ORIGINAL RESEARCH

Comparison of the Efficacy of Ketotifen Fumarate 0.02% and Azelastine 0.05% in the Treatment of Vernal Kera-toconjunctivitis

Ashish Chander[1], Shilpa Patrick[2]

ABSTRACT

Introduction: Vernal Keratoconjunctivitis (VKC) is an ocular disorder that primarily affects children and adolescents. Various treatment modalities of VKC are topical mast cell stabilizers, anti-histaminics, corticosteroids, and immunomodulators.
Material and methods: The efficacy of the two drugs Ketotifen 0.02% and Azelastine 0.05% was compared in this prospective trial. The study included 50 patients of vernal Keratoconjunctivitis (VKC) in whom one eye was randomly assigned to Ketotifen fumarate and other to Azelastine. Symptoms and signs were assessed at day 0, 7, 14 and 28.
Results: Both drugs were found to significantly improve symptoms such as watering, itching, redness and discharge and signs such as conjunctival mucus, congestion and discharge. No difference was found in the efficacy of the two drugs.
Conclusion: In our study all the symptoms improved significantly with both the drugs, with Ketotifen being better in reducing ropy discharge.

Key words: Vernal Keratoconjunctivitis, Ketotifen, Azelastine.

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[1]Assistant Professor Department of Ophthalmology, [2]Assistant Professor Department of Pharmacology Christian Medical College, Ludhiana, India

Corresponding author: Dr Shilpa Patrick: Assistant Professor Department of Pharmacology Christian Medical College Ludhiana.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent, bilateral inflammatory disease of cornea and conjunctiva affecting young children, mostly in their first decade.[1] VKC is a disease of warm climate and warm weather months.[2] Boys are affected more commonly than girls. The disease is characterized predominantly by itching, photophobia, foreign body sensation and thick mucus discharge from the eyes. Diagnosis of this Allergic condition is done by the presence of characteristic clinical features which consist of itching, cobblestone papillae seen over upper tarsal conjunctiva, Tranta's spots over the limbus and superficial keratitis.[3]
Management of this condition varies according to symptom severity. A number of therapeutic options available for the treatment of VKC range from the prophylactic use of topical mast cell stabilizers to the therapeutic use of corticosteroids in extreme cases.[4]
Mast cell stabilizers are characterized by a slow onset of action and mantainence of therapy is essential. This can lead to poor patient compliance. Antihistaminics on the other hand provide rapid symptomatic relief but their effect is short lasting. The dual action drugs which stabilize the mast cell membranes as well as block the various inflammatory mediators released are the newest drugs in our armamentarium for the treatment of this condition. The present study was undertaken to compare the efficacy of two drugs Ketotifen fumarate 0.02% and Azelastine 0.05% belonging to this category of dual action drugs. The aim of this study was to compare the efficacy of Ketotifen fumarate 0.02% and Azelastine 0.05% in the treatment of vernal Keratoconjunctivitis.

MATERIAL AND METHODS

The prospective trial was carried out in the department of ophthalmology, in a tertiary care hospital. VKC was diagnosed on the basis of itching, ropy discharge, presence of papillae in upper tarsal conjunctiva and limbal changes. A total of 50 patients were enrolled in the study. Informed consent was taken from the patients and prior treatment was stopped for all patients for a period of one week before inclusion in the study.

All patients underwent complete ophthalmic examination including recording of details of symptom, visual acuity and a complete slit-lamp examination. One eye of each patient was randomly assigned to Ketotifen fumarate and other to azelastine. Patients were adviced to use both drugs twice daily.

Symptom and signs were assessed at baseline (day 0 i.e. one week after stopping prior treatment), day

Signs	Mild (1)	Moderate (2)	Severe (3)
Lid edoma	Minimal	Moderate	Interpalpebral fissure decreased
Chemosis	Minimal	Focal areas chemosis	Obvious chemosis
Bulbar congestion	Minimal	Obvious but not diffuse	Diffuse redness
Conj.mucus	Min mucus strands	Few	Diffuse
Papillary hypertrophy	Mosaic, flat appearance <0.4mm	Elevated with definite depression 0.4-1mm	cobblestone
Limbal infiltrates	Upto 1 quadrant	2 quadrant	More than 2 quadrant
Keratitis	Few erosions	Macroerosions	Vernal ulcer

Table 1: Sign severity scale

Symptom	Baseline	Day 7 score	p-value	Day 14 score	p-value	Day 28 score	p-value
Itching							
Azelastine	1.18	0.69	<0.001	0.39	<0.001	0.17	<0.001
Ketotifen	1.04	0.47	<0.001	0.26	<0.001	0.13	<0.001
	p>0.05	P<0.05		P<0.05		p>0.05	
Watering							
Azelastine	0.95	0.60	<0.05	0.39	<0.05	0.22	<0.001
Ketotifen	0.78	0.56	<0.05	0.30	<0.05	0.17	<0.001
	p>0.05	P>0.05		P>0.05		p>0.05	
Redness							
Azelastine	1.26	0.82	>0.05	0.52	<0.05	0.21	<0.005
Ketotifen	1.24	0.65	<0.05	0.52	<0.05	0.21	<0.005
	p>0.05	P<0.05		P>0.05		p>0.05	
Ropy discharge							
Azelastine	0.82	0.65	<0.05	0.34	<0.001	0.21	<0.001
Ketotifen	0.78	0.60	<0.05	0.34	<0.001	0.13	<0.001
	p>0.05	P>0.05		P>0.05		P<0.05	

Table 2: Symptom severity score

Signs	Baseline	Day 7 score	P value	Day 14 score	P value	Day 28 score	P value
Conj.mucus							
Azelastine	0.91	0.73	>0.05	0.52	>0.05	0.34	<0.05
Ketotifen	0.88	0.65	>0.05	0.56	>0.05	0.21	<0.05
	p>0.05	p>0.05		p>0.05		p<0.05	
Bulbar congestion							
Azelastine	0.96	0.78	>0.05	0.47	<0.05	0.21	<0.05
Ketotifen	0.91	0.65	>0.05	0.39	<0.05	0.17	<0.05
	P>0.05	P<0.05		p>0.05		p>0.05	
Palpebral congestion							
Azelastine	1.08	0.87	<0.001	0.52	<0.001	0.30	<0.01
Ketotifen	1.0	0.83	<0.001	0.52	<0.001	0.30	<0.01
	p>0.05	p>0.05		p>0.05		p>0.05	
Papillary hypertrophy							
Azelastine	1.30	1.30	>0.05	1.17	>0.05	1.08	>0.05
Ketotifen	1.26	1.26	>0.05	1.13	>0.05	1.04	>0.05
	p>0.05	p>0.05		p>0.05		p>0.05	
Keratitis							
Azelastine	0.74	0.61	>0.05	0.48	<0.05	0.22	<0.05
Ketotifen	0.79	0.55	>0.05	0.42	<0.05	0.19	<0.05
	p>0.05	p>0.05		p>0.05		p>0.05	

Table 3: Sign severity score

7, day 14 and day 28. Patient complaints/adverse effects regarding the use of drugs were also recorded.

Presence of symptoms such as itching, redness, watering, ropy discharge, lid swelling, foreign body sensation and photophobia were graded on a scale of 0-3 subjectively by the patient at each visit. Signs were graded as mild, moderate and severe according to the sign severity score scale given in table 1. [5]

STATISTICAL ANALYSIS

Data obtained were analysed using unpaired student's t test for within group and paired test for between group comparisons.

RESULTS

Our study included a total of 50 patients. Average age of the patients was 12.3 years (6-23 years). There were 36 males and 14 females in our study 16 patients had palpebral type, 14 had bulbar type and 20 had mixed type of vernal conjunctivitis.

Scores for each symptom and sign were compared within the group at day 7, 14, 28 as well as between the 2 groups (Table 2 and Table 3)

All the symptoms and signs which had a baseline score of less than 0.75 were excluded.

Symptoms

Watering and itching: Both the groups significantly reduced watering and itching at day 7 itself and the effect continued through out the 4 weeks with no difference between the groups.

Redness: Decrease in redness occurred earlier in Ketotifen group as compared to azelastine group, where significant improvement was seen only at 2 weeks but no difference was seen at 4 weeks be-

tween the groups.

Discharge: Both groups significantly decreased discharge only at 4 weeks with Ketotifen showing better response.

Signs

Conjunctival mucus: Conjunctival mucus decreased significantly only at 4 weeks for both groups with Ketotifen being slightly better.

Bulbal congestion: Bulbar congestion decreased for both groups at 2 weeks and palpebral congestion at 1 week itself with no difference between the 2 groups at any point of time.

Papillary hypertrophy: No significant change was noticed in papillary hypertrophy between the 2 groups at any visit.

Keratitis: Keratitis showed significant improvement in the 2 groups only at 2 weeks with no significant difference between the 2 groups.

DISCUSSION

VKC is an allergic disorder in which IgE mediated mechanism play a role. The early allergic response results from allergen mediated cross linking of pairs of immunoglobulin's (IgE) on the surface of conjunctival mast cells. This leads to mast cell degranulation and release of inflammatory mediators like histamine, tryptanase, leukotrienes, cytokines and platelet activating factor. Histamine binds to H1 receptor on the conjunctival epithelial cells and stimulates the parasympathetic nerve endings and dilates the blood vessels and recruits eosinophilia to the site resulting in redness and swelling and a prolonged allergic response.[6,7] As allergen avoidance is unachievable, there is often need for therapeutic intervention that offers effective and sustained symptomatic relief.

The conventional treatment for VKC involves instillation of antihistamines or mast cell stabilizers. Both treatment options have benefits and considerable limitations as well. Antihistamines block histamine only and mast cell stabilizers have a slow onset of action and have to be administered prophylactically.

This led to the development of newer selective H1 receptor antagonist which have a dual mode of action: stabilize the mast cells and block various inflammatory mediators.

Ketotifen fumarate is a potent non competitive histamine receptor antagonist with higher affinity to histamine receptors. It has three independent pharmacological mechanisms that appear to contribute to its antiallergic effect.[8]

1. Inhibition of H1 receptors
2. Mast cell stabilization
3. Prevention of eosinophilic accumulation
4. Inhibits platelet activating factor

Azelastine on the other hand acts through the following mechanism:[9]

1. Inhibits mast cell activation
2. H1 receptor antagonistic activity
3. Inhibits leucotrienes biosynthesis and release
4. Inhibits activation of eosinophils
5. Downregulates ICAM 1(intercellular adhesion molecule).

ICAM 1 is known as a hallmark of allergic inflammation. It plays a crucial role in the recruitment and migration of inflammatory cells and is rapidly expresses following ocular allergen provocation. It is a convenient and meaningful marker for evaluation of ocular anti allergic therapies. Topical administration of azelastine to the eye has been found to reduce the ICAM 1 expression significantly after specific allergen challenge test and during natural seasonal allergenic exposure.[10]

In our study all the symptoms improved significantly with both the drugs, with Ketotifen being better in reducing ropy discharge. All signs except papillary hypertrophy improved significantly with both drugs with Ketotifen being better in reducing conjunctival mucus.

CONCLUSION

VKC is a common form of allergic conjunctivitis in India like other tropical countries affecting young male children below 16 years. Predominant features are seasonal occurrence and Itching. The composite symptom and sign score for the two drugs was not significantly different at any point of time. Thus the two drugs, though act on different mediators of inflammation proved to be equally efficacious in the treatment of vernal Keratoconjunctivitis.

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