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A review of the use of olopatadine in allergic conjunctivitis

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Abstract

Ocular allergies are very common and range in intensity from mild, self-resolving, acute conditions to serious, chronic disease that can severely affect vision. The vast majority of sufferers experience relatively mild symptoms, which are often seasonal in nature. Treatments should be simple, comfortable and very safe. They should be able to respond to an ongoing attack but also provide long-term relief from symptoms. Mast cell degranulation is central to all forms of ocular allergic disease and so treatment has concentrated on preventing this process or antagonizing the effects of the primary mediator, histamine. Olopatadine is a relatively new selective H_1 antagonist that has mast cell stabilizing properties and has been shown to affect release of TNF_α and various cytokines from conjunctival epithelial cells. This paper reviews the local ocular use of olopatadine and discusses the place of the drug in the treatment of allergic eye disease.

Introduction

Allergic eye disease is a common ocular problem affecting many people worldwide [1]. It is part of a whole spectrum of allergic diseases that share a common initiating mechanism and a characteristic pattern of inflammation. Morbidity from atopic conditions, particularly asthma, has increased in recent years [1, 2, 3] with no corresponding rise in the underlying rate of atopy itself, possibly as the result of environmental factors [4]. Although there is no direct evidence of an increase in the incidence of allergic eye disease, it is probable that the true incidence is higher than suggested in the literature [5].

The symptoms of ocular allergies range from mild to severe. The milder forms of acute seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are most common and have symptoms of itch tearing, mucus discharge and redness, which are irritating but not sight threatening. The more severe forms of the disease include vernal keratoconjunctivitis (VKC), which unless adequately treated, can be sight threatening, and giant papillary conjunctivitis (GPC), which is related to the presence of local foreign bodies such as contact lenses. The chronic forms of the disease, atopic blepharo-conjunctivitis (ABC) and atopic keratoconjunctivitis (AKC), have a prolonged relapsing sight threatening clinical course, and are often associated with atopic dermatitis and asthma.

In all forms of allergic eye disease, the clinical response is due to mast cell activation either directly via antigen–mast cell linkage, or by T-cell activation of mast cells [5, 6, 7]. Conjunctival mast cell activation leads to the release of histamine and locally synthesized mediators prostaglandin D2, the leukotriene C4, tryptase, chymase, carboxypeptidase-A, cathepsin-G, platelet activating factor (PAF) and other chemoattractants resulting in the recruitment of eosinophils and neutrophils into the area [6, 7, 8]. Recent work has also shown that mast cells store and release proinflammatory cytokines including IL4, IL6, IL8, IL 13 and TNF_α [7, 9, 10]. The exact nature of the involvement of these cytokines in the varying types of allergic eye disease is still to be fully elucidated. IL4, which is involved in the control of adhesion molecule up-regulation, is present in two forms, a stored form in quiescent disease and a different form in active disease. The expression of all types of adhesion

molecules (E-selectin, ICAM-1 and VCAM-1) is increased in active allergic disease [11]. Stem cell factor (SCF), an essential growth factor for mast cells, that enhances IgE-dependant -mast cell mediator release, cytokine generation and release, and is a chemoattractant for mast cells, is also manufactured and stored in mast cells. It has been shown that there is a fourfold increase of SCF in SAC [12], giving the mast cell the potential for its own autoregulation.

Allergen challenge in atopic patients has also demonstrated that the ocular allergic response can be divided into an early phase, characterized by a significant increase in tear histamine and tryptase levels [13] and a dose dependent later response (at about 6 h) featuring a second peak in tear histamine and a cellular infiltrate of mast cells, neutrophils, eosinophils, macrophages and basophils [13, 14].

The response to an allergen challenge in the eye is, therefore, a very complex process potentially involving a large variety of chemical mediators. However, in SAC and PAC topical antihistamines, such as antazoline, levocabastine and emedastine, remain the most popular treatment [5, 15]. They reduce itching, redness and swelling and can be used to treat an ongoing allergic reaction. The non-steroidal anti-inflammatory drug, ketorolac 0.5%, is also available for topical use for the relief of itch in SAC in some countries [15]. Oral histamine H_1-receptor antagonists (antihistamines) such as astemizole, terfanidine and loratadine have been shown to be effective, but they are not ideal because they take several hours to act and may have some systemic side effects such as sedation [16].

Mast cell stabilizers, such as sodium cromoglycate, are effective in SAC and PAC and carry very few side effects [5], but patients need to receive treatment for several days before the expected exposure to allergen. In the T cell dependent AKC and VKC, the existing mast cell stabilizer sodium cromoglycate is ineffective. In these conditions, the newer mast cell stabilizers, such as lodoxamide [17] and nedocromil [18, 19], have been found to be effective as maintenance therapy, but in acute exacerbations, steroids (dexamethasone) in doses up to one drop hourly are required to control the disease process, especially if a keratopathy is present.

Recently drugs such as ketotifen, and azelastine, that have multiple modes of action, have been introduced. In addition to a potent antihistaminic effect, they also demonstrate mast cell-stabilizing properties [15]. Olopatadine represents the latest drug that can be added to this particular class of anti-allergic agent. It displays antihistaminic and membrane stabilizing properties, but also has effects on other mediators involved in the allergic response.

Olopatadine: a new anti-allergic agent

Olopatadine is a tricyclic drug containing an alkylamino moiety that inhibits mast cell mediator release and possesses histamine H_1-receptor antagonist activity. It was first synthesized in Japan and was approved in that country for treatment of allergic rhinitis, chronic urticaria, eczema dermatitis, prurigo, pruritis cutaneous, psoriasis vulgaris and erythema exsudativum multiforme in December 2000 [20].

Olopatadine is rapidly absorbed when given orally, and urinary excretion of olopatadine accounts for over 50% of total drug clearance. The contribution of metabolism to clearance of the drug is low in humans [20], and olopatadine has been found to have no significant effect on cytochrome P450 enzyme systems [21].

Olopatadine has been shown to be a selective histamine H_1-receptor antagonist and to possess inhibitory effects on the release of inflammatory lipid mediators such as leukotriene and thromboxane from human polymorphonuclear leukocytes and eosinophils [20]. The specificity of olopatadine for the H_1-receptor in ocular tissues has been studied in equilibrium radioligand binding experiments [22, 23]. Olopatadine has been shown to have a high affinity for H_1-receptors (IC_{50} 31.6–41.1 nM) and a significantly lower affinity for H_2(IC_{50} > 40,000 nM) and H_3 (IC_{50} > 75,000 nM) receptors. It has also been shown to react significantly with only two of 42 non-histamine binding sites examined [23]. In comparative studies the H_1 selectivity of olopatadine was superior to that of other ocularly used antihistamines studied, such as ketotifen, levocabastine, antazoline and pheniramine [22, 23].

These properties indicated that olopatadine was a suitable candidate for trial in ocular allergy. Antihistaminic activity *in vivo* was demonstrated using a model of histamine-induced vascular permeability in guinea pig conjunctiva. Olopatadine applied topically from 5 min to 24 h prior to

histamine challenge inhibited the vascular permeability response in a dose-dependent fashion, indicating that the compound has an acceptable onset and a long duration of action [24]. Drug concentrations five times greater than those that were effective against histamine-stimulated conjunctival responses failed to inhibit vascular permeability responses that were induced with either serotonin or PAF, indicating the specificity of the action [24].

Functional potency in ocular tissues

The relative functional potency of olopatadine at ocular H_1-receptors has been measured by looking at intracellular phospoinositide (PI) turnover or calcium mobilization (both involved in mast cell degranulation) and by measuring extracellular release of appropriate cytokines. In studies of this type, olopatadine has been shown to antagonize histamine-induced PI turnover in cultured human conjunctival epithelial cells ($IC_{50} = 9.5$–10 nM), human corneal fibroblasts ($IC_{50} = 15.8$–19 nM) and transformed human trabecular meshwork cells ($IC_{50} = 31.6$–39.9 nM) [22, 23]. In a further comparative study, primary human conjunctival epithelial cell cultures were stimulated with histamine in the presence or absence of a variety of antihistamines [25]. Antazoline hydrochloride, emedastine difumarate, levocabastine hydrochloride, olopatadine hydrochloride and pheniramine maleate were all shown to attenuate histamine-stimulated phosphatidylinositol turnover and IL-6 and IL-8 secretion. Emedastine was the most potent, with IC_{50} 1–3 nM, while olopatadine was of similar potency to levocabastine and far more potent than antazoline and pheniramine. Olopatadine was of similar potency to emedastine as an inhibitor of cytokine secretion (IC_{50} 1.7–5.5 nM) and more potent than the other three antihistamines tested.

Mast cell stabilizing activity

The mast cell stabilizing properties of olopatadine in ocular tissues have been investigated by challenging conjunctival mast cells with anti-human IgE in the presence and absence of the drug and measuring the release of various proinflammatory mediators [23]. Olopatadine was shown to inhibit the release of histamine, tryptase and prostaglandin D_2, in a concentration-dependant manner.

In another study, a monodispersed suspension of partially purified human conjunctival mast cells was prepared from cadaver conjunctival tissue and challenged with anti-human IgE in the presence or absence of test drugs, and histamine content of the cell supernatants was determined using a specific radioimmuno assay [26]. Olopatadine inhibited histamine release in a concentration-dependent fashion, while nedocromil demonstrated limited activity. Cromolyn and pemirolast (100 nM to 1 mM) failed to significantly inhibit histamine release from human conjunctival mast cells.

Some antihistamines have been shown to stimulate histamine release from human conjunctival mast cells at concentrations only slightly higher than effective inhibitory concentrations. In contrast, histamine release was not stimulated by olopatadine at concentrations as high as 10 mM [24]. Olopatadine, therefore, has a low potential to cause ocular toxicity. The interactions of olopatadine and other antihistamines with phospholipid model membranes and natural membranes of erythrocytes, human corneal epithelial cells and conjunctival mast cells have been compared in an effort to understand the differences in their ability to stimulate histamine release [27, 28]. All molecules tested were intrinsically surface active and interacted with phospholipid monolayers. However, the surface activity of olopatadine was much lower than the other antihistamines tested. For these molecules the order of activity was clemastine $\geq$ desloratadine > azelastine > ketotifen > epinastine. The effects of the drugs on cell membranes were also dramatically different. Exposure of bovine erythrocytes to increasing concentrations of ketotifen (1–10 mM) resulted in complete hemolysis of the cells, while olopatadine (1–10 mM) caused only minimal hemolysis ($< 8\%$). Marketed concentrations of ketotifen (0.025%), azelastine (0.05%) and epinastine (0.05%), but not olopatadine (0.1%), produced significant disturbance of the membranes of human conjunctival mast cells and human corneal epithelial cells [27, 28]. These data demonstrate fundamental differences between olopatadine and many other antihistamines in their effects on cell membranes and offer an explanation for the biphasic, non-specific, cytotoxic effect of many antihistamines on mast cells. They may also

explain the non-lytic, mast cell stabilizing activity of olopatadine.

Other actions

Cook and co-workers have demonstrated the release of TNF_α from purified human conjunctival mast cells in response to a challenge from anti-lgE antibody, in a concentration-dependent manner [29]. Pre-incubation of cells with olopatadine resulted in a dose-dependent decrease in TNF_α release [29]. In a subsequent study it was demonstrated that TNF_α released from stimulated human conjunctival mast cells upregulated the expression of ICAM-1 on human conjunctival epithelial cells. Preincubation of the conjunctival mast cells with olopatadine was also found to significantly block this activity [30]. The blocking of TNF_α release and ICAM-1 upregulation by olopatadine may have implications for the longer-term activity of the molecule.

Clinical activity in allergic conjunctivitis

The activity of olopatadine in allergic conjunctivitis has been examined in the conjunctival allergen challenge (CAC) model and in a number of clinical trials.

The CAC model is a clinically validated method of testing the efficacy of drugs used to treat Type I hypersensitivity reactions and closely mimics the clinical spectrum of allergic conjunctivitis [15]. In most cases active drug will be given to one eye and placebo to the other, so that each subject acts as his or her own control.

CAC test results

Initial dose ranging studies on olopatadine have been reported by Abelson and Spitalny [31, 32]. In these studies concentrations of olopatadine ranging from 0.01 to 0.15% were instilled, with placebo, given in the contralateral eye, acting as a control. Subjects were randomly assigned to receive a particular concentration of drug at each visit and eyes were challenged with the allergen at times ranging from 3 to 27 min (to measure early response) and 4 to 8 h (to measure duration of action) after drug instillation on different study days. Itching and redness were scored at 3, 10 and 20 min after challenge. Olopatadine was found to be significantly superior to placebo at reducing the response to allergen challenge and a 0.1% concentration of olopatadine was found to be optimal.

The activity of olopatadine in the CAC model has been directly compared with nedocromil sodium 2%, ketotifen 0.05%, azelastine 0.05%, loteprednol 0.2% and ketorolac 0.5%. Thus olopatadine has been compared with representative examples from all other classes of drugs commonly used to treat ocular allergies. Olopatadine has been shown to be statistically significantly more effective than azelastine in the prevention of itching from 3.5 to 20 min post-challenge, when both drugs were given 5 min before the allergen was administered [33]. Compared to ketotifen, efficacy scores after allergen challenge for olopatadine were superior after 3 and 5 min when assessed 12 h after dosing [34]. Olopatadine treated eyes were also significantly more comfortable than ketotifen treated eyes immediately after instillation and 12 h later. Olopatadine was found to be more effective at reducing itching and redness and more comfortable than ketorolac [35], and more effective and better tolerated than loteprednol [36]. In the case of ketorolac, challenge was conducted 15 min after dosing while for loteprednol the delay prior to challenge was 27 min. When compared with the mast cell stabilizing drug nedocromil, olopatadine was clinically and statistically superior at reducing itching at 3, 5 and 10 min after a challenge and eyes were also rated as being more comfortable [37]. In this case nedocromil was given twice daily for 2 weeks to allow for drug loading and the challenge was conducted 15 min after a dose of nedocromil or olopatadine on the test day. In these studies, both the short [31–37] and long-term [32] efficacy of olopatadine to suppress conjunctival redness and itching have been confirmed.

The benefit of adding olopatadine 0.1% to a standard selective oral antihistamine in allergic conjunctivitis has been demonstrated in a number of studies [38, 39]. In these studies, addition of olopatadine to loratadine provided better early relief from itching than when loratadine was used with placebo. In another study, the combined effect of the inhaled steroid fluticasone and topical ophthalmic olopatadine was compared with that of fluticasone and the antihistamine, fexofenadine on the ocular and nasal symptoms of patients with

atopic disease [40]. Itching scores were improved with olopatadine, but there was no difference in redness or nasal symptoms. Recently, the clinical effects of olopatadine in the CAC model have been correlated with known indices of mast cell stabilization [41]. Ten patients had a suitable dose of allergen determined and confirmed in the normal way and then commenced twice daily olopatadine 0.1% in one eye and placebo in the contralateral eye for 5 days. They then underwent CAC 15 min after the final dose, and clinical signs and symptoms were recorded 5, 10, 20, 30 min and 5 h after CAC. The 5-hour time point was selected as it has been shown in previous studies to represent the peak effect of mast cell chemotactic agents and cellular infiltration. Itching and hyperaemia were reduced by olopatadine at all time points, compared to placebo. It also significantly reduced the number of neutrophils and total cells at 30 min and number of eosinophils, neutrophils, lymphocytes and total cells at 5 h. Histamine levels in tears and ICAM-1 expression on epithelial cells were also significantly reduced in olopatadine treated eyes in comparison to placebo [41]. These results clearly correlate the long-term clinical effects of olopatadine with its mast cell stabilizing properties.

Clinical studies

Clinical trials in patients with allergic conjunctivitis have compared olopatadine 0.1% with cromolyn 2%, nedocromil 2%, ketotifen 0.05% and placebo. These trials, in which drugs have been given for 1–6 weeks have generally confirmed the results expected from the performance in the CAC model.

Abelson and Turner reviewed a multicentre, parallel group study comparing olopatadine 0.1% with placebo, given twice daily for 10 weeks to 131 patients with seasonal allergic conjunctivitis and rhinoconjunctivitis [42]. Mean scores for ocular itching and redness were lower at all assessment times for olopatadine than placebo and similar results were obtained for rhinorrhea, sneezing and nasal itching. In a 2-week cross-over study, no significant difference was found in clinical performance or comfort between olopatadine 0.1% and nedocromil 2%, both given twice daily [43]. However, in a longer-term (6-week) parallel group comparison of olopatadine twice-daily with cromolyn four-times daily, reductions in itching and redness from baseline were significantly greater in the olopatadine group by day 42 and the doctor's assessment of patients condition was better for olopatadine at days 30 and 42 [44]. In a 14-day parallel group study comparing olopatadine with ketotifen, olopatadine was found to control symptoms more rapidly and to a greater extent [45]. However, in a 3-week parallel group study in 66 patients with allergic conjunctivitis, responder rate was judged to be higher with ketotifen than with olopatadine at days 5 and 21 [46]. In another 2-week, cross-over study, in which a combination of topical olopatadine and oral loratadine was compared with loratadine alone in 94 patients with seasonal allergic conjunctivitis, the addition of olopatadine was found to reduce itching and redness 20 min after the initial dose [47]. Patient quality of life scores at 7 days were also superior in the presence of olopatadine.

In a further open clinical study, the efficacy of olopatadine 0.1%, twice daily was evaluated in patients with allergic conjunctivitis due to contact lens wear and in patients with SAC, vernal conjunctivitis and AKC over a 28-day period [48]. Treatment with olopatadine rapidly alleviated the signs and symptoms of allergic conjunctivitis in both groups of patients. Patients with ocular allergies due to contact lens wear were able to continue to wear their contact lenses during treatment.

In allergic conjunctivitis, disorders of tear function and conjunctival cytology occur. The effects of olopatadine 0.1%, twice daily on corneal sensitivity, tear function and cell morphology were investigated in a single centre study in which the drug was given to 21 patients with allergic conjunctivitis for 3 weeks [49]. The eyes of 30 healthy volunteers acted as controls. Patients in the treatment group experienced improvements in fluorescein staining score, corneal sensitivity, mean BUT, squamous cell metaplasia grade and goblet cell density.

The recommended dose of olopatadine for treatment of allergic eye disease is currently one drop of a 0.1% solution instilled twice daily. Recently, clinical studies have been conducted in allergic conjunctivitis using a 0.2% concentration given once a day [50, 51]. Initial results have been encouraging, but further work needs to be

conducted on this concentration of the drug to confirm safety and efficacy.

Ocular comfort

In addition to the good clinical efficacy demonstrated in clinical studies and the CAC model, comfort upon instillation for olopatadine has been rated highly. This is particularly important since treatments for allergic conjunctivitis are often given frequently or for long periods and the eye may be in a highly sensitive state when treatment is commenced. In CAC studies, olopatadine was reported to be more comfortable or better tolerated than ketotifen [34], ketorolac [35], lotoprednol [36] and nedocromil [37]. A direct comparison of comfort between olopatadine and ketotifen fumarate 0.05% was conducted in a double-masked, multi-centered, randomized trial in 80 subjects who had one drop of each medication instilled into separate eyes [52]. When asked to make a "forced choice" between the products, based on ocular comfort, 100% of subjects selected olopatadine as the more comfortable formulation. In contrast, in a study involving 92 subjects with a history and current diagnosis of allergic conjunctivitis randomized to receive a single dose of either olopatadine 0.1% or ketotifen 0.025%, Patterson and co-workers found no difference in tolerability between the two products [53].

Conclusions

Ocular allergies are very common and range in intensity from mild, self-resolving, acute conditions to serious, chronic disease that can severely affect vision. The vast majority of sufferers experience the relatively mild but annoying symptoms of itching and redness, which are often seasonal in nature. Ideally, treatments for these conditions should be simple, comfortable and very safe. They should also be able to respond to an ongoing attack but provide long-term relief from symptoms. Mast cell degranulation is central to all forms of the disease and so treatment has concentrated on preventing this process or antagonizing the effects of the primary mediator, histamine.

Olopatadine is a selective H_1 antagonist that has mast cell stabilizing properties and also has been shown to affect release of TNF_α and various cytokines from conjunctival epithelial cells. It is more selective for the H_1-receptor than other commonly used antihistamines such as ketotifen, levocabastine, antazoline and pheniramine and has been demonstrated to have a higher functional potency to arrest histamine-stimulated reactions in conjunctival epithelial cells than levocabastine, antazoline and pheniramine.

Olopatadine has been shown to demonstrate significant mast cell stabilizing activity in conjunctival preparations at much lower doses than cromolyn, nedocromil and pemirolast. Unlike many other antihistamines, olopatadine does not cause histamine release from mast cells when applied at concentrations close to the clinically effective concentration. This difference can possibly be explained by a difference in the way in which olopatadine reacts with cell membranes and provides a reduced potential for ocular toxicity.

In the CAC model, olopatadine has been shown to be very effective in suppressing signs and symptoms of ocular allergic response, with a rapid onset and long duration of action. It has been shown to be more effective than the mast cell stabilizing drug, nedocromil, the steroid, loteprednol and the non-steroidal anti-inflammatory drug, ketorolac. When compared with other drugs, which also claimed to have multiple modes of action (antihistaminic and mast cell stabilizing), olopatadine was more effective than azelastine at reducing the symptoms of itching and gave more immediate relief than ketotifen.

Clinical studies have confirmed the effectiveness of olopatadine 0.1% given twice daily in patients with mild allergic conjunctivitis and with more serious ocular allergic conditions such as contact lens related allergic conjunctivitis and vernal conjunctivitis. It has also been shown to have a positive effect on the decreased corneal sensitivity, mean BUT and goblet cell density that accompany allergic conjunctivitis and to reverse changes in squamous cell morphology. In comparative clinical studies twice-daily olopatadine 0.1% has been shown to be more effective than cromolyn given four times daily at controlling itching and redness and to control symptoms more rapidly and to a greater extent than ketotifen. Importantly olopatadine 0.1% is very comfortable upon instillation. It has been shown to be better

tolerated than lotoprednol, ketotifen, ketorolac and nedocromil, in CAC studies.

The use of rapidly acting, highly selective H_1 antagonists is to be preferred when providing relief from the symptoms of acute allergic conjunctivitis. However, mast cell stabilizing drugs are of benefit in addressing longer-term control of this condition and chronic forms of the disease. Drugs with actions on other mediators, such as TNF_α, that are probably important in potentiating the effects of an allergic response, undoubtedly also have a role in the treatment of chronic allergic eye disease. Azelastine and ketotifen are two drugs reported to have both antihistaminic and mast cell stabilizing properties that are now understandably popular in the treatment of allergic eye disease. However, studies have shown that olopatadine is pharmacologically and clinically superior to both of these drugs. It is also very comfortable upon instillation.

In summary, olopatadine is a potent, highly selective, well-tolerated topical antihistamine with powerful conventional mast cell stabilizing properties and a number of other useful additional properties that affect the allergic cascade. It acts rapidly but has a long duration of action and represents a useful addition for the treatment of acute forms of allergic eye disease. Further work is required to fully elucidate its pharmacological properties and method of action and to clarify its role in the treatment of chronic ocular allergic conditions.

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