

Fluticasone furoate nasal spray reduces the nasal-ocular reflex: A mechanism for the efficacy of topical steroids in controlling allergic eye symptoms

Fuad M. Baroody, MD, Deanna Shenaq, BSc, Marcy DeTineo, BSN, JiangHong Wang, MD, and Robert M. Naclerio, MD *Chicago, Ill*

Background: Eye symptoms frequently occur in patients with allergic rhinitis and are among the most bothersome symptoms. Intranasal steroids have been shown to reduce ocular symptoms associated with allergic nasal symptoms, even though they do not reach the eye.

Objective: To elucidate a mechanism to explain these observations.

Methods: We performed a double-blind, placebo-controlled, crossover experiment in 20 subjects with seasonal allergic rhinitis. Nasal antigen challenge was performed consecutively for 3 days after 1 week of treatment with either placebo or fluticasone furoate nasal spray (FFNS). Subjects recorded their nasal and ocular symptoms, and nasal secretions were quantified. Nasal scrapings to quantify eosinophils were obtained before each antigen challenge.

Results: Nasal challenge with antigen led to sneezing, a nasonasal, and a nasal-ocular reflex. Priming in the number of sneezes, contralateral nasal secretion weights, and total eye symptoms were observed. Treatment with FFNS reduced sneezing, the nasonasal and nasal-ocular reflexes, and the amount of eosinophils in nasal secretions.

Conclusions: We confirmed that a nasal-ocular reflex follows nasal challenge with allergen and that it can contribute to the ocular symptoms associated with allergic rhinitis. FFNS reduced eosinophil infiltration, priming, and ocular symptoms. Furthermore, our results support a mechanism by which control of eye symptoms can be achieved during nasal administration of an intranasal steroid in patients with seasonal allergic rhinitis. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Allergic rhinoconjunctivitis, nasal-ocular reflex, fluticasone furoate nasal spray, nasal challenge, priming, eosinophils

Allergic rhinitis is a common disease, affecting about 20% of the American population,¹ and is ranked as the fifth most costly chronic disease in the United States.² Allergic rhinitis greatly affects patients' quality of life, cognitive and learning functions, decision-making, and self-perception.³ Quality of life impairments related to allergic rhinitis also lead to decreased work productivity and classroom activity.^{4,5} Therefore, cost-effective treatment for the disease is important for both patient and society.

Clinical symptoms of allergic rhinitis include sneezing, rhinorrhea, nasal itching, and nasal congestion. According to an analysis of National Health and Nutrition Examination Survey III data, more than 40% of the US population with allergic rhinitis experienced ocular symptoms, primarily manifesting as itchy and watery eyes, regardless of age or geographic location.⁶ In a study performed by Wuthrich et al,⁷ the authors evaluated 509 symptomatic patients with hay fever who were not currently receiving medical treatment and found that conjunctivitis symptoms were at least as severe as rhinitis symptoms in approximately 70% of the patients. Furthermore, when the recent Allergies in America survey asked 2500 adults with allergic rhinitis, on treatment, who had bothersome symptoms to identify the most bothersome of these symptoms, 15% described eye symptoms (watering or red, itching eyes) compared with 14% who described postnasal drip and 14% who described headaches.⁸ This was exceeded only by the symptom of stuffy nose described by 22% of the respondents.

The mechanism underlying the development of eye symptoms associated with allergic rhinitis remains ambiguous and is probably multifactorial. Allergen contacting the conjunctiva of an allergic individual will induce an allergic reaction, the pathophysiology of which parallels that of the nasal response. This reaction probably accounts for part of the eye symptoms in patients with allergic rhinoconjunctivitis. The ocular challenge system was first used by Noon⁹ in 1911 to demonstrate the efficacy of immunotherapy. Another hypothesized mechanism involves a nasal-ocular reflex—that is, pollen is inhaled into the nose and initiates a neural reflex, which produces ocular symptoms.

The nasal-ocular reflex theory is based on the fact that nasal afferent nerves are stimulated by released histamine, and lead to an efferent parasympathetic response that not only causes the well established nasonasal reflex, but also causes a nasal-ocular reflex.¹⁰ In support of this theory, the lacrimal gland is richly innervated by parasympathetic nerves, which enter the orbit in

From the Section of Otolaryngology—Head and Neck Surgery, Department of Surgery, Pritzker School of Medicine, University of Chicago.

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Reprint requests: Fuad M. Baroody, MD, Section of Otolaryngology—Head and Neck Surgery, 5841 S. Maryland Ave, MC1035, Chicago, IL 60637. E-mail: fbaroody@surgery.bsd.uchicago.edu.

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Abbreviations used

FFNS: Fluticasone furoate nasal spray
SPT: Skin prick test

conjunction with parasympathetic input to the nasal cavity. Supporting this theory is our recent experiment using a localized nasal challenge model, in which we demonstrated that challenge of 1 nasal cavity with allergen causes a significant ocular symptomatic response.¹⁰ This response was inhibited by premedicating the nose with a topical antihistamine, supporting the role of histamine in the initiation of this response.

Patients with symptoms of allergic rhinitis become increasingly reactive to pollen as the season progresses, a phenomenon referred to as *priming*, first described by Connell.¹¹ Priming has been mimicked in the laboratory by showing increased nasal reactivity of allergic volunteers to progressively lower doses of allergens when administered on consecutive days.¹² Priming is related to underlying nasal inflammation that occurs during repeated exposure, and we speculated that this priming response of symptoms would also translate into a priming of the nasonasal and nasal-ocular reflexes.

Intranasal steroids demonstrate effectiveness in treating eye symptoms of allergic rhinitis and, for many preparations, achieve this effect with systemic bioavailability of less than 1%.¹³ In a meta-analysis performed by Weiner et al,¹⁴ intranasal steroids proved superior to antihistamines in controlling all nasal symptoms and were equally effective compared to oral antihistamines in reducing allergic eye symptoms. This beneficial effect of intranasal steroids on eye symptoms occurs even though they are applied to the nasal mucosa. The mechanism of this favorable effect has not been explored yet. This study was designed to elucidate one of the potential mechanisms by which intranasal steroids alleviate ocular symptoms. We hypothesized that the nasal-ocular reflex will prime after repeated nasal antigen exposure. In addition, we hypothesized that treatment with fluticasone furoate nasal spray (FFNS), an intranasal steroid that has consistently reduced eye symptoms in clinical trials and has less than 1% systemic bioavailability, before and during repetitive nasal antigen stimulation, will inhibit cellular inflammation and subsequently reduce nasal and ocular symptoms by inhibiting priming of the nasal-ocular reflex.

METHODS

Subjects

We performed a double-blind, placebo-controlled, 2-way crossover study in 20 subjects with a history of grass and/or ragweed seasonal allergic rhinitis. Subjects between the ages of 18 and 35 years were recruited if they had history of allergic rhinitis to grass or ragweed over the period of the past 2 years and a positive skin prick test (SPT) result to either allergen. They underwent a screening nasal challenge with timothy grass or ragweed allergen outside their allergy season. Twenty subjects who passed nasal challenge screening, defined as exhibiting nasal and ocular symptoms postantigen challenge, were enrolled. All subjects also had positive skin test results to other allergens (molds, dust mite, trees, and cat), but their symptom distribution over the period of the 12 months of the year was commensurate with peak symptoms during either the grass or ragweed seasons as determined by their replies to a screening questionnaire. Nine subjects were challenged with grass and 11 with ragweed, and all were challenged outside of their pollen seasons. In the ragweed-challenged patients, mean ragweed SPT wheal diameter was 10.2 ± 1.0 mm,

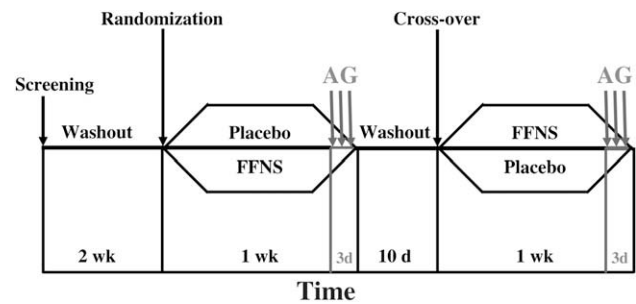


FIG 1. Study design. The timeline appears at the bottom. The 3 arrows labeled AG denote the 3 consecutive allergen challenges performed on 3 consecutive days while patients were still on intranasal treatment. During each of these challenges, the subjects were challenged with the diluent for the allergen extract, followed 10 minutes later by challenge with either ragweed or grass antigen extracts. All challenge solutions (diluent or allergen) were placed on the nasal septum by using filter paper discs.

and in the grass-challenged patients, the mean wheal diameter to grass SPT was 10.6 ± 1.1 mm. Histamine SPT wheal diameter for these patients was 7.0 ± 0.2 mm. When asked to grade the severity of their symptoms during the months of the relevant season on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe), 13 of 20 (65%) patients reported severe symptoms, 5 of 20 (25%) moderate symptoms, and 1 of 20 (5%) mild symptoms, and there were no data available for 1 subject (5%). Duration of disease was reported by 17 of 20 patients and was a median of 13 years, with a range of 3 to 35 years. Subjects completed written informed consent before participation in the study, which was approved by the Institutional Review Board at the University of Chicago (Institutional Review Board no. 15061B). The trial was registered at <http://ClinicalTrials.gov> (registration no. NCT00473915). An investigational new drug designation from the US Food and Drug Administration was obtained to perform the antigen challenges.

Study design

After a 2-week washout period from the screening challenge, enrolled subjects were randomized to receive intranasal administration of either placebo or FFNS (Veramyst nasal spray; GlaxoSmithKline, Philadelphia, Pa) at 2 puffs per nostril, once daily (110 μ g) for 1 week. Subjects returned to the Nasal Physiology Laboratory the following week to undergo nasal challenge with diluent and grass or ragweed allergen as in the screening procedure (Fig 1). Identical nasal antigen challenges were performed consecutively for 3 days. After each challenge, participants were treated with their assigned medication. Next, subjects washed out for 10 days and then crossed over to the administration of the other treatment for 1 week, followed by a similar nasal challenge for 3 consecutive days.

Nasal antigen challenge

Filter paper discs were used to deliver challenge solutions to the nasal septum and collect generated secretions from both nostrils as previously described.¹⁵ The diluent for the allergen extracts was 0.9% phenol-buffered saline, and the allergens were grass (10,000 biologically active units/mL) or ragweed (1:20 wt/vol) extracts. All subjects received a single dose (50 μ L on a filter paper disc) of ragweed or grass extracts. In the case of grass extract, the dose placed on the disc in 50 μ L would be 500 biologically active units. How much of the allergen doses actually elute off the disc and are effectively generating the observed response is not known.

Nasal and eye symptoms

Ten minutes after each challenge, participants recorded the number of sneezes elicited, bilateral nasal symptoms (congestion, rhinorrhea, itchy nose/throat), and bilateral ocular symptoms (watery and itchy eyes). Nasal and ocular symptoms were rated on the following scale: 0, none; 1, mild; 2, moderate; and 3, severe.

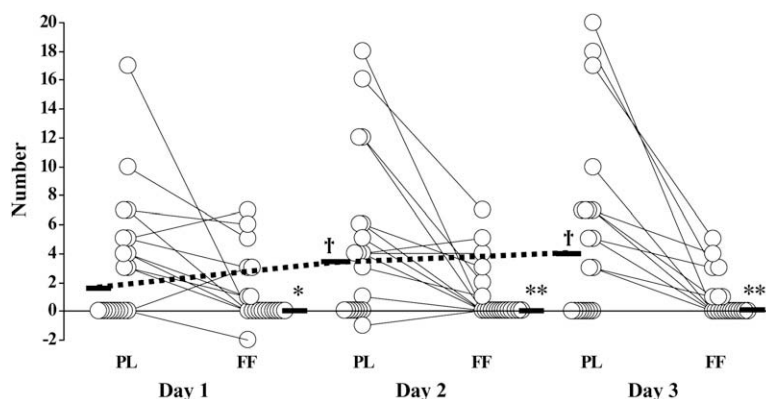


FIG 2. The effect of FFNS on the sneezing response after allergen challenge. The x-axis shows the time scale and pretreatment. Net change from diluent is depicted as individual data ($n = 20$). The solid bars represent median levels. The dashed line represents the priming response. † $P \leq .03$ vs day 1, illustrating priming, and ** $P < .01$ and * $P < .03$ vs placebo, demonstrating the inhibitory effect of active treatment. FF, Fluticasone furoate nasal spray; PL, placebo.

Nasal secretions

Nasal secretions after both diluent and allergen challenges were collected from the site of stimulation and the contralateral nasal septum by using filter paper discs placed for 30 seconds.¹⁵ The discs were then placed in microtubes. The disc/tube combination was weighed before and after collection, allowing the computation of the weight of generated secretions.

Eosinophil evaluation

Before each nasal antigen challenge, a mucosal sample was obtained from the same spot the challenge disc was placed at by using a Rhinoprobe (Arlington Scientific Inc, Springville, Utah). The mucosal sample was then spread on a microscope slide and stained by using a modified Wright stain (Diff Quick Stain Set; Dade Behring Inc, Newark, De). Two hundred cells excluding epithelial cells were counted by an investigator blind to the treatment allocation. The percentage of eosinophils was then calculated.

Statistics

Before initiating the study, we performed a power calculation to estimate the number of subjects required on the basis of the objective measure of the nasosnasal reflex and our previous work.¹⁰ We speculated that the reduction in weight of nasal secretions after FFNS administration would be 8 mg compared with placebo. Assuming a population SD of 10 mg and $P < .05$ as significant, 20 subjects were estimated to be adequate to yield an 80% power of detecting a difference.

Because the data did not follow a normal distribution, we used nonparametric statistics to analyze the responses. To evaluate the effect of allergen challenge, we compared the responses obtained after allergen challenge with those after diluent challenge on different challenge days using a Wilcoxon matched-pairs signed-ranks test. To evaluate the priming effect, we compared the net change from the diluent response obtained on the 3 consecutive challenge days with the patients on placebo treatment by using a Wilcoxon matched-pairs signed-ranks test. To evaluate the effect of treatment, we compared the net change from diluent during placebo or FFNS for each set of data by using the Wilcoxon matched-pairs signed-ranks test. $P < .05$ was considered significant. Analysis was performed by using the Systat 11 package (Systat Software Inc, Richmond, Calif). Data are depicted as individual points for each subject with median values.

RESULTS

Twenty-one subjects were enrolled, and 20 completed the protocol. One participant was excluded for noncompliance. There were 13 men and 7 women with a median age of 24.5 years,

ranging from 19 to 44 years. Races included 11 white, 6 black, and 3 Asian. No adverse events were reported or observed with either the challenges or the treatment medications. A total of 32 volunteers were screened to identify the study participants.

Sneezing

Compared with challenge with diluent, antigen challenge during placebo treatment led to a significant increase in sneezing on all 3 challenge days ($P < .005$). When the change over diluent in sneezing was compared on the 3 days of challenge, the response exhibited priming with the patients on placebo: the sneezing response on day 1 (1.5) increased significantly on days 2 (3.5; $P = .03$ vs day1) and 3 (4.0; $P = .01$ vs day 1; Fig 2). When the subjects were on FFNS, the change from diluent in the sneezing response was reduced significantly compared with placebo on all 3 challenge days ($P < .03$), and there was no significant priming of the response on the 3 consecutive days. The change from diluent in the number of sneezes was 0 for all 3 days (day1 vs days 2 and 3, $P > .5$; Fig 2).

Nasal symptoms

Nasal symptoms of bilateral runny and stuffy nose and itchy nose/throat were added together and showed a significant increase after allergen compared with diluent challenges with the patients on placebo ($P \leq .0001$) and FFNS ($P \leq .001$) on all challenge days (Table I). There was no priming of total nasal symptoms after repeated challenges on either treatment. When the net change from diluent was evaluated, premedication with FFNS resulted in a significant reduction in total nasal symptoms on days 2 and 3 of challenge compared with placebo ($P \leq .004$; Table I).

Nasal secretion weights

After pretreatment with placebo, nasal secretion weights on days 1 to 3 showed a significant increase after allergen challenge compared with the diluent response in both the challenged ($P < .0001$) and contralateral ($P \leq .009$) nostrils. When the net change from diluent was examined on placebo treatment, secretion weights increased bilaterally while on placebo, but priming over the 3-day period was observed only with the contralateral

TABLE I. Total nasal symptoms (SXS; bilateral runny/stuffy nose and itchy nose/throat) and ipsilateral nasal secretion weights (SW)

	Day 1			Day 2			Day 3		
	Diluent	Allergen	Change	Diluent	Allergen	Change	Diluent	Allergen	Change
SXS challenge									
Placebo	1 (0-13)	6 (1-15)*	5 (-2-13)	2 (0-5)	7 (3-13)*	5 (0-10)	2 (0-6)	7 (2-13)*	6 (0-11)
FFNS	1 (0-4)	4 (0-13)†	3 (0-11)	1 (0-4)	4 (0-9)†	3 (-1-9)‡	1 (0-9)	4 (0-13)†	3 (-1-11)‡
SW challenge									
Placebo	8 (4-17)	26 (12-69)*	16 (6-53)	10 (3-32)	37 (7-67)*	21 (0-50)	11 (4-33)	35 (6-66)*	20 (-1-52)
FFNS	8 (2-46)	21 (5-46)*	9 (-4-41)§	6 (2-42)	19 (4-66)*	13 (-2-42)§	6 (2-35)	16 (3-56)*	11 (-4-36)§

Data presented as median (range). Total possible symptom score, 15.

Change, Net change over diluent.

* $P < .0001$.

† $P < .001$ vs diluent.

‡ $P < .004$ FFNS vs placebo.

§ $P < .059$ FFNS vs placebo.

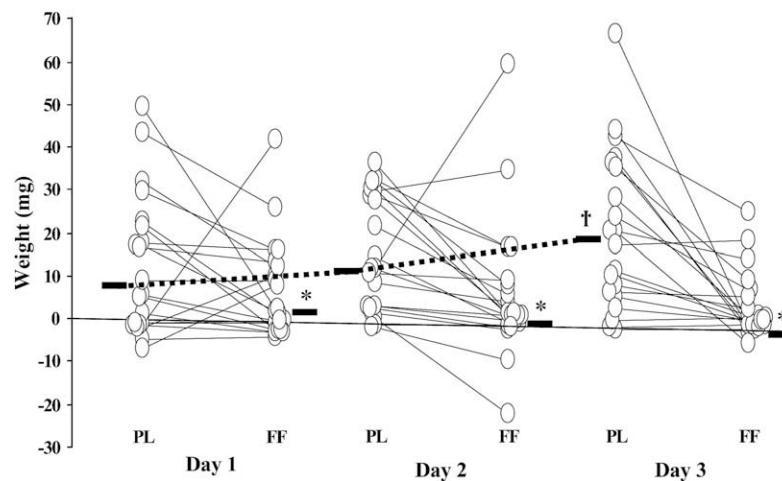


FIG 3. The effect of FFNS on contralateral nasal secretion weights after allergen challenge. The x-axis shows the time scale and pretreatment. Net change from diluent is depicted as individual data ($n = 20$). The solid bars represent median levels. The dashed line represents the priming response. † $P \leq .04$ vs day 1 and day 2, illustrating priming, and * $P < .04$ vs placebo, demonstrating the inhibitory effect of active treatment. FF, Fluticasone furoate nasal spray; PL, placebo.

reflex response on day 3 (day 3 vs day 1, $P = .012$; day 3 vs day 2, $P = .04$; Fig 3). FFNS treatment inhibited priming on the contralateral side and also inhibited the contralateral secretory response compared with placebo on all challenge days ($P \leq .04$; Fig 3). FFNS also reduced the ipsilateral secretory response, and this effect tended to approach statistical significance on all challenge days ($0.057 \leq P \leq .059$; Table I).

Ocular symptoms

The eye symptoms represent the sum of both watery and itchy eye symptoms for both eyes. Compared with the diluent response, subjects reported an increase in total eye symptoms after antigen challenge while on placebo ($P \leq .01$). When the net change over diluent for total eye symptoms was evaluated with the patients on placebo, the symptoms were higher on day 3 than day 1 of challenge ($P \leq .04$). Pretreatment with FFNS reduced total eye symptoms compared with placebo on all days, with the response on days 2 and 3 ($P \leq .004$) reaching statistical significance (Fig 4).

Eosinophils

There was an increase in the percentage of eosinophils on the third day of challenge compared with the first day while the

patients were on placebo, but the difference was not statistically significant ($P = .12$). Pretreatment with FFNS significantly reduced the percentage of eosinophils recovered on all 3 days ($P < .05$; Fig 5).

DISCUSSION

A localized unilateral nasal challenge with antigen led to sneezing and a nasopalmar reflex, which increased after 3 repetitive antigen challenges, demonstrating priming. Ocular symptoms also increased after each nasal challenge with antigen, supporting the existence of a nasal-ocular reflex response and its ability to prime in response to nasal inflammation. All these responses to a localized nasal antigen challenge were reduced by treatment with the intranasal steroid, FFNS. Eosinophils in nasal scrapings, a local biomarker of allergic inflammation, were also reduced by the intranasal steroid, suggesting that the reduction in allergic inflammation reduced the neurologic reflexes originating at the site of challenge, including the nasal-ocular reflex. A reduction in allergic inflammation and a reduction in the nasal-ocular reflex provide a potential mechanism to explain how treatment with an intranasal steroid may work locally in the nose to reduce the

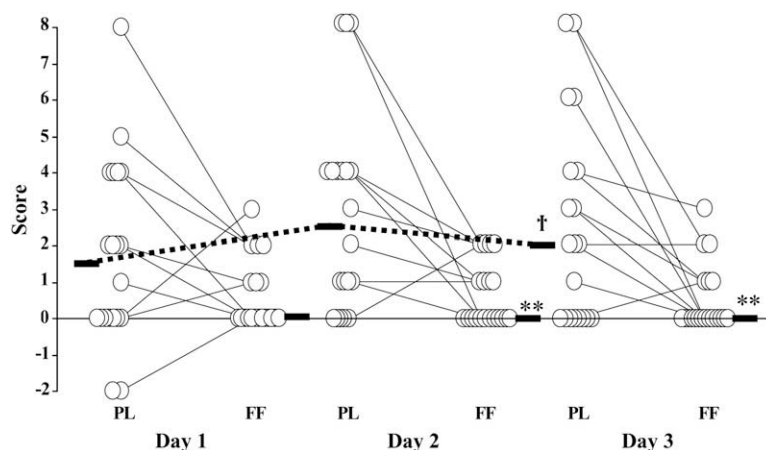


FIG 4. The effect of FFNS on the total eye symptom score after allergen challenge. The x-axis shows the time scale and pretreatment. Net change from diluent is depicted as individual data ($n = 20$). The solid bars represent median levels. The dashed line represents the priming response. $†P \leq .04$ vs day 1, illustrating priming, and $**P \leq .01$ vs placebo, demonstrating the inhibitory effect of active treatment. FF, Fluticasone furoate nasal spray; PL, placebo.

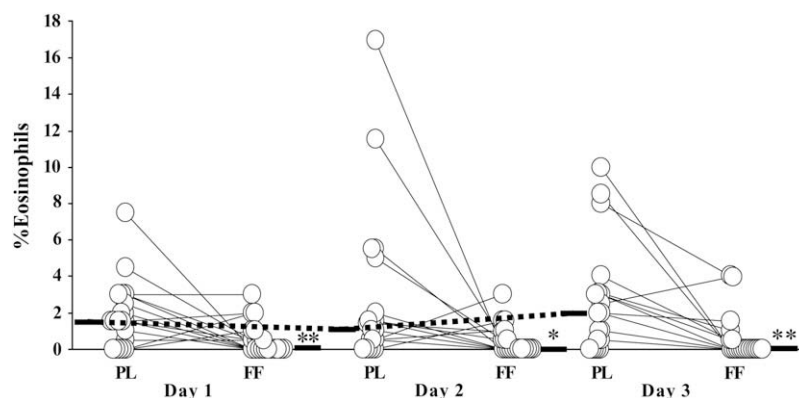


FIG 5. The effect of FFNS on the percentage of eosinophils in nasal scrapings. The x-axis shows the time scale and pretreatment. Percent eosinophils in scrapings obtained at the beginning of each challenge are depicted as individual data ($n = 20$). The solid bars represent median levels. The dashed line represents the priming response. $**P \leq .01$ and $*P \leq .05$ vs placebo, demonstrating the inhibitory effect of active treatment. FF, Fluticasone furoate nasal spray; PL, placebo.

ocular symptoms associated with allergic rhinitis. These findings also emphasize that not all ocular symptoms associated with allergic rhinitis originate from direct contact of antigen with the conjunctiva.

Because eosinophils were significantly reduced by active treatment before the first antigen challenge on day 1, even though the subjects were asymptomatic, it is possible that our subjects had some minimal inflammation present before challenge, which partially primed the neural reflex and made FFNS almost effective in reducing eye symptoms on day 1. Another explanation for the effectiveness of FFNS in inhibiting the reflex response on each day of antigen challenge is that a week of intranasal steroids has been shown to reduce the release of mast cell mediators in the nasal mucosa after allergen challenge, and thus histamine, which initiates the reflex.^{10,16}

The induction of the nasosnasal secretory reflex after unilateral antigen challenge has been well described.^{14,17-21} In this study we showed, for the first time, priming of the nasosnasal reflex and its inhibition by an intranasal steroid. The nasosnasal reflex also

served as a positive control for the nasal-ocular reflex. Sneezing, another neural reflex, also exhibited priming, and reduction by FFNS. Thus, the fact that the ocular response exhibited similar behavior to the other allergen-induced reflexes supports our hypothesis that eye symptoms can be generated after nasal allergen challenge by a nasal-ocular reflex.

Total nasal symptoms and ipsilateral secretion weights did not demonstrate priming. We suspect that total nasal symptoms did not prime because nasal congestion (scores obtained reflect both nostrils) primarily occurs on the side of challenge and is not reflex-mediated. Ipsilateral nasal secretions clearly increased, but did not reach significance, probably because generated secretions were larger than the collection capacity of the discs. We also suspect that inclusion of a higher number of subjects might have led to a demonstration of priming.

We are proposing that the beneficial effect of intranasal steroids in reducing eye symptoms in allergic rhinoconjunctivitis is, at least in part, related to its inhibition of nasal priming and, subsequently, a nasal-ocular reflex. However, several other

mechanisms of this beneficial action have been proposed. By inhibiting local nasal inflammation—that is, production of cytokines and infiltration of inflammatory cells—intranasal steroids may have indirect systemic effects that reduce inflammation in other tissues, including the eyes.²² This hypothesis would require exposure in the nose and a subsequent antigen exposure in the conjunctiva, which would cause an influx of cells that were primed by the nasal allergic reaction. Although this is feasible, it does not explain the results of our study because antigen was not applied to the eye. Another possible explanation is that intranasal steroids may reduce inflammation of the nasolacrimal duct, thereby improving nasolacrimal drainage and reducing conjunctival exposure to allergens and inflammatory mediators.²³ This hypothesis is undermined by the finding that nasolacrimal duct blockage does not increase the response to ocular antigen challenge, and by the Jones test, which shows continued patency of the nasolacrimal duct during allergic reactions in the nose.²⁴ It has also been suggested that intranasal steroids may travel through the nasolacrimal duct and thereby have direct anti-inflammatory effects on the conjunctiva. The lack of steroid-related ocular side effects, such as glaucoma and cataract, indicates that movement through the nasolacrimal duct is not a viable mechanism for the ocular effects of intranasal steroids. Although corticosteroids have potent systemic anti-inflammatory effects, systemic absorption of these agents after topical administration is below the level that would be expected to produce systemic effects, especially after the drug has been diluted by the blood before it can be delivered to the eye. Of direct relevance to our study, the systemic bioavailability of fluticasone furoate after intranasal administration is less than 0.5%. Therefore, it is unlikely that intranasal steroids act systemically to relieve ocular symptoms, especially those caused within minutes of antigen challenge.^{23,25}

Although our study investigated the effect of one of the available intranasal steroids, FFNS, it is likely that the observed beneficial effect on eye symptoms in patients with allergic rhinoconjunctivitis extends to other agents within this class. This is evidenced by several clinical studies using other intranasal steroids that demonstrate similar beneficial effects on eye symptoms.^{26,27}

Our study provides further evidence for the existence of a nasal-ocular reflex in the etiology of ocular symptoms during seasonal allergic rhinitis and shows how allergic inflammation augments this response. It also provides a potential mechanism, among many possible ones, by which intranasal steroids may reduce the ocular symptoms associated with allergic rhinitis without being systemically absorbed. It is interesting to speculate that seasonal allergic eye symptoms are a combination of a nasal-ocular reflex after nasal inhalation of allergen and the direct ocular response to antigen stimulation. The percent contribution of each mechanism is unknown, but is a critical clinical question. We speculate that the nasal-ocular reflex is the primary mechanism because active nasal breathing leads to much more pollen landing on the nasal mucosa compared with the conjunctiva and intranasal steroids effectively treat eye symptoms.

It would be useful to identify patients who have a greater contribution to their eye symptoms from the nasal-ocular reflex mechanism versus direct allergen deposition to help further refine treatment choices on the first visit to the clinician. Of relevance to this point is the interesting observation from our experiments that our volunteers had eye symptoms but little, if any, ocular redness.

It is therefore reasonable to speculate that the presence of redness, in the context of allergic symptoms, may be a sign of direct antigen stimulation or another ocular disease such as keratoconjunctivitis, which can cause significant ocular discomfort and impaired vision if not properly treated. If redness serves as a useful marker to identify subjects whose ocular symptoms might not respond to intranasal steroids alone, then we suggest that patients with allergic rhinitis and eye symptoms without prominent redness should be initially treated with an intranasal steroid alone. This would be the most effective treatment to eliminate nasal inflammation and nasal symptoms and reduce ocular symptoms, a strategy that would reduce the overall health costs for allergic rhinitis.

Clinical implications: This study demonstrates a potential mechanism to explain the efficacy of intranasal steroids in reducing eye symptoms in allergic rhinoconjunctivitis.

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