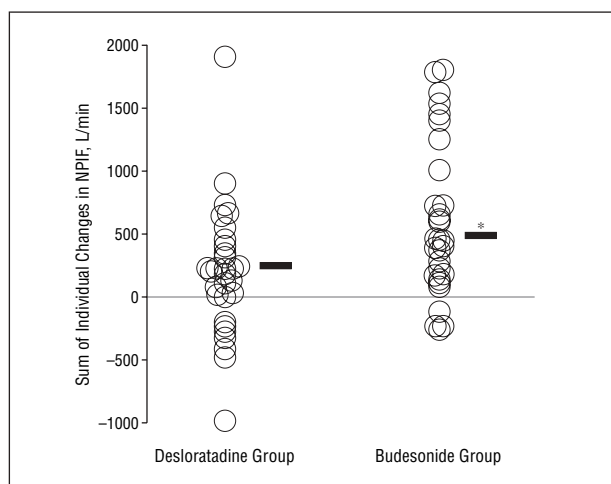


Figure 4. Total change from baseline for nasal peak inspiratory flow (NPIF). For individual changes from baseline for all measurements of NPIF, a negative number represents worsening, and a positive number represents improvement. The individual patients are represented by the circles. The bars represent the medians. Asterisk indicates $P = .01$ vs desloratadine.

dine. The total NPIF values (sum of the morning and evening NPIFs) improved significantly in the desloratadine group on day 6 and days 8 through 12, whereas the budesonide group's total NPIFs had significant increases on all of the treatment days ($P \leq .05$) (**Figure 3**). Comparing the total NPIF between budesonide and desloratadine showed a significant difference on all of the treatment days except days 5 and 6, with budesonide providing more improvement in nasal airflow than desloratadine. The total change over the baseline showed a significantly greater improvement for budesonide than for desloratadine ($P = .01$) (**Figure 4**).

For each domain of the RQLQ, both treatments led to significant improvement. Differences between the treatment groups at the baseline visit and at the second visit were not significant ($P \geq .05$). The change from baseline was not significantly different between the treatment groups ($P \geq .05$). The overall quality-of-life score showed similar results (**Figure 5**). Further, clinically meaning-

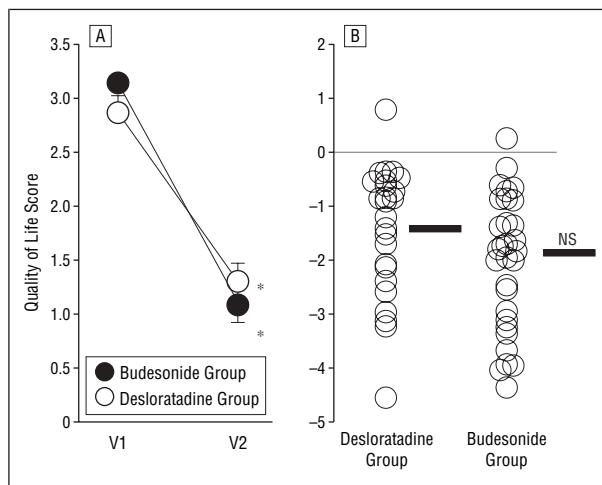


Figure 5. Change in rhinitis quality of life. The overall quality-of-life score calculated from the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is shown. A, Mean $\pm$ SEM for the 2 groups at enrollment (V1) and after 2 weeks of treatment (V2). Larger numbers on the y-axis indicate worse quality of life. Asterisk indicates $P < .05$ vs visit 1. B, Individual changes from baseline for the overall quality-of-life score of the RQLQ. Bars represent the mean, and NS represents a nonsignificant difference between treatments ($P = .27$).

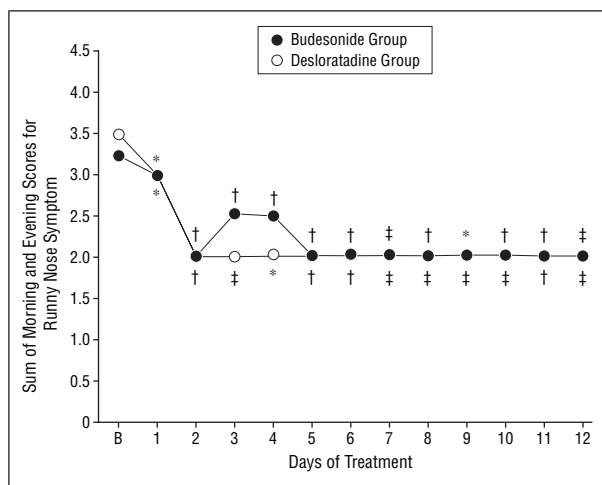


Figure 6. Change in symptom of stuffy nose. Data are presented as medians. Measurement of symptom scores is described in the "Outcome Measures" subsection of the "Methods" section. Baseline (B) is the average of the measurements of the 2 pretreatment days. Asterisk indicates $P < .05$, dagger, $P < .01$, and double dagger, $P < .001$ comparing treatment days vs the average of the baseline measurements.

ful changes, defined as a drop of 0.5 in the overall score, occurred in 28 of the 30 subjects treated with budesonide and 27 of the 31 subjects treated with desloratadine. The average drop in the overall domain was 1.5 for desloratadine and 2.0 for budesonide, both of which were significant and clinically meaningful.

Symptom scores on the treatment days were compared with the baseline days and between treatments. Both groups showed improvement from baseline for the individual and total symptoms, but there were no significant differences between the groups (**Figure 6** and **Figure 7**). **Table 2** shows the total change from the average of the baseline measurements for individual symptoms.

Seasonal allergic rhinitis produces several characteristic symptoms in patients, including sneezing, runny nose, stuffy nose, and itchy eyes and nose. Nasal stuffiness is usually considered the most bothersome symptom. Nasal stuffiness usually becomes more prevalent during the late-phase immune response and later in the allergy season.²⁶ The mechanisms underlying the symptom of stuffiness are considered to be more complex than just histamine release. The cause of nasal stuffiness probably relates to the interaction of multiple mediators released from resident cells within the nasal mucosa and cells trafficking into the nose. This increased mediator release is accompanied by hyperresponsiveness of the nasal mucosa to the mediators.²⁷ Therefore, treatments that antagonize histamine binding and inhibit other immune processes involved in the hypersensitivity reaction should be the most effective in treating nasal stuffiness and improving airflow.

The H₁-blocking antihistamine desloratadine has been shown in several studies to affect some of these processes, in addition to its role as an H₁ receptor antagonist.¹³⁻¹⁷ Unlike other antihistamines, which offer minor relief of nasal stuffiness, this drug has been promoted for treatment of stuffiness.

In our study, the data for the NPIF suggest that, although desloratadine improved NPIF, budesonide improved it to a significantly greater extent. Thus, intranasal corticosteroids like budesonide should remain the preferred treatment for stuffiness associated with seasonal allergic rhinitis.

For the evening NPIF measurements reflective of the past 12 hours, the desloratadine group had significant improvement on nearly all days, including the first. However, when taking into account the morning measurements, one can see from the total NPIF results that a significant improvement takes much longer to develop. A possible reason for this disparity is that the medication was taken in the morning, and so the evening measurement was obtained during higher serum levels of desloratadine compared with the morning measurement, which was obtained almost 24 hours after dosing, suggesting that desloratadine did not improve airflow for 24 hours. Another possibility is the greater level of symptoms reported by subjects with allergic rhinitis in the morning. Budesonide, which has stronger anti-inflammatory effects than desloratadine, including blockage of priming and cellular influx, provides a full 24 hours of efficacy.

The subjective variable of symptom scores, in particular stuffiness, did not show the difference between the 2 groups. Similarly, the RQLQ data showed no significant differences for any points between the 2 treatment groups.

A few possibilities might explain why the desloratadine group improved compared with the budesonide group in symptoms and quality of life, but not NPIF. First, the subjective and objective measures do not always correlate. For example, a patient may still feel stuffy after removal of the inferior turbinates, although measurements of nasal airflow increase dramatically. Second, the

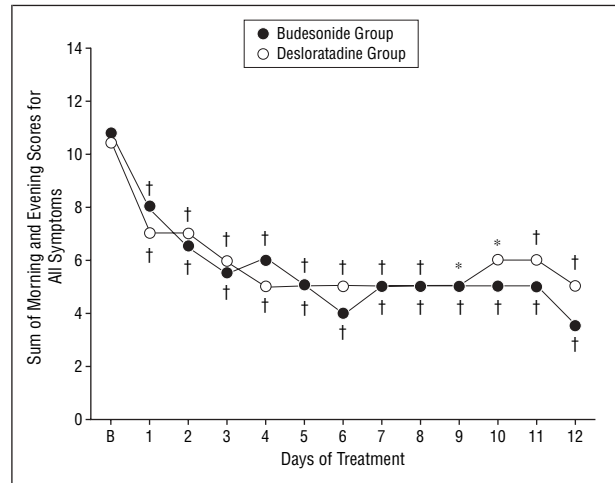


Figure 7. Total symptoms. Baseline (B) is the average of the measurements of the 2 pretreatment days. Measurement of symptom scores is described in the "Outcome Measures" subsection of the "Methods" section. Asterisk indicates $P < .01$, and dagger, $P < .001$, comparing treatment days vs the average of the baseline measurements.

Table 2. Total Individual Symptoms*

Symptom	Treatment Group, Median (Range) of Total Change		P Value
	Desloratadine	Budesonide	
Sneezing	-10 (-48 to 24)	-15.5 (-56 to 25)	.06
Runny nose	-15 (-52 to 32)	-12 (-45 to 9)	.40
Stuffy nose	-12 (-51 to 35)	-13 (-38 to 10)	.80
Itchy eyes/nose	-11 (-50 to 17)	-16.5 (-51 to 18)	>.99

*Symptoms are measured as the sum of morning and evening individual symptoms; median and range are calculated as the total change in scores from the average of the baselines. Measurement of symptom scores is described in the "Outcome Measures" subsection of the "Methods" section.

number of patients enrolled in this study was powered to show a statistical difference in the primary variable, NPIF, whereas symptom scores typically require more subjects to show significant differences between groups, owing to the higher variability compared with that of NPIF. Third, the pollen season was relatively mild, with tree counts going into the moderate range and grass counts remaining light to moderate on most days. Such a season may not have provided an adequate allergen challenge to the subjects to produce a high symptom baseline. Without severe symptoms and an extremely compromised quality of life at the start of treatment, both medications have less room to improve the symptoms and show a difference between them. Fourth, the subjective nature of the variables themselves creates the possibility that patients simply feel that they improve when any medication is taken, without truly considering the degree of improvement. Fifth, the dose of budesonide used in this study was the lowest starting dose, and a higher dose might have shown greater effect in all of the variables studied.

All of these reasons that possibly explain why the subjective variables showed similar results, whereas the objective variable showed a difference, are limitations of the study. These issues should be accounted for in future stud-

ies, such as enrolling more patients to better differentiate between treatment effects, or performing the study at multiple locations to increase the chance that some patients will be exposed to a more severe pollen season. Other limitations include the lack of a placebo arm to see how much of the improvement in the subjective measurements could be secondary to a placebo effect. With more enrollees, a placebo arm could have been incorporated into this 2-week study. However, NPIF, a measure previously shown to correlate with the symptom of nasal airflow obstruction,¹⁰ showed that intranasal corticosteroids are the preferred treatment for seasonal allergic rhinitis.

In conclusion, desloratadine, an H₁-blocking antihistamine, improves airflow in patients with seasonal allergic rhinitis. However, budesonide, an intranasal corticosteroid, improves airflow to a significantly larger extent.

Submitted for Publication: July 13, 2004; final revision received October 5, 2004; accepted November 3, 2004.

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Funding/Support: This study was supported by a grant from the Investigator Sponsored Studies Program of AstraZeneca, Westborough, Mass.

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