Comparison of the Efficacy of Combined Fluticasone Propionate and Olopatadine Versus Combined Fluticasone Propionate and Fexofenadine for the Treatment of Allergic Rhinoconjunctivitis Induced by Conjunctival Allergen Challenge

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ABSTRACT

Background: One approach to treating allergic rhinoconjunctivitis is the concomitant use of an intranasal spray such as fluticasone propionate to alleviate nasal symptoms and a topical or systemic agent to relieve ocular symptoms. It has not yet been determined whether a topical or systemic agent is more effective for the latter purpose.

Objective: This study compared the efficacy of combined use of fluticasone and olopatadine with combined use of fluticasone and fexofenadine in the treatment of the signs and symptoms of allergic rhinoconjunctivitis.

Methods: This 2-site, randomized, double-masked, placebo-controlled, parallel-group study employed the conjunctival allergen challenge (CAC) model, a standardized method of inducing ocular and nasal signs and symptoms of allergic rhinoconjunctivitis. At visit 1, subjects underwent CAC to determine the dose of allergen required to elicit a positive reaction. The allergen dose was confirmed at visit 2, and, according to a randomization schedule, subjects were dispensed fluticasone, olopatadine, and placebo pill; fluticasone, fexofenadine, and tear substitute; or placebo nasal spray, placebo pill, and tear substitute. CAC took place at visit 3, after patients had used the assigned medications for 2 weeks. Study medication was instilled 2 hours before CAC, after which allergic signs and symptoms were graded on standardized scales. The primary efficacy variables were ocular itching, ocular redness, and overall nasal symptoms.

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Results: Eighty subjects completed the study: 30 received fluticasone and olopatadine, 30 fluticasone and fexofenadine, and 20 placebo. Women constituted 63.8% of the study population and men 36.3%; 91.3% were white, 3.8% black, 2.5% Hispanic, 1.3% Asian, and 1.3% other. Concomitant use of fluticasone and olopatadine produced significantly greater improvements in ocular itching at 3 and 7 minutes after CAC compared with fluticasone and fexofenadine (P < 0.05). There were no significant differences in redness scores between groups; however, concomitant use of fluticasone and olopatadine produced significantly greater improvements in redness at 2 time points in each of the 3 vessel beds (ciliary, conjunctival, and episcleral) compared with placebo, and fluticasone and fexofenadine produced significantly greater improvement in redness at 1 time point in 1 vessel bed compared with placebo (both comparisons, P < 0.05). The 2 treatments had similar effects on total nasal symptom efficacy scores.

Conclusions: In this study, concomitant use of the topical agents fluticasone and olopatadine was more effective than concomitant use of fluticasone plus fexofenadine for overall treatment of the signs and symptoms of induced allergic rhinoconjunctivitis.

Key words: fluticasone, olopatadine, fexofenadine, conjunctival allergen challenge, ocular allergy. (Clin Ther. 2002;24:1161-1174)

INTRODUCTION

More than one third of Americans experience allergic rhinoconjunctivitis after exposure to specific allergens or pollens. The allergen first binds allergen-specific immunoglobulin E (IgE) on the surface of conjunctival or nasal mast cells, which initiates the allergic cascade. The allergen-bound IgE then cross-links, leading to mast-cell degranulation and release of allergic and inflammatory mediators. Among these is histamine, the primary mediator of the ocular itching and hyperemia associated with an early-phase allergic reaction.

One approach to relieving the nasal signs and symptoms of allergic rhinoconjunctivitis is combined use of an intranasal spray and a systemic antihistamine. A novel alternative is concomitant use of a topical ophthalmic preparation and a nasal spray, which has the advantages of avoiding the drying effects of systemic antihistamines and delivering direct site-specific treatment for both ocular and nasal signs and symptoms. The relative efficacy of these 2 approaches is not well documented.

Some commonly used medications for allergic rhinoconjunctivitis were included in the present study. Fluticasone propionate nasal spray is a corticosteroid approved for the treatment of nasal symptoms associated with perennial or seasonal allergic and nonallergic rhinitis. The exact mechanism of its anti-inflammatory action is unknown, but intranasal steroids have been shown to moderate the increase in serum levels of antigen-specific IgE antibodies during allergy season, and fluticasone has been shown to reduce the number of nasal mast cells in nasal provocation tests. Fexofenadine hydrochloride, a second-generation antihistamine, is a non-sedating selective antagonist of the hist-
tamine type 1 (H₁) receptor that has been approved for the relief of symptoms associated with seasonal allergic rhinitis. Olopatadine hydrochloride,* a topical ophthalmic solution, is a combination mast-cell stabilizer and antihistamine approved for treatment of the signs and symptoms of allergic conjunctivitis; it has demonstrated statistically significant efficacy in studies using the conjunctival allergen challenge (CAC) model ($P < 0.05$). 8,9

The objective of this study was to evaluate the relative efficacy of combined fluticasone and olopatadine, combined fluticasone and fexofenadine, and placebo in the treatment of the signs and symptoms of allergic rhinoconjunctivitis induced by CAC.

SUBJECTS AND METHODS

This was a 2-site, randomized, double-masked, placebo-controlled, parallel-group CAC study. Potential subjects were identified from an allergy patient database and recruited through telephone contact. The protocol was approved by the IntegReview Institutional Review Board, Austin, Texas. Written informed consent was obtained from all subjects, who received prorated reimbursement.

The study consisted of 3 visits per patient (Figure 1). CAC, which has been accepted by the US Food and Drug Administration as a clinically relevant model for evaluating the efficacy of antiallergic agents, was performed according to previously described methods. 10 This model uses 25 μL of specific allergens (cat hair and/or dander, ragweed pollen, tree pollen, or grass pollen) to initiate a reproducible inflammatory response that produces the ocular and nasal signs and symptoms of allergic rhinoconjunctivitis. The choice of allergen for each patient is based on the results of prior skin testing. Under these reproducible conditions, antiallergic agents can be evaluated for efficacy (change in mean scores between visit 2 and visit 3) using standardized scales.

Visit 1

At visit 1, demographic data, medication and medical histories, and visual acuity (Early Treatment of Diabetic Retinopathy Study 11 methodology) were recorded. Subjects participating in this study may have participated in previous ocular allergen challenge studies, but those who had participated in a study evaluating nasal spray or involving evaluation of nasal symptoms were excluded. The presence of inclusion or exclusion criteria was reviewed at the beginning and end of each study visit, and any subject found to be unqualified was discontinued. Subjects were excluded if they were aged <18 years; if they were taking antihistamines, corticosteroids, mast-cell stabilizers, decongestants, topical ophthalmic preparations, or nasal sprays; or if they had illnesses or ocular conditions or infections that might, in the investigators' opinion, interfere with study assessments. In addition, use of any investigational drug or device within 30 days, any known allergy or contraindication to study medications, or any ocular and/or nasal surgery within 3 months of enrollment were exclusionary factors. A urine pregnancy test was given to all women of childbearing potential.

A slit-lamp examination was performed to exclude subjects having any disallowed
Figure 1. Study design. CAC = conjunctival allergen challenge.

ocular conditions or exhibiting any signs of active allergic rhinoconjunctivitis (presence of itching in either eye, redness score >1 in any vessel bed, or nasal symptom score >3). The scales used to assess ocular itching, ocular redness, and nasal symptoms are described in the following section.

CAC was then performed by bilateral instillation of cat hair and/or dander, ragweed pollen, tree pollen, or grass pollen in buffered saline solution. Dosing was initiated at the lowest available concentration of the specific allergen. If, after 10 minutes, the patient’s allergic reaction was insufficient, the allergen concentration was increased every 10 minutes until a qualifying reaction was obtained (ocular itching score ≥2, redness score ≥2 in any vessel bed, and nasal symptom score ≥5).

Ocular itching was graded by subjects on a scale from 0 (no itching) to 4 (severe itching), and ocular redness in each vessel bed (ciliary, conjunctival, and episcleral) was graded by the investigator on a scale from 0 (no redness) to 4 (extremely severe redness). Nasal symptoms were graded by subjects over 10-minute periods using standardized scales for 4 categories: sneezing (0 = <2 sneezes; 0.5 = 2 sneezes; 1.0 = 3–4 sneezes; 1.5 = 5 sneezes; 2.0 = >5 sneezes); rhinorrhea (0 = no symptoms; 1 = either runny nose or postnasal drip; 3 = both runny nose and postnasal drip); pruritus (0 = absent; 1 = present in nose or ear/palate; 2 = present in both nose and ear/palate); and congestion (0 = breathing freely; 1 = breathing without difficulty; 2 = one nostril blocked; 3 = both nostrils blocked). The nasal scales and use of their summed scores as exclusion criteria and for data analysis were adapted from previous nasal allergen challenge studies.12,13 Subjects who did not develop sufficient ocular itching, redness, or nasal symptoms to indicate active allergic rhinoconjunctivitis were excluded from the study. If needed, 1 drop of a currently marketed topical antiallergic medication (naphazoline<sup>®</sup>) was administered at the end of the visit to relieve immediate discomfort due to allergen challenge.

*Trademark: Vasocon<sup>®</sup> (Novartis Ophthalmics, Duluth, Georgia).

"Trademark: Visine<sup>®</sup>-A<sup>TM</sup> (Pfizer Inc, Morris Plains, New Jersey)."
Visit 2

At visit 2, patients' medical and medication histories were updated, their visual acuity was measured as at visit 1, and slit-lamp examination was repeated. One drop of the allergen solution that had elicited a positive reaction at visit 1 was instilled bilaterally. Subjects were asked to evaluate ocular itching at 3, 7, and 10 minutes after challenge. Investigators evaluated redness in each of the 3 vessel beds at 10, 15, and 20 minutes after challenge. Subjects evaluated nasal symptoms at 10, 20, and 30 minutes after challenge.

Subjects who continued to meet the inclusion criteria at visit 2 were assigned to treatment groups according to a randomization schedule generated before commencement of the study by qualified staff uninvolved in the conduct or monitoring of the study. Subjects were randomized to treatment in a 3:3:2 ratio (fluticasone + olopatadine: fluticasone + fexofenadine: placebo), and sequential numbers were assigned to all qualified subjects before separation by site.

The treatment groups consisted of fluticasone, olopatadine, and placebo pill; fluticasone, fexofenadine, and tear substitute; or placebo nasal spray, placebo pill, and tear substitute. The active preparations were fluticasone propionate 50 μg/spray, olopatadine hydrochloride 0.1% ophthalmic solution, and fexofenadine hydrochloride 60 mg capsule. The placebo preparations were sugar pills, tear-substitute eye drops,* and saline nasal spray, respectively.

Patients were instructed to administer all study medications twice daily, in the morning (within 2 hours of waking) and in the evening (8–12 hours after the morning dose), beginning on the morning after visit 2 and continuing for 2 weeks until the night before visit 3. Medications were to be administered as 1 drop in each eye, 1 spray in each nostril, and 1 pill each morning and evening. Within each medication type, all eye drops, nasal sprays, and pills were of identical appearance.

Visit 3

At visit 3, medical and medication histories were updated, visual acuity measured, and slit-lamp examination repeated. Study personnel administered the eye drops and observed patients' administration of nasal spray and pills. The medications were taken from the supply dispensed to each patient at visit 2. Two hours after administration of all medications, 1 drop of the allergen solution that had elicited a positive response at visit 1 was instilled bilaterally. Ocular itching, redness, and nasal symptoms were evaluated at the same time points as at visit 2. If needed, naphazoline was administered topically to relieve any immediate discomfort caused by the allergic reaction.

Statistical Analysis

Data from all subjects who completed the study were included in the efficacy analyses. Mean baseline-corrected scores for ocular itching, ocular redness in each vessel bed, and total nasal symptoms were calculated at visits 2 and 3, and the change from visit 2 to visit 3 was compared between treatments. Greater magnitude of change between visit 2 (untreated) and visit 3 CAC (treated) would indicate greater medication efficacy. Two-sided Wilcoxon rank sum tests were used to

*Trademark: Tears Naturale® (Alcon Laboratories, Inc, Fort Worth, Texas).
determine $P$ values, and statistical significance was set at $P < 0.05$.

RESULTS

Eighty subjects completed the study, of whom 30 received fluticasone, olopatadine, and placebo pill; 30 received fluticasone, fexofenadine, and tear substitute; and 20 received placebo nasal spray, placebo pill, and tear substitute. Forty-three subjects did not complete the study, either because of failure to meet the inclusion criteria at visit 1 or visit 2 (33) or because of limited allowed enrollment (80 patients were required to complete the randomization scheme) at visit 2 (10). The demographic characteristics of the study population are summarized in the table.

The combination of fluticasone and olopatadine produced significantly greater improvement in ocular itching at 3 and 7 minutes after challenge compared with the combination of fluticasone and fexofenadine ($P < 0.05$) (Figure 2). Both treatments were significantly more effective than placebo at 3, 7, and 10 minutes after challenge ($P < 0.05$).

With respect to redness in the ciliary (Figure 3), conjunctival (Figure 4), and episcleral (Figure 5) vessel beds, there were no significant differences between combined fluticasone and olopatadine and combined fluticasone and fexofenadine at 10, 15, or 20 minutes after challenge. Fluticasone and olopatadine produced significantly greater improvements in redness at 10 and 15 minutes after challenge in all 3 vessel beds compared with placebo (all, $P < 0.05$); fluticasone and fexofenadine produced significantly greater improvement at 10 minutes after challenge.

### Table. Demographic characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluticasone + Olopatadine</th>
<th>Fluticasone + Fexofenadine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of patients</td>
<td>30 (37.5)</td>
<td>30 (37.5)</td>
<td>20 (25.0)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>40.9</td>
<td>43.8</td>
<td>39.5</td>
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<tr>
<td>Sex, no. (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (36.7)</td>
<td>7 (23.3)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (63.3)</td>
<td>23 (76.7)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Race, no. (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28 (93.3)</td>
<td>28 (93.3)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Black</td>
<td>–</td>
<td>2 (6.7)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3.3)</td>
<td>–</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>–</td>
<td>–</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Allergen, no. (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass pollen</td>
<td>12 (40.0)</td>
<td>4 (13.3)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Ragweed pollen</td>
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<td>16 (53.3)</td>
<td>9 (45.0)</td>
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<tr>
<td>Cat dander/hair</td>
<td>6 (20.0)</td>
<td>7 (23.3)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Tree pollen</td>
<td>1 (3.3)</td>
<td>3 (10.0)</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>

*Percentages may not total 100 due to rounding error.
Figure 2. Change from visit 2 (untreated) to visit 3 (treated) in baseline-corrected mean ocular itching scores at (A) 3 minutes, (B) 7 minutes, and (C) 10 minutes after conjunctival allergen challenge. *P < 0.001 versus fluticasone and fexofenadine; †P < 0.001 versus placebo; ‡P = 0.019 versus fluticasone and fexofenadine.
Figure 3. Change from visit 2 (untreated) to visit 3 (treated) in baseline-corrected mean ciliary redness scores at (A) 10 minutes, (B) 15 minutes, and (C) 20 minutes after conjunctival allergen challenge. *P = 0.002 versus placebo; †P = 0.043 versus placebo; ‡P = 0.035 versus placebo.
Figure 4. Change from visit 2 (untreated) to visit 3 (treated) in baseline-corrected mean conjunctival redness scores at (A) 10 minutes, (B) 15 minutes, and (C) 20 minutes after conjunctival allergen challenge. *P = 0.023 versus placebo; †P = 0.039 versus placebo.
Figure 5. Change from visit 2 (untreated) to visit 3 (treated) in baseline-corrected mean episcleral redness scores at (A) 10 minutes, (B) 15 minutes, and (C) 20 minutes after conjunctival allergen challenge. *P = 0.023 versus placebo; †P = 0.029 versus placebo.
in the ciliary vessel bed compared with placebo ($P < 0.05$).

In the analysis of total nasal symptoms (sneezing, rhinorrhea, pruritus, congestion), no statistically significant differences were demonstrated between the combination of fluticasone and olopatadine and the combination of fluticasone and fexofenadine (Figure 6). Combined fluticasone and olopatadine were significantly more effective than placebo at 20 and 30 minutes after challenge, and combined fluticasone and fexofenadine were significantly more effective than placebo at 10 and 20 minutes after challenge (all, $P < 0.05$).

**DISCUSSION**

It has been demonstrated that concomitant use of such allergy medications as olopatadine eye drops and loratadine tablets can produce greater improvements in rhinoconjunctival symptoms than a single agent.\(^4\) However, the comparable efficacy of specific combination regimens has not been determined. The present study was designed to compare the efficacy of combined use of 2 site-specific topical medications (fluticasone and olopatadine) with combined use of a topical and a systemic medication (fluticasone and fexofenadine) versus placebo in the CAC model of allergic rhinoconjunctivitis. The overall efficacy of these regimens was determined based on separate evaluations of the ocular and nasal components of allergic rhinoconjunctivitis.

Fluticasone and olopatadine had greater efficacy against the ocular signs and symptoms of induced allergic rhinoconjunctivitis than did fluticasone and fexofenadine, whereas the 2 treatments exhibited comparable efficacy against nasal symptoms. The combination of fluticasone and olopatadine provided greater overall relief. The intranasal steroid fluticasone, which was used in both treatment arms, specifically targets the nasal allergic reaction, and topical olopatadine specifically targets the signs and symptoms of allergy localized to the eye. It cannot be determined from this study what proportion of the relief of nasal discomfort was produced by each medication. It is highly unlikely that any ocular relief was produced by the nasal spray, because little medication (mean, 8.7%) is delivered even as far as the middle meatus with nasal spray administration,\(^15\) and the majority (>60%) is cleared from the nose via rapid drainage and ciliary and mucosal clearance of drug.\(^16\) However, olopatadine has been shown to be effective in reducing nasal symptoms,\(^17\) since a certain amount of eye drop delivery to the inferior turbinate occurs as a result of the contiguity of the ocular and nasal membranes and their connection through the channels of the lacrimal drainage system.

In the present study, the strategy of specifically targeting therapy to the sites of allergic reaction produced greater overall relief from the signs and symptoms of induced allergic rhinoconjunctivitis. Treating the ocular component of allergic rhinoconjunctivitis with a systemic medication, which must travel through the bloodstream, results in delivery of only a fraction of drug to the intended site, whereas use of a topical medication, which disperses directly through the tear film, provides greater bioavailability at the site of action.\(^18,19\) Previous research has indicated that olopatadine alone produces greater and longer-lasting improvements in the ocular symptoms of allergic rhinoconjunctivitis compared with sys-
Figure 6. Change from visit 2 (untreated) to visit 3 (treated) in baseline-corrected mean total nasal symptom scores (including sneezing, rhinorrhea, pruritus, and congestion) at (A) 10 minutes, (B) 20 minutes, and (C) 30 minutes after conjunctival allergen challenge. \(*P = 0.003\) versus placebo; \(^{+}P = 0.014\) versus placebo; \(\dagger P = 0.015\) versus placebo.
temic antihistamines.\textsuperscript{18} Eye drops have the additional nonspecific antiallergic effect of stabilizing the ocular tear film, providing a surface barrier against the binding of allergen to the conjunctiva.\textsuperscript{3} In contrast, an ocular drying effect has been observed with use of second-generation systemic antihistamines, increasing the probability of allergen binding to the relatively dry, unprotected conjunctiva.\textsuperscript{3}

**CONCLUSIONS**

In the subjects in this CAC study, the use of combined fluticasone and olopatadine produced greater improvements in the ocular signs and symptoms of allergic rhinoconjunctivitis compared with combined use of fluticasone and fexofenadine. Both treatments produced comparable improvements in nasal symptoms. Therefore, the combination of the 2 topical medications provided greater overall relief.

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**REFERENCES**


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