An Evaluation of Onset and Duration of Action of Patanol® (Olopatadine Hydrochloride Ophthalmic Solution 0.1%) Compared to Claritin® (Loratadine 10 mg) Tablets in Acute Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model

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ABSTRACT.

Purpose: **To compare the clinical efficacy of Patanol® (olopatadine hydrochloride ophthalmic solution 0.1%) to Claritin® (loratadine 10 mg) tablets, in the conjunctival allergen challenge model.**

Methods: **This was a randomized, double-masked, single center, contralateral controlled, antigen challenge model study. The concentration of allergen that elicited a positive response was determined at Visits 1 and 2 (itching $\geq$2 and redness $\geq$2 OU). At Visit 3, 29 subjects were randomized into two groups. Fifteen subjects received Claritin® tablet and Patanol® ophthalmic solution 0.1% in one eye and placebo in the contralateral eye. Fourteen subjects received placebo tablet and Patanol® in one eye and placebo in the contralateral eye. One hour after drug administration, subjects were challenged with the antigen that elicited a positive response. At 3, 7, and 10 minutes, itching was subjectively evaluated. At Visit 4, the same procedure was followed as in Visit 3, but antigen challenge occurred 8 hours after drug instillation.**

Results: **Results were analyzed by eye. Eyes treated with Patanol® (concomitant with placebo tablet) had significantly lower ocular itching scores when compared to eyes treated with placebo (concomitant with Claritin®) at 3, 7 and 10 minutes in the onset of action evaluation ($p<0.05$). Eyes treated with Patanol® (concomitant with placebo tablet) had significantly lower ocular itching scores at 7 minutes and there was a statistical trend ($0.05<p<0.1$) at 10 minutes in duration of action evaluation.**

Conclusions: **Patanol® therapy was significantly more efficacious than Claritin® in reducing ocular itching related to allergic conjunctivitis.**

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Introduction

Allergic conjunctivitis occurs in atopic individuals exposed to specific antigens and manifests primarily as ocular itching and conjunctival hyperemia. Chemosis, lid hyperemia and edema, tearing and mucous discharge are also frequently part of the symptom complex. A myriad of agents with different mechanisms are used to treat ocular allergy including antihistamines, antihistamine/vasoconstrictor combinations, mast cell stabilizers, mast cell stabilizer/antihistamine combinations, NSAIDs, and steroids (1, 2). Among the most recent additions to the anti-allergic arsenal is Patanol® (olopatadine hydrochloride 0.1%, Alcon Laboratories, Inc Forth Worth, TX), a long lasting mast cell stabilizer and antihistamine (3–5). Patanol® has been shown to be very effective against ocular itching for up to eight hours, significantly longer than most topical agents indicated for use in allergic conjunctivitis (6).

When rhinitis accompanies ocular allergy, a systemic antihistamine becomes necessary for control of the disease. Claritin® (loratadine 10mg, Schering, Kenilworth, NJ), has been shown to be an effective tool in controlling the nasal signs and symptoms associated with allergic rhinoconjunctivitis. In spite of its efficacy, Claritin® may not be sufficient for patients suffering from signs and symptoms in the eyes.

The conjunctival allergen challenge (CAC) model is a clinically validated and FDA recognized method of testing the efficacy of various drugs used to treat Type I hypersensitivity reactions, as it closely

Table 1. Itching values, standard deviation and p-values for onset of action evaluation of Claritin® with placebo (n=15) compared to Patanol® with placebo (n=14).

Claritin® with placebo	3 minutes	7 minutes	10 minutes
Mean	1.9	2.0	1.5
Std	0.8	0.9	0.8
Patanol® with placebo			
Mean	0.8	0.6	0.4
Std	1.1	0.6	0.6
p value	0.0002	0.0001	0.0004

mimics the clinical spectrum of allergic conjunctivitis (7–10). This method elicits a natural immunological mast cell degranulation through the instillation of a known concentration of allergen to a sensitized subject. There is subsequent binding of the antigen to IgE molecules on the surface of the mast cell inducing the release of allergic mediators, including histamine, the mediator responsible for the itching and redness of ocular allergy. This study implements a precise clinical model for ocular allergy to determine whether Patanol® is more effective in controlling itching than Claritin®.

Methods and Materials

This was a randomized, double-masked, contralateral controlled, paired comparison. Twenty-nine (29) subjects were randomized to receive either one Claritin® 10 mg tablet and one drop of Patanol® in one eye and placebo in the contralateral eye (n=15) or placebo tablet and one drop of Patanol® drop in one eye and placebo in the contralateral eye (n=14).

Day 1, Visit 1

Demographic data, medical and medication history were captured and informed consent was obtained. A pregnancy test was performed on all women of childbearing potential. A baseline slit-lamp exam was performed and any subject exhibiting the signs or symptoms of allergic conjunctivitis, defined as >1+ redness and any itching in either eye, was excluded. A bilateral conjunctival antigen challenge test was performed with allergen selected according to the results of a skin test. One drop of 25 µl allergen at the lowest concentration was instilled into the culde-sac of each eye. After ten minutes, if the subject did not react sufficiently, defined as 2+ itching and 2+ redness in any vessel bed bilaterally, the allergen concentration was increased every 10 minutes until a sufficient reaction occurred. If the subject did not have a sufficient reaction to any concentration, the subject was excluded from the study. Itching was graded using a standardized scale.

Day 7, Visit 2

After seven days, subjects returned to confirm the allergen concentration that elicited a positive reaction at the initial visit. Medical and medication history were updated. A slit-lamp exam was performed to discontinue any subjects exhibiting the signs or symptoms of allergic conjunctivitis. The conjunctival allergen challenge was performed using the allergen concentration that elicited a positive reaction at the first visit. Those subjects who met all inclusion and exclusion criteria and had a positive reaction to the allergen challenge were permitted to continue to Visit 3.

Day 14, Visit 3

Medical and medication history were updated. A slit-lamp exam was performed to discontinue subjects suffering from allergic conjunctivitis. All subjects received Patanol® in one eye and a placebo drop in the contralateral eye. In a randomized, double-masked fashion, 15 subjects each received one Claritin® tablet and 14 subjects each received one placebo tablet. One hour after drug administration, the allergen challenge was performed bilaterally using the concentration that elicited a positive response at the first 2 visits. Itching was subjectively graded at 3, 7, and 10 minutes after the challenge.

Day 28, Visit 4

Medical and medication history were updated. A slit-lamp exam was performed to discontinue subjects suffering from allergic conjunctivitis. All subjects received Patanol® in one eye and a placebo drop in the contralateral eye. In a randomized, double-masked fashion, 15 subjects each received one Claritin® tablet and 14 subjects each received one placebo tablet. Eight hours after drug administration, the allergen challenge was performed bilaterally using the concentration that elicited a positive response at the first 2 visits. Itching was subjectively graded at 3, 7, and 10 minutes after the challenge.

Statistical analysis

Statistical analysis of the difference in mean response scores between treatment groups for redness and for itching were done using repeated Measures Analysis of Variance (ANOVA). All repeated measures were implemented in PROC MIXED, SAS PC, Version 6.12. Statistical significance was defined as $p \leq 0.05$. A statistical trend was defined as $0.05 < p < 0.1$.

Results

Subjects

Twenty-nine (29) subjects were randomized to one of two treatment groups. All subjects received study drugs and none were discontinued from the study after randomization. Therefore, all subjects were included in the analysis of safety and efficacy parameters.

Efficacy

Itching

Efficacy evaluations comparing Patanol® to Claritin® were done by eye (n=29). In

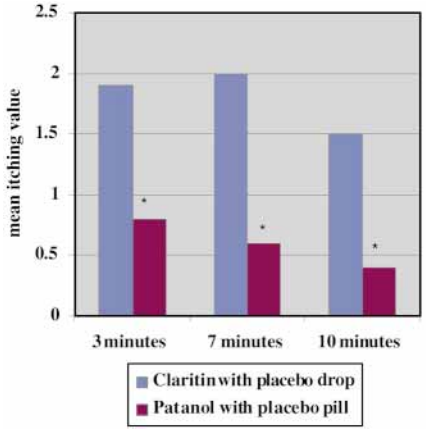

Fig. 1. Mean itching values for onset of action evaluation at 3, 7, and 10 minutes post-challenge in eyes treated with Claritin® with placebo drops (n=15) and Patanol® with placebo tablet (n=14). Results were statistically significant at all time points ($p<0.05$). Results were clinically significant at all time points (score unit difference of at least 1 unit). *=statistical significance

Table 2. Itching values, standard deviation and p-values for duration of action evaluation of Claritin® with placebo (n=15) compared to Patanol® with placebo (n=14).

Claritin® with placebo	3 minutes	7 minutes	10 minutes
Mean	0.8	1.2	0.8
Std	0.5	0.8	0.7
Patanol® with placebo			
Mean	0.5	0.5	0.4
Std	0.7	0.7	0.6
p value	0.2209	0.0052	0.0906

the onset of action evaluation, scores for itching in Group 1, eyes treated with placebo drops concomitant with Claritin® tablet (n=14), were compared to itching scores in Group 2, eyes treated with Patanol® concomitant with placebo tablet, (n=15). A statistically significant difference was seen in favor of Patanol® at 3 minutes (p=0.0002), 7 minutes (p=0.0001), and 10 minutes (p=0.0004). Itching results were also clinically relevant (score unit decrease of at least 1) at 3, 7 and 10 minutes. (Table 1, Figure 1).

In the duration of action evaluation, scores for itching in Group 1, eyes treated with placebo drops concomitant with Claritin® (n=14), were compared to itching scores in Group 2, eyes treated with Patanol® concomitant with placebo tablet, (n=15). A statistically significant difference was seen in favor of Patanol® at 7 minutes (p=0.0052). A statistical trend was seen at 10 minutes (p=0.0906) (Table 2, Figure 2).

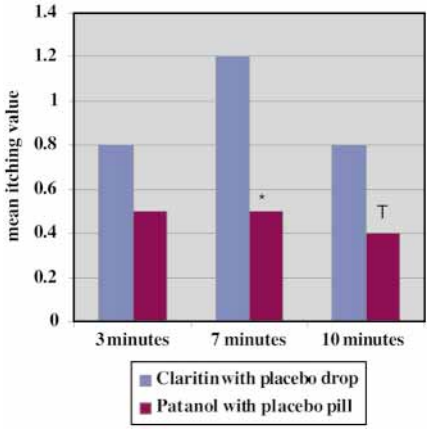

Fig. 2. Mean itching values for duration of action evaluation at 3, 7, and 10 minutes post-challenge in subjects treated with Claritin® with placebo drops (n=15) and Patanol® with placebo tablet (n=14). Results were statistically significant at 7 minutes ($p<0.05$). There was a statistical trend at 10 minutes ($0.05<p<0.1$).
*=statistical significance
T=statistical trend

Discussion

Recently, the practice of treating topical diseases with systemic medications has come under evaluation. While the new potent H1 antihistamines such as Claritin® have been shown to be effective in controlling the signs and symptoms of rhinitis, there has yet to be a well-controlled study evaluating the effectiveness of Claritin® in allergic conjunctivitis and comparing Claritin® to the efficacy of newer topical agents such as Patanol®. Claritin® has been shown to produce ocular drying (11) by decreasing the tear film. The tear films acts as a diluent and eye wash and provides a protective function. This drying effect enhances the likelihood of antigen binding to the conjunctival surface. The lubricating effect of any eye drop is an added benefit to the active drug.

Additional studies have shown that other topical agents have enhanced activity in controlling ocular itching when compared to Claritin®. When Claritin® was compared to Ocuhist® eye drops (0.025% naphazoline/0.3% pheniramine), results showed that Ocuhist® was significantly better at controlling itching and was clinically superior (12). Claritin® is not the only systemic antihistamine that has reduced activity in controlling ocular itching when compared to topical agents. Ocuhist® was shown to be significantly better than Benadryl® (25 mg diphenhydramine) at controlling ocular itching (13). These additional studies further support the results of this Patanol® versus Claritin® study, and confirm that itch associated with ocular allergy, a topical disease, is better controlled using a topical medication.

There are several possible explanations for the augmented performance of Patanol®. Patanol®, in addition to being an antihistamine, is also a mast cell stabilizer (14). There are numerous potential mechanisms for mast cell stabilization, and we are still understanding the process that may lead to this. Patanol® inhibits the release of the inflammatory mediators, histamine, tryptase and prostaglandin D_2, from human mast cells in a concentration dependant manner (14) and has an extremely high H_1 affinity, significantly higher than other topical antihistamines (15). The binding affinity of olopatadine for the H_1 histamine receptor is greater (≈3-fold) than that of loratadine. The Ki for olopatadine is 36 nM and the Ki for loratadine is 111.9 nM. In guinea pig conjunctiva, olopatadine was shown to reduce conjunctival histamine-induced vascular permeability at a concentration considerably lower (0.002%) than its market concentration of 0.1% (16). Patanol® may be more efficacious than Claritin®. Patanol's increased activity may also be explained by pharmacokinetics. It is to be expected that the amount of Claritin® that can be delivered to the eye after it has been diluted through the entire body, cannot be as efficacious as a drug delivered directly to the affected tissue. Patanol® is also more readily available to the eye and can therefore almost immediately relieve ocular allergy.

Conclusion

This study, to our knowledge, is the first effort to examine the effects of Claritin® in a precisely controlled ocular allergy model and to compare it to a topical agent. The use of topical agents in ocular allergy seems to be preferred in terms of efficacy and in terms of safety, as topical agents to do not produce drying as Claritin® does (11). Clinicians should be encouraged to treat topical diseases topically, using an effective agent such as Patanol®.

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