Comparative study of 0.1% olopatadine hydrochloride and 0.5% ketorolac tromethamine in the treatment of seasonal allergic conjunctivitis

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ABSTRACT.

Purpose: **To compare the therapeutic effects of two ophthalmic solutions (0.1% olopatadine hydrochloride and 0.5% ketorolac tromethamine) with different pharmacological mechanisms on the clinical signs and Symptoms of seasonal allergic conjunctivitis (SAC).**

Methods: **Forty patients with the signs and symptoms of SAC (i.e. hyperaemia, itching, mucus discharge, tearing) were included in this placebo-controlled, randomized, parallel group, single centre study. In group 1 (20 patients) one eye of each patient was treated with olopatadine and the other with placebo. In group 2 (20 patients) one eye of each patient was treated with ketorolac solution and the other with placebo. The principal signs and symptoms of SAC (hyperaemia and itching) were evaluated at 30 mins and at 2, 7 and 15 days.**

Results: **In group 1, both parameters improved significantly in eyes treated with olopatadine compared with those receiving placebo at all control examinations (all $p < 0.05$). Similarly, eyes treated with ketorolac showed significant reductions in signs and symptoms compared with those receiving placebo (all $p < 0.05$). When the clinical parameters of eyes treated with olopatadine were compared with those treated with ketorolac, the mean score of hyperaemia was found to be lower in the olopatadine group, but the difference was not statistically significant (all $p > 0.05$). However, the itching score was significantly lower in the olopatadine group from the second day through to the end of the study ($p < 0.05$).**

Conclusions: **Both olopatadine and ketorolac ophthalmic solutions were found to be effective in alleviating the clinical signs and symptoms of SAC compared to placebo. However, olopatadine reduces ocular itching significantly more than ketorolac.**

Key words: ocular allergy – seasonal allergic conjunctivitis – olopatadine – ketorolac

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Introduction

Seasonal allergic conjunctivitis (SAC) or hay fever is a common allergic disease typically elicited by airborne allergens such as pollen, grass, weeds and animal dander (Abelson & Schaefer 1993). It is a type 1 hypersensitivity reaction mediated by IgE in response to these environmental antigens. The principal symptom of SAC is ocular itching (Abelson & Schaefer 1993). Other signs and symptoms include conjunctival hyperaemia, tearing, mucus discharge, chemosis and lid oedema.

Mast cells play an important role in the pathophysiology of this condition. When specific allergens bind to sensitized mast cells in the conjunctiva, degranulation of mast cells, and release of preformed (histamine, eosinophil chemotactic factor, tryptase) and newly synthesized mediators (prostaglandins, leukotrines) occur. Hence, typical signs and symptoms of SAC appear. Histamine, which is a preformed agent, is accepted as the predominant mediator (Berdy et al. 1991). On the other hand, prostaglandin D_2 is produced by the arachidonic acid pathway, and has a role in the pathogenesis of SAC (Woodward et al. 1995). Prostaglandin D_2 has been shown to induce conjunctival hyperaemia, oedema and mucus discharge; prostaglandins,

particularly D_2 and E_2, have a pruritogenic effect on the conjunctiva (Woodward et al. 1995).

Topically applied ophthalmic agents are the principal treatment method for SAC. Currently available topical drugs include H_1 antihistamines such as levocobastine, H_1 antihistamine-vasoconstrictor combinations such as antazoline-naphazoline, mast cell stabilizors such as cromolyn sodium and lodoxamide, and non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin synthesis, such as ketorolac tromethamine. Inhibition of prostaglandin synthesis, including prostaglandins D_2 and E_2, may play a role in the treatment of SAC. Ketorolac is an NSAID approved in the USA for the relief of ocular itching associated with SAC which works by inhibiting the prostaglandins' pruritogenic effects on the conjunctiva. A new topical drug, olopatadine, has been shown to have a dual action, in terms of both mast cell degranulation inhibition and histamine H_1 receptor blockage (Sharif et al. 1996; Yanni et al. 1996; Abelson 1998; Abelson & Spitalny 1998; Deschenes et al. 1999). This agent has a rapid onset due to antihistamine activity and prolonged duration of action due to mast cell stabilization, which allows for a twice daily dosage.

The aim of the current study was to compare the therapeutic effectiveness of two ophthalmic solutions (0.1% olopatadine hydrochloride; Patanol® (Alcon Laboratories, Fort Worth, TX, USA) and 0.5% ketorolac tromethamine; Acular® (Allergan, Irvine, CA, USA) with different pharmacological mechanisms on the clinical signs and symptoms of SAC.

Material and Methods

A total of 40 patients with the signs and symptoms of SAC (ocular itching, hyperaemia, mucus discharge and tearing) were involved in this placebo-controlled, randomized, parallel group, single centre study. All subjects had a history of SAC over the previous 2 years and showed the same classical signs and symptoms of SAC during the study period. None of the patients had a systemic or ocular (dry eye, uveitis, viral-bacterial infection) illness, and none had received systemic or topical ocular medication during the 4 weeks prior to the study. All patients started and completed the study within the month of April in order to avoid a major variance in allergen counts. In our region, April is the period when patients with SAC display maximum signs and symptoms, indicating a heavy allergen exposure.

Group 1 comprised 20 patients. One eye of each of these patients received olopatadine and the other eye received placebo (Tears Naturale II®, Alcon, Fort Worth, TX, USA), both twice daily. Group 2 (20 patients) used ketorolac solution in one eye and the placebo (Tears Naturale II®, Alcon) in the fellow eye, four times daily. Informed consent was obtained from all patients. In order to achieve better rates of compliance, patients were given 15-day timetables indicating the control days and drop instillation times. Patients were asked to mark each medication administration on these schedules and these lists were checked at each control visit.

Clinical signs and symptoms were evaluated at baseline, and at 30 mins and 2, 7 and 15 days. The main parameters assessed were ocular itching and hyperaemia. The grading of signs and symptoms are shown in Table 1.

Statistical analysis was performed using the paired *t*-test. A p-value < 0.05 was accepted as statistically significant.

Results

Of the 40 subjects, 21 were male and 19 were female. Their average age was 19 years (range 15–25 years). All patients completed the study. Overall topical drop application compliance was 100% in the olopatadine group and 90% in the ketorolac group (i.e. two patients missed three applications).

The mean scores of the clinical parameters were computed for each examination (Table 2). The baseline scores were found to be similar in both groups ($p > 0.05$). In group 1, both itching and hyperaemia improved significantly in eyes receiving olopatadine solution compared to placebo eyes at all control examinations ($p < 0.05$) (Figs 1 and 2). Similarly, eyes receiving ketorolac solution showed a significant reduction in signs and symptoms compared to placebo eyes at all examinations ($p < 0.05$) (Figs 1 and 2). When the mean scores of olopatadine treated eyes were compared to the scores of ketorolac treated eyes, the mean scores of hyperaemia were found to be lower in the olopatadine group, indicating better therapeutic effectiveness, although the difference did not reach statistical significance ($p = 0.154$, 0.9, 0.65, 0.79, 0.79, for baseline, 30 mins, 2, 7 and 15 days scores, respectively) (Figs 1 and 2). Itching scores, however, were found to be significantly lower in the olopatadine group at 2, 7 and 15 days ($p = 0.339$, 0.446, 0.018, 0.007, 0.036, for baseline, 30 mins, 2, 7 and 15 days, respectively) (Figs 1 and 2).

Discussion

Both olopatadine and ketorolac ophthalmic solutions were found to be effective in the treatment of SAC compared to placebo. These two drugs act

Table 1. Scoring of signs and symptoms of allergic conjunctivitis.

Score		
Itching*	0	None
	1	Intermittent tickling sensation, involving more than corner of eye
	2	Mild, continuous itch without desire to rub
	3	Severe itch with desire to rub
Hyperaemia	0	None
	1	Mild, slightly dilated blood vessels, pink in colour, may be quadrantal
	2	Moderate, more apparent vessel dilatation, vessel colour is more intense, involves most of vessel bed
	3	Severe, numerous and obvious dilated blood vessels, colour deep red, not quadrantic

* Itching was scored by the patients.

Table 2. Mean itching and hyperaemia scores (SD).

	Baseline	30 mins	2nd day	7th day	15th day
Itching					
Olopatadine	2.3 (0.9)	0.4 (0.8)	0.05 (0.2)	0	0
Placebo	2.2 (1.1)	1.3 (1.2)	1.1 (1.2)	1 (1.1)	1 (1.1)
p-value	0.76	0.011	0.0001	0.0001	0.0001
Ketorolac	2.5 (0.5)	0.6 (0.8)	0.4 (0.6)	0.3 (0.4)	0.2 (0.4)
Placebo	2.6 (0.5)	1.8 (1.1)	1.4 (0.9)	1.4 (1.0)	1.2 (1.0)
p-value	0.791	0.0001	0.001	0.0001	0.0001
Hyperaemia					
Olopatadine	2.0 (0.7)	1.2 (0.6)	0.7 (0.5)	0.4 (0.5)	0.3 (0.4)
Placebo	2.1 (0.7)	1.8 (0.7)	1.6 (0.5)	1.4 (0.6)	1.3 (0.7)
p-value	0.664	0.014	0.0001	0.0001	0.0001
Ketorolac	2.2 (0.5)	1.2 (0.7)	0.8 (0.8)	0.5 (0.6)	0.4 (0.6)
Placebo	2.2 (0.6)	2.0 (0.7)	1.8 (0.8)	1.8 (0.7)	1.8 (0.7)
p-value	0.796	0.002	0.0001	0.0001	0.0001

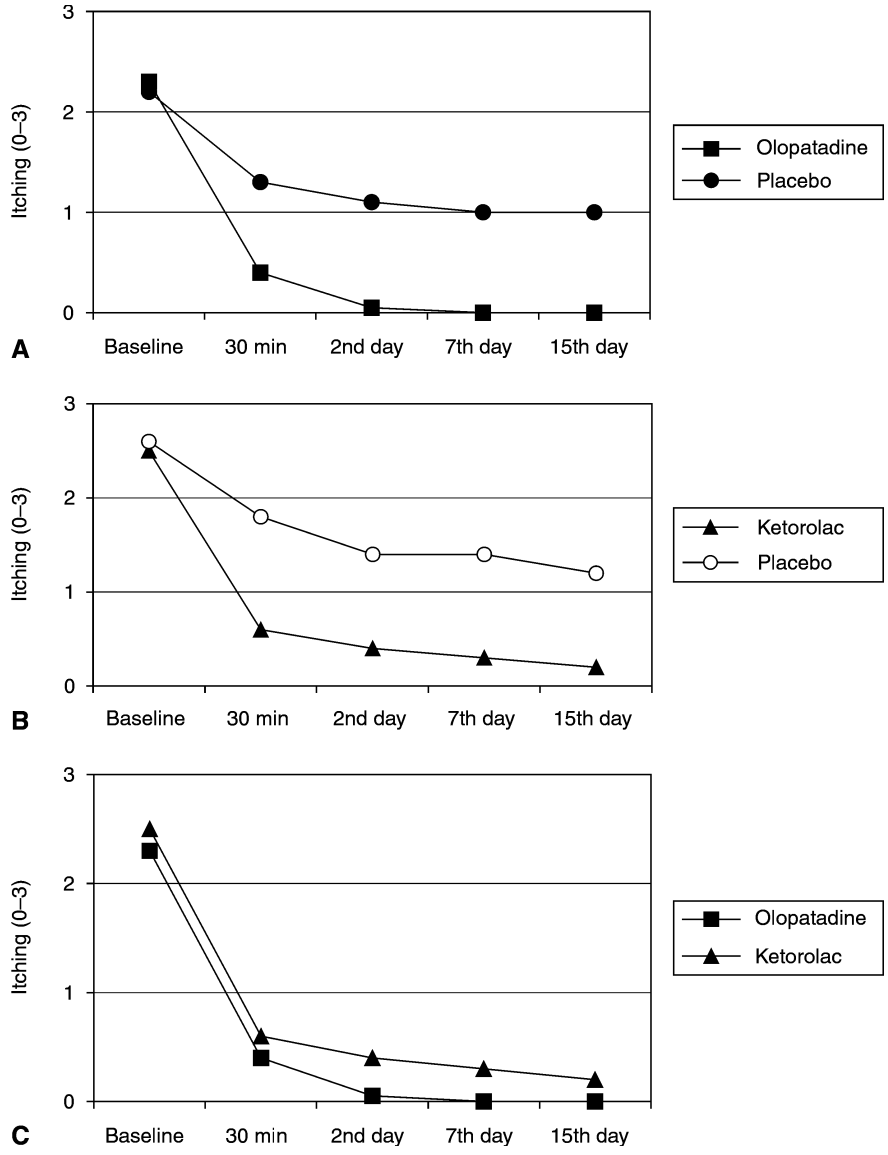

Fig. 1. Ocular itching scores. (A) Olopatadine versus placebo. (B) Ketorolac versus placebo. (C) Olopatadine versus ketorolac.

via different pharmacological mechanisms. Olopatadine is a new topical ocular dibenzoxepin derivative (Yanni et al. 1996). It inhibits the release of preformed and newly synthesized inflammatory mediators from mast cells upon allergen challenge, and also has antihistaminic properties towards H_1 receptors. Its dual activity is an advantage and the drug may be used both as a therapeutic and prophylactic agent. The dual action also renders the drug superior in terms of clinical effectiveness, rapid onset and length of duration of action (Abelson 1998; Abelson & Spitalny 1998; Deschenes et al. 1999). On the other hand, ketorolac is an NSAID; it works through the inhibition of cyclooxygenase, which produces prostaglandins. Prostaglandin D_2 is among the newly synthesized mediators released by mast cells following antigen stimulation, and inhibition of the production of this mediator can decrease the signs and symptoms of SAC (Woodward et al. 1995). Antipruritogenic and antihyperaemic actions of ketorolac in the treatment of SAC can be explained by inhibition of prostaglandin synthesis, particularly prostaglandins D_2 and E_2 (Woodward et al. 1995).

Prior placebo-controlled, randomized studies have demonstrated the effectiveness of olopatadine in the treatment of allergic conjunctivitis (Abelson 1998; Abelson & Spitalny 1998; Deschenes et al. 1999). Ketorolac ophthalmic solution has also been found to be more effective than placebo in the therapy of SAC (Ballas et al. 1993; Tinkelman et al. 1993).

In a previous study, the efficacy of olopatadine ophthalmic solution was compared to that of ketorolac solution in a clinical model of acute allergic conjunctivitis (Deschenes et al. 1999). The study used the provocative antigen challenge model and subjects were randomized to receive either olopatadine in one eye and placebo in the contralateral eye, or ketorolac in one eye and placebo in the fellow eye. At 27 mins after drug administration, the eyes were challenged with allergen, and ocular itching and hyperaemia were graded at 3, 10 and 20 mins. Olopatadine was found to be significantly more effective than ketorolac in the alleviation of the clinical parameters studied. This study has some differences compared to our trial. It was performed as a clinical

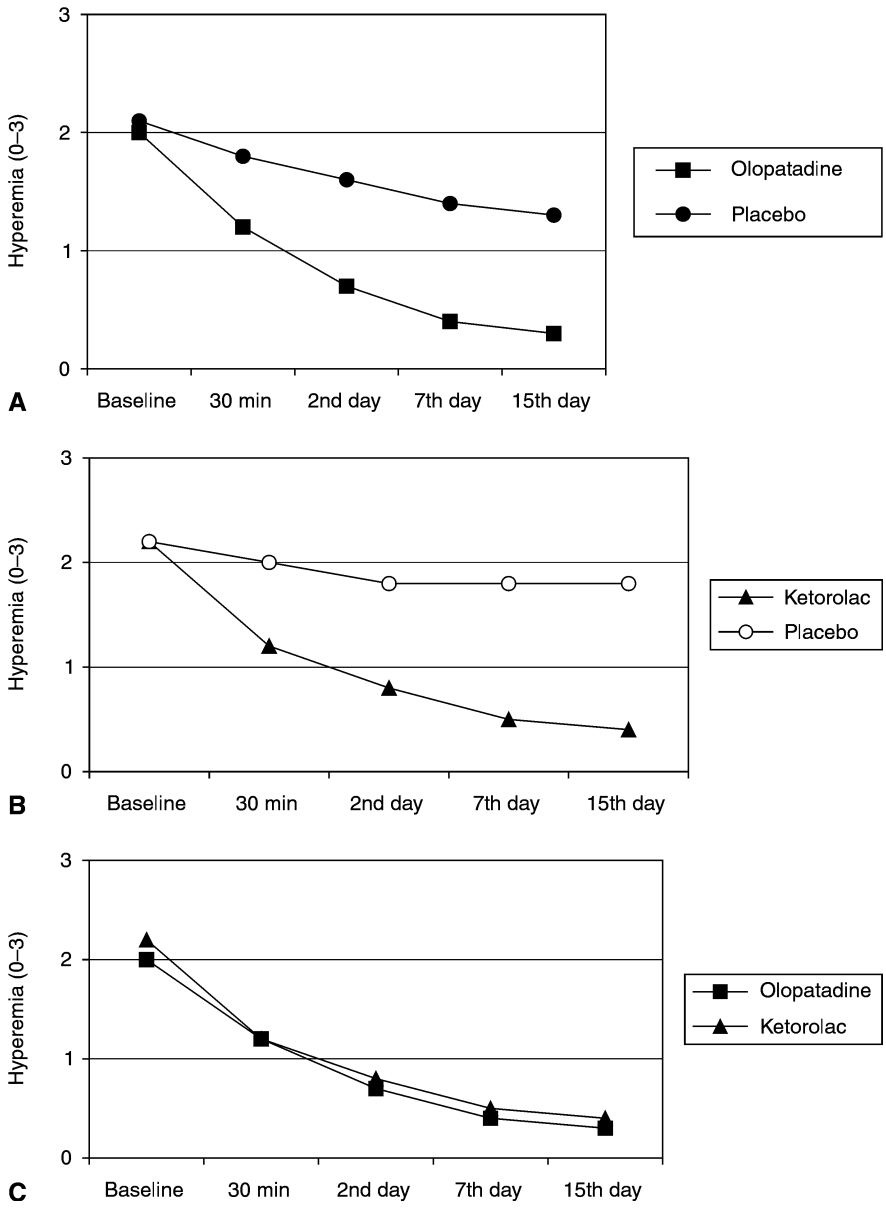

Fig. 2. Conjunctival hyperaemia scores. (A) Olopatadine versus placebo. (B) Ketorolac versus placebo. (C) Olopatadine versus ketorolac.

model of acute allergic conjunctivitis elicited by antigen challenge, the drug was applied once and its effectiveness was evaluated over a 20-min period. Our study included patients with SAC and the drugs were administered and their efficacy evaluated over a 15-day period. According to Deschenes et al. (1999), ketorolac did not significantly reduce itching and increased the hyperaemia compared to placebo. The authors explained ketorolac's lack of effectiveness in the inhibition of allergic response in the human conjuctiva on the basis that either prostaglandin D_2, which is important in guinea pig allergic conjunctivitis, might have a limited role to play in human allergic conjunctivitis, or that the dosing regimen employed (one application only, approximately 30 mins before allergen) was not enough for the drug to show its effect. The first explanation contradicts other studies which have clinically demonstrated the effectiveness of ketorolac in the treatment of SAC (Ballas et al. 1993; Tinkelman et al. 1993). In these studies, ketorolac was used four times daily for 1 week, in a similar manner to our study. In our study, the effectiveness of ketorolac was observed right from the 30-min check, a finding which contradicts the second proposal made by Deschenes et al. (1999). The paradoxical increment in the hyperaemia was explained by ocular irritation upon ketorolac solution administration (Deschenes et al. 1999).

The mean scores for hyperaemia were found to be lower in the olopatadine group than in the ketorolac group in our study. As for ocular itching, the difference reached statistical significance, indicating that olopatadine was superior to ketorolac in inhibiting ocular pruritus. The higher clinical effectiveness of olopatadine compared to ketorolac in alleviation of signs and symptoms of SAC, particularly of itching, may be explained by the dual action of this drug. Histamine is accepted as the principal mediator in allergic conjunctivitis, and is responsible for the characteristic symptom of itching (Berdy et al. 1991). It has been shown that selective stimulation of H_1 receptors in the conjunctiva results in itching (Weston et al. 1980). However, other mediators such as prostaglandins D_2 and E_2 have also been shown to have pruritogenic properties (Woodward et al. 1995). Ketorolac, unlike olopatadine, does not inhibit mast cell degranulation and does not possess antihistamine activity. Although ketorolac inhibits pruritogenic prostaglandin synthesis, and thus has antipruritogenic effectiveness in the treatment of SAC, the resultant anti-itching effect is less than that of olopatadine, which is a potent antihistaminic agent.

Our study has some limitations. Firstly, this is an environmental study and thus differs from the conjunctival allergen challenge (CAC) model. The CAC model was reported to provide standardized, reproducible results, thereby avoiding the possible variability in signs and symptoms inherent in naturally occurring conditions (Abelson & Spitalny 1998). Our study included patients who had SAC under natural conditions, implying that they might have been exposed to varying amounts of allergen during the study. In order to minimize a large fluctuation of pollens, all subjects were evaluted within the same month and were observed on the same day at all control visits. Moreover, the patients included in the study came from different parts of our region, both rural and urban, and taking pollen counts at many different areas would not have been feasible. It might be argued that the observed results in this study were due to decreased allergen exposure during the study and that the reduction in placebo scores serves as

evidence of this proposal. Even if the pollen counts decreased during the study period, which we do not believe to be the case, the differences observed between study drugs and placebo, and between study medications, cannot be explained solely on the basis of decreased antigen exposure. As for the effect of placebo on the clinical parameters of SAC, it is well known that artificial tear preparations have diluting and flushing effects on allergens and inflammatory mediators present on ocular surface. One last problem related to environmental studies is the issue of compliance. In our study, patient compliance was stimulated by asking each patient to use a diary.

In conclusion, both olopatadine and ketorolac ophthalmic solutions were found to be effective in alleviating the clinical signs and symptoms of SAC compared to placebo. However, the improvement in clinical parameters, particularly ocular itching, was more significant in olopatadine group.

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