Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis

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Fluticasone propionate (FP) is a topical corticosteroid with minimal systemic activity. We examined safety and compared the efficacy of FP aqueous nasal spray, 200 μg every day with loratadine tablets, 10 mg by mouth every day in 240 adolescents with ragweed pollen–induced seasonal allergic rhinitis for 4 weeks in a randomized, double-blind, parallel-group study. Nasal and eye symptoms were recorded daily on a 4-point (0 to 3) scale. A higher percentage of symptom-free days was observed for nasal blockage on waking during treatment with FP ($p < 0.0001$). Significant results were also obtained for all other nasal symptoms when analyzed for both symptom-free days and symptom scores. No differences were found for eye irritation symptoms ($p = 0.14$). Morning and evening nasal peak inspiratory flow (PIF) was recorded daily by 57 subjects. FP treatment was associated with significantly higher PIF values than loratadine both morning ($p = 0.0051$) and evening ($p = 0.0036$). A greater improvement over 4 weeks was observed for PIF morning values in the FP group ($p = 0.008$) but not for evening values ($p = 0.358$). Statistically significant correlations were found for nasal blockage and PIF in the morning ($r = -0.54$, $p = 0.0001$) and in the evening ($r = -0.46$, $p = 0.008$). (J ALLERGY CLIN IMMUNOL 1996;97:588-95.)

Key words: *Fluticasone propionate, loratadine, intranasal corticosteroid, antihistamine, nasal peak inspiratory flow, seasonal allergic rhinitis*

Allergic rhinitis is the most common allergic disease, with an estimated prevalence of 10% to 15%. Changes in nasal mucosal vasculature and secretory cell function contribute to nasal symptoms. A large number of inflammatory cells, especially eosinophils, are present in the inflamed nasal mucosa, and some 50 different chemical mediators have now been identified either in the mucosa or in the nasal lavage fluid. The involvement of many mediators may explain limitations of therapeutic agents that inhibit only one mediator.

Abbreviations used
FP: Fluticasone propionate
PIF: Peak inspiratory flow

Topical intranasal corticosteroids have proven highly effective for the treatment of allergic rhinitis.[1, 2] The inhibition of the influx of inflammatory cells, a major source of cytokines and mediators, probably explains the efficacy of this treatment.[3, 4] Fluticasone propionate (FP) is a new, highly active topical corticosteroid. FP has been developed to provide a high ratio of local antiinflammatory to systemic activity. Studies in volunteers have demonstrated a skin vasoconstrictor potency approximately twice that of beclomethasone dipropionate.[5] Systemic bioavailability of FP is extremely low because of an extensive first-pass clearance by

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the liver. Pharmacokinetic studies in human beings have shown that morning plasma cortisol and 24-hour urinary cortisol excretion are unaffected by oral doses as high as 16 mg daily.[6] Intranasal administrations of 2 mg twice a day for 7 days failed to change morning plasma cortisol concentrations.[6]

A dose tolerance study has shown that even at the highest intranasal dose studied, 1600 μg/day for a period of 4 weeks, no hypothalamo-pituitary-adrenocortical–axis suppression was observed.[7] The excellent safety profile of FP has been supported in several studies.[8] FP aqueous nasal spray at a dose of 200 μg administered once a day has proven effective, with a good safety profile, in controlling nasal symptoms in patients with allergic rhinitis.[8]

Antihistamines are widely used in the treatment of allergic rhinitis.[9] Loratadine is a new, long-acting, selective H_1-receptor antagonist with minimal sedative and anticholinergic side effects. This study was conducted to examine safety and compare efficacy of FP aqueous spray, administered once daily, with loratadine tablets administered once daily in adolescent patients with moderate to severe ragweed-induced seasonal allergic rhinitis.

METHODS

Study population

Two hundred and fifty-seven patients between the ages of 12 and 17 years with a history of moderate to severe ragweed-induced seasonal allergic rhinitis entered the trial. Allergy to ragweed was confirmed with a ragweed extract skin prick test showing a wheal and flare response with a wheal at least 3 mm in diameter greater than the buffer control. Subjects were excluded if they had concurrent perennial rhinitis or if they had taken the following drugs: long-acting histamine antagonists within the past 6 weeks; inhaled, intranasal, or systemic corticosteroids or inhaled sodium cromoglycate within the past 4 weeks; or loratadine or another over-the-counter antihistamine within the last week. Subjects were also excluded if they had received any other therapy for their rhinitis or if they had clinical evidence of infection of the paranasal sinuses and/or of the upper or lower respiratory tract. Other exclusion criteria included nasal surgery within the past year, structural nasal abnormalities or concurrent disease that could interfere with the validity of the study results. Patients were also excluded if they were pregnant, lactating, or were not using reliable contraceptive measures.

Study medications

Subjects received either FP aqueous nasal spray (50 μg per actuation) 200 μg daily or loratadine tablets, 10 mg daily, throughout the 4-week treatment period. Subjects were also given rescue medications in the form of terfenadine (60 mg), a naphazoline and pheniramine combination eye drops, and the bronchodilator salbutamol to be used when required. No other medication for rhinitis was permitted during the trial.

Study design

This multicenter, randomized, double-blind, parallel-group study was conducted during the ragweed season at five allergy clinics located in southern Ontario. The study protocol was approved by the local ethics committee at each participating center, and informed consent was obtained before inclusion of patients in the study. All subjects attended the clinics on five occasions: a pretrial visit up to 1 month before the allergy season to establish eligibility, a pretreatment visit 1 week after the start of the allergy season to reassess patient eligibility and randomization, after 2 and 4 weeks of treatment, and 2 weeks after completion of the study.

Subjects were randomly assigned to receive either FP aqueous nasal spray, 200 μg plus placebo oral tablet, once daily each morning or placebo aqueous nasal spray and loratadine oral tablet, 10 mg, once daily each morning for the duration of the treatment period. Subjects were randomized as a cohort; all were began receiving medication during a 5-day period. Centers documented local daily pollen counts from August 1 to September 30.

On admission to the trial and after 4 weeks of treatment, a complete physical examination, clinical history, laboratory tests, and rhinoscopy were performed. The rhinoscopy was performed to detect a mechanical abnormality or possible adverse effect of treatment.

Subjects were issued diary cards on which to record the severity of five symptoms: (1) nasal blockage on awakening, recorded in the morning; (2) nasal blockage for the rest of the day; (3) sneezing; (4) nasal itch; and (5) eye watering or irritation for the whole day, recorded in the evening. Symptoms were assessed daily on a 4-point scale, ranging from absent (0) to severe (3).

Fifty-seven subjects from one center, after initial training in taking nasal peak inspiratory flow (PIF) measurements with a Youlten portable PIF meter, provided diary card data for morning and evening nasal PIF. Morning PIF measurements were taken immediately on awakening before any medication was taken and in the evening at the time of daily completion of the diary cards.

The primary efficacy assessment was the percentage of symptom-free days (score of 0) for nasal blockage during the day. Throughout the trial period, the subjects were also asked to keep a daily record of all medications taken and any side effects or problems they experienced.

Three population samples were analyzed: an "intent-to-treat" population, comprising all subjects receiving treatment; a "per-protocol" sample, which included only subjects that followed the protocol closely (n = 200);

TABLE I. Study populations

	No. of subjects	Group	
		FP	Loratadine
Total recruited	257	NA	NA
Total randomized	242	NA	NA
Intent to treat	240	121	119
Per protocol	200	107	93
Testing for PIF	57	29	28

NA, Not applicable.

and a sample of all subjects randomized, excluding data recorded during the time that pollen counts were observed to decline. Results were similar for all three samples. The results of primary interest, reported here, are the analysis of data for the intent-to-treat population stratified by center (Table I). Data were used for those days for which there were valid diary entries.

Statistical analysis

Each symptom recorded on the diary card was analyzed separately to determine the percentage of symptom-free days, the mean symptom score, and the median symptom score. The percentage of symptom-free days and median symptom scores was summarized by using the interquartile range (Q3-Q1) percentile as a measurement of dispersion. Results were analyzed with the Wilcoxon rank sum test and the van Elteran test, which stratifies by center for the percentage of symptom-free days and median symptom scores. Mean symptom scores were analyzed by analysis of variance with and without center in the model.

The use of rescue medication was summarized for each patient by calculating the mean number of doses over 28 days of each medication and the percentage of days when no rescue medication was used. Each of these responses was analyzed with the Wilcoxon rank sum test and the van Elteran method.

Nasal PIF data were summarized by taking the mean of the subjects' three morning measurements and the mean of the three evening measurements and averaging these means over the treatment period. Results were analyzed by using unpaired Student's t test. Pearson's correlation coefficient was used to examine the relationship between symptom scores and PIF measurements in the first week of treatment. Additionally, repeated measures analysis of variance was used to test for a difference between the groups in PIF change between the first and last week of treatment.

To characterize findings during the ragweed season, diary card data recorded before August 20 or after September 21 were excluded from the analysis.

The critical level of significance was $\alpha = 0.05$ (two-sided) with a power of 90% to detect a 20% difference between treatment regimens. All statistical analyses were performed with SAS software programs and procedures (SAS Institute, Cary, N.C.).

TABLE II. Demographic characteristics

	FP 200 μg o.d.	Loratadine 10 mg o.d.
No. of subjects	121	119
Sex (n)		
Male	64	71
Female	57	48
Age in years (n)		
12 to 14	61	59
15 to 17	60	50
Weight (kg)		
Mean	59	56
SD	15	14
Medical history (n)		
Asthma	45	46
Rhinitis symptoms		
Moderate	45	43
Severe	76	76

RESULTS

Six patients were withdrawn from the study because of violation of inclusion or exclusion criteria, and nine were withdrawn before randomization. Two hundred and forty-two patients were randomized to treatment. Two patients elected not to participate in the trial just before the study medications were issued. Thus 240 subjects were included in the study: 121 received FP aqueous spray and 119 received loratadine. The treatment groups were comparable in demographic characteristics (Table II). Twelve subjects discontinued the study (five from the FP group and seven from the loratadine group). Four subjects were withdrawn because of suspected adverse events: three from the loratadine group (infectious mononucleosis, angioedema, sinus headache), one from the FP group, (asthma exacerbation), and another three from the FP group (failure to return, broken spray bottle, violation of exclusion criteria). Four subjects in the loratadine group and one in the FP group elected to withdraw because of ineffectiveness of study medication.

Results for the intent-to-treat population (n = 240), the per protocol population (n = 210), and the analysis for high pollen periods only were similar, and the intent-to-treat population results are presented here. In addition, there were differences between centers in differences between the groups, but the direction of treatment differences was the same for all centers.

The percentage of symptom-free days for nasal and eye symptoms is presented in Fig. 1. For the primary analysis variable, nasal blockage during

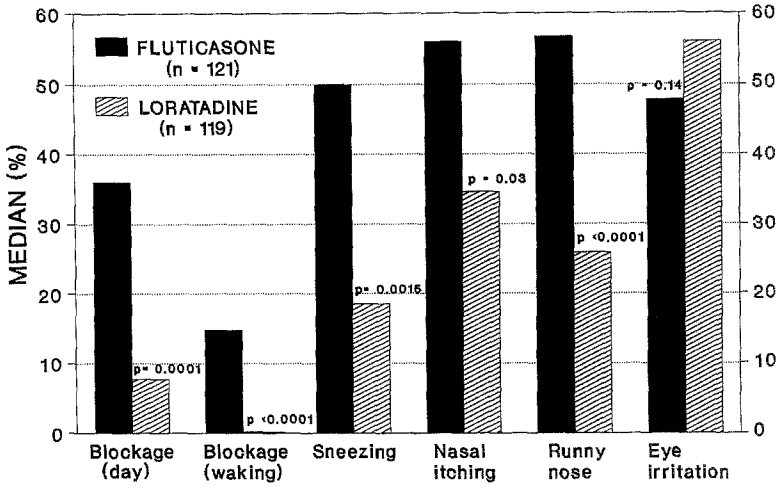

FIG. 1. Median percentage of symptom-free days. Half the patients treated with FP were free of symptoms (symptom score of 0) 36% of 28 days for nasal blockage during the day. FP had significantly higher percentages of symptom-free days than loratadine for all nasal symptoms scored. No difference was found for eye symptoms.

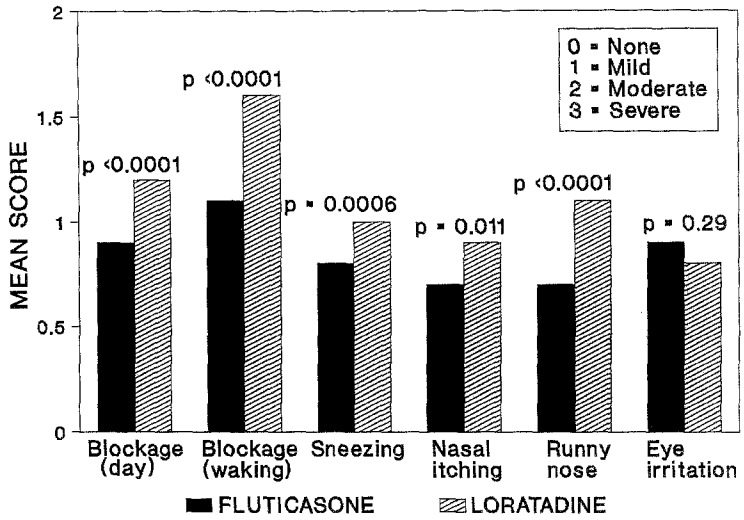

FIG. 2. Mean symptom scores (FP, $n = 121$; loratadine, $n = 119$). A mean symptom score (more than 28 days) was calculated for each patient. This figure represents the overall mean symptom score for FP and loratadine groups over the 28-day treatment.

the day, the median percentages and interquartile ranges (Q3-Q1) were 36.0 and 64.3, and 7.7 and 36.0 for FP and loratadine, respectively ($p = 0.0001$). The percentage of symptom-free days for the FP group was higher than for the loratadine group for all nasal symptoms scored. In contrast, no difference was found for eye watering or irritation ($p = 0.14$).

Mean symptom scores are presented in Fig. 2. Similar results were found, with statistically significant lower symptom scores in the FP group for all nasal symptoms scored. No statistically significant difference was found for eye symptoms.

The FP group had statistically significantly lower median symptom scores than the loratadine group for nasal blockage during the day ($p = 0.0006$), sneezing ($p = 0.0054$), runny nose ($p < 0.0001$), and nasal itching ($p = 0.029$). For both treatment groups, few patients had scores in the severe category, except for in the loratadine group, in which 13% of the patients scored severe (Fig. 3) for nasal blockage on waking. There was no statis-

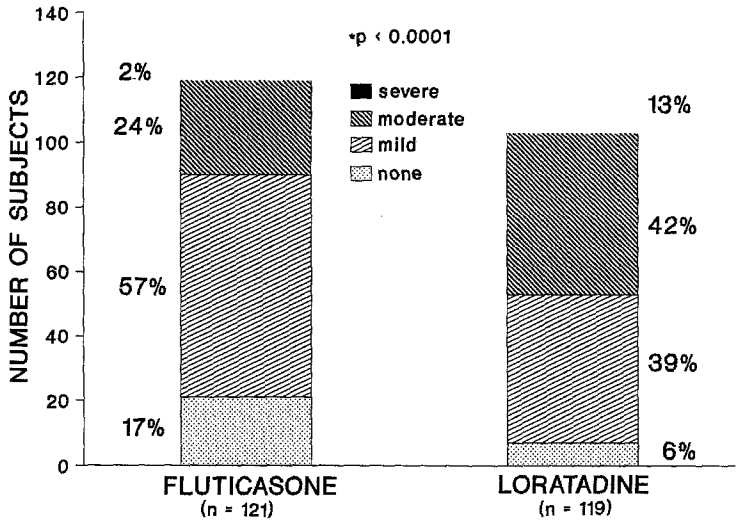

FIG. 3. Median symptom scores for nasal blockage on waking. If the median fell between two levels, the more severe level was taken as the median.

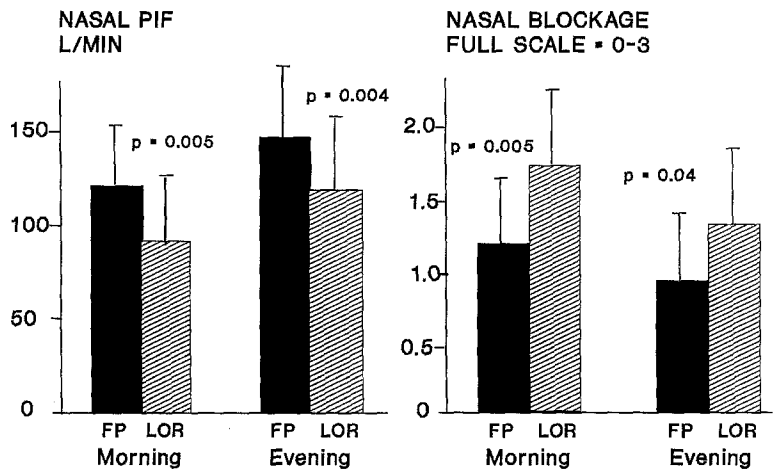

FIG. 4. Diurnal variation (FP, $n = 29$; loratadine, $n = 27$): nasal PIF and nasal blockage over 28 days of treatment. *LOR,* Loratadine.

tically significant difference detected for eye symptoms.

There were no statistically significant differences between the groups for percentage of rescue-free days (median and interquartile range) (93, 25%) and (96, 33%) for FP and loratadine, respectively ($p = 0.61$).

Twenty-six (21%) subjects receiving FP used rescue antihistamine versus 47 (39%) receiving loratadine ($p < 0.0025$). This result, however, may only reflect a pretrial trend because 77% of subjects receiving FP used antihistamine previously compared with 85% receiving loratadine.

There was no statistically significant difference between groups for mean use of rescue eye drops ($p = 0.70$) or rescue bronchodilator ($p = 0.78$).

Fifty six subjects (29 receiving FP and 27 receiving loratadine) provided valid nasal PIF results with a variation of less than 10% between the three measurements at any particular reading. All but three subjects recorded valid data for at least 28 days.

Nasal PIF values (mean and standard deviation) in liters were higher for FP than loratadine both in the morning (123.0, 34.6 and 94.0, 37.9, respectively, $p = 0.0051$) and in the evening (145.9, 39.5 and 112.3, 41.9, respectively, $p = 0.0036$). For both FP and loratadine, morning blockage symptom

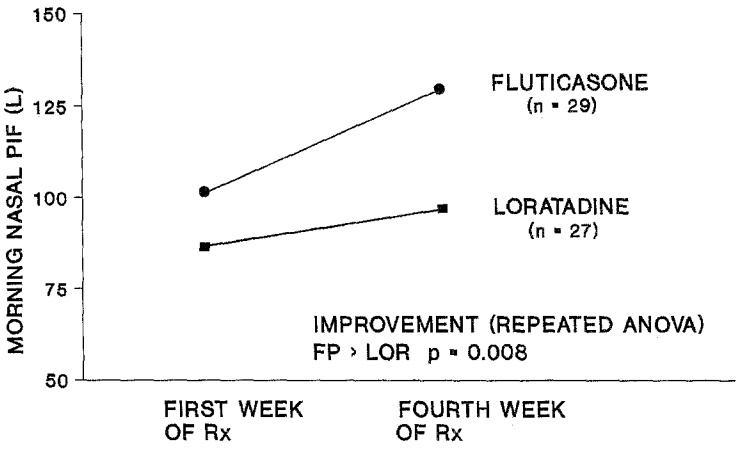

FIG. 5. Morning nasal PIF improvement during the ragweed season. *LOR,* Loratadine.

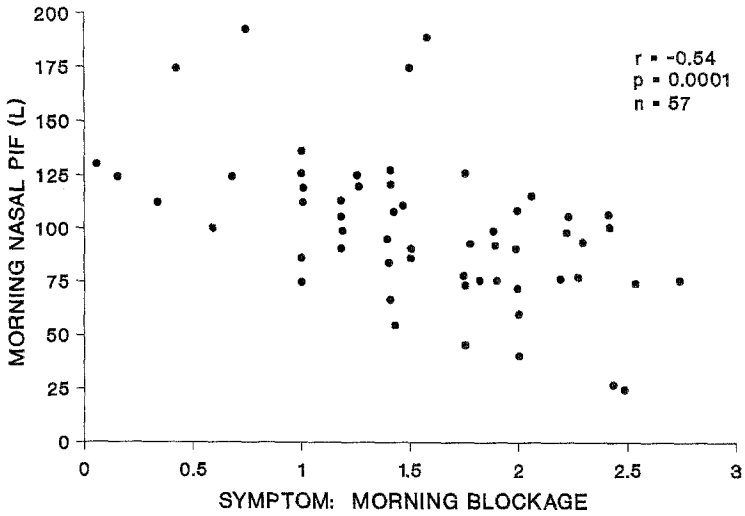

FIG. 6. Mean morning nasal PIF versus mean nasal blockage during the first week of treatment. Symptom scores: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe.

scores were higher and morning PIF values were lower than evening values (Fig. 4). Morning and evening mean nasal PIF results were observed to increase over the 28-day period (more for FP than loratadine) during a period when pollen counts were decreasing, showing a greater improvement over the treatment period in the FP group. A significant treatment-week interaction ($p = 0.008$), indicating progressive improvement during treatment, was found for mean morning PIF measures (Fig. 5). No statistically significant difference in PIF increase between the groups was found for evening PIF measures ($p = 0.358$). Relationships between nasal PIF and the symptom of nasal blockage were examined during the first week when PIF was lowest. Negative correlations were found for evening nasal PIF and evening nasal blockage during the first week of treatment ($n = 56$, $r = -0.46$; $p = 0.0004$). Similar results were observed with morning measures (Fig. 6). Morning and evening PIF rates measured during the first week of treatment were highly correlated ($n = 56$, $r = 0.88, p = 0.0001$).

The most common adverse events in both treatment groups were headache and pharyngitis (42% and 16%, respectively, in the FP group and 25% and 10% in the loratadine group, respectively). Headaches occurred in 50 subjects in the FP group and 27 subjects in the loratadine group. Headaches were classified in FP and loratadine ($p = 0.003$) groups, respectively, as severe in nine and six subjects (not significant), moderate in 29 and 14

subjects ($p = 0.002$), and mild in 66 and 29 subjects ($p < 0.001$). The event most frequently reported by the investigator as "drug-related" was epistaxis (7% and 4%, respectively). As determined by nasal and oropharyngeal examination there was no evidence of candidiasis or nasal septal perforation and no difference between the groups in prevalence of crusting or bleeding of the mucosa. Laboratory values at baseline and at the end of treatment were similar for both treatment groups. Abnormal values were considered by the investigators to be unrelated to treatment.

DISCUSSION

Previous comparisons have suggested that nasal symptoms are more effectively controlled with FP aqueous nasal spray than with terfenadine, 60 mg twice daily,[9, 10] or astemizole.[11] Comparisons of FP with these antihistamines generally favored FP for the treatment of various individual nasal symptoms.

We set out to compare FP aqueous nasal spray given once daily (200 μg) with loratadine given once daily (10 mg) in a double-blind, randomized, parallel-group study in adolescent patients with allergic rhinitis caused by ragweed. Treatment with FP aqueous nasal spray was associated with better control of nasal symptoms than treatment with loratadine throughout the study. When symptoms were present, they tended to be mild in the FP group, whereas they were more likely to be of moderate or severe intensity in the loratadine group. The same conclusions were reached with mean symptom scores and median symptom scores, suggesting that perhaps only one such analysis is necessary in studies of this type.

One center had pollen counts much lower than the others. As a result of reduced symptoms at the one center, there was a treatment-center interaction that was significant for some nasal symptoms, in particular mean nasal blockage during the day. Because the allergy season was less pronounced, it would be expected that treatment differences among the groups would be smaller at that center. Nevertheless, the direction of treatment differences was the same for all centers.

FP aqueous nasal spray treatment was also associated with higher values for nasal airflow. The high correlation observed between morning and evening PIF measures in this study suggests that with appropriate patient training, nasal inspiratory flow rates measured at home on a Youlten peak flow meter have good reproducibility. Symptoms of allergic rhinitis tend to be worse in the morning, and although lower symptom levels and higher PIF values were obtained with FP aqueous nasal spray treatment, the diurnal variation in both nasal obstruction and PIF persisted in the FP group during the study. It is worth noting that morning PIF measurements were taken before the use of any medications. The lower level of nasal blockage and the higher PIF values were the consequence of treatment received 24 hours earlier and possibly in the preceding days.

During the course of the 4-week treatment in the ragweed pollen season, the magnitude of improvement in PIF was greater with FP aqueous nasal spray than with loratadine. These results provide support for those obtained from the symptom diary.

Patients receiving loratadine used more rescue antihistamine, and more patients withdrew because of lack of control of symptoms (four in the loratadine group, one in the FP group), but the sample size was too small to apply statistics. The lower prevalence of headaches in the loratadine group could indicate that the antihistamine partially prevents headaches in season in these patients with allergic rhinitis.

The preparations were generally well tolerated. No treatment-related laboratory abnormalities were identified.

The opportunity to use FP aqueous nasal spray once daily, rather than the usually recommended twice or more daily application of intranasal corticosteroid therapy, may improve patient compliance. The results of the type of comparison reported here indicate that topical nasal corticosteroid is a reasonable first choice for the treatment of seasonal allergic rhinitis.

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