

Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis

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Summary

Background If monotherapy with an intranasal corticosteroid can alleviate both nasal and ocular symptoms of allergic rhinitis, treatment may be simplified and costs may be reduced.

Objective The purpose of this study was to evaluate the efficacy of once-daily fluticasone propionate (FP) aqueous nasal spray 200 µg compared with vehicle placebo and oral loratadine (LOR) 10 mg in reducing ocular symptoms associated with seasonal allergic rhinitis.

Methods A total of 471 patients received vehicle placebo, LOR, or FP in this multi-centre, double-blind, double-dummy, randomized study. Patients were ≥12 years old with a history of seasonal allergic rhinitis and a positive skin test for a relevant allergen. During the baseline and treatment periods, patients rated the severity of eye itching, tearing, and redness via visual analogue scales that ranged from 0 (no symptoms) to 100 (most severe symptoms). The three ocular ratings were added to derive the total ocular symptom score (TOSS). Patients with a TOSS ≥120 on at least 4 of the 7 days before the randomization visit were enrolled. The primary outcome was the difference between FP and vehicle placebo in the mean change from baseline in the reflective TOSS overall (averaged over the 28-day treatment period). A difference between FP and vehicle placebo of 25.5 was considered clinically significant.

Results The overall mean change from baseline in the TOSS was significantly greater in the FP group compared with vehicle placebo (clinically significant difference of 28.8; $P < 0.001$) and compared with LOR (difference of 16.2; $P = 0.028$). Overall mean (SEM) changes were –59.9 (5.4) for the placebo group, –72.5 (5.4) for the LOR group, and –88.7 (5.3) for the FP group. The FP treatment group also showed significantly greater overall mean changes in ocular itching, tearing, and redness compared with vehicle placebo ($P < 0.001$) and compared with LOR ($P \leq 0.045$).

Conclusion Patients treated with intranasal FP had clinically and statistically significant decreases in ocular symptom scores compared with vehicle placebo. Data also suggest that FP reduced ocular symptoms more than or comparable with oral LOR. Patients experiencing ocular symptoms associated with allergic rhinitis may benefit from monotherapy with intranasal FP.

Keywords allergic rhinitis, corticosteroids, eye, fluticasone propionate, intranasal administration, loratadine, ocular

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Introduction

Guidelines for the management of rhinitis suggest that intranasal corticosteroids are the most effective medication for improving nasal symptoms of allergic rhinitis [1]. Because many patients with allergic rhinitis also experience ocular symptoms, [2–4] an oral antihistamine may be prescribed in addition to an intranasal corticosteroid to treat the ocular symptoms. However, there is growing evidence suggesting that some intranasal corticosteroids may reduce ocular

symptoms along with nasal symptoms [5–9]. If monotherapy with an intranasal corticosteroid could effectively alleviate both nasal and ocular symptoms of allergic rhinitis, management of symptoms would be simplified and costs may be reduced.

Evidence supporting the efficacy of intranasal corticosteroid sprays on ocular symptoms is derived from rhinitis studies specifically designed to show efficacy with nasal symptoms [5–9]. However, the percentage of patients experiencing ocular symptoms at baseline is not reported in most of these studies and may not have been collected during the baseline symptom assessment. In other studies, rescue medications such as eye drops or oral antihistamines were allowed, which confounded the interpretation of ocular efficacy. Nonetheless, some studies have shown that the beneficial effect of intranasal

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corticosteroids on ocular symptoms may be comparable with the effect of some oral antihistamines [10–14]. Two systematic reviews of comparative, randomized clinical trials found no differences between the two classes of medication in the treatment of ocular symptoms associated with allergic rhinitis [15, 16]. In the meta-analysis reported by Weiner, Abramson, and Puy, 11 studies included an assessment of ocular symptoms. Pooled data indicated that there were no significant differences between intranasal corticosteroids and antihistamines in reducing ocular symptoms. In the review by Stempel and Thomas, nine of the 10 studies that evaluated ocular symptoms found no statistically significant effects between intranasal corticosteroids and non-sedating antihistamines on ocular symptoms, with one study [17] showing a statistical difference favouring the use of an antihistamine [16].

Fluticasone propionate (FP) aqueous nasal spray is a topical corticosteroid [18, 19] that has been proven to significantly decrease the nasal symptoms of allergic and non-allergic rhinitis [20–23]. In studies assessing the effect of FP on nasal symptoms due to allergic rhinitis, a beneficial effect of treatment on ocular symptoms was also observed [6, 7, 20]. In a pooled analysis of seven double-blind, placebo-controlled studies originally designed to assess nasal symptom reduction, patients with seasonal allergic rhinitis who were treated with FP 200 µg once daily for up to 14 days experienced significantly greater and clinically relevant reductions in the total ocular symptom score (TOSS) compared with vehicle placebo [24]. Despite a large placebo response, patients treated with FP showed greater decreases in the TOSS and in all four individual symptoms assessed (eye itching, tearing, redness, and puffiness) compared with vehicle placebo.

To our knowledge, there has been no placebo-controlled study designed specifically to evaluate the efficacy of intranasal corticosteroid sprays in treating ocular symptoms associated with allergic rhinitis. We report the results of the first randomized, double-blind, placebo-controlled study prospectively designed to evaluate the efficacy of FP aqueous nasal spray, an intranasal corticosteroid, in decreasing the severity of ocular symptoms associated with seasonal allergic rhinitis. An oral loratadine (LOR) arm was included as an active control known to provide clinically relevant improvement in ocular symptoms.

Methods

Study Design

This multi-centre, randomized, double-blind, double-dummy, parallel-group study was conducted at 14 investigative sites in the US. The protocol was approved by an institutional review board for each participating centre and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Eligible patients were at least 12 years of age with a history of allergic rhinitis for ≥ 2 years and a positive skin test to at least one allergen relevant to the spring pollen season and geographic region. For the purposes of this study, a positive skin test reaction was defined as a weal diameter at least 3 mm greater than diluent control using 1:20 W:V glycerinated solution. Patients meeting inclusion criteria entered a 7–14-day baseline

period designed to assess the severity of ocular itching, tearing, and redness and nasal congestion through the use of a daily diary card. At the end of the baseline period (Visit 2), patients with a TOSS (the sum of ocular itching, tearing, and redness scores) of 120 out of a maximum 300 points, and a nasal congestion symptom severity score of 50 out of a maximum 100 points, on at least 4 of 7 days immediately preceding Visit 2 were eligible for randomization to study medication.

Eligible patients were randomly assigned (in a 1:1:1 ratio) to one of the following treatment groups for 28 days: (1) Placebo group (vehicle placebo spray + placebo capsule); (2) LOR group (encapsulated LOR 10 mg tablet + vehicle placebo spray); (3) FP aqueous nasal spray group (FP aqueous nasal spray 200 µg + placebo capsule). To maintain blinding, a double-dummy scheme was used; the device that contained FP aqueous nasal spray was identical to the device that contained vehicle placebo spray and the encapsulated LOR 10 mg tablets matched the placebo capsules. Both the patients and investigators were blinded to study treatment allocation. Study medication was taken once daily in the morning. FP (50 µg strength) or vehicle placebo spray was administered as two sprays per nostril. No rescue medications were allowed during the study. During the baseline and treatment periods, patients were not allowed to take any prescription or over-the-counter medications (e.g. oral antihistamines or artificial tears) that might affect ocular or nasal symptoms.

Study procedures

Each evening at bedtime, patients completed a diary card on which they reflectively rated the severity of ocular itching, tearing, and redness throughout the day using visual analogue scales [25]. Patients indicated the severity of each symptom by making a vertical mark on an unmarked horizontal 100 mm line that represented a continuum from 0 (none) to 100 (most severe). For each symptom, the distance in millimeters between the left end of each line (representing 0) and the patient's vertical mark made on the scale was measured by site personnel, and the number was recorded to represent the severity of each of the symptoms. Patients also rated the severity of nasal congestion on a visual analogue scale (0–100).

Patients returned for clinic visits at Day 15 and at Day 29; if treatment was prematurely discontinued, patients returned to the clinic for a final visit. Between clinic visits, patients recorded symptoms and documented their compliance with study medication on diary cards. At each clinic visit, investigators collected diary cards and evaluated adverse events. To calculate compliance, the number of days that both nasal spray and capsule were taken were divided by the number of days they should have been taken. At the final visit, patients were asked to evaluate their overall response to the double-blind therapy for relief of eye symptoms over the entire treatment period using a seven-point categorical scale ranging from significant improvement to significant worsening.

Endpoints

The primary efficacy measure was the difference between FP and vehicle placebo in the mean change from baseline in the

reflective patient-rated TOSS averaged over Days 1–28 (overall mean change). Other efficacy measures included pairwise treatment comparisons of (1) the mean change from baseline in TOSS over each week of treatment, (2) the mean change from baseline in the three individual ocular symptom scores overall and over each week of treatment, (3) the mean change from baseline in nasal congestion overall and over each week of treatment, and (4) the patient-rated overall evaluation of response to therapy.

Statistical analysis

Enrollment was planned for approximately 474 patients (158 patients per treatment group) to ensure 152 completed patients per treatment group. A sample size of 152 completed patients per treatment group provided at least 85% power to detect a difference between FP and vehicle placebo of 25.5 in the mean change from baseline in the TOSS, based on a change of 8.5 in each individual symptom (assuming each symptom is weighted equally). The sample size calculation used a two-sided *t*-test with a significance level of $\alpha = 0.05$ and assumed a standard deviation of 73.8.

A difference in mean change from baseline between FP and placebo of 25.5 was chosen as a conservative estimate of a clinically meaningful difference for visual analogue scale ratings of ocular symptoms. In previous rhinitis studies using a visual analogue scale with a total nasal symptom score (TNSS) of 300, differences as low as 20 (approximately 20–26) represented clinically relevant differences that were detectable by the patients. This determination of clinical relevance was established by observing the difference in response to a global evaluation of efficacy in which patients used a categorical scale to describe their level of improvement. In these studies in which differences as low as 20 for TNSS were observed, a greater percentage (45–59%) of patients treated with FP rated their improvement in symptoms as significantly or moderately improved compared with placebo (30–32%) and the comparison of responses for FP vs. placebo were statistically significant ($P < 0.01$).

The TOSS was derived by the statistician for each patient by adding the three ocular symptom scores for each day recorded on the diary card. The maximum score for each ocular symptom was 100 points, and the maximum TOSS possible was 300 points. Baseline was defined as the average symptom score over the 7 days immediately preceding Day 1 (i.e. treatment start date).

Analyses used all available data from the intent-to-treat population, defined as all patients who were randomized to receive study drug. *P*-values were based on analysis of covariance on change from baseline, adjusting for investigator, treatment, and baseline value, using linear contrasts for pairwise comparisons. The comparison of the overall mean change from baseline in TOSS between FP and vehicle placebo was assessed at a significance level of $\alpha = 0.05$. Results of the FP–vehicle placebo comparisons were adjusted for multiplicity by assessing other efficacy measures for statistical significance using a hierarchical closed testing strategy (TOSS, then each individual ocular symptom; within each endpoint, overall, and then by descending week). Multiplicity adjustment was not applied to the exploratory endpoints, which included nasal congestion, end of treatment

patient-rated overall response to therapy, and the FP–LOR and LOR–vehicle placebo comparisons of all endpoints.

Results

A total of 471 patients received vehicle placebo ($n = 155$), LOR ($n = 158$), or FP ($n = 158$). The majority of patients, 91% of the placebo group, 87% of the LOR group, and 94% of the FP group, completed the 28-day treatment period. The most common reasons for premature discontinuation were adverse events (2% in the placebo group, 4% in the LOR group, and 3% in the FP group) and lack of efficacy (3% in the placebo group, 4% in the LOR group, and 0% in the FP group). Daily diary cards indicated mean rates of compliance to blinded study medication for each group ranging from 97% to 99%. At least 96% of patients in each treatment group reported at least 80% compliance with their study medication.

Demographic and baseline characteristics were similar among treatment groups. The majority of patients were Caucasian (80–89% of each group); 58–62% of each group were female. Eighty percent of the patients were between the ages of 18 and 64. Symptom severity at baseline was similar among the three groups for both ocular symptoms and nasal congestion (Table 1).

Total ocular symptom score

The overall (Days 1–28) mean change from baseline in the TOSS was significantly greater in the FP group compared with placebo ($P < 0.001$) and with LOR ($P = 0.028$; Table 1). Overall mean (SEM) changes from baseline in the TOSS were -59.9 (5.4) for the placebo group, -72.5 (5.4) for the LOR group, and -88.7 (5.3) for the FP group. The difference in the overall mean change between FP and placebo (28.8) was considered clinically significant. The FP group demonstrated

Table 1. Mean ($\pm$ SEM) change from baseline in symptom scores for Days 1–28

Efficacy variable	Placebo (<i>N</i> = 155)	LOR 10 mg QD (<i>N</i> = 158)	FP 200 μ g QD (<i>N</i> = 158)
TOSS			
Baseline	207.9 $\pm$ 3.8	204.3 $\pm$ 3.8	209.4 $\pm$ 3.8
Mean change	-59.9 ± 5.4	-72.5 ± 5.4	$-88.7 \pm 5.3^{*†}$
Itching			
Baseline	72.9 $\pm$ 1.2	74.4 $\pm$ 1.2	73.6 $\pm$ 1.2
Mean change	-21.7 ± 1.9	-26.3 ± 1.8	$-31.3 \pm 1.8^{*†}$
Tearing			
Baseline	66.5 $\pm$ 1.6	65.3 $\pm$ 1.6	68.0 $\pm$ 1.6
Mean change	-19.8 ± 1.9	-23.6 ± 1.8	$-28.8 \pm 1.8^{*†}$
Redness			
Baseline	68.5 $\pm$ 1.6	64.6 $\pm$ 1.5	67.8 $\pm$ 1.5
Mean change	-18.6 ± 1.9	-23.1 ± 1.8	$-28.6 \pm 1.8^{*†}$
Nasal congestion			
Baseline	78.5 $\pm$ 1.1	78.3 $\pm$ 1.1	79.0 $\pm$ 1.1
Mean change	-21.7 ± 1.9	-25.0 ± 1.9	$-35.3 \pm 1.9^{*†}$

SEM, standard error of the mean; FP, fluticasone propionate; QD, once-daily; LOR, loratadine; TOSS, total ocular symptom score.

* $P < 0.05$ for FP vs. vehicle placebo. † $P < 0.05$ for FP vs. loratadine.

a statistically significant mean change in TOSS compared with placebo throughout all 4 weeks of treatment and compared with LOR over Weeks 2–4 (Fig. 1). The LOR group demonstrated consistently greater mean change in the TOSS compared with placebo over each week of treatment and significantly greater change compared with placebo over Week 1 only ($P = 0.036$). Differences between LOR and placebo were not significant over Weeks 2–4 or for the overall (Day 1–28) assessment.

Individual ocular symptom scores

The FP treatment group showed significantly greater overall (Days 1–28) mean change in ocular itching, tearing, and redness compared with placebo ($P < 0.001$) and compared with LOR ($P \leq 0.045$) (Figs 2–4). Differences between FP and placebo were both clinically and statistically significant during each week of treatment for each of the three symptoms ($P \leq 0.008$). The LOR group had greater, but non-significant, overall mean changes than placebo for each individual symptom.

Nasal congestion

The FP group had significantly greater mean change from baseline in nasal congestion overall (Days 1–28) and for each

week of treatment compared with placebo ($P < 0.001$) and also compared with LOR ($P \leq 0.003$). Overall mean changes from baseline were -21.7 (1.9) for the placebo group, -25.0 (1.9) for the LOR group, and -35.3 (1.9) for the FP group. Differences between LOR and placebo were not significant.

Patient-rated overall evaluation of response to therapy

Patients' overall assessment of the effectiveness of the double-blind therapy for relief of eye symptoms over the entire treatment period were significantly different between the FP and placebo groups and between the FP and LOR groups ($P < 0.001$) but not between the LOR and placebo groups. The seven-point categorical scale used for this assessment ranged from significant improvement to significant worsening. More patients in the FP group (82%) reported improvement (significant, moderate, or mild improvement) compared with patients in the placebo group (65%) or LOR group (64%).

Adverse events

The incidence of adverse events was similar among the three treatment groups, with 40% of the placebo group, 42% of the LOR group, and 44% of the FP group reporting at least one

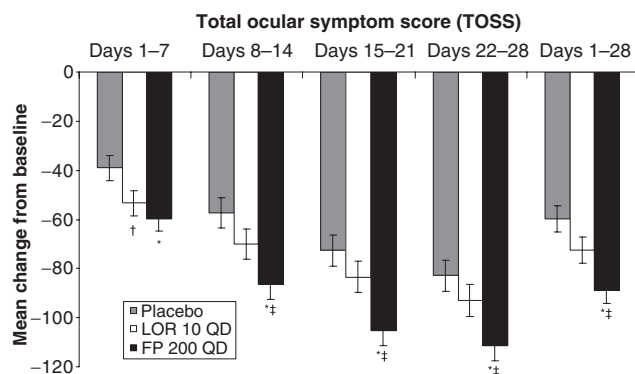


Fig. 1. Mean change ($\pm$ SEM) from baseline in total ocular symptom score (TOSS) during each week of treatment and overall (Days 1–28) for placebo, LOR 10 mg QD (loratadine), and FP 200 μ g QD (fluticasone propionate aqueous nasal spray): * $P < 0.05$ for FP vs. placebo, † $P < 0.05$ for LOR vs. placebo, and ‡ $P < 0.05$ for FP vs. LOR.

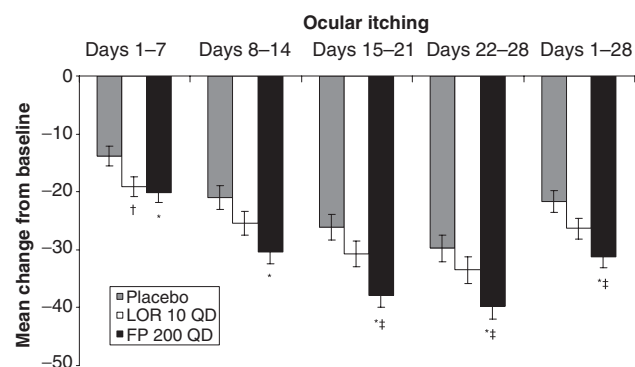


Fig. 2. Mean change ($\pm$ SEM) from baseline in ocular itching during each week of treatment and overall (Days 1–28) for placebo, LOR 10 mg QD (loratadine), and FP 200 μ g QD (fluticasone propionate aqueous nasal spray): * $P < 0.05$ for FP vs. placebo, † $P < 0.05$ for LOR vs. placebo, and ‡ $P < 0.05$ for FP vs. LOR.

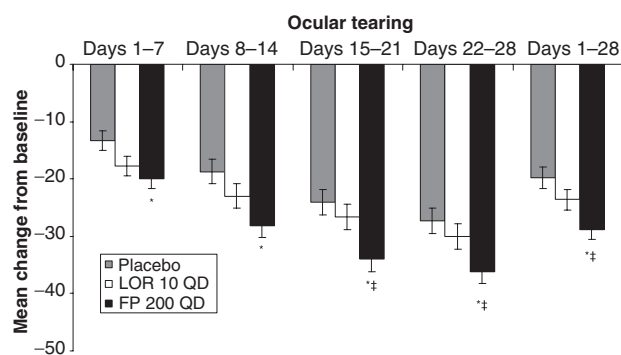


Fig. 3. Mean change ($\pm$ SEM) from baseline in ocular tearing during each week of treatment and overall (Days 1–28) for placebo, LOR 10 mg QD (loratadine), and FP 200 μ g QD (fluticasone propionate aqueous nasal spray): * $P < 0.05$ for FP vs. placebo and ‡ $P < 0.05$ for FP vs. LOR.

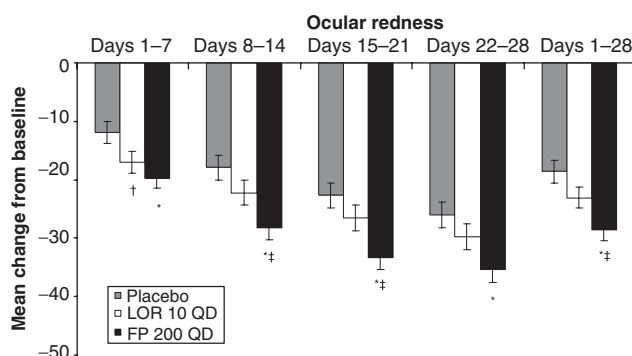


Fig. 4. Mean change ($\pm$ SEM) from baseline in ocular redness during each week of treatment and overall (Days 1–28) for placebo, LOR 10 mg QD (loratadine), and FP 200 μ g QD (fluticasone propionate aqueous nasal spray): * $P < 0.05$ for FP vs. placebo, † $P < 0.05$ for LOR vs. placebo, and ‡ $P < 0.05$ for FP vs. LOR.

adverse event during the study. The most common event was headache (12% in the placebo group, 18% in the LOR group, and 17% in the FP group).

Discussion

This is the first report of a placebo-controlled study prospectively designed and statistically powered to assess the effect of an intranasal corticosteroid on the severity of ocular symptoms associated with allergic rhinitis. Patients receiving once-daily FP 200 µg aqueous nasal spray reported clinically and statistically significant mean changes in ocular symptoms compared with vehicle placebo. This was true for the TOSS, as well as for the scores for the individual symptoms of ocular itching, redness, and tearing. These data are consistent with a retrospective analysis of ocular data from seven allergic rhinitis studies designed to evaluate the efficacy of FP in reducing nasal symptoms. In the pooled analysis, the FP group showed significant decreases in both clinician-rated and patient-rated composite ocular symptom scores compared with vehicle placebo [24]. However, like most allergic rhinitis studies, patients were enrolled in those studies on the basis of nasal symptoms; ocular symptoms were recorded but not required for enrollment. In the current study, only patients showing a clinically relevant degree of ocular itching, redness, or tearing associated with their seasonal allergic rhinitis were enrolled.

The encapsulated oral LOR was added as a third treatment arm in this study to include an active control known to provide clinically relevant improvements in ocular allergy symptoms. The FP group demonstrated significantly greater mean change from baseline in the TOSS compared with LOR overall and over Weeks 2–4. During Week 1, the LOR group showed mean changes in TOSS that were significantly greater than placebo and comparable with changes demonstrated by the FP group. Decreases in the overall TOSS and overall nasal congestion scores, respectively, were approximately 29% and 28% for the placebo group. Other allergic rhinitis studies have reported response rates (improvement in nasal symptom scores) for patients who were treated with nasal saline or vehicle placebo that ranged from 20% to 30% [26]. Due to the possible flushing action of unmedicated spray on the nasal passages, there may be a beneficial effect of the vehicle placebo spray on nasal symptoms, and in turn on ocular symptoms, as secretions containing mediators and inflammatory cells are removed from the nose [20, 27, 28]. Similar to the findings of this study, other allergic rhinitis studies have shown non-sedating oral antihistamines to be no more effective than vehicle placebo aqueous nasal spray [20, 29, 30].

There are several plausible explanations of how an intranasal corticosteroid might improve eye symptoms, although the exact mechanism is unknown. Retention of allergen in the conjunctiva could be reduced by enhancing drainage of the nasolacrimal duct and thereby reducing edema and inflammation surrounding the opening of the nasolacrimal duct. In the current study, the similarity of results between decreases in the TOSS and decreases in nasal congestion may lend support to this theory: decreases in the overall TOSS and nasal congestion scores, respectively, were

approximately 29% and 28% for the placebo group, 35% and 32% for the LOR group, and 42% and 45% for the FP group. Another possibility is that the anti-inflammatory properties of intranasal corticosteroids may decrease ocular irritation through modulation or normalization of allergen-induced increases in reflex neuronal activity [24, 31–33]. It is highly unlikely that intranasal FP alleviates eye symptoms due to systemic absorption and recirculation of the drug. FP has been shown to work topically, [18, 19] with the intranasal formulation having a mean absolute bioavailability estimated at 0.51% [34]. A review of adverse effects reported in four studies, from 6 months to a year in duration, support the topical vs. systemic action of intranasal FP; [7, 19, 35, 36] there were no reports of cataracts or clinically significant increases in intraocular pressure with administration of FP. Studies have shown other intranasal sprays also exert their effects through topical administration vs. systemic absorption. In a study evaluating the topical vs. systemic effect of the intranasal corticosteroid budesonide, patients given oral budesonide had a higher plasma level of the drug compared with patients who received intranasal budesonide, yet there was a significant reduction in both nasal and ocular symptoms only in the intranasal treatment group [37]. The topical action of intranasal corticosteroids is consistent with the relative lack of systemic adverse events with this class of medication. Derby [38] found that the use of intranasal corticosteroids in patients less than 70 years old was not associated with an increased risk of cataracts. In the current study, adverse effects were similar among groups.

In conclusion, intranasal FP significantly decreased the severity of ocular symptoms associated with allergic rhinitis compared with vehicle placebo. Intranasal FP also reduced ocular symptom scores more than oral LOR, a product currently indicated for relief of nasal and non-nasal symptoms due to allergic rhinitis. FP's effect on ocular symptoms is likely indirect and secondary to a reduction in nasal inflammation and congestion. Our findings suggest that patients experiencing ocular symptoms associated with allergic rhinitis may benefit from monotherapy with intranasal FP.

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