Randomized, Double-Masked Comparison of Olopatadine Ophthalmic Solution, Mometasone Furoate Monohydrate Nasal Spray, and Fexofenadine Hydrochloride Tablets Using the Conjunctival and Nasal Allergen Challenge Models

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ABSTRACT

Background: It is presumed that exposure to allergens in the environment occurs through both the eyes and the nose. Allergic rhinoconjunctivitis is typically treated with a nasal spray or systemic antihistamine, neither of which may provide adequate relief of the ocular component of the disease.

Objective: This study was designed to gain a better understanding of the physiologic interaction between the conjunctival and nasal mucosa and thus help establish a profile for the most effective ocular treatment in patients whose allergies have both an ocular and a nasal component.

Methods: This was a single-center, randomized, double-masked clinical study using the conjunctival allergen challenge (CAC) and nasal allergen challenge (NAC) models. It compared the clinical signs and symptoms induced by CAC and NAC, the effects of drugs administered by 3 different routes, and the movement of fluorescein after instillation into the eye and nose (Jones test), and assessed levels of inflammatory mediators in tears and nasal secretions. At visit 1, subjects previously identified as CAC responders underwent NAC to determine the dose of allergen necessary to elicit a sufficient positive reaction. At visit 2, which took place 1 week later, subjects with a positive reaction at visit 1 were randomized to group A (CAC) or group B (NAC), and underwent challenge to confirm the allergen dose necessary to produce a positive reaction. Subjects who qualified were randomized to receive 1 of 3 treatments: olopatadine 0.1% ophthalmic solution,
placebo nasal spray, and placebo tablets; mometasone furoate monohydrate 50-µg nasal spray, placebo topical solution, and placebo tablets; or fexofenadine hydrochloride 180-mg tablets, placebo topical solution, and placebo nasal spray. All study medications were administered according to their approved labeling: drops were administered twice daily in the eyes, and the nasal sprays and tablets were administered once daily. At visit 3, which took place 1 week after visit 2, subjects received study medication and 15 minutes later underwent CAC or NAC as before. The primary efficacy variables were ocular itching, ocular redness, and overall nasal symptoms (sneezing, rhinorrhea/postnasal drip, nasal pruritus, palatal pruritus, and nasal congestion) rated on standard scales. Peak nasal inspiratory flow (PNIF) was measured at each visit, and the Jones test was performed at visits 1 and 3. At baseline and after challenge at visits 2 and 3, tear and nasal lavage samples were collected from a subset of randomly selected subjects for analysis of eosinophil cationic protein and tryptase.

Results: Seventy-three subjects (42 women, 31 men; mean age, 45.26 years [range, 21–73 years]) were screened, and all were randomized to treatment. Two subjects did not complete the study. CAC induced clinically significant (>1 unit difference) ocular and nasal signs and symptoms, whereas NAC induced clinically significant nasal signs and symptoms only. In group A, there was a greater reduction in ocular itching with olopatadine compared with mometasone and fexofenadine at 3 minutes (P = 0.003 and P = 0.008, respectively) and 5 minutes (P = 0.007 and P = 0.013) after challenge. Although the difference was not statistically significant, overall relief of conjunctival redness (average of 3 vessel beds) was greatest in the olopatadine group, followed by fexofenadine. In group B, prevention of total nasal symptoms was significantly greater with mometasone compared with fexofenadine at 20 minutes (P = 0.006) and 30 minutes (P = 0.014) after challenge. There were no statistically significant differences between treatment groups in nasal symptom scores at any time point after CAC. There were also no significant differences in PNIF between treatment groups. Fluorescein was present in nasal secretions within 5 minutes of being instilled into the eye; no fluorescein was detected in the eye after instillation into the nose.

Conclusions: In this study, exposure of the nasal mucosa to allergen resulted in allergic rhinitis, and exposure of the ocular surface to allergen resulted in conjunctivitis with a secondary effect in the nose. These results suggest movement of allergens, their mediators, and antiallergy drugs from the ocular surface into the nasal cavity, with no meaningful movement from the nasal cavity to the ocular surface. In this controlled model, both the systemic agent and the nasal spray failed to control ocular symptoms. The topical ophthalmic solution provided the most effective management of allergic ocular signs and symptoms, and the nasal spray was most effective for nasal symptoms. Combined use of a nasal spray and topical ophthalmic solution may provide maximal relief in patients whose aller-
INTRODUCTION
The conjunctival and nasal mucosa are similar in terms of the underlying immunologic pathways through which environmental allergens induce an immunoglobulin E (IgE)/mast cell–mediated event, although the signs and symptoms may be different. Whereas some patients experience only conjunctivitis and some only rhinitis, the majority experience both ocular and nasal symptoms.

The eye and the nose are connected anatomically by the nasolacrimal drainage system, which allows drainage of fluid from the eye into the inferior turbinate of the nasal cavity. The nasolacrimal duct provides a route for allergen, inflammatory mediators released by mast cells in the eye, and topically applied pharmaceutical agents to move from the eyes to the nose. The immunologic pathway by which both nasal and ocular signs and symptoms are triggered involves exposure to allergen, followed by IgE antibody cross-linkage and binding to mast cells. This cross-linkage activates mast cells and leads to release of a cascade of allergic and inflammatory mediators. In the eye, the release of these mediators causes the classic signs and symptoms of allergic conjunctivitis—itching, redness, chemosis, and eyelid swelling; in the nose, it causes sneezing, postnasal drip, congestion, and nasal and palatal pruritus.

Conventional treatments for rhinoconjunctivitis include nasal sprays and systemic antihistamines. However, these treatments overlook the ocular component of rhinoconjunctivitis. Based on the quantity of over-the-counter antihistamine topical ophthalmic solutions purchased, it is evident that the ocular component is an important concern for millions of patients. The general perception is that when nasal symptoms are addressed, the problem is solved; however, this is not true for the 50% of rhinitis patients who also experience ocular symptoms that are untreated by systemic antihistamines or nasal sprays.

Current treatment options for the control of symptoms of rhinoconjunctivitis include nasal sprays, systemic agents, topical ocular medications, and immunotherapy for nasal allergy. For the present study, we selected 1 standard, widely used product from each of 3 categories: nasal spray, systemic agent, and topical ocular medication. Olopatadine hydrochloride 0.1% ophthalmic solution*

*Trademark: Patanol® (Alcon Laboratories, Inc., Fort Worth, Texas)
is approved for the treatment of the signs and symptoms of allergic conjunctivitis; it reduces allergic symptoms through its antihistaminic properties and through inhibition of the release of histamine and other proinflammatory allergic mediators from mast cells.\textsuperscript{3-5} Mometasone furoate monohydrate nasal spray\textsuperscript{7} is a steroidal product indicated for the treatment of the nasal symptoms of seasonal and perennial rhinitis in patients aged \( \geq 3 \) years and for prophylaxis against nasal symptoms in patients aged \( \geq 12 \) years.\textsuperscript{6} Steroidal nasal sprays such as mometasone furoate are potent anti-inflammatory agents that work by suppressing production of proinflammatory mediators such as cytokines and prostaglandins.\textsuperscript{7} Nasal sprays are not indicated for the treatment of ocular signs or symptoms. Fexofenadine hydrochloride\textsuperscript{7} is a systemic antihistamine indicated for the relief of symptoms associated with allergic rhinitis. As with other agents in its class (desloratadine,\textsuperscript{8} loratadine,\textsuperscript{8} and cetirizine\textsuperscript{7}), the indications for fexofenadine include an ocular component, in its case itchy, watery, or red eyes.\textsuperscript{8}

The approval of these systemic antihistamines for use in the treatment of certain ocular symptoms was based on the use of grouped or summed symptom scores for both ocular and nasal symptoms. This method may allow observation of subtle differences within the class of systemic antihistamines, but the differences do not reach acceptable levels of clinical relevance based on US Food and Drug Administration (FDA) guidelines for the approval of ophthalmic agents. It has been reported that more efficacious treatment of topical disease is achieved with the use of topical treatments.\textsuperscript{9,10} Topical therapies directly applied to the tissue achieve high drug concentrations, whereas systemic agents are absorbed into the bloodstream, with only a small fraction of drug reaching the intended site of action. It has also been reported that systemic antihistamines have drying effects on the eyes, which may lead to exacerbation of ocular allergies.\textsuperscript{9,10}

Patients with rhinoconjunctivitis may be prescribed a nasal spray or systemic agent alone or a combination of the 2 on the assumption that this therapy will address their ocular symptoms. However, this may not be the most effective method for managing both the nasal and ocular symptoms of allergy. This study was designed to investigate the relationship between the eye and nose in allergic rhinoconjunctivitis and how this relationship contributes to the patterns of efficacy of drugs administered by 3 different routes—ocular, nasal, and systemic—in the conjunctival allergen challenge (CAC) and nasal allergen challenge (NAC) models. In these standard models, allergen is instilled into either the conjunctiva or nasal cavity to produce a controlled allergic reaction. With control of other

\textsuperscript{1}Trademark: Nasonex\textsuperscript{®} (Schering Corporation, Kenilworth, New Jersey).
\textsuperscript{2}Trademark: Allegra\textsuperscript{®} (Aventis Pharmaceuticals Inc., Bridgewater, New Jersey).
\textsuperscript{3}Trademark: Clarinex\textsuperscript{®} (Schering Corporation).
\textsuperscript{4}Trademark: Claritin\textsuperscript{®} (Schering Corporation).
\textsuperscript{5}Trademark: Zyrtec\textsuperscript{®} (Pfizer Inc, New York, New York).
variables, these models are precise tools for the assessment and comparison of therapies.\textsuperscript{11,12}

**SUBJECTS AND METHODS**

Eligible subjects were aged ≥18 years, able to follow study instructions, and willing to avoid disallowed medications (systemic or topical antihistamines, corticosteroids, mast-cell stabilizers, acetylsalicylic acid, decongestants, or any other ophthalmic or nasal preparations) during a prestudy washout period and during the study itself. They had a positive history of allergic rhinoconjunctivitis, a positive skin test result within 2 years of visit 1, and a positive CAC within the past year. Subjects who wore contact lenses were required to discontinue their use 3 days before visit 1 and throughout the study.

The protocol for this single-center, randomized, double-masked, 3-visit study was reviewed and approved by an independent review board (IntegReview, Inc., Austin, Texas). Written informed consent was obtained from each subject. The study design is illustrated in Figure 1.

**Study Assessments**

*The CAC Model*

The CAC model has been used extensively to assess the efficacy of ocular anti-allergic agents and is accepted by the FDA for this purpose. It provides a controlled environment in which to simulate an acute ocular allergic reaction.\textsuperscript{11} The model uses results of previous skin testing to determine the allergen to which the subject is most sensitive. Allergen is then placed in the subject’s eyes to elicit a reproducible reaction.

In this study, CAC was performed according to methods that have been described elsewhere.\textsuperscript{11} Subjects rated ocular itching on a scale from 0 to 4 and eyelid swelling on a scale from 0 to 3. Using slit-lamp biomicroscopy, the investigator rated redness and chemosis on a scale from 0 = none to 4 = extremely severe.

*The NAC Model*

The NAC is the standard model used to assess anti-allergic agents for the treatment of rhinitis.\textsuperscript{13–19} It involves delivery of 100 μL of the allergen to which a subject is sensitized (as indicated by a positive skin test result) into each nostril via a nasal spray pump.\textsuperscript{18–20}

In the present study, NAC was performed with ragweed, cat hair/dander, tree pollen, or grass pollen. Subjects rated the following nasal symptoms using adapted versions of standard NAC scales:\textsuperscript{18–20} sneezing (scale from 0 = no sneezes to 2 = >5 sneezes), rhinorrhea and postnasal drip (0 = neither to 3 = both), nasal pruritus (0 = absent to 1 = present), palatal pruritus (0 = absent to 1 = present), and
Figure 1. Study design. NAC = nasal allergen challenge; PNIF = peak nasal inspiratory flow; CAC = conjunctival allergen challenge.
nasal congestion (0 = no congestion to 3 = both nostrils blocked). The highest possible total nasal symptom score was 10, and the lowest was 0 (no symptoms).

**Peak Nasal Inspiratory Flow**

At each visit, peak nasal inspiratory flow (PNIF) was measured on a standard scale using an In-Check™ inspiratory flowmeter (Clement Clarke International, Harlow, United Kingdom) with a nasal adaptor. Measurements were taken with the subject in the standing position. Subjects were instructed to exhale to residual volume, place a face mask over the mouth and nose, and then inhale forcefully through the nose to total lung capacity. Three consecutive measurements were made at 30 and 60 minutes after administration of allergen.

**The Jones Test**

The Jones test was performed at visits 1 and 3. At visit 1, 1 drop of fluorescein was instilled in each eye, and a cobalt blue light was used to determine drainage of fluorescein into the nasal secretions 5 minutes after instillation. At visit 3, fluorescein was instilled into the nose via nasal spray, and again the ocular surface was examined for the presence of fluorescence 5 minutes after instillation. This sequence was designed to test the hypothesis of the unidirectional nature of the nasolacrimal duct; namely, the occurrence of downward flow from the eye to the nose through this duct and the lack of upward flow.

**Determination of Eosinophil Cationic Protein and Tryptase Levels**

Levels of eosinophil cationic protein (ECP) and tryptase were determined from tear and nasal lavage samples obtained from a subset of subjects selected based on a predetermined randomization schedule, the timing of their scheduled visits, and the availability of the assay equipment. ECP is released by eosinophils, and tryptase is a specific marker for mast-cell degranulation. Mast cells release chemotactic factors that recruit and activate eosinophils; thus, the presence of ECP, signifying the presence of eosinophils, is also an indicator of mast-cell activity. Although eosinophils do not have clinical significance in most patients with allergic conjunctivitis, they do play a role in the progression of nasal signs and symptoms.

Tear samples were collected from subjects’ unanesthetized eyes at baseline and after challenge at visits 2 and 3. Twenty milliliters of phosphate-buffered saline (PBS) was instilled into the cul-de-sac, and the subject was asked to move the eye for 5 seconds to mix the tear fluid content. A 10-µL sample of tears was extracted using a micropipette. Tear samples were transferred into 100 µL of 4°C PBS and stored frozen at −40°C. Tear samples from the right eye were used to measure ECP levels, and tear samples from the left eye were used to determine tryptase levels. Levels of ECP and tryptase were measured by immunofluorescence assay (UniCAP
tryptase fluoroenzymeimmunoassay, Pharmacia Diagnostics, Uppsala, Sweden). The lower limits of detection of this system are 2 μg/L for ECP and 1 μg/L for tryptase.

Nasal lavage was performed in the same subset of subjects at baseline and after challenge at visits 2 and 3. With the subject in a sitting position, leaning forward with the neck flexed at 60°, sterile PBS was instilled into 1 of the nasal cavities using a nasal pool device.13,23 After 10 seconds, the PBS was withdrawn. This procedure was repeated and the 2 initial lavages were discarded. After 5 minutes, a third lavage was performed and saved. The final lavage was performed 60 minutes after challenge. Lavage samples were immediately chilled and centrifuged. The supernatants were separated, and aliquots were taken and stored at −40°C for subsequent analysis of ECP and tryptase content as described in the preceding section.

Visit 1—NAC Screening

At visit 1 (day 0), each subject's medical and medication history was obtained, and visual acuity (LogMAR) was measured. Women of childbearing potential were excluded if they were unwilling to use a reliable form of contraception throughout the study or if they had a positive pregnancy test result at this visit. Nasal and ocular examinations were performed to exclude subjects with disallowed conditions (ie, preauricular lymphadenopathy, clinically significant blepharitis, follicular conjunctivitis, iritis, nasal or ocular infection) or signs and symptoms of active allergic rhinoconjunctivitis. A baseline PNIF was obtained.

Subjects were challenged with PBS in both nostrils, and those who reacted positively were excluded. Qualifying subjects were challenged nasally with the allergen that had previously caused a reaction on CAC. Ten minutes after this challenge, subjects rated their nasal symptoms using the scales described earlier. A subject who failed to have a reaction after 10 minutes was challenged with increasingly higher doses of allergen at 10-minute intervals until a sufficient positive reaction was achieved within 10 minutes of challenge. Subjects who did not have a sufficient reaction at the highest available concentration of allergen were excluded from the study. A positive reaction was defined as a total nasal symptom score ≥5.

At the end of NAC, the investigator assessed nasal signs of allergic rhinoconjunctivitis (nasal swelling, internal nasal color, and nasal discharge) using an otoscope and ocular signs of allergic rhinoconjunctivitis (ocular redness and chemosis) using slit-lamp biomicroscopy. Subjects were asked to assess ocular itching and eyelid swelling using the previously described scales.

The Jones test was performed after NAC. Subjects were offered an antiallergic eyedrop, a nasal decongestant spray, and/or pseudoephedrine tablets as needed to relieve immediate discomfort caused by allergen challenge.

1Trademark: Naphcon A® (Alcon Laboratories, Inc., Fort Worth, Texas).
2Trademark: Afrin® (Scherling-Plough HealthCare Products, Inc., Memphis, Tennessee).
Visit 2—Confirmation of Allergen Dose

At visit 2 (day 7 ± 2 days), medical and medication history were updated and visual acuity was measured. Slit-lamp and nasal examinations were performed to exclude subjects with disallowed conditions. A baseline PNIF was obtained. Baseline tear collection and nasal lavage were performed in the selected subset of subjects.

After baseline data collection, eligible subjects were randomized into 2 groups according to screening numbers assigned before commencement of the study, based on their order of arrival, by a technician uninvolved in any other aspect of the study. Group A was randomized to undergo CAC and group B to undergo NAC. To confirm the allergen doses needed to produce a positive reaction, subjects in group A were challenged ocularly with the dose of allergen that had previously been shown to induce a sufficient reaction, and subjects in group B were challenged nasally with the allergen that had induced a positive response at visit 1. Ocular and nasal signs and symptoms were assessed after both CAC and NAC.

Subjects assessed ocular itching at 3, 5, and 7 minutes after challenge and eyelid swelling at 20, 30, 40, and 60 minutes after challenge. The investigator assessed redness at 10, 15, 20, and 60 minutes after challenge and chemosis at 20, 30, 40, and 60 minutes after challenge.

Nasal symptoms (frequency of sneezing, rhinorrhea and postnasal drip, nasal and palatal pruritus, and nasal congestion) were assessed by subjects at 10, 20, 30, 40, 50; and 60 minutes after challenge. Nasal swelling, discharge, and color were assessed by the investigator at 20, 30, 40, 50, and 60 minutes after challenge.

PNIF was measured at 30 and 60 minutes after administration of allergen. Sixty minutes after challenge, tear and nasal lavage samples were obtained from the selected subset of subjects.

Subjects in group A who had a qualifying response to CAC (defined as an itching score ≥2, a redness score ≥2 in any vessel bed, and a composite nasal symptom score ≥5) and those in group B with a qualifying response to NAC (defined as a composite nasal symptom score ≥5 at any point) continued in the study. Qualifying subjects were randomized equally to 1 of 3 treatment arms: olopatadine 0.1% ophthalmic solution, placebo nasal spray, and placebo tablets; mometasone furoate monohydrate 50-μg nasal spray, placebo topical solution, and placebo tablets; or fexofenadine hydrochloride 180-mg tablets, placebo topical solution, and placebo nasal spray. Subjects were instructed to instill 1 drop of the ophthalmic solution into each eye twice daily, take 1 tablet once daily, and administer 2 sprays of the nasal spray once daily. The regimens were consistent with the approved dosing recommendations for the study drugs.

A loading period was included so that drug levels would reach pharmacokinetic steady state before visit 3. A 1-week period was chosen because, in our experience, a majority of subjects show clinical improvement after 1 week. Although in clinical practice up to 4 weeks of treatment may be necessary in cases in...
which nasal decongestants and systemic steroids are also required to relieve congestion, subjects in this study had clear nasal passages, as indicated by the results of Jones testing. Intranasal steroids have been reported to offer relief within 12 to 24 hours.\textsuperscript{24,25}

**Visit 3—Drug Assessment**

At visit 3 (day 14 ± 2 days), subjects' medical history and visual acuity were updated, and baseline nasal and ocular examinations were performed to exclude subjects with disallowed conditions. Subjects were questioned about compliance with their assigned study regimen. Baseline PNIF and tear and nasal lavage samples were obtained as at visit 2.

Each subject was then administered the assigned study medications. Fifteen minutes later, group A underwent CAC and group B underwent NAC. Ocular and nasal signs and symptoms were assessed at the same time points as at visit 2. Tear and nasal lavage samples were collected 60 minutes after challenge in the selected subset of subjects. The Jones test was performed with fluorescein instilled into the nose. Subjects were offered an antiallergic agent as before and were questioned regarding adverse events.

**Statistical Analysis**

Data from all enrolled subjects who completed the study were included in the study analyses. Mean scores for each efficacy variable at each time point were calculated by challenge type at visit 2 and by treatment arm within challenge type at visit 3. One-way analysis of variance with the Tukey adjustment for multiple comparisons was performed to determine $P$ values, and nonparametric analyses (Wilcoxon rank sum test) were conducted as a check on the normality assumption. Statistical significance was set at $P < 0.05$, and mean score differences of $\geq 1$ unit were considered clinically significant.

**RESULTS**

**Subject Disposition**

Seventy-three subjects (42 women, 31 men; mean age, 45.26 years [range, 21–73 years]) were screened; and all were randomized to receive treatment. Thirty-four subjects were assigned to group A and 39 to group B. Two subjects did not complete the study; 1 was lost to follow-up at visit 3 (group A), and 1 took a disallowed medication after NAC at visit 3 (group B). The characteristics of study subjects are shown in Table I. Tear and nasal lavage samples were collected from 64 subjects, but adequate sample volume was obtained from only 48 (23 CAC, 25 NAC).

**Jones Testing**

All subjects underwent Jones testing. After ocular instillation of fluorescein, fluorescence was detected in the nasal secretions of 100% of subjects within

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Table I. Characteristics of subjects randomized to receive study medication (N = 73).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</tr>
<tr>
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</tr>
<tr>
<td>Range</td>
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<tr>
<td>Sex, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42 (57.5)</td>
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<tr>
<td>Male</td>
<td>31 (42.5)</td>
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<td>Race, no. (%)</td>
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<tr>
<td>White</td>
<td>65 (89.0)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Iris color, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>40 (54.8)</td>
</tr>
<tr>
<td>Blue</td>
<td>17 (23.3)</td>
</tr>
<tr>
<td>Hazel</td>
<td>10 (13.7)</td>
</tr>
<tr>
<td>Green</td>
<td>6 (8.2)</td>
</tr>
</tbody>
</table>

*Percentages do not total 100 due to rounding error.

5 minutes. After nasal administration of fluorescein, no fluorescence was detected in any subject’s eyes 5 minutes after instillation.

**Effects of Allergen Challenge on the Eye and Nose**

CAC induced significant ocular signs and symptoms compared with NAC. Among ocular signs, P values were as follows: total redness, P < 0.001 at all time points; conjunctival redness, P < 0.001 at all time points (Figure 2); chemosis, P < 0.001 at all time points; and eyelid swelling, P < 0.001 at 20 minutes, P = 0.003 at 30 minutes, P = 0.002 at 40 minutes, and P < 0.001 at 60 minutes. Among ocular symptoms, itching was significant at all time points for CAC compared with NAC (P < 0.001) (Figure 3).

NAC yielded no clinically significant (>1 unit difference) ocular signs and symptoms. Interestingly, the nasal response was similar whether an identical allergen dose was instilled in the eye or the nose. With the exception of a significant difference after NAC compared with CAC at the earliest time point (P = 0.002), representing a lag in movement of allergen and/or mediators from the eye through the nasolacrimal duct into the nose, overall nasal symptoms were similar after CAC and NAC (Figure 4). There were no statistically significant differences in PNIF induced by CAC or NAC (Figure 5).
Figure 2. Comparison of mean conjunctival redness scores (scale from 0–4) after conjunctival allergen challenge (CAC) and nasal allergen challenge (NAC). *P < 0.001.

Figure 3. Comparison of mean ocular itching scores (scale from 0–4) after conjunctival allergen challenge (CAC) and nasal allergen challenge (NAC). *P < 0.001.
Figure 4. Comparison of mean total nasal symptom scores (scale from 0–10) after conjunctival allergen challenge (CAC) and nasal allergen challenge (NAC). *P = 0.002.

**Treatment Efficacy**

**CAC**

There was a significantly greater reduction in ocular itching with olopatadine compared with mometasone and fexofenadine at 3 minutes (P = 0.003 and P = 0.008, respectively) and 5 minutes (P = 0.007 and P = 0.013) after challenge (Figure 6). Although the difference was not statistically significant, overall relief of conjunctival redness (average of 3 vessel beds) was greatest with olopatadine, followed by fexofenadine; the effect was negligible with mometasone. There were no statistically significant between-group differences in the prevention of nasal symptoms at any time point after CAC (Figure 7).

**NAC**

Total nasal symptom scores were significantly better with mometasone compared with fexofenadine at 20 minutes (P = 0.006) and 30 minutes (P = 0.014) after challenge (Figure 8). There were no statistically significant between-group differences in PNIF at any time point after NAC (Figure 9).
Figure 5. Comparison of percentage of peak nasal inspiratory flow (PNIF) after conjunctival allergen challenge (CAC) and nasal allergen challenge (NAC).

**Presence of Eosinophil Cationic Protein and Tryptase**

ECP or tryptase was present in the tears or nasal lavage samples from 11 (47.8%) CAC subjects and 15 (60.0%) NAC subjects (Table II).

**DISCUSSION**

This study was designed to investigate the relationship between the eye and nose in allergic rhinoconjunctivitis and how this relationship contributes to the patterns of efficacy of drugs administered by 3 different routes—ocular, nasal, and systemic. The eye-nose relationship was assessed in 4 ways: by monitoring the movement of fluorescein after instillation in the eye and nose; by assessing clinical signs and symptoms induced by allergen instilled in the eye and nose; by evaluating the effect of the 3 routes of drug administration on signs and symptoms in the eye and nose; and by monitoring levels of inflammatory mediators in tears and nasal lavage fluid after allergen challenge in the eye and nose. The results indicate that there is movement of substances from the ocular surface into the nasal cavity, but no meaningful movement from the nasal cavity to the ocular surface.
Figure 6. Mean ocular itching scores (scale from 0–4) after conjunctival allergen challenge (N = 32). *P = 0.003 versus mometasone, †P = 0.008 versus fexofenadine, ‡P = 0.007 versus mometasone, §P = 0.013 versus fexofenadine.

After instillation of fluorescein into the eye, fluorescence was detected in nasal secretions within 5 minutes, indicating that this chemical marker drained rapidly from the ocular surface into the nasal cavity. Furthermore, CAC induced not only ocular signs and symptoms of allergy but also significant nasal allergic signs and symptoms (P < 0.05), as indicated by a nasal symptom score that would constitute a sufficient positive reaction to NAC and a clinical picture identical to that after NAC. The presence of the eosinophil marker ECP and the mast-cell marker tryptase in both tears and nasal secretions after instillation of allergen onto the ocular surface confirmed the movement of allergen and/or allergic mediators from the eye into the nose. This is not unexpected, as the anatomic connection from the eye to the nose is well established.126,27 Drainage of allergens or allergic mediators from the ocular surface occurs through the nasolacrimal ducts and into the inferior turbinate of the nose.

Based on a search of MEDLINE for controlled clinical trials in which ocular signs and symptoms were assessed after NAC or in which CAC was performed after administration of nasal drugs, the flow of substance from the nose into the
Figure 7. Mean total nasal symptom scores (scale from 0–10) after conjunctival allergen challenge (N = 32).

eye has not been studied extensively under controlled conditions. In the present study, fluorescein instilled directly into the nasal cavity did not appear on the ocular surface. In addition, instillation of allergen into the nose with a spray pump produced no significant ocular signs or symptoms (ie, did not induce a sufficient reaction, as defined for CAC) and no detectable tryptase in tears.

Olopatadine ophthalmic solution, mometasone nasal spray, and fexofenadine tablets were chosen for this comparison of their therapeutic effects on the eye and nose based on their pharmacology, their current indications for components of rhinoconjunctivitis, and their widespread use. Treatment delivered to the site of allergen exposure showed the greatest efficacy. For ocular itching, olopatadine instilled into the eye was superior to either the systemic antihistamine or the topical nasal steroid, neither of which produced notable reductions in symptoms. Mometasone applied directly to the nasal cavity reduced nasal symptoms to the greatest degree. This finding supports the conclusion of an analysis of data from 11 randomized, controlled trials that topical nasal steroids were superior to systemic agents for the treatment of allergic rhinitis.28 It is possible that other drugs from these 3 classes, with different pharmacokinetic properties and effects on
mast cells and histamine receptors, might have different treatment profiles from those included in this study.

Although fexofenadine, like other systemic antihistamines of its class, is indicated for the treatment of itchy, watery, and red eyes, as well as for nasal symptoms, in the clinical trial supporting fexofenadine’s ocular indication\textsuperscript{8} and in a clinical trial comparing fexofenadine with other therapies,\textsuperscript{29} itchy, watery, and red eyes were grouped with nasal symptoms (eg, sneezing, rhinorrhea, and itchy nose, palate, and throat), and the signs and symptoms of ocular and nasal allergies were combined in total symptom scores. However, grouping ocular signs and symptoms with nasal symptoms does not give an accurate indication of the efficacy of fexofenadine, particularly in terms of reducing ocular signs and symptoms. Analyses of data that have been grouped in this manner do not meet FDA standards for the approval of ophthalmic agents.

One review found no difference between intranasal corticosteroids and systemic agents in the management of ocular allergic symptoms.\textsuperscript{28} However, the data on which the review was based were heterogeneous, the ocular symptom scales used were imprecise, and there was no evidence that either type of agent would
Figure 9. Percentage of peak nasal inspiratory flow (PNIF) after nasal allergen challenge (N = 38).

Table II. Subjects (no. [%]) with measurable levels of eosinophil cationic protein (ECP) or tryptase in tears and nasal secretions after conjunctival allergen challenge (CAC) or nasal allergen challenge (NAC) at visit 2.*

<table>
<thead>
<tr>
<th>Challenge</th>
<th>ECP</th>
<th>Tryptase</th>
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<tbody>
<tr>
<td></td>
<td>Tears</td>
<td>Nasal Secretions</td>
</tr>
<tr>
<td>CAC (n = 23)</td>
<td>4 (17.4)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>NAC (n = 25)</td>
<td>1 (4.0)</td>
<td>14 (56.0)</td>
</tr>
</tbody>
</table>

*Samples were obtained from 64 subjects, but sample volume was sufficient for immunofluorescence analysis in only 48 subjects. Subjects may have had both ECP and tryptase in both tears and nasal secretions.
have reduced ocular symptoms compared with placebo, as several of the studies did not include a placebo group. Furthermore, in environmental studies, the nature of allergic disease and exposure patterns makes comparisons to baseline imprecise.

It has been postulated that decongestion of the nose may enhance tear flow, helping to wash allergens and mediators from the ocular surface. This may explain the minimal ocular effects reported by small numbers of patients using topical nasal medications in published studies. However, as indicated by the lack of efficacy of nasal drugs for ocular signs and symptoms in the present study, the active drug was not able to bind to receptors or actively block mediators sufficiently to reduce ocular symptoms. Furthermore, studies have reported significant ocular drying effects of systemic antihistamines (P < 0.05), with a 50% reduction in tear flow and volume after their use. Drying of the ocular surface is not desirable in patients with allergic conjunctivitis, because the tear film helps wash the surface of the eye, acts as a barrier, and dilutes mediators and allergens in the tears.

Other studies have found the topical ocular agent olopatadine to be effective in the reduction of allergic nasal signs and symptoms. As well as having antihistaminic activity, olopatadine has been shown to be a potent mast-cell stabilizer both in vitro and in humans. Olopatadine has been studied extensively in the CAC model and has demonstrated efficacy in the management of all signs and symptoms of allergic conjunctivitis. As indicated by the results of CAC in the present study, allergen and/or allergic mediators released from mast cells in the eye can drain into the nose, compounding nasal symptoms. Olopatadine may have blocked the release of mediators from conjunctival mast cells and subsequent drainage into the nose, or the drug may have drained into the nasal cavity, inhibiting mast cells and histamine receptors in the nose.

The results of this study highlight the importance of topical treatment of the eye in patients whose allergies have both ocular and nasal components. A previous study using the CAC model found that combined use of a nasal spray and a topical ocular medication was significantly more effective in managing both the nasal and ocular symptoms of rhinoconjunctivitis than the combination of a nasal spray and a systemic antihistamine (P < 0.05). Studies have also reported the secondary action of an ocular solution in the nose, confirming the movement of substances from the ocular surface into the nasal cavity. A study of olopatadine use during grass pollen season indicated significant control of rhinorrhea (P < 0.006), sneezing (P < 0.012), and nasal pruritus (P < 0.034), in addition to control of ocular signs and symptoms.

Approximately 50% of patients with allergic rhinitis also have ocular allergic signs and symptoms. Ocular itching is the primary sign of ocular allergy and is a distinguishing symptom that can help confirm the diagnosis of allergy. In patients
with rhinoconjunctivitis, complete treatment of symptoms in both the eye and nose may require the addition of a topical ophthalmic drug to existing therapy. Topical diseases are best treated topically. From a pharmacokinetic point of view, targeted therapy is good clinical practice. In the case of allergic rhinoconjunctivitis, targeted therapy may provide more complete management of signs and symptoms, including ocular symptoms.\textsuperscript{2}

**CONCLUSIONS**

Patients with allergic rhinoconjunctivitis are by definition exposed to allergen both through the nose and through the surface of the eye, which causes ocular reaction and contributes to mediator flow into the nose. The results of this study suggest that the most effective way to treat ocular allergic symptoms is with a topical ophthalmic medication. The results of CAC and NAC, as well as the Jones test, confirmed that flow through the nasolacrimal duct is unidirectional, explaining how an ocularly instilled antiallergic medication can exert a secondary effect on nasal symptoms. The systemic agent or the nasal spray alone was not sufficient to treat ocular symptoms, which were most effectively managed with a topical ophthalmic medication.

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**REFERENCES**


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