Original Article

Comparison of efficacy and safety of topical Ketotifen (Zaditen) with Cromolyn sodium in the treatment of Vernal keratoconjunctivitis

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ABSTRACT

Background: This study compared the efficacy of Ketotifen fumarate .025% (Zaditen) with Cromolyn sodium 4% (Opticrom) eye drops in prevention of itching, tearing, and redness in Vernal Keratoconjunctivitis (VKC).

Methods: This double blind randomized single center clinical trial conducted between April and August 2004 in Yazd. One hundred eligible patients with clinical diagnosis of moderate VKC were randomly prescribed Zaditen (group A: n=50) and Cromolyn sodium (group B: n=50) eye drops for a 4 weeks period. Itching, lacrimation, redness, and photophobia were scored on a 4-points severity scale.

Results: After 7 days of treatment, the response rates based on subjects assessment of global efficacy was significantly greater in Ketotifen group (61.5%) than in Cromolyn group(53%).A clear response to treatment occurred in 94.4 of Zaditen and 81.2% of Sodium Cromoglycate treated patients. The investigator's assessment of response rates also showed that Ketotifen was superior to Cromolyn sodium (P=0.001). Ketotifen produced a significantly better outcome than Cromolyn for relief of signs and symptoms of VKC (P<0.05). Ketotifen fumarate treatment significantly reduced the total signs and symptoms score for each patients, in compare with day 0.

Conclusion: Ketotifen had a faster onset of action and provided better symptom relief than Cromolyn. The rapid onset of action and symptom control, make Zaditen a valuable treatment for VKC.

Keywords : VKC , allergic conjuctivitis , zaditen

Vernal keratoconjunctivitis (VKC) is a bilateral ocular allergic disease tends to occur in children during spring and summer months [1]. The disease occurs in warm temperate zones and is more common in the Middle East, Mediterranean area, and Iran [2].

VKC can certainly pose a threat to vision due to corneal involvement [3].It's immunopathogenesis appears to involve both type I and IV hypersensitivity [4,5]. The treatment of VKC is quite prolonged and demand good compliance.

Presently, moderate to severe cases are treated with a mastcell stabilizer such as cromolyn sodium and topical corticosteroid [6]. However, prolonged use of corticosteroids have risks such as cataract and glaucoma, and this drug should be reserved for treatment of severe ophthalmic symptoms of VKC. Mast cell degranulation and release of histamine in VKC stimulates nerve endings and dilates the blood vessels, causing itching and redness [7]. Mast cell stabilizing drops (Cromolyn) have an important role in treatment of VKC. More recently, the interset has focused on the possibility of topical application of histamine (H1) antagonists.

Ketotifen, a benzocycloheptathiophene derivate, has been used in the treatment of Asthma [8]. It blocks H1 receptors, stabilizes mast cells, and prevents eosinophil accumulation and degranulation [9, 10].

Ketotifen fumarte 0.025% ophthalmic solution (Zaditen, Novartis Ophthalmics) has been developed recently for alleviating the ocular signs and symptoms of VKC [11]. Recent clinical trials demonstrated that Zaditen 0.025% eye drop was efficacious and safe, providing a rapid onset and long duration of action [12, 13, 14].

This study was conducted for the first time in our country.

The purpose of this study was to compare the

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efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution (Zaditen) with Cromolyn sodium 4% in the treatment of moderate VKC.

Subjects and Methods

Subjects

This study was performed between April and August 2004 in yazd provinence.

One hundred subjects (68 males and 32 females) enrolled in this research. Eligible cases were assigned randomly to one of two treatment sequences according to a computer- generated randomization list. Eligible cases for inclusion were between ages of 8 and 25 years old.

Criteria of moderate VKC were papilla on upper tarsus, limbal hypertrophy, and conjunctival chemosis. Cases with the following conditions were excluded: history of dry eye, other form of allergic conjunctivitis, allergy to antihistamines, the ocular surgery within 2 months before study, and using systemic or ocular corticosteroids or mast cell stabilizer within 4 weeks of randomization .Patients written informed consent was required.

The trial was conducted in accordance with the declaration of Helsinki .

Study Design

This was a single center, double blind, randomized, comparative clinical trial, and the patients were randomly divided into two equal groups (groups A and B).

Group A patients (n=50) received topical Zaditen(Novartis Ophthalmicus) 0.025%, twice daily and placebo, one time daily .To maintain study blindness, placebo medication were supplied in empty bottles of Zadietn so that the appearance and application regimen of placebo was identical to Zaditen. Placebo was artificial eye drop. Topical Cromolyn sodium 4% or Opticrom (Fisons Pharmaceuticals, Loughborough,UK) was prescribed for group B (n=50) three times daily. Both drops were made in foreign factories.The packaging of all medications has indented appearance for each group.

Each group contained 34 males and 16 females. Treatment was given in each group for 4weeks. The study contained three visits, a screening visit and two treatment visits. Primary analysis was done at the follow-up visit held between day 7 and 15.

Response rates were also assessed at the termination visit held at day 30.

Ocular Status Assessment

Different symptoms (itching, tearing, burning, redness) and signs (limbal hypertrophy ,conjunctival chemosis, and presence of follicle) of VKC were evaluated at their enrolment (day zero) and at different times after starting the treatment(days 7, 15, and 30). Symptoms and signs were classified in four stages: 0-Absent; 1-Mild; 2-Moderate; and 3-Severe. The Total Symptoms and Signs Score (TSSS) for each case were obtained by adding the values of each symptom and sign together and dividing the outcome by the total number of them. Each patient was instructed to grade his or her symptoms of itching, photophia , watering , and mucoidal discharge on a scale from 0 to 3 . The patients scored their symptoms for both eyes .Clinical signs (conjuntival erythema and chemosis, papillae , limbal hypertrophy , lid follicles) were also collected from the right eye of each patient at the beginning, follow-up, and at the end of the study. Each patient was examined and clinically scored by an ophthalmologist who did not know the clinical status in the pre or post treatment period in the two groups. Cases were asked to assess the overall effect of treatment using a five point grading scale (Table 1).

Table 1. Case and investigator assesment of global efficacy (relative to baseline).

Score	Change from baseline	Description
0	Excellent	Complete relief from ocular symptoms
1	Good	Distinct relief from ocular symptoms
2	Fair	Some relief from ocular symptoms
3	poor	No relief from ocular symptoms
4	Deterioration	Worsening of ocular symptoms

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Tolerability and Safety

Assesment of tolerability was based on finding adverse effects by the case and physician. At the end of the treatment, investigator provided a global assessment of safety and tolerability using the same 5- points scale as efficacy (Table 1).

Statistical Analysis

The Kaplan-Meier technique was used to describe the time-to-onset distributions of the two treatments. The time-to-onset distributions were compared between the two treatment groups, using a log-rank test. The log-rank test was used to test the variable factor of primary efficacy. The response rate, signs, and symptoms were analyzed using logistic regression for binary and ordinary data.

Results

One hundred cases (68 males, 32 females) were screened. The homogeneity of treatment groups was checked with regard to age, sex, and baseline sum score. No significant difference was noted between groups. Study participants were between ages of 8 and 25 years old (mean 16.3) and had a duration of disease ranging from 1 to 15 years (median duration of 8.3).

Response Rate

Responders were patients whose sum score of three main eye symptoms decreased by at least 3 points from a baseline score.After 7 days of treatment, 61.5% of Zaditen treated patients and 53% of Cromolyn treated patients showed improvements of their symptoms and signs . With continued treatment untill day 14, symptoms control was achieved in 81% of group A and 63% of group B and this difference was significant (P<0.001) .

Primary Efficacy Variable

The primary efficacy variables were physicians clinical judgment scales and patients overall judgment scales of improvement from baseline.

The median time to onset of action were 15 minutes for Zaditen versus 45 minutes for Cromolyn. Onset of action was defined as first time interval in which a decrease of at least 20% in composite ocular symptom score. At each post-dose time-point, cases receiving Zaditen who had 20% or more symptom reduction were more than those receiving Cromolyn. Analysis of the time to onset distribution (Figure 1) showed Zaditen to be statiscally superior to Cromolyn (P=0.028).

Both primary efficacy variables showed significantly greater overall improvement of VKC from baseline with Zaditen than Cromolyn.

At the final visit, the respondse rate as judged by the case was significantly greater with Zaditen Compared with Cromolyn (P=0.001).

Moreover administration of Zaditen eye drop for thirty days, significantly (P<0.0001) reduced the TSSS for each patient between days 0 and 30.

A clear response to treatment (an improvement of sum scores of $\geq$ 3 points compared to base line)

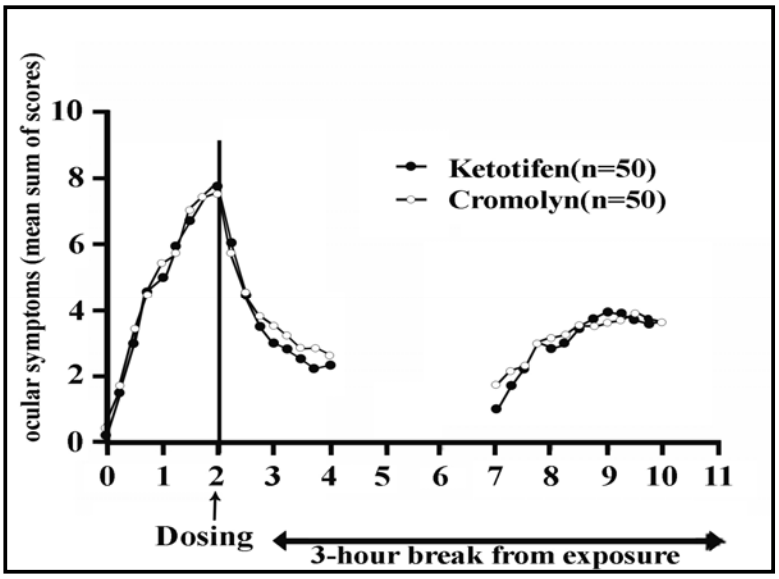

Figure 1. Onset of action in treatment groups.

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occurred in 94.4% of Zaditen and 81.2% of Cromolyn treated patients. Based on cases daily records the superiority of Zaditen in relieving signs and symptoms including redness and tearing was observed from the beginning of the treatment and was most marked during the first days. Zaditen was superior to Cromolyn in preventing itching ($p<.001$) and redness ($p<0.005$) at most assessment.

Mean scores for eyelid swelling and mucous discharge were generally low for Zaditen group (Table 2).

At the termination visit the analysis showed significantly better relief of signs and symptoms with Zaditen than Cromolyn ($p=0.0$), with mean composite sign and symptom score of 2.92 and 3.89 respectively (Table2).

Table 2. Mean of ocular signs and symptoms at days 5-8 visits

	Mean Score		P-value
Sings and symptoms	**Zaditen(n=50)**	**Cromlyn(n=50)**	**Zadetin Vs Cromolyn**
Redness	0.68	0.90	0.03
Itching	1.25	1.44	0.27
Tearing	0.53	0.88	0.01
Lid Swelling	0.40	0.43	0.85
Discharge	0.12	0.24	0.82
Composite Score	2.98	3.89	0.02

Analysis of the mean composite ocular symptoms score versus the time showed Zaditen to have a faster onset of action in the relief of ocular symptoms (2 hours post-dose) than Cromolyn sodium (figure 2). At the end of treatment global assessment of efficacy by investigator was considered at least 91.4% for Zaditin and 78% for Cromolyn sodium.

Safety

Both treatments were generally well tolerated and majority of adverse events were of mild transient irritation and burning. However the droup-out rate due to adverse events was lower in the Zaditen group (n=2.4%) compared with Cromolyn (n= 4.8%)

Investigator global assessment of tolerability gave an opinion of at least satisfactory in 95.6% of Zaditen –and 86.3% on Cromolyn sodium, treated patients.

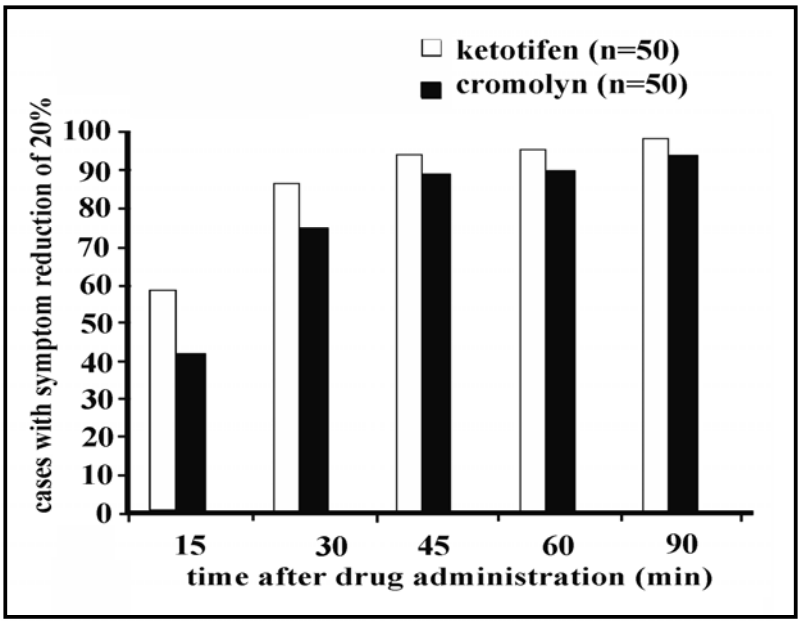

Figure 2. Change in mean of composite ocular symtom scores over the time

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Discussion

VKC is a common, prevalent, and clinically significant IgE mediated hypersensivity response. VKC is an immunopatholgic disease in which the number of mast cells increases in substantia propria [15-16]. Activation of mast cells by IgE bound receptor cross-linking by allergen promotes the release of several mediators such as histamine , prostaglandins, and cytokinase, which all of them are responsible for the symptoms of VKC [17,18]. The mast cell is considered to play a pivotal role in causing symptoms and signs of VKC [19]. Current therapy of VKC foccuses on modulation of the immune system and pharmacologic inhibition of the chemical mediators involved in the immune response. Mast cell stabilizers and antihistamines are two of the most commonly used groups of therapeutic agents, they stabilize mast cell membranes by preventing calcium influx across the mast cell membranes, there by preventing mast cell degranulation and mediator release. The new antihistamines have been demonstrated to be capable of affecting several phenomena of the allergic inflammation including mediator release [20,21].

Among these drugs, new multiple - action agents like Ketotifen fumarate (Zaditen) is histamine (H1) receptor antagonist , as well as mast cell stabilizer .

In addition, in vitro and animal studies [22] have shown that Zaditen inhibits the activation and chemotaxis of eosinophils into the conjunctiva, which is an important step in the late phase of the immune response [23].

Cromolyn sodium, as a mast cell stabilizer is effective and safe in the treatment of VKC, but topical steroids which are often required, increase the chance of bacterial keratitis, cataract, and glaucoma, so we decided to perform this study in order to investigate and compare the effect of the topical Ketotifen with Cromolyn sodium in moderate VKC.

In the present study main VKC symptoms decreased significantly by day 3 with sustained improvement on days 7 and 14.

The result of this study showed that Zaditen 0.025% applied topically twice daily was superior to Cromolyn three times daily (P=0.001). Zaditen produced a significantly better outcome than Cromolyn (P<0.05) for relief of signs and symptoms of VKC. Leonardi's study [24] showed that investigators assessment of response rates for Zaditen was superior to Cromolyn which is similar to our study. A recent study by Andren petal [25] reported a clear response rate of 91.2% for zaditen and 83.5% for Cromolyn treatment groups that were same to our study.

In the current study, as Friedrich Horak's report [12], Zaditen was found to have a faster onset of action than Cromolyn . In term of efficacy, Zaditen was numerically superior to Cromolyn for the majority of the individual symptoms score [26].

We can conclude that at the 15 minutes and 4-hours periods of time, Zaditen was superior to Cromolyn in preventing itching and redness that was same as Greiner's research [27].

In this study, the response rate after 7 days of treatment was 61.5% for Zaditen and 53% for Cromolyn treated patients, however in Mkidd's report [28] these were 56.5% and 49.3% respectively. Cases, assessment of global efficacy was significantly greater in Zaditen group(71.5%) than in Cromolyn group (51%).

Although the efficacy of ketotifen fumarate in seasonal allergic conjunctivitis (SAC) has already been shown. the findings of our study confrim effectiveness of Ketotifen in VKC .

Zaditen, two times daily was significantly more effective than sodium Cromolyn three times daily in alleviating symptoms and signs of moderate VKC . The faster onset of action (within 15 minutes) and better symptoms relief observed with Ketotifen during the initial 2 hours , along with favourably safety and tolerability profile make Zaditen a new valuable treatment option for patients with moderate VKC.

References

1. *Allansmetl MR, Intasman W, Jaeger EA. Duane's Cinical Ophthalmology, revised. Philadelpia: Lippincott;1995.*
2. *Buckley RY. Vernal keratoconjunctivitis (review). Int Ophthalmol Clin 1998;66:112-7.*
3. *Cameron JA. Shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. Ophthalmology 1995;102:985-93.*
4. *Bonini S, Bonini S. JgE and non – JgE mechanisms in ocular allergy. Ann Allergy 1993 Sep;71(3):296-9.*
5. *Foster CS. Atopic keratoconjunctivitis. Ophthalmology 1990;99:992-1000.*

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6. *Abelson MB, George MA, Smith LM. Evaluation of 0.05% levocabastine versus 4% sodium cromolyn in the allergen challenge model. Ophthalmology 1995 Feb;102(2):310-6.*
7. *Leonardi A. Role of Histamine in allergic conjunctivitis. Acta Ophthalmol Scand 2000;230:18-21.*
8. *Cartier A, Bernstein IL, Burge PS, Cohn JR, Fabbri LM, Hargreave FE et al. Guidelines for bronchoprovocation on the investigation of occupational asthma. Report of the Subcommittee on Bronchoprovocation for Occupational Asthma. J Allergy Clin Immunol 1989 Nov;84(5 Pt 2):823-9.*
9. *Grant SM, Goa KL, Fitton A, Sorkin EM. Ketotifen: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma and allergic disorders. Drugs 1990 Sep;40(3):412-48.*
10. *Nabe M, Miyagawa H, Agrawal DK, Sugiyama H, Townley RG. The effect of ketotifen on eosinophils as measured at LTC4 release and by chemotaxis. Allergy Proc 1991 Jul-Aug;12(4):267-71.*
11. *Fsadim MG, Lanz R, Taylor HR et al. Efficacy and safety of Ketotifen fumarate eye drops versus vihicle placebo and levocabastino in an environmental. Study of patients with seasonal allergic conjunctivitis (abstract). Invest Ophthalmal Vis Sci 2000;41:S368.*
12. *Horak F, Stubner P. Onset and duration of action of ketotifen 0.025% and Emedastine 4% in (SAC). Clin Drug Invest 2000;23(5):329-37.*
13. *D'Arienzo PA, Leonardi A, Bensch G. Randomized, double-masked, placebo-controlled comparison of the efficacy of emedastine difumarate 0.05% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the human conjunctival allergen challenge model. Clin Ther 2002 Mar;24(3):409-16.*
14. *Gomes PJ, Welch DL, Abelson MB. Evaluation of the efficacy and safety of Ketotifen in the allergen challenge model. Eur J Ophthalmol 2003 Mar; 13(2):128-33.*
15. *Macleod JD, Anderson DF, Baddeley SM, Holgate ST, McGill JF, Roch WR. Immunolocalization of cytokines to mast cell in normal and allergic conjunctiva. Clin Exp Allergy 1997;27:1328-34.*
16. *Irani AM. Ocular mast cells and mediators in ocular allergy. Immunology and allergy clinics of North America (Edited by:Bielory):WB sounders; 1997.*
17. *MacDonal SM. Histamine-releasing factor. Curr Opin Immunol 1996;8:778-83.*
18. *Desreumaux P, Capron M. Eosinophils in allergic reactions. Curr Opin Immunol 1996,8:790-5.*
19. *Anderson DF, MacLeod JD, Baddeley SM, Bacon AS, McGill JI, Holgate ST et al. Seasonal allergic conjunctivitis is accompanied by increased mast cell numbers in the absence of leucocyte infiltration. Clin Exp Allergy 1997 Sep;27(9):1060-6.*
20. *Abelson MB, Schaefer K. Conjunctivitis of allergic origin: immunologic mechanisms and current approaches to therapy. Surv Ophthalmol 1993 Jul-Aug;38 Suppl:115-32.*
21. *Ciprandi G, Passalacqua G, Canonica GW. Effects of HI antihistamines on adhesion molecules: a possible rationale for long term treatment. Clin Exp Allergy 1999;29:49-53.*
22. *Sanjar S, Aoki S, Boubekeur K, Burrows L, Colditz I, Chapman I et al. Inhibition of PAF-induced eosinophil acculation in pulmonary airways of guinea pigs by anti-asthma drugs. Jpn J Pharmacol 1989 Oct;51(2):167-72.*
23. *Arnoux B, Denjean A, Page CP, Nolibe D, Morley J, Benveniste J. Accumulation of platelets and eosinophils in baboon iung after paf-acetger challenge.inhibition by ketotifen. Am Rev Respir Dis 1988 Apr;137(4):855-60.*
24. *Leonardi A, Busca F, Tavolato M, Secchi AG. The anti-allergic effects of a chlorphiniramine sodium-chlorp combination compared to ketotifen in the conjuctiva challege model. Eur J Ophthalmol 2003 Mar;13(2):128-33.*
25. *Martin AP, Urrets-Zavalia J, Berra A, Mariani AL, Gallino N, Gomez Demel E et al. The effect of ketotifen on inflammatory markers in allergic conjunctivitis. BMC Ophthalmol 2003 Jan;3(1):2-6.*
26. *Greiner JV, Minno G. A placebo-controlled comparison of ketotifen fumarate and nedocromil sodium ophthalmic solutions for the prevention of ocular itching with the conjunctival allergen challenge model. Clin Ther 2003 Jul;25(7):1988-2005.*
27. *Greiner JV, Michaelson C, McWhirter CL, Shams NB. Single dose of ketotifen fumarate .025% vs 2 weeks of cromolyn sodium 4% for allergic conjunctivitis. Adv Ther 2002 Jul-Aug;19(4):185-93.*
28. *Kidd M, McKenzie SH, Steven I, Cooper C, Lanz R; Australian Ketotifen Study Group. Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. Br J Ophthalmol 2003 Oct;87(10):1206-11.*

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