Superiority of an Intranasal Corticosteroid Compared With an Oral Antihistamine in the As-Needed Treatment of Seasonal Allergic Rhinitis

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Background: The daily use of either intranasal corticosteroids or histamine1 (H1) receptor antagonists has proved to be efficacious in the treatment of seasonal allergic rhinitis. Most patients, however, use these medications as needed. Our objective was to compare the effectiveness of as-needed use of H1 receptor antagonists with that of intranasal corticosteroids in the treatment of seasonal allergic rhinitis.

Methods: We performed a randomized, open-label, parallel-group study comparing the as-needed use of an H1 receptor antagonist (loratadine) with that of an intranasal corticosteroid (fluticasone propionate) in the management of fall seasonal allergic rhinitis in the fall of 1999. Subjects kept a diary of their daily symptoms and were examined at enrollment into the study and biweekly for 4 weeks during treatment. Outcome measures were the Rhinoconjunctivitis Quality of Life Questionnaire score, daily symptom diary scores, and the number of eosinophils and the levels of eosinophilic cationic protein in nasal lavage samples.

Results: Patients in the fluticasone-treated group reported significantly better scores in the activity, sleep, practical, nasal, and overall domains (P < .05) of the Rhinoconjunctivitis Quality of Life Questionnaire. The median total symptom score in the fluticasone-treated group was significantly lower than that in the loratadine-treated group (4.0 vs 7.0; P < .01). After treatment, the number of eosinophils was significantly smaller in the fluticasone-treated group compared with the loratadine-treated group (P = .001). Eosinophilic cationic protein levels followed the same pattern, with a significant correlation between the levels of eosinophilic cationic protein and the number of eosinophils (r = 0.70, P < .01).

Conclusion: As-needed intranasal corticosteroids reduce allergic inflammation and are more effective than as-needed H1 receptor antagonists in the treatment of seasonal allergic rhinitis.

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Allergic rhinitis affects about 20% of the US population, sparing no age group.1 It has a negative impact on the quality of life, and billions of dollars are spent annually on the treatment of this disease and its associated conditions. Furthermore, its incidence is increasing, and this will increase health care expenditures.2 The treatment of this common ailment, therefore, is increasingly being subjected to guidelines, some of which are evidence based.3,4

The typical guidelines recommend the use of histamine1 (H1) receptor antagonists as the first-line treatment of mild disease, whereas more severe disease is usually treated with daily intranasal corticosteroids.3,4 The rationale for these recommendations is that H1 receptor antagonists have a rapid onset of action (within hours) and are, thus, suitable for as-needed treatment when the patient is seeking immediate relief of symptoms. Fluticasone propionate nasal spray (Flonase), an intranasal corticosteroid, has an onset of action within 12 hours and a peak effect that occurs after several days.5 We questioned the logic of these guidelines based on our understanding of the pathophysiological features of seasonal allergic rhinitis.

Allergic individuals challenged with an appropriate allergen in the laboratory react within minutes with an early response, characterized by mast cell degranulation, histamine release, and typical symptoms of sneezing, rhinorrhea, and congestion.1 This early response is followed hours later by a cellular influx, including eosinophils, and an increase in nasal reactivity to further antigen exposure, called priming. The late response, with congestion as the primary symptom, is less dramatic than the early reaction. Although histamine is increased during the late reaction, its role is not clearly defined. Antihistamines have not been shown...
SUBJECTS AND METHODS

STUDY DESIGN

We performed a randomized, open-label, parallel-group study. We recruited 88 individuals with fall seasonal allergic rhinitis who were older than 18 years. All subjects had a history of rhinitis during at least the last 2 ragweed seasons in Chicago, Ill, and a positive puncture skin test result to ragweed antigen extract. The subjects were in good health except for a few who had mild asthma. Patients were excluded if they had symptoms or physical signs suggestive of renal, hepatic, or cardiovascular disease; nasal polyps; a displaced septum; or perennial rhinitis. Furthermore, patients who had used topical or systemic corticosteroids, antihistamines, decongestants, or cromolyn sodium in the preceding 2 weeks or who underwent immunotherapy in the past 2 years were excluded. Pregnant or lactating women were not permitted to join the study. Enrollment occurred before and during the ragweed pollen season. Written informed consent was obtained from all participants, and the Institutional Review Board of the University of Chicago, Chicago, approved the study.

During their first visit to the nasal physiology laboratory, patients completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), which is a validated quality-of-life measure for patients with allergic rhinitis. Subjects also had their nose lavaged with 10 mL of lactated Ringer solution. We used the lavage sample to obtain a total eosinophil count and to measure the level of eosinophil cationic protein (ECP). Each subject was given either treatment and instructed in its use. Patients who enrolled before August 15th were instructed not to begin treatment or begin their diaries until that date. Fluticasone aqueous nasal spray (Flonase), an intranasal corticosteroid, and loratadine (Claritin), an H1 receptor antagonist, were chosen because they are the market leaders in their respective categories.

The subjects were randomized in balanced blocks of 4 to receive fluticasone propionate nasal spray (100 µg/d per nostril) or a loratadine tablet (10 mg/d) as needed for 4 weeks during the ragweed season. If the patients had bothersome nasal symptoms, they were instructed to use two 50-µg sprays in each nostril in the fluticasone-treated group or to take 1 tablet (10 mg) in the loratadine-treated group, not more frequently than once a day. If the patients continued to have significant problems, they were asked to see one of the participating physicians (F.M.B. or R.M.N.). No rescue medications were allowed. Patients kept a daily symptom and medication diary during the season in which they recorded the severity, over 12 hours, of episodes of sneezing, rhinorrhea, itchy eyes, and nasal congestion and medication use. The subjects returned in another 2 weeks and underwent a nasal lavage and completed the RQLQ. Diaries were collected and new ones issued. The patients continued in the study and returned in 2 weeks for a final visit, in which the nose was lavaged, an RQLQ was completed, and medications and diary cards were collected.

POLLEN COUNTS

Ragweed pollen counts for the Chicago area during the study were recorded by the Grant Hospital Pulmonary Physiology Laboratory by use of the Rotorod method.

NASAL LAVAGE SAMPLES

Five milliliters of warmed (37°C) lactated Ringer solution was instilled into each nostril and, after 10 seconds, the subjects expelled the lavage fluid into a plastic collection vessel. All samples were first vigorously shaken for homogenization of the mixture of sol and gel phases and were stored on ice in plastic tubes until cell counts were performed. After the total cell count was obtained, the samples were centrifuged at 5000g for 15 minutes at 4°C. Aliquots for ECP determination were stored at −20°C until assayed.

EOSINOPHIL QUANTIFICATION IN NASAL LAVAGE FLUIDS

Total counts of eosinophils recovered from lavage samples were performed by use of a modification of a previously to reduce eosinophil influx into the nasal mucosa, block priming, or reduce symptoms of the late reaction. In contrast, intranasal corticosteroids have profound inhibitory effects on the late response.

We reasoned that those allergic individuals who use medications as needed would treat themselves after sensing an early reaction. Taking an antihistamine at this point would not affect the symptoms of the immediate response, because the symptoms dissipate within minutes and antihistamines do not affect the late response. In essence, the antihistamine would be effective against the sneezing and rhinorrhea associated with the next immediate response to antigen exposure, provided the drug is present at therapeutic levels at that time. The effectiveness of antihistamines when given before a nasal challenge with antigen has been shown repeatedly. The antihistamine, however, would not prevent allergic inflammation and priming from developing. Thus, as the season progressed, the immediate symptoms in response to further antigen exposure would increase.

An intranasal corticosteroid, taken after sensing the symptoms of an immediate response, would be expected to block eosinophil infiltration and priming, as Anderson and colleagues demonstrated in the laboratory. The intranasal corticosteroid would also be expected to reduce any contribution of the symptoms of the late reaction to clinical disease, such as congestion. We also speculated that, as the season progresses, priming would not occur, and the symptoms experienced by patients on repeated pollen exposure would be less severe and last for a shorter interval as the pollen counts dissipated. Therefore, we hypothesized that the as-needed use of intranasal corticosteroids would reduce allergic inflammation and provide superior symptom relief compared with the as-needed use of an antihistamine.

As a first step toward testing the stated hypothesis, a parallel, placebo-controlled, randomized study to test whether symptoms of patients with seasonal allergic rhinitis are reduced by treatment with as-needed intranasal corticosteroids vs placebo was performed. The re-
described method. If sufficient cells were present on a slide, 200 cells were counted and a differential count was obtained. When 200 cells could not be counted, as many cells as possible were examined for differential determination. If the total number of cells available for differential estimation was less than 50, the slide was considered technically inadequate for interpretation, and no value was available for analysis. If the slide had a sufficient number of cells to be examined, but no eosinophils were counted among these cells, then 50 was assigned as the number of eosinophils because this was the lowest number of eosinophils obtained among all the technically adequate specimens.

EOSINOPHILIC CATIONIC PROTEIN

Eosinophil cationic protein, a marker of eosinophil secretion, was measured by a commercially available double-antibody radioimmunoassay (Pharmacia AB, Uppsala, Sweden). The assay has a sensitivity detection limit of 2 µg/L. Values lower than the detection limit were arbitrarily assigned a value of 1 µg/L.

SYMPTOM DIARIES

Each subject recorded symptom scores in a diary twice daily. Subjects reported itchy eyes and 3 symptoms for each nostril (rhinorrhea, nasal congestion, and sneezing) on a scale from 0 to 3 (0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms). Symptom scores were evaluated separately for each symptom category, and the total symptom score (the sum of individual symptoms) was also evaluated.

QUALITY-OF-LIFE ASSESSMENT

Quality of life was assessed with the self-administered RQLQ as described and validated by Juniper and Guyatt. In brief, the RQLQ has 7 domains: sleep, non–nasal/eye, practical, nasal, eye, emotional, and activity. The average score for each domain was computed and used for data analysis. The overall quality of life is determined as the average of the 7 domains on the RQLQ. Higher scores indicate a worse quality of life.

STATISTICAL ANALYSIS

Because the data were not normally distributed, nonparametric statistics were used for analysis. The primary variable analyzed was the RQLQ score. The number of subjects to be enrolled was arrived at from a power calculation based on the results of a previous study comparing as-needed fluticasone with as-needed isotonic sodium chloride solution. We chose the global score for the RQLQ as the primary variable because it had the smallest SD. Because Juniper and Guyatt define a 0.5 shift as clinically significant in the RQLQ, we chose this level of difference for our power calculation. Assuming a value of P<.05, a difference of 0.5 in the overall score, and a population SD of 0.8, having 40 completed patients in each group would have 80% power of detecting a difference. We assumed a 10% dropout rate.

The secondary variables were the symptom diary scores, ECP levels, total eosinophil counts, and individual symptom scores. The median total daily symptom scores were calculated by addition of the individual scores. The difference between the intranasal corticosteroid– and the H₁ receptor antagonist–treated groups was analyzed for each day of the study by a Mann-Whitney test. The median total symptom score for all 28 days of treatment was also calculated and compared between the treatment groups by use of the Mann-Whitney test. Other symptoms were analyzed similarly. When different points within a group were analyzed, and if repeated measures were being considered (eg, total eosinophils on 3 visits for the same treatment group), a Friedman analysis of variance was first performed. If significant changes were detected, a post hoc analysis was performed by use of the Wilcoxon signed rank test. Data are presented as the median and range or the median with 25th and 75th percentiles as error bars. Correlation was performed using the Spearman rank test. A 2-tailed P<.05 was considered to indicate significance.

RESULTS

The ragweed counts for the 1999 season were typical for the Chicago area (Figure 1). The number of subjects enrolled in the study on a particular day is superimposed on this figure. Most subjects were recruited before or during the beginning of the season, with all subjects being recruited before peak pollen counts occurred. Eighty-eight subjects were enrolled into the study.

There were 44 subjects randomized to each arm of the study, and, because randomization was blocked in groups of 4, the number of subjects enrolled at any point was divided equally between intranasal corticosteroid and H₁ receptor antagonist treatments. The groups were matched for age, sex, race, and skin test sensitivity (Table 1). Two patients from each treatment group dropped out before completing the protocol. One patient moved away from Chicago, and 3 were noncompliant with respect to returning for their appointments.

During the 28 days in which subjects were allowed to take their medication, the intranasal corticosteroid–treated group used medicine on 17.0 (3–28) days, and the H₁ receptor antagonist–treated group used medicine on 18.0 (5–28) days. The correlation between symptoms and medication use for each individual patient was rₛ = 0.34 (−0.44 to 0.82) for fluticasone and rₛ = 0.39 (−0.26 to 0.79) for loratadine. The overall correlation for all subjects was rₛ = 0.41 (P<.001) in the fluticasone-treated group and rₛ = 0.46 (P<.001) in the loratadine-treated group.

The RQLQ scores were similar between groups at enrollment into the study. The intranasal corticosteroid–treated group had significant improvement on the second and third visits in the activity, sleep, practical, nau-
sal, and overall domains (P < .05) (Figure 2). Eye symptoms were better in the intranasal corticosteroid–treated group than in the loratadine-treated group during the second visit.

Total symptoms were similar at enrollment into the study. We analyzed the score based on the day of enrollment, instead of the calendar day; this permitted ease of matching. Significant differences between the intranasal corticosteroid– and the H1 receptor antagonist–treated groups in total symptom scores started to be evident after 5 days of enrollment and remained significantly different at most points until the 28th day (Figure 3). The median score for the H1 receptor antagonist–treated group during the 28-day duration of the study was 7.0, whereas the score for the intranasal corticosteroid–treated group was 4.0, the difference being highly significant (P = .005). The results for the individual symptoms were similar, with the intranasal corticosteroid–treated group reporting fewer symptoms than the H1 receptor antagonist–treated group (Table 2).

The number of eosinophils and the level of ECP were not different between the groups at enrollment. The fluticasone-treated subjects had fewer eosinophils during visit 3 compared with visit 1 (P = .001) and during visit 2 compared with visit 1 (P = .005). The data from the subjects receiving the H1 receptor antagonist showed that the subjects in this group had an increase in eosinophils during visit 3 compared with visit 1 (P = .02) and during visit 2 compared with visit 1 (P = .002). When a comparison of the number of total eosinophils was performed at each visit between the 2 treatment groups, the group receiving fluticasone propionate nasal spray had significantly fewer eosinophils during the second (P = .004) and third (P = .001) visits compared with the H1 receptor antagonist–treated group (Figure 4). The ECP levels followed the same pattern, with significant decreases in the intranasal corticosteroid–treated group and significant increases in the H1 receptor antagonist–treated group (Figure 5). There was a significant correlation between the levels of ECP and the number of eosinophils (r = 0.70, P < .01).

Although instructed to use intranasal corticosteroids or antihistamines daily, most patients are probably not compliant. The as-needed use of these agents has been studied to a limited extent. Juniper and colleagues compared regular with as-needed use of intranasal corticosteroids and found regular use to be superior. In a more recent study in which a quality-of-life questionnaire was used, the differences between as-needed and regular use were statistically significant, but the researchers found that the degree of improvement with regular use was not clinically significant compared with as-needed use. Another previous study showed that the as-needed use of intranasal corticosteroids is more effective than placebo in the treatment of seasonal allergic rhinitis. To our knowledge, the present study is the first to demonstrate the superiority of as-needed intranasal corticosteroid use compared with as-needed H1 receptor antagonist use.

We used multiple subjective and objective outcome variables to support our conclusion. The difference in the RQLQ scores between the intranasal corticosteroid– and H1 receptor antagonist–treated groups suggests not only statistical differences but clinical significance as well. Furthermore, the subjects’ responses were supported by the measures of eosinophil counts and the ECP levels. These provide an objective measure and a pathophysiological explanation for our results.

Whereas a double-blind double-dummy study might have been more elegant, we doubt that the results would have differed. The lack of availability of placebo loratadine tablets or data on the pharmacokinetics of the dissolution of loratadine from opaque capsules precluded that approach. Thus, our study was more like real life in that each subject was given a medication and instructed in its use. Because patients knew after randomization which treatment they were receiving, individual biases could have affected their responses. Our impression, however, was that biases were equally likely to favor either treatment, because both are heavily advertised directly to consumers. The consistency of the results strengthens our observations. Also, the use of blindly assessed objective measures reinforces our findings.

There was a low dropout rate in both groups and no difference between them, even though we did not pro-
vide any rescue medication. The absence of rescue medication in our study design made the analysis simpler and the results more clear-cut.

We reasoned that patients would elect to take their medication after the antigen caused symptoms. In absence, patients chose to medicate after the immediate reaction and before eosinophil infiltration and changes in reactivity occurred. Thus, as the season progressed, subjects receiving fluticasone propionate nasal spray did not have an eosinophil infiltration or an increase in their reactivity to antigen and, subsequently, had fewer symptoms and a better quality of life on exposure to antigen. In contrast, the use of H1 receptor antagonist did not block eosinophil infiltration and priming and, therefore, the patients reported more symptoms and a worse quality of life as the season progressed. The data we collected support this hypothesis.

The study supports the concept of the pathophysiological features of allergic rhinitis as elucidated through nasal provocation studies. Our study emphasizes the rela-

Figure 2. The individual domains for the Rhinoconjunctivitis Quality of Life Questionnaire (A, activity; B, sleep; C, non–nasal/eye; D, practical; E, nasal; F, eye; G, emotional; and H, overall). Median responses and 25th and 75th percentiles at each visit are shown for the 2 treatment groups. The asterisk indicates \( P < 0.01 \) vs the loratadine-treated group; the dagger, \( P < 0.05 \) vs the loratadine-treated group.

Figure 3. Median total symptom scores and 25th and 75th percentiles are shown for the 2 treatment groups for the duration of the study. The asterisk indicates \( P < 0.05 \) vs the loratadine-treated group; the dagger, \( P < 0.01 \) vs the loratadine-treated group.
we predict a benefit if H1 receptor antagonists were given before exposure, such as before going golfing or visiting a friend with a pet, or during an environmental chamber antigen exposure. However, we question the efficacy of intermittent use of H1 receptor antagonists when taken after exposure and the benefit of this class when used in an as-needed fashion as rescue therapy in clinical trials.

The major message from our study relates to guidelines for treating seasonal allergic rhinitis. Our data support the efficacy of fluticasone propionate nasal spray in the treatment of seasonal allergic rhinitis and the superiority of its as-needed use compared with that of an as-needed H1 receptor antagonist. Weiner and colleagues18 reached a similar conclusion when they performed a meta-analysis comparing the regular use of intranasal corticosteroids with that of H1 receptor antagonist. Thus, it would seem logical to use intranasal corticosteroids as first-line treatment for seasonal allergic rhinitis. The medication would be recommended for regular use in patients with severe disease and for as-needed use in patients with mild disease. This recommendation is not the prescribing trend, as suggested by the observation that H3 receptor antagonists outsell intranasal corticosteroids 3 to 1. In addition, a 30-day supply of nonsedating H1 receptor antagonists costs more than a 30-day supply of intranasal corticosteroids.19 The reduced cost and superior efficacy of either continuous or as-needed use of intranasal corticosteroids compared with nonsedating H1 receptor antagonist suggests that the cost-benefit ratio favors intranasal corticosteroids. A change in guidelines would benefit more patients and reduce health care costs.

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