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≤.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.

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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.3 Most antihistamines have not been especially effective in treating the symptom of obstructed airflow.2 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-
fектов на производство цитокинов, включая интерлейкин 4 и интерлейкин 13, а также на выработку гистамина и лейкотриенов. Все эти анти-инфамматорные эффекты могут сказываться на симптомах нарушения воздухоносной перегородки.

Интратраханальные стероиды являются средством выбора в большинстве случаев аллергического ринита, вызывающего нарушение воздухоносной перегородки. Мета-анализ, сравнивающий эффекты интратраханальных стероидов и оральных антигистаминов, показал, что стероиды обеспечивают более значительное улучшение симптомов, включая носовые проявления, особенно при бронхоспазме и отеке слизистой оболочки.

В исследовании сравнивался объективный эффект деслоратадина и бudesонида в сезонном исследовании, используя жизнеспособность (NPIF) как основной показатель. Рациональю для этого исследования явилось сравнение объективных эффектов деслоратадина и интратраханального стероида на воздухоносной перегородке, так что врачи могут быть информированы об относительной величине этих двух агентов. Благодаря доказанной эффективности улучшения качества жизни и облегчения носовых симптомов, мы выбрали бudesонид как интратраханальный стероид. Мы сравнили эффекты интратраханального стероида, бudesонида, и деслоратадина в сезонном исследовании, используя NPIF как основной параметр. Цель исследования — сравнить эффективность бudesонида с носовым стероидом, деслоратадина и бudesонида.20 Мы выбрали бudesонид носовой спреем в более высокой степени, чем placebo в дне, и будесонид в интратраханальном стероиде, что позволяет врачам быть информированными о относительной величине этих двух агентов.

Из-за доказанной эффективности улучшения качества жизни и облегчения носовых симптомов, мы выбрали бudesонид как интратраханальный стероид. Day et al21 показали, что бudesонид носовой спрей был более эффективен, чем placebo в дне, и педерсен et al22 показали в сезонном исследовании, что бudesонид был значительно лучше, чем placebo в лечении нескольких носовых симптомов, включая насморк, чихание, и заложенность носа. В дополнение, его эффект на лечение аллергических симптомов, включая заложенность носа, исчезал в течение 7 до 12 часов после начала лечения.22

### METHODS

#### SUBJECTS

Мы набрали пациентов в возрасте от 18 до 45 лет, имеющих клинический анамнез аллергии на деревянные и травяные вещества. Пациенты прошли испытания на чувствительность к деревянным и травяным веществам. Позитивный тест на реакцию на дерматомикоз и носовые симптомы в сезонный период для последних 2 лет были необходимы для участия в исследовании. Пациенты исключены из исследования, если у них были системные стероиды в предыдущие 30 дней, оральные антигистаминовые или деоконгестанты в последние 7 дней, и аллергические антитела или деоконгестанты в последние 24 часа. Мы также исключили индивидуумов, которые использовали долгосрочные анти-аллергические препараты или иммунотерапию в предыдущие 2 года. Женщины были исключены из исследования, если они были беременными или кормили грудью. Все пациенты прошли урологическую пробу, и только те, которые оставались без симптомов, были включены в исследование. Если у пациентов были симптомы, они получали препараты, медроциклид и оральный антигистамин.25 Мы выбрали деслоратадин как антагонист аллергии, принимая во внимание его качество жизни, и его выраженные анти-инфамматорные свойства, мы выбрали бudesонид как интратраханальный стероид. Day et al22 показали, что бudesонид носовой спрей был более эффективен, чем placebo в дне, и pedersen et al22 показали в сезонном исследовании, что бudesонид был значительно лучше, чем placebo в лечении нескольких носовых симптомов, включая насморк, чихание, и заложенность носа. В дополнение, его эффект на лечение аллергических симптомов, включая заложенность носа, исчезал в течение 7 до 12 часов после начала лечения.22

#### STUDY DESIGN

Мы организовали 2-недельное, рандомизированное, двойное-слепое, двойное-дummies, параллельное клиническое исследование, сравнивающее эффекты деслоратадина (Clarinex; Schering Corp, Kennilworth, NJ) и бudesонида (Rhinocort Aqua; AxtraZeneca, Westborough, Mass) на симптомы, качество жизни, и NPIF во время сезона аллергии в Чикаго. Пациенты должны были быть симптоматичными в течение всей недели. После набора в исследование, пациенты получали их препараты. Если у пациентов не было симптомов, они получали препараты, медроциклид и оральный антигистамин.25 Мы выбрали деслоратадин как антагонист аллергии, принимая во внимание его качество жизни, и его выраженные анти-инфамматорные свойства, мы выбрали бudesонид как интратраханальный стероид. Day et al22 показали, что бudesонид носовой спрей был более эффективен, чем placebo в дне, и pedersen et al22 показали в сезонном исследовании, что бudesонид был значительно лучше, чем placebo в лечении нескольких носовых симптомов, включая насморк, чихание, и заложенность носа. В дополнение, его эффект на лечение аллергических симптомов, включая заложенность носа, исчезал в течение 7 до 12 часов после начала лечения.22

#### OUTCOME MEASURES

**Rhinocconjunctivitis Quality of Life Questionnaire**

RQLQ включает 7 доменов, которые включают активность, сон, и нос/другое, практические, аллергические, и эмоциональные проблемы. Было несколько вопросов в каждом домене, и пациенты рейтинг их симптомов на шкале от 0 до 6, с 6 представляя худшее качество жизни. Общий показатель качества жизни был рассчитан путем оценки 7 индивидуальных доменов.24

**Peak Flow**

An In-Check peak и инспираторный флюметр (Ferraris Medical, Inc, Louisville, Colo) использовались для измерения пиковых значений NPIF в литрах в минуту.26 У пациентов был дан список измерений и результаты были записаны в каждый временной отрезок.

**Symptom Diary**

Симптомы были включены на шкале от 0 до 3, с 0 означающим отсутствие симптомов и 3 означающим сильные симптомы. Симптомы включали чихание, насморк, зудящий нос, и зудящие глаза/нос. Каждый регистр симптомов отражался на времени после последней записи. Для утренних записей, пациенты записывали симптомы перед началом дня, и для вечерних записей, пациенты записывали симптомы после окончания дня.22

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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 4 symptoms were also compared between the treatment arms by use of a nonpaired t test. The Mann-Whitney test was used for comparing these changes from baseline for each day of treatment within each treatment group. Wilcoxon signed rank test was used to analyze the change from baseline on days 8, 10, and 12, whereas the budesonide 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<.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<.05) (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=.05). The morning NPIFs from the desloratadine group showed a significant increase from baseline 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<.01) (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-
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 \((P = .27)\). The change from baseline was not significantly different between the treatment groups \((P = .05)\). The overall quality-of-life score showed similar results \((P = .01)\) (Figure 5). Further, clinically meaningful 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. 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. 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. 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 blocking 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 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,\(^1\) showed that intranasal corticosteroids are the preferred treatment for seasonal allergic rhinitis.

In conclusion, desloratadine, an H\(_1\)-blocking antihista

H\(_1\)-blocking antihistamine, improves airflow in patients with seasonal allergic rhinitis. However, budesonide, an intranasal corticosteroid, improves airflow to a significantly larger extent.

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