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.34

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.34 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...
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-
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 was 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 \( r_s = 0.34 (0.44 to 0.82) \) for fluticasone and \( r_s = 0.39 (0.26 to 0.79) \) for loratadine. The overall correlation for all subjects was \( r_s = 0.41 (P<.001) \) in the fluticasone-treated group and \( r_s = 0.46 (P<.001) \) in the loratadinetreated 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, na-
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 colleagues12 compared regular with as-needed use of intranasal corticosteroids and found regular use to be superior. In a more recent study13 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 study13 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.11 Furthermore, the subjects’ responses were supported by the measures of eosinophil counts and the ECP levels. These provide an objective measure and a pathophysiologic 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-

![Figure 1. Ragweed counts and number of subjects enrolled for the duration of the study. The x-axis represents various days during the ragweed season, and the y-axes represent the number of subjects enrolled on each day (closed circles) and the ragweed counts on those days (shaded area). Levels of ragweed less than 40 grains per cubic millimeter are considered low.](image-url)
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 essence, 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 relevance of these findings in clinical practice.

Figure 2. The individual domains for the Rhinocconjunctivitis 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 $P<.01$ vs the loratadine-treated group; the dagger, $P<.05$ 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 $P<.05$ vs the loratadine-treated group; the dagger, $P<.01$ vs the loratadine-treated group.
There have been numerous clinical trials demonstrating the efficacy and success of H<sub>1</sub> receptor antagonist in the treatment of seasonal allergic rhinitis. However, in these studies, H<sub>1</sub> receptor antagonist were used continually and, thus, the medication was in essence given prophylactically. When antihistamines are given in this manner, our concept of the pathophysiological features of allergic rhinitis would predict a benefit. Likewise, we would predict a benefit if H<sub>1</sub> 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 H<sub>1</sub> 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 H<sub>1</sub> receptor antagonist. Weiner and colleagues reached a similar conclusion when they performed a meta-analysis comparing the regular use of intranasal corticosteroids with that of H<sub>1</sub> 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 H<sub>1</sub> receptor antagonists outsell intranasal corticosteroids 3 to 1. In addition, a 30-day supply of non-sedating H<sub>1</sub> receptor antagonists costs more than a 30-day supply of intranasal corticosteroids. The reduced cost and superior efficacy of either continuous or as-needed use of intranasal corticosteroids compared with non-sedating H<sub>1</sub> 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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Table 2. Individual Nasal Symptoms*

<table>
<thead>
<tr>
<th>Nasal Symptoms</th>
<th>Fluticasone Propionate-Treated Group</th>
<th>Loratadine-Treated Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezing</td>
<td>0 (0-1.5)</td>
<td>1 (0-2)</td>
<td>.009</td>
</tr>
<tr>
<td>Runny nose</td>
<td>0 (0-2)</td>
<td>1 (0-3)</td>
<td>.02</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Data are given as the median (range). The medians of median total symptom scores during the 28 days of treatment with either loratadine or fluticasone are presented.
REFERENCES