Comparative Study of Clinical Efficacy and Tolerance in Seasonal Allergic Conjunctivitis Management with 0.1% Olopatadine Hydrochloride versus 0.05% Ketotifen Fumarate

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ABSTRACT.

Objective: **To compare the clinical efficacy and tolerance of 0.1% olopatadine hydrochloride (OHC) versus 0.05% ketotifen fumarate (KF) in the management of allergic conjunctivitis.**

Materials and Methods: **Eighty adult patients with a history of allergy (allergic conjunctivitis, hay fever, asthmatic bronchitis and dermatitis) that were showing allergic conjunctivitis signs and symptoms (itching, hyperemia, mucous discharge and tearing) at the time of inclusion in this study were evaluated. Patients were divided in two groups, A and B. Group A patients were treated with OHC and group B patients were treated with KF. Both groups received one drop in the affected eye every 12 hrs. The start time of this study was the first patient visit, in which the medication was instilled for the first time. Both groups of patients were evaluated 30 min, 48 hr., 7 days and 14 days later. Local tolerance of each medication was evaluated.**

Results: **Clinical improvement of the signs and symptoms of allergic conjunctivitis occurred in 42.5% to 62.5% of the patients in Group A when assessed 30 min following the first topical ocular dose of olopatadine. However, mucous discharge was not affected. Forty-eight (48) hrs. after the first instillation, improvements in 57.5% to 75% of the patients were shown in every evaluated parameter. After 7 days of treatment, positive clinical results were observed in 80% to 87.5% of the treated patients. Except for the patients that were dismissed from the study before the seventh day of treatment due to the absence of therapeutic response (4/40), all patients satisfactorily completed the therapeutic plan by the seventh day. No intolerance reactions were observed in patients of this group.**

In Group B patients (KF), clinical improvement of the signs and symptoms measured in the study was shown in 20.0% to 47.5% 30 min after instillation. As observed with olopatadine, no improvement in the number of patients showing mucous discharge was noted at the 30-min time point. At 48 hr. after the first instillation, 27.5% to 48% of patients showed improvement in every evaluated parameter. After 7 days of treatment, improvement was observed in 60% to 75% of patients. On Day 14, positive responses were observed in 67.5% to 75% of patients. Seventeen and one-half percent of the patients were dismissed from the study before the seventh day of treatment due to the absence of a therapeutic response. Approximately 23% of the patients had mild reactions of intolerance (stinging) which was not a cause to discontinue the treatment.

Conclusion: **Olopatadine hydrochloride controlled allergic conjunctivitis symptoms and signs more rapidly and to a greater extent than ketotifen fumarate.**

Fewer cases of treatment failure were noted with OHC, and no local intolerance reactions were observed, while KF triggered mild reactions (stinging) in 23% of patients.

Key words: seasonal allergic conjunctivitis – olopatadine – ketotifen.

Acta Ophthalmol. Scand. 2000: 78: 52–55
 ISSN 1395-3907

Introduction

Allergic conjunctivitis is an ocular surface inflammatory disease that affects approximately 25% of the general population (1) and has a significant impact on the social and economic aspects of life. It can appear alone or associated with other allergic diseases, especially allergic rhinitis.

Allergic conjunctivitis is an immunopathological disease. It is a typical Type I hypersensitivity reaction mediated by IgE and results from a series of biological responses (2): 1) environment allergen sensitization; 2) IgE mast cell activation and consequent mediators release; 3) conjunctival inflammation with eosinophil prevalence; 4) cytokine production, and 5) increased mucous secretion.

Mast cells play an important role in this physiopathology. Nearly 100% of the mast cell population found in the conjunctival surface of allergic conjunctivitis patients are the tryptase-chymase type (3). Their number is significantly increased (higher than 200,000/mm^3) in both conjunctival epithelium and stroma, and mediators are elevated in these patients' tears (4). Mast cell activity is not only related to the development of the acute allergic reaction but is also involved in the metabolic modulation of the connective tissue following this response (fibrosis). In both phases, acute and chronic, the main characteristic is the presence of inflammatory cells (neutrophils, eosinophils and lymphocytes) in tears approximately 6 to 24 hours after the reaction is initiated. The principal mediator present is histamine (5). This vasoactive amine induces the major signs and symptoms of allergic conjunctivitis.

Main signs include keratic and perikeratic conjunctival congestion, conjunctival chemosis, mucous secretion, epiphora and papillae. The principal symptoms include tearing, photophobia, blurry vision, foreign body sensation and itching, the last one being the distinctive indicator of allergic conjunctivitis.

Allergic conjunctivitis can be treated with local anti-allergic agents such as antihistamines, either alone or in combination with alpha (α) adrenergic agents (6) and mast cell stabilizers. Some antihistaminic agents with mast cell stabilizing properties have recently been added to the Ophthalmological Pharmacopeia. This dual action allows control of the allergic conjunctivitis signs and symptoms during the acute phase (antihistaminic action), and also allows prevention of the long-term mast cell degranulation response (membrane stabilizing action).

Within this group of drugs we can find 0.1% olopatadine hydrochloride (Patanol®) and 0.05% ketotifen fumarate solutions (Zaditor™).

Olopatadine hydrochloride 0.1% has a rapid initial action (minutes) that extends for hours, which allows a BID dosing schedule. It has strong, selective antihistaminic and mast cell stabilizing action with an important inhibitory effect on pro-inflammatory cytokine production (7, 8). It is very well tolerated (less than 5% incidence of mild discomfort) when instillated. It is indicated for children as young as 3 years of age.

Ketotifen fumarate 0.05% is derived from cyproheptadine, a serotonin and histamine antagonist. Its clinical use has been widely studied in relation to bronchial asthma. Its antihistaminic action is the result of a non-competitive and non-selective antagonistic mechanism and the mast cell stabilizing action is comparable to that of sodium cromoglycate in asthmatic patients. When used as a topical antihistaminic in ophthalmology, the dosage varies from 2 to 4 daily instillations. At 0.1%, its efficacy increases, but so does the incidence of adverse effects. Clinical efficacy data in children are not available.

Materials and Methods

From August 1998 to July 1999, 80 adult patients with positive allergy records (allergic conjunctivitis, hay fever, asthmatic bronchitis and dermatitis) were evaluated. At the moment of being included in this study they were showing signs and symptoms of allergic conjunctivitis which were classified in four stages: 0-Absent; 1-

Table 1. Allergic conjunctivitis signs and symptoms classification.

Hyperemia:
0 Absent
1 Mild: small vascular dilatations, pink color, distributed in quadrants.
2 Moderate: medium size vascular dilatations, generally red color, generalized and randomly located in conjunctiva.
3 Severe: Numerous vascular generalized dilatations, red color with or without chemosis.

Mucous discharge:
0 Absent
1 Mild: small mucous conglomerates, preferably concentrated in the inferior conjunctival cul-de-sac.
2 Moderate: Bigger mucous conglomerates in the inferior conjunctival cul-de-sac, producing discomfort generally in the morning.
3 Severe: Big mucous conglomerates in cul-de-sac with discharge in palpebral edges and at the caruncle level, accompanied with sticky eyes in the morning.

Itching:
0 Absent
1 Mild: occasional, tendency to scratch or rub the eyes.
2 Moderate: always present with tendency to scratch or rub the eyes.
3 Severe: continuous, frequently drying the eyes.

Tearing:
0 Absent.
1 Mild: sporadic.
2 Moderate: perceived by patient, felt as discomfort.
3 Severe: permanent and frequently accompanied by drying of the eyes and palpebral edges.

Table 2. No tolerance reactions.

0	Absent.
1	Mild: mild stinging or foreign body sensation at instillation.
2	Moderate: mild stinging or foreign body sensation at instillation which persists.
3	Severe: important stinging or foreign body sensation at instillation and persisting to the point that treatment has to be discontinued.

Mild; 2-Moderate, and 3-Severe (Table 1). There were 58 women and 22 men whose ages ranged from 19 to 68 years of age, with an average of 40.

Patients with a history of hypersensitivity to other anti-allergic agents (including corticosteroids), and those that were receiving any other type of medication (local or systemic) related or not with the allergic pathology, were excluded from this study. Women who suspected they were pregnant were also excluded. Patients were divided into two groups (A and B) of 40 persons each. Group A patients were treated with 0.1% olopatadine hydrochloride (OHC) and group B patients were treated with 0.05% ketotifen fumarate (KF).

Each patient received one drop in the affected eye every 12 hrs.

In order to evaluate the starting point of action for each drug, patients' signs and symptoms were recorded, and then the first instillation of drug was performed during the initial patient consultation visit. Clinical responses to this first drug treatment were recorded during the next 30 minutes. After that, each group of patients was evaluated 48 hr, 7 days and 14 days after treatment initiation.

Responses were evaluated according to the following criteria: 0- Totally controlled, 1- Controlled, 2- Slight improvement, 3- No changes, and 4- Worsened. Based upon clinical experience, the final point of evaluation was the time when the patient reached a score between 0 and 1. Patients were instructed to report any type of adverse reaction or intolerance that appeared after administration of test drug. The evaluation scheme was as follows: 0- Absent, 1- Mild, 2- Moderate, and 3- Severe (Table 2).

Results and Discussion

Improvements in symptoms – itching and tearing – and signs – hyperemia and mucous discharge – of allergic conjunctivitis were evaluated at 30 min, 48 hrs, 7 days, and 14 days after initiation of treatment. Data are shown in Figure 1.

In group A (OHC), 42.5% to 62.5% of patients showed improvement between 0 min and 30 min after instillation in the signs and symptoms assessed in the study, with the exception of mucous discharge, which did not show any changes. 48 hr after the first instillation, improvements in every evaluated parameter were observed in 57.5% to 75% of patients. After 7 days of treatment, complete control of all evaluated signs and symptoms was achieved in 80% to 87.5% of patients.

With the exception of 4 patients (10%) excluded from the study because of the absence of therapeutic response after 7 days of treatment, every patient completed the treatment satisfactorily by the seventh day after initiation of olopatadine therapy. *NOTE: Patients of this group satisfactorily finished the treatment on Day 7 and it was not necessary to continue treatment for 14 days. This rapid improvement was not noted in the KF group.* No intolerance reactions were observed in any of the patients of this group.

In Group B (KF), 20.0% to 47.5% of patients showed improvement in the signs and symptoms evaluated between 0 min and 30 min after instillation, with the exception of mucous discharge, which did not show any improvement. By 48 hrs after the first instillation, improvements in every evaluated parameter were ob-

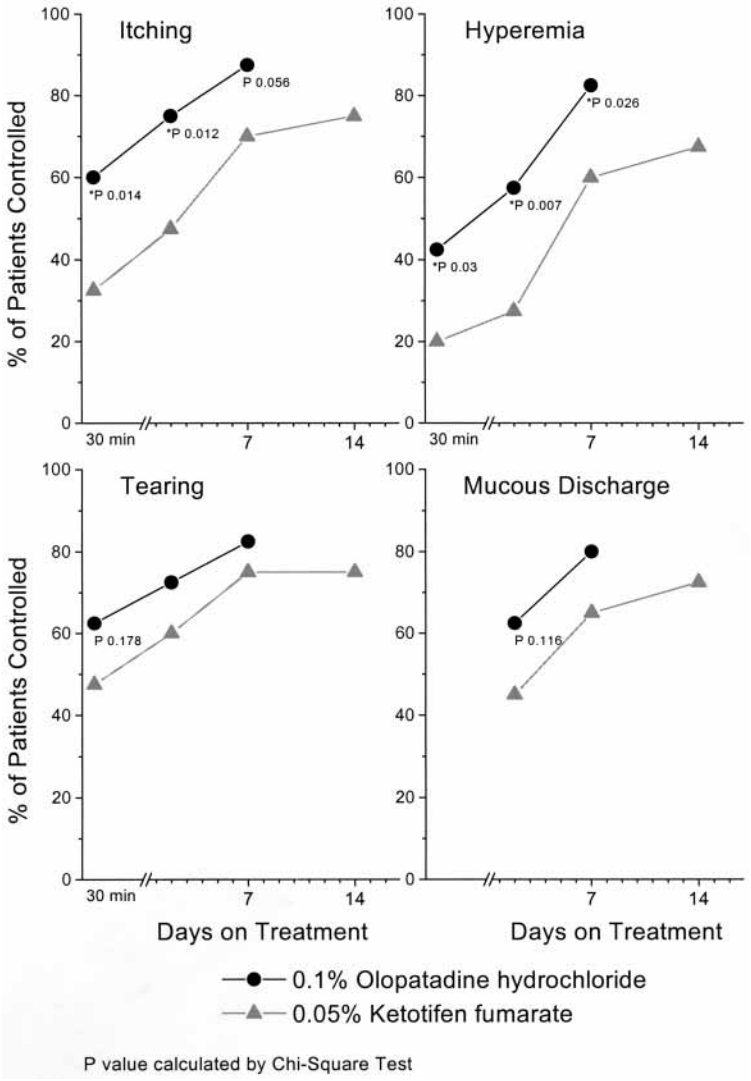

Fig. 1. Comparative efficacy of olopatadine hydrochloride and ketotifen fumarate on the signs and symptoms of allergic conjunctivitis.

served in 27.5% to 48% of patients. After 7 days of treatment, 60% to 75% of patients showed improvements. With continued treatment through Day 14, control of all signs and symptoms evaluated was observed in 67.5% to 75% of patients. In this study ketotifen was less effective than expected based on its purported preclinical activities. However, these results could be explained if, in fact, ketotifen's effects result only from its antihistaminic activity, as reported by Majchel et al. (9).

Seven patients (17.5%) of this group were excluded from this study due to the lack of a therapeutic response within 7 days of treatment.

Mild intolerance was observed in 9 patients (22.5%) in the form of stinging, but treatment did not have to be discontinued in any of the cases.

Conclusions

Olopatadine hydrochloride 0.1% provided superior efficacy and a more rapid resolution of the signs and symptoms of allergic conjunctivitis compared to ketotifen fumarate 0.05%.

No local intolerance reactions were observed in any of the patients treated with 0.1% olopatadine hydrochloride. Twenty-two and one-half percent of the patients reported mild adverse reactions (stinging) with 0.05% ketotifen fumarate.

The lack of therapeutic response was higher in the 0.05% ketotifen fumarate group than in the 0.1% olopatadine hydrochloride group.

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