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ORIGINAL ARTICLE

Efficacy and Tolerability of Ketotifen in the Treatment Of Seasonal Allergic Conjunctivitis: Comparison between Ketotifen 0.025% and 0.05% Eye Drops

Andrea Leonardi¹, Decio Capobianco², Nicola Benedetti³, Antonio Capobianco⁴, Fabiano Cavarzeran¹, Tania Scalora¹, Rocco Modugno¹, and Oren Mark Feuerman¹

¹Department of Neuroscience, Ophthalmology Unit, University of Padova, Padova, Italy, ²Ophthalmology Service, ASL Napoli-1, Napoli, Italy, ³Ophthalmology Service, Casa di Cura Don Lorenzo Avezzano, L'Aquila, Italy, and ⁴Ophthalmology Service, Fondazione Gemelli, Roma, Italy

ABSTRACT

Purpose: To study the tolerability and efficacy of two formulations of topical ketotifen ophthalmic solutions for the treatment of seasonal allergic conjunctivitis (SAC).

Methods: 81 active SAC patients were treated with either ketotifen 0.025% or 0.05% eye drops for 3 weeks. Allergic signs and symptoms were evaluated at baseline (V0), after 7 (V1) and 21 days (V2). Drugs tolerability and ratings of global efficacy were recorded.

Results: Both concentrations of ketotifen were highly effective. The total signs and symptoms scores (TSSS) were significantly better reduced by ketotifen 0.025% compared to 0.05% at both V1 and V2 ($p < 0.001$). Ketotifen 0.025% was better tolerated than 0.05% at the first instillation and at days 2, 4, and 6 ($p < 0.0001$), and had a better responder rate ($p < 0.001$) according to the patient's and investigator's assessments.

Conclusions: Ketotifen 0.025% was more effective and better tolerated than 0.05% in SAC.

Keywords: Environmental study, ketotifen, ocular allergy, seasonal allergic conjunctivitis, tolerability

Ocular allergies (OA), either seasonal/intermittent or perennial/persistent, are characterized by a clinical reaction involving the conjunctiva and the eyelids always associated with ocular itching, the quintessential symptom of allergy consequence of mast cell degranulation. In fact, IgE-mediated mast cell activation and release of the main mediator, histamine, has been described in all allergic ocular diseases: seasonal allergic conjunctivitis (SAC), perennial conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC).¹ In addition to histamine, conjunctival mast cells have been shown to release several mediators and cytokines, and to be heterogeneous in phenotype, biochemical properties, and functional responses.² Histamine release is a rapid process

accompanied by immediate ocular itching,² with tear histamine values peaking 5 minutes after conjunctival allergen challenge.³ Redness and chemosis have a slower onset after challenge but persist for a longer period of time. Therefore mast cells and histamine receptors are the main targets for anti-allergic treatment in all forms of OA. Mast cell stabilizers inhibit mast cell degranulation by blocking calcium-mediated release of inflammatory mediators, including histamine, from mast cells.⁴ The first approved drug in its class was cromolyn sodium 4%, approved in 1984 for use in VKC. Others that followed include lodoxamide tromethamine 0.1%, nedocromil sodium 2%, and permir-olast potassium 0.1% and N-spaglumic acid 4%, are beneficial because they can target both early and late

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Correspondence: Andrea Leonardi, MD, Department of Neuroscience, Ophthalmology Unit, University of Padua, via Giustiniani 2 35128, Padua, Italy. E-mail: andrea.leonardi@unipd.it

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phase allergic reactions. However, they are only effective if mast cells are deactivated prior to an allergic response. Thus, therapy must be initiated at least 2 weeks prior to antigen exposure.

First generation antihistamines are still used in combination with vasoconstrictors for the treatment of OA because of their rapid onset of action and easy over the counter accessibility. However, due to the short duration of effects, usually 2 hours, dosing may be necessary up to four times per day. In addition, the vasoconstrictor causes stinging upon instillation, can lead to rebound congestion and local toxicity, and are contraindicated in the presence of narrow angles. The second-generation of topical antihistamines levocabastine and emedastine eye drops share several benefits including longer duration of action, lasting 4 hours, and less stinging upon instillation.

The last generation of anti-allergic ophthalmic compounds share the mast cell stabilization and the antihistaminic activity in the same molecule: azelastine hydrochloride 0.05%, epinastine hydrochloride 0.05%, ketotifen fumarate 0.025% and 0.05%, and olopatadine hydrochloride 0.1%. Olopatadine 0.2%, the first daily dosing ocular anti-allergic compound, bepotastine besilate 1.5%, and once daily dosing alcaftadine 0.25%, approved by FDA, are not available in the European countries. These agents combine the season-long prevention of allergy attacks by mast cell stability with the instant gratification afforded by the antihistamine, alleviating the immediate signs and symptoms of the patient. Because of their long duration of action, they are prescribed for twice daily dosing; these are considerable advantages over mast cell stabilizers. All topical antihistamines and mast cell stabilizers reduce symptoms and signs of seasonal allergic conjunctivitis when compared with placebo in the short term.⁵

Among these drugs, ketotifen fumarate ophthalmic solution is a cyproheptadine derived anti-allergic drug that possesses both a mast cell stabilizing effect and H1-receptor antagonistic activity.⁶ Ketotifen fumarate attenuated the local allergic reaction in patients with SAC⁷ and in human conjunctival allergen challenge model both in adults and pediatric populations.⁸⁻¹³

The aim of this study was to evaluate the efficacy and tolerability of two different concentrations of ketotifene eye drops in patients affected by active SAC as they present in the common clinical outpatient practice.

MATERIAL AND METHODS

A single-masked, randomized, multicenter study was performed in four centers. A total of 81 patients who

suffered from active mild-to-moderate SAC, defined by an ocular itching score of at least 2+ and total symptom score of at least 5, were treated with two different concentrations of ketotifen eye drops. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board. Patients enrolled in the study were adults with a clinical history of SAC and a previous positive skin test or radioallergosorbent test (RAST) within the past 36 months to at least one common allergen prevalent during the study period: blue grass or ragweed pollen, alternaria, or other local weed pollens. Women of childbearing potential were required to use an adequate birth control method during the study period. Patients suspended all systemic and local drugs for at least five days prior to study commencement. Exclusion criteria were the following: the presence of any ocular pathology other than acute SAC (i.e. dry eye, chronic allergic conjunctivitis, VKC, viral or bacterial conjunctivitis); history of herpes keratitis; use of contact lenses during the course of the study; any other medical condition that could have interfered with the results of the study; use of non-steroidal anti-inflammatory agents, mast cell stabilizers, antihistamines, decongestants, or α -adrenoreceptor antagonists; use of topical (ocular) or systemic corticosteroids within two weeks before the start of the study; intraocular pressure (IOP) greater than 21 mmHg in either eye or any type of glaucoma; history of ocular surgery or laser within the previous 6 months; best-corrected visual acuity (Snellen) in either eye worse than 20/100.

On the day of enrollment, the signs (conjunctival redness, conjunctival chemosis, watery discharge increase, eyelid swelling) and symptoms (itching, tearing, burning) were reported according to a scoring system of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) and considered as baseline (V0). The total signs score, the total symptoms score and the total signs and symptoms scores (TSSS) for each subject were obtained adding the values of each symptoms and signs. Patients who met inclusion and exclusion criteria scores were randomized into two groups of subjects to receive either 0.025% ketotifen (Zaditen Oftabak, Thea, France) or 0.05% ketotifen (Ketoftil, Farmigee, Italy). They were instructed to administer bilaterally two drops/eye twice a day (at approximately 08.00 and 20.00 hours) from day 0 (V0, baseline) to day 21. Signs and symptoms of SAC were then evaluated on days 7 (V1) and 21 (V2) approximately at the same time of day (± 2 hours) as on V0.

Following the patients' random assignment to treatment groups, a trained nurse coordinator instilled the first dose of medication, one drop in each eye, at the study center. One minute later patients were queried about the ocular comfort of the medication rating ocular comfort/tolerability on a 4-point scale assessing the

degree of burning/stinging sensation (0 = absence of burning sensation or discomfort at instillation; 1 = mild (slightly perceptible); 2 = moderate (uncomfortable); 3 = severe (intense/extremely intense).

Using a daily diary at home, patients were asked to evaluate the local tolerability to the eye drops using the same 0–3 discomfort scale on days 2, 4, and 6 of treatment. The global assessment of the treatment was also evaluated by both the investigator and the patients at V1 and V2 using a –1 to 3 scale: –1 = deterioration/worsening; 0 = no relief; 1 = poor, but some relief; 2 = good/distinct relief; 3 = excellent/complete or almost complete relief of ocular allergy symptoms. According to this assessment scale a responder was defined by a score of 2 or 3 (complete or distinct relief).

The primary efficacy outcome was the reduction of TSSS at V2 between the two treatments. Other secondary efficacy outcomes were individual scores for signs and symptoms, the patients and investigators' assessment of global efficacy, and the responder rate (patient assessment at V2 and investigator assessment at V1 and V2). Local safety evaluation was assessed by the difference in tolerability of both treatments after the first instillation and during the study period.

Other ocular safety evaluations included external and slit-lamp evaluation, applanation tonometry, visual acuity, and fundus examination. Subjects were asked to report any adverse events or side effects that may have occurred between visits.

Signs, symptoms, ratings of global efficacy and tolerability were compared between groups with a two-factor (treatment and time) ANOVA with repeated measures on time factor and Bonferroni post-hoc test for multiple comparisons using a mixed-model procedure. The intention to treat population (all subjects that receive any study drug and who participated in at least one assessment) coincided with the full analyses set since all the patients concluded the study. All tests were two sided; a p value less than or equal to 0.05 was considered statistically significant. All statistics were performed using the SAS version 9.4 software (SAS Institute, Cary, NC).

RESULTS

All 81 enrolled patients concluded the study (40 in the ketotifen 0.025% group and 41 in the ketotifen 0.05% group). No statistical differences in demographics or baseline characteristics were found between the two groups. Both ketotifen 0.025% and 0.05% were effective in reducing the TSSS, the total sign score, the total symptom score and single signs and symptoms at V2 compared to V0 ($p < 0.001$).

The TSSS was significantly better reduced by ketotifen 0.025% compared to 0.05% at both V1 and V2

Total signs and symptoms score

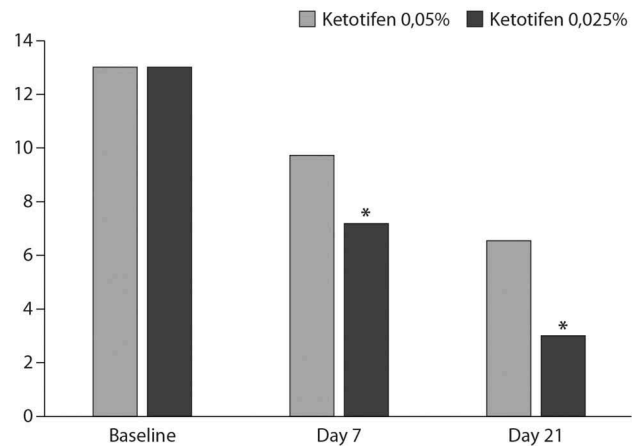


FIGURE 1. Total score of signs (conjunctival redness, conjunctival chemosis, watery discharge increase, eyelid swelling) and symptoms (itching, tearing, burning) according to the scoring system of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe), assessed on day 0, Day 7 and Day 21. * = $p < 0.0001$.

($p < 0.001$) (Figure 1). The total symptom score was also in favor of the 0.025% formulation at both V1 ($p < 0.0003$) and V2 ($p < 0.0001$). Similarly, the total sign score was better reduced by the 0.025% formulation at both V1 and V2 ($p < 0.0001$). Ketotifen 0.025% was statistically significant more effective than ketotifen 0.05% in reducing all signs and symptoms at V2 compared to baseline (Table 1).

Ketotifen 0.025% was better tolerated than ketotifen 0.05% at the first instillation (1.57 ± 0.9 vs 2.12 ± 0.7 , $p < 0.0001$) and at days 2, 4, and 6 ($p < 0.0001$) (Figure 2).

At each follow-up visit, patients and investigators found ketotifen 0.025% superior to ketotifen 0.05% in relieving the signs and symptoms of allergic conjunctivitis.

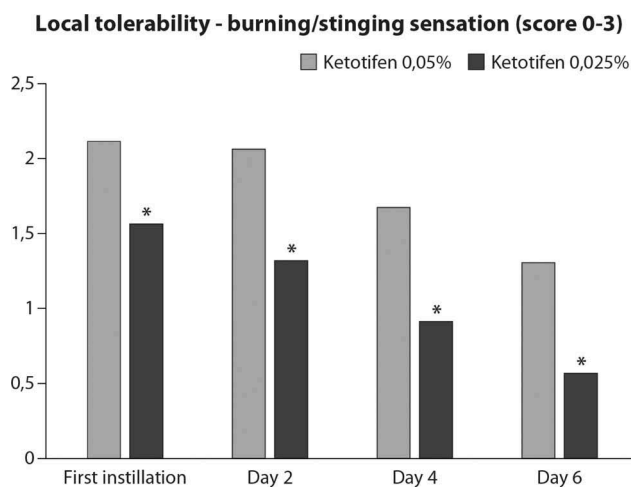
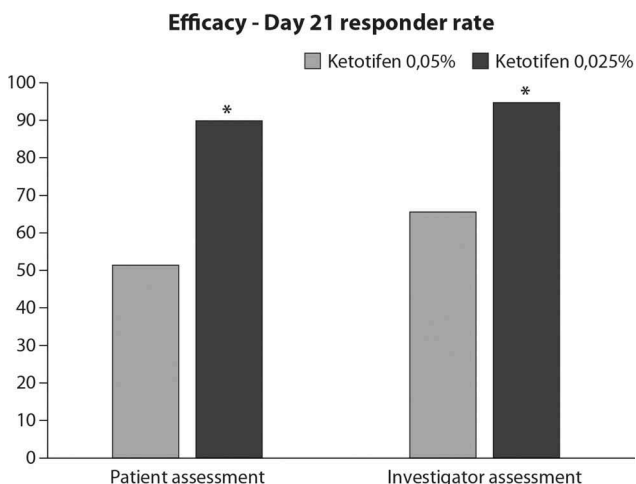
In fact, the mean global efficacy based on patient and investigator assessments for each treatment group, showed a significant better response for ketotifen 0.025% at V1 and at V2 for both patients and investigator assessments ($p < 0.001$) (Figure 3). No ocular or systemic side effects were reported by the patients in both groups.

DISCUSSION

Deciding on which therapy to prescribe for the treatment of SAC, the efficacy is heavily dependent on compliance. Patient perception data can be helpful in selecting the therapy that will be most accepted and thus most adhered to. The objective of this study was to examine two concentrations available in the market of the anti-allergy ophthalmic agent, ketotifen, to determine which was more effective in reducing signs and symptoms, and which the patients

TABLE 1. Signs and symptoms of SAC assessed according to a scoring system of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

	Baseline (Visit 0)		Day 21 (Visit 2)		<i>P</i> value
	<i>Ketotifen 0.05%</i> Mean (SD)	<i>Ketotifen 0.025%</i> Mean (SD)	<i>Ketotifen 0.05%</i> Mean (SD)	<i>Ketotifen 0.025%</i> Mean (SD)	
Itching	2.24 (0.7)	2.25 (0.9)	1.17 (0.9)	0.75 (0.6)	0.0004
Tearing	1.85 (1.0)	1.75 (1.1)	1.04 (0.9)	0.37 (0.5)	< 0.0001
Burning	1.82 (0.7)	2.00 (0.7)	0.87 (0.7)	0.35 (0.5)	< 0.0001
Conjunctival hyperemia	2.03 (0.9)	2.10 (0.8)	1.17 (0.8)	0.17 (0.3)	< 0.0001
Conjunctival chemosis	1.68 (0.6)	1.67 (0.8)	0.70 (0.7)	0.17 (0.3)	< 0.0001
Eyelid swelling	1.73 (0.8)	1.65 (0.9)	0.780 (0.8)	0.137 (0.7)	0.0043
Watery discharge	1.58 (1.0)	1.647 (0.9)	0.70 (0.8)	0.22 (0.4)	0.0009

FIGURE 2. Responder rate on day 21 according to patient assessment and investigator assessment. * = $p < 0.001$.FIGURE 3. Burning/stinging sensation after first instillation, at days 2, 4 and 6 scored according to a 4-point scale. * = $p < 0.0001$.

preferred in terms of tolerability and subjective global efficacy under a real-life condition.

Fourth-generation antihistamines include dual mechanism topical antihistamine-mast cell stabilizer medications. They offer the rapid onset of symptom relief through H1 receptor blockade and provide long-term inhibition of mediator release via mast cell stabilization.⁵ Typically, compliance is better when compared to mast cell stabilizers alone because pretreatment is not required and the long duration of action, usually 8 hours, requires only twice daily dosing.

In this study, both concentrations of ketotifen were effective in reducing ocular allergic TSSS, ocular itching and hyperemia associated with allergic conjunctivitis. However, it is clear that patients had a better response using ketotifen 0.025% over 0.05%. In fact not only TSSS and single signs and symptoms were better reduced by the 0.025% formulation but also tolerability and subjective global assessment were significantly in favor of ketotifen 0.025%. In the present study, ketotifen 0.025% was in its preservative-free formulation while ketotifen 0.05% was in the preserved ophthalmic solutions. This may have been one reason of the better tolerance of the 0.025% formulation.¹⁴

Ketotifen's rapid onset of action (within 15 minutes) and extended duration of action (at least 8 hours) make it a valuable treatment for allergic conjunctivitis.¹⁰ Ketotifen significantly decreased the signs and symptoms of ocular and nasal allergic rhinoconjunctivitis in the allergen challenge model with an adjunctive improvement of its effect when oral desloratadine was added.¹⁵ Besides the well-known effect in reducing signs and symptoms of OA, significantly diminished production of eotaxin and expression of CD29 by epithelial cells in patients with SAC.¹⁶

In conclusions, ketotifen eye drop, a dual acting antihistamine-mast cell stabilizers with rapid-onset of symptom relief, was shown to be an effective in reducing signs and symptoms of allergic conjunctivitis in this positive controlled seasonal study. Of the two concentrations available, the 0.025% was shown to be not only more effective but also preferred by the patients. This study gives some new perspectives on

the decision of the ophthalmic anti-allergy options available. The results of this study can be kept in mind as useful pieces of information to consider when making therapy choices.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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