
Nasal ocular reflexes and eye symptoms in patients with allergic rhinitis

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Background: Allergic patients often complain of eye symptoms during the allergy season. A possible mechanism for these eye symptoms is a nasal ocular reflex.

Objective: To demonstrate eye symptoms after nasal allergen challenge.

Methods: In a double-blind, placebo-controlled, crossover, clinical trial, 20 patients with seasonal allergic rhinitis were challenged in 1 nostril with antigen, and the response was monitored in both nostrils and in both eyes. Symptoms were recorded. Filter paper disks (intranasally) and Schirmer strips (intraocularly) were used for collecting secretions, which were subsequently eluted for the measurement of histamine and albumin levels. Patients were treated once topically at the site of challenge with azelastine or placebo.

Results: After placebo treatment, ipsilateral nasal challenge caused nasal symptoms and an increase in secretion weights; both were blocked by treatment with azelastine. Histamine and albumin levels increased only at the site of nasal challenge. Azelastine pretreatment inhibited the increase in albumin but not histamine levels. Symptoms of itchy and watery eyes increased significantly compared with symptoms with sham challenge after nasal allergen and were blocked by azelastine use. Ocular secretion weights increased bilaterally after placebo use and were not inhibited by azelastine use.

Conclusions: Nasal allergen challenge releases histamine at the site of the challenge, which probably initiates a nasonasal and a nasal ocular reflex. This reflex is reduced by an H₁-receptor antagonist applied at the site of the challenge. The eye symptoms associated with allergic rhinitis probably arise, in part, from a naso-ocular reflex.

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INTRODUCTION

Symptoms of conjunctivitis (tearing and itching) occur frequently in patients with allergic rhinitis. The pathogenesis underlying these symptoms remains to be elucidated. We hypothesize that eye symptoms arise via a combination of mechanisms, including direct contact of natural pollen with the conjunctiva and reflex mechanisms originating in the nose.

Reflex mechanisms in the nose have been shown to occur commonly in response to nasal challenge with antigen, which induces a reflex in the contralateral nasal cavity.¹ The contralateral response to antigen is blocked by topical anticholinergic agents applied to the contralateral nostril, suggesting that the efferent limb is parasympathetically mediated.² Histamine is released only on the side of challenge with antigen, but oral H₁ antihistamines reduce the contralateral response to unilateral nasal allergen challenge, suggesting that histamine contributes to initiation of the reflex.³ A nasonasal reflex also

follows a unilateral challenge with cold dry air,⁴ histamine,⁵ and capsaicin⁶ but not with methacholine.⁵

The eye is richly innervated by parasympathetic nerves, which enter the eye after traveling in conjunction with the parasympathetic input to the nasal cavity. We, therefore, hypothesized that the conjunctiva will respond to nasal allergen in a manner similar to the response of the contralateral nasal cavity and that an intranasal H₁ antihistamine would at least partially block this response.

MATERIALS AND METHODS

Study Design

We performed a double-blind, placebo-controlled, 2-way crossover study in 20 healthy patients who had a history of grass or ragweed allergy symptoms. Patients came to the Nasal Physiology Laboratory at The University of Chicago for screening, where they completed an allergy questionnaire and underwent skin prick testing for confirmation of a positive grass or ragweed allergy. Depending on skin test results, eligible patients then underwent a screening nasal challenge with either grass or ragweed allergen outside their allergy season. This study was approved by the institutional review board of The University of Chicago, and all the patients gave written informed consent before entry.

Patients who passed the screening challenge (ie, exhibited an ocular reflex after nasal allergen challenge as determined by increased secretions) had a 2-week washout period, and 20 responders were asked to return to the Nasal Physiology

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Laboratory, where they were randomized to receive either placebo or azelastine hydrochloride (274 µg) delivered intranasally via a metered-dose spray bottle. Ten minutes after treatment, patients underwent a nasal challenge with diluent and with the dose of allergen that caused the ocular reflex during the screening challenge. Next, the patients had a 2-week washout period and then crossed over to administration of the other treatment followed by a similar challenge.

Nasal Challenge

The localized nasal challenges and evaluation of the nasal reflex response were performed using filter paper disks.² In brief, each challenge consisted of placement of a disk on the anterior nasal septum beyond the mucocutaneous junction. Fifty microliters of challenge solution was placed on the disk, and it was kept on 1 side of the nasal septum for 1 minute. Grass antigen extract concentrations were 333 and 1,000 BAU/mL, and ragweed antigen extract concentrations were 1:666 and 1:200 wt/vol. Thirty seconds after removal, 2 preweighed collection disks were placed on both sides of the nasal septum for 30 seconds. After removal of the collection disks from the nose, preweighed Schirmer strips (Haag-Streit UK Ltd, Harlow, Essex, England) were placed in each eye for collecting ocular secretions for 4 minutes. Nasal and ocular symptoms were recorded by the patients.

The next challenge was performed approximately 10 minutes after the previous nasal challenge. The first challenge in a given experiment was always performed with the diluent for the allergen extracts followed by single or increasing doses of grass or ragweed extracts. In pilot experiments, Schirmer strips caused significant eye irritation and tearing; therefore, proparacaine hydrochloride ophthalmic solution, USP 0.5% (Akorn Inc, Buffalo Grove, Illinois), was applied, 2 drops in each eye repeated twice (total of 4 drops in each eye) at a 5-minute interval 1 to 2 minutes before the initial challenge began.

The screening challenge was usually performed using 2 increasing doses of allergen after diluent challenge. Screening responders, who would qualify for the full study, were defined as having an increase in eye secretions after allergen challenge compared with diluent challenge and an increase in nasal symptoms and nasal secretion weights. The study challenges were then performed using only the allergen challenge dose that resulted in the ocular reflex response, which was 1,000 BAU/mL of grass extract or 1:200 wt/vol of ragweed extract in all cases.

Symptoms

Nasal symptoms (congestion, rhinorrhea, itchy nose/throat, and sneezing) and eye symptoms (watery and itchy) were rated on a scale from 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe) and recorded by the patients. The number of sneezes after each challenge was also recorded. Nasal symptoms were recorded for each nasal cavity separately, whereas eye symptoms reflected the status of both eyes.

Secretions and Mediators

Before collection of secretions, the filter paper disks and the Schirmer strips had been placed in sealed Eppendorf tubes, and the tube-filter paper combinations were weighed. After collection, the filter paper disks or strips were replaced in their respective tubes and weighed again. The change in weight represents the amount of secretions collected during the time of placement. Three hundred microliters of phosphate-buffered saline was added to the tubes, and they were stored at 4°C for 24 hours for elution of secretions. After 24 hours, the tubes were vortexed, the filter papers were squeezed to the bottom of the tubes, and the supernatants were aliquoted to plastic tubes and frozen at -20°C until being assayed for histamine and albumin. Histamine levels were measured using a commercially available competitive direct enzyme-linked immunosorbent assay sensitive to 2.5 ng/mL (Oxford Biomedical Research Inc, Oxford, Michigan). Levels below the detection limit were assigned a value of 1.25 ng/mL, and all the samples were run in 1:5 dilution. Albumin levels were measured using an enzyme-linked immunosorbent assay sensitive to 1 ng/mL, as previously described.⁷ The samples for the albumin assay were run in 3 dilutions (1:50, 1:500, and 1:2,500), and the values in the range of the standard curve were used. Levels below the detection limit were assigned a value of 0.5 ng/mL.

After the concentration of the mediator in the eluate was obtained, and because the volumes of the eluate and the generated nasal secretions were known, it was possible to calculate the total amount of mediator recovered, and these data are reported.² For example, if the concentration of histamine obtained from the assay is referred to as *X* (ng/mL) and the volume of eluate used in the experiments is referred to as *Y* (µL), then to convert the value of histamine obtained from the assay to total histamine (*Z*) (ng) during each specific time point we used the following formula:

$$Z \text{ (ng)} = X \text{ (ng/mL)} \times [Y \text{ (}\mu\text{L)} + \text{Secretion Weight (mg)}] / 1,000 \text{ (}\mu\text{L/mL)}$$

Statistical Analyses

We performed a power calculation to estimate the number of patients. We speculated that the reduction in the weight of ocular secretions after azelastine administration would be 8 mg compared with placebo use. We speculated that the SD for the weight would be 10 mg. If we assume that *P* < .05 is statistically significant, a difference of 8 mg is a clinically significant reduction in secretion weight, and the population SD is 10 mg, then having 20 patients in each group would have 80% power to detect a difference.

Because the data were not distributed normally, nonparametric statistical analyses (Wilcoxon signed rank tests) were used for evaluating the responses. The data are presented as individual points connected by lines to indicate the paired nature of the data. When numerical data are reported, the median (range) is given. To compare the 2 treatments, we calculated the change from the diluent response induced by

antigen by subtracting the response after diluent challenge from that after antigen challenge. $P < .05$ was considered statistically significant.

RESULTS

We screened 32 patients. One patient decided not to participate, 4 failed the screening on the basis of lack of eye symptoms, and 6 failed screening for lack of nose and eye symptoms. Twenty-one patients enrolled, and 20 completed the protocol. One patient did not comply with study procedures and was dropped. There were 12 women and 8 men. The median patient age was 26.5 years (range, 20–42 years). There were 14 white patients, 3 African American patients, and 3 others. No adverse events were reported or observed.

Nasal Symptoms

Antigen challenge led to a significant increase in sneezing, which was blocked by treatment with azelastine (Fig 1). Patients reported an increase in scores for rhinorrhea on the challenge side, and also on the contralateral side when they received placebo. These symptoms were reduced bilaterally by treatment with azelastine, and the difference in reduction was significantly greater after azelastine use compared with placebo use. Allergen challenge led to significant increases in nasal congestion on the challenge side and on the contralateral side compared with responses after diluent challenge. Pretreatment with azelastine had no effect on the allergen-induced increase in nasal congestion (Table 1). When symptoms of itchy nose or throat were examined, there were modest increases after allergen challenge after placebo pretreatment, which were inhibited by pretreatment with azelastine ($P = .03$).

Ocular Symptoms

Patients reported an increase in scores for itchy (Fig 2) and watery eyes when they received placebo. These symptoms were reduced bilaterally by treatment with azelastine, and the difference in reduction was significantly greater after azelastine use than after placebo use (Fig 2).

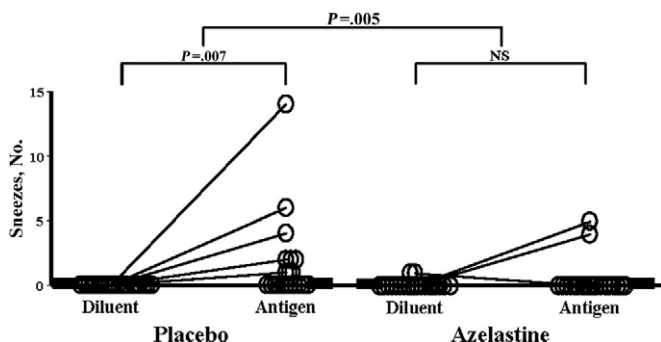


Figure 1. Effect of premedication with azelastine on the sneezing response after allergen challenge ($n = 20$). The x-axis shows the type of challenge and pretreatment. Thick horizontal bars represent medians. NS indicates nonsignificant.

Secretion Weights

Nasal secretion weights ipsilateral to allergen challenge showed a significant increase after allergen challenge compared with the diluent response. When the patients were premedicated with azelastine, there was no significant increase in ipsilateral secretion weights compared with diluent challenge. The net change from diluent challenge in ipsilateral secretion weights was significantly lower after azelastine pretreatment compared with placebo pretreatment. There was an increase in contralateral secretions after allergen challenge only after placebo treatment, and the change from diluent challenge showed a significant inhibitory effect of azelastine (Fig 3).

In the eye ipsilateral to the allergen-challenged nostril, secretion weight results showed a significant allergen-induced increase compared with diluent challenge when patients were pretreated with placebo and azelastine (Fig 4). Although the change in secretion weights between allergen and diluent challenges was lower after azelastine pretreatment (4.25 mg; -3 to 24 mg) compared with placebo pretreatment (6.65 mg; -10.4 to 34.2 mg), the change was not statistically significant ($P = .18$). Similar results occurred in the contralateral eye. The change from diluent challenge was also decreased after azelastine use (2.4 mg; -3.7 to 26.4 mg) compared with placebo use (8.8 mg; -17.9 to 28.4 mg), but the difference was not statistically significant ($P = .2$).

Mediators

Histamine results are reported for 19 patients because 1 set of samples was unavailable for assay. Histamine levels were significantly increased only in the secretions collected at the site of challenge (Fig 5). This increase in histamine levels was not affected by pretreatment with azelastine. There was no significant increase in histamine levels in the nasal cavity contralateral to the challenge. Ocular histamine levels were essentially undetectable after all challenges.

Nasal albumin levels increased significantly on the challenge side when allergen responses were compared with diluent responses after placebo pretreatment and after azelastine pretreatment (Fig 6). Azelastine use led to a significant reduction in nasal albumin levels after allergen challenge (Fig 6). There were modest but significant increases in allergen-induced albumin levels in the nostril contralateral to challenge compared with diluent responses after placebo and azelastine pretreatment. Azelastine had no effect on this response.

On the side ipsilateral to the nasal challenge, allergen challenge resulted in a significant increase in ocular albumin levels ($10.4 \mu\text{g}$; 0.5 to $62.1 \mu\text{g}$) compared with diluent challenge ($3.6 \mu\text{g}$; 0.1 to $28.4 \mu\text{g}$) after pretreatment with placebo ($P = .03$). There were no significant changes after azelastine treatment in ocular albumin levels ipsilateral to nasal allergen challenge, and when the changes from diluent challenge were compared, there was no significant effect of active treatment. On the side contralateral to the nasal chal-

Table 1. Stuffy Nose Symptoms^a

Treatment	Ipsilateral symptoms			Contralateral symptoms		
	Diluent	Allergen	Change	Diluent	Allergen	Change
Placebo	0 (0–2)	1 (0–3) ^b	0 (0–3)	0 (0–3)	1 (0–3) ^b	0 (0–3)
Azelastine	0.5 (0–3)	1 (0–3) ^c	0 (0–3)	0 (0–3)	1 (0–3) ^c	0 (0–3)

^a Data are given as median (range) nasal congestion scores.

^b $P < .01$ vs responses after diluent challenge.

^c $P < .05$ vs responses after diluent challenge.

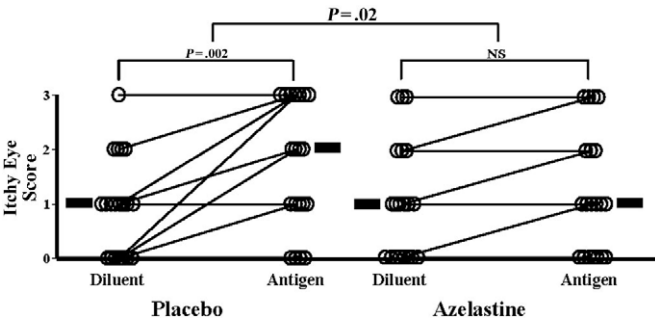


Figure 2. Effect of premedication with azelastine on itchy eye symptoms after allergen challenge ($n = 20$). The x-axis shows the type of challenge and pretreatment. Thick horizontal bars represent medians. NS indicates nonsignificant.

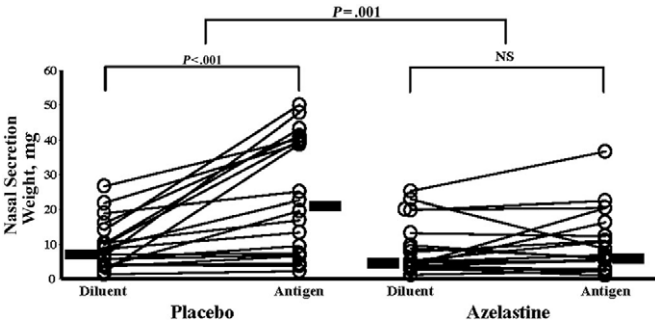


Figure 3. Effect of premedication with azelastine on contralateral nasal secretion weights after allergen challenge ($n = 20$). The x-axis shows the type of challenge and pretreatment. Thick horizontal bars represent medians. NS indicates nonsignificant.

lenge, there were no significant increases in ocular albumin levels after allergen challenge.

DISCUSSION

To summarize, a unilateral nasal challenge with antigen leads to localized histamine release, an increase in nasal vascular permeability, a nasonasal secretory reflex, and increased eye itching and lacrimation bilaterally, which was detected by diary and secretion weights. The symptom and secretion response in the nose was significantly inhibited by a topical H_1 antihistamine applied only to the side of antigen challenge. Active treatment inhibited the ipsilateral allergen-induced increase in vascular permeability but had no effect on hista-

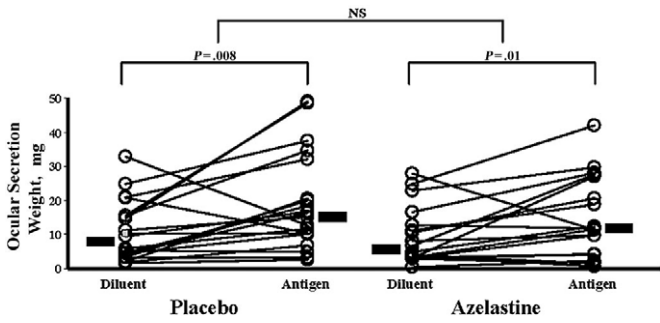


Figure 4. Effect of premedication with azelastine on ipsilateral ocular secretion weights after allergen challenge ($n = 20$). The x-axis shows the type of challenge and pretreatment. Thick horizontal bars represent medians. NS indicates nonsignificant.

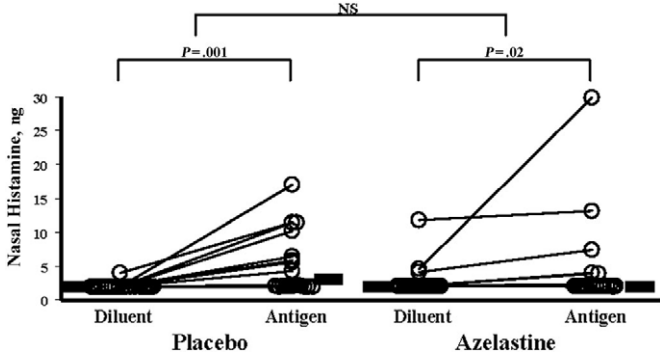


Figure 5. Effect of premedication with azelastine on ipsilateral nasal histamine level after allergen challenge ($n = 19$). The x-axis shows the type of challenge and pretreatment. Thick horizontal bars represent medians. NS indicates nonsignificant.

mine release. The intranasally applied H_1 antihistamine also resulted in a significant reduction in ocular symptoms. Ocular secretions were reduced, but not significantly, by active treatment.

Because tearing was increased equally in both eyes, we postulate that it occurred secondary to a cholinergically mediated central reflex. Because a topical intranasal H_1 antihistamine was effective in inhibiting the response, we conclude that histamine released during the acute response to antigen contributes to initiation of the reflex. The possibility that histamine released in the nose was absorbed systemically and reached the eye, thus leading to the ocular symptoms, is not

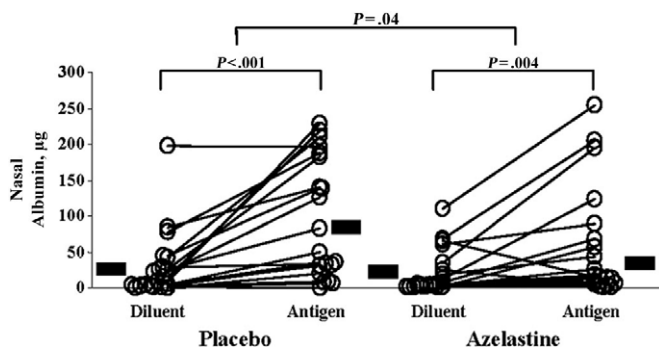


Figure 6. Effect of premedication with azelastine on ipsilateral nasal albumin levels after allergen challenge ($n = 20$). The x-axis shows the type of challenge and pretreatment. Thick horizontal bars represent medians.

likely because the small amounts of histamine generated in the nose after allergen challenge would be diluted significantly, and, thus, several-fold lower concentrations would reach the eye, and these are probably not likely to cause the observed symptoms. Furthermore, previously published studies on the nasonasal reflex have shown that the most potent inhibitor of the contralateral nasal secretory response in response to ipsilateral allergen challenge is atropine.² This supports the role of an efferent parasympathetic reflex arm in the contralateral secretory response. We chose not to apply atropine to the eye because atropine causes prolonged pupillary dilatation, and the parasympathetic innervations to the lacrimal glands is posterior and would be difficult, if not impossible, to block with a topically applied anticholinergic agent.

The inhibitory effects of azelastine on the eye response were significant with the eye symptoms but not with the objective measure of eye secretion production. We speculate that the reason for this discrepancy is related to the larger variability in the secretion weights collected by the Schirmer strips after diluent challenge, which prevented us from showing a significant reduction in the eye secretory response. Other explanations might include the importance of other mediators in initiating the reflex, the use of a single dose of azelastine, and the fact that only a single antigen challenge rather than a dose-response challenge was used. One could speculate that the positive effect of azelastine on eye symptoms might be related to systemic absorption of the drug after intranasal administration. This is unlikely for 2 reasons: (1) the amount of drug delivered to the nose was small and would undergo significant dilution in the bloodstream, likely to result in a negligible concentration in the eye, and (2) there was no significant histamine release in the eye after allergen challenge of the nose. One could also speculate that azelastine could have reached the eyes directly via aerosolized particles or via the nasolacrimal duct. The tip of the spray bottle was placed carefully inside the nostril during activation, and no aerosolized particles are likely in this case to reach the eye directly. Furthermore, the flow of tears from the

eye to the nose and the location of the opening of the nasolacrimal duct in the inferior meatus precluded the azelastine from reaching the eye directly through the nasolacrimal duct. In addition, only 1 nostril was treated, making bilateral effects unlikely.

Although antihistamines at high concentrations have been shown *in vitro* and *in vivo* to reduce histamine release from basophils and mast cells,^{8,9} this inhibition has not been consistent for all antihistamines. Indeed, the results of this study are similar to those of a previous nasal challenge study¹⁰ in which histamine release was not blocked by pretreatment with intranasal azelastine.

The nasonasal reflex after unilateral challenge with allergen has been described and studied extensively.^{1,3,11-14} Histamine initiates this parasympathetic reflex.² In this study, we used the nasonasal reflex as a positive control and confirmed the previous findings as they relate to secretion weights, histamine release, and ipsilateral albumin levels.

Previous studies of the nasal ocular reflex after antigen stimulation have presented mixed results. Zilstorff-Pedersen¹⁵ reported bilateral lacrimation after unilateral irritation of the nasal mucosa. Using capsaicin as a stimulant and as a desensitizer, Philip and colleagues⁶ showed that unilateral nasal challenge with capsaicin produced ocular tearing and watering, which was reduced significantly after repeated capsaicin challenges, which led to desensitization of the response. Lebel and colleagues¹⁶ reported that approximately 20% of patients with allergic rhinitis experienced ocular symptoms during nasal provocation, suggesting that allergic ocular symptoms can occur without direct exposure of the conjunctiva to allergen. Loth and Bende¹⁷ concluded that nasal challenge with allergen does not increase lacrimal gland secretion because inhibition of parasympathetic nerves by lidocaine did not reduce tears. The conclusions of this study can be questioned because the placebo arm did not demonstrate a significant increase in lacrimation after allergen challenge. For the present study, we preselected individuals who had a nasal ocular reflex, and the results confirmed a positive nasonasal reflex, showed a nasal ocular reflex, and demonstrated subjective inhibition of the nasal ocular reflex by pretreatment with an intranasal H_1 -receptor antagonist.

There is ample evidence that symptoms of conjunctivitis can be produced by application of antigen into the eye of an allergic individual.¹⁸⁻²¹ However, what is not known is the relative contribution of direct allergen stimulation vs nasolacrimal reflexes in the genesis of ocular symptoms in patients with rhinoconjunctivitis. The amount of allergen deposited on the nasal mucosa with active inhalation of air is expected to be much higher than the amount of pollen deposited on the ocular conjunctiva without inhalation. One would suspect that even less allergen would be recovered indoors or on nonwindy days. Therefore, the nasal ocular reflex has to be at least a partial contributor to the eye symptoms in rhinoconjunctivitis. Further support for this speculation is that intranasal corticosteroids have been shown to reduce the ocular symptoms of allergic rhinoconjunctivitis to an extent compa-

table with that provided by oral antihistamines.²² We hypothesized that the nasal ocular reflex is augmented by allergic inflammation and that treatment with an intranasal corticosteroid reduces nasal inflammation and decreases the strength of the nasal ocular reflex and the eye symptoms perceived by the patient.

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