Ocular Allergy Treatment Comparisons: Azelastine and Olopatadine

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Azelastine hydrochloride 0.05% and olopatadine hydrochloride 0.1% are topical ocular allergy treatments that have demonstrated multiple pharmacologic actions, including antihistamine, mast cell stabilization, and inhibition of proinflammatory mediators. In this article, the mechanisms of action, efficacy, and tolerability of these two agents on ocular signs and symptoms are examined. By studying the various target sites of drug action, an enhanced clinical response algorithm of these topical ocular agents can be implemented to maximize the response for patients suffering from ocular allergy.

Introduction

Allergic conjunctivitis is characterized by ocular inflammation in response to an allergen–mast cell interaction. Mast cells are an integral part of the ocular allergic response reactions that cause the various signs of inflammation in the eye. Human ocular mast cells are primarily mast cell tryptase+, chymase+ (MC_{TC}), and, therefore, it has been suggested that therapies targeting MC_{TC} could improve treatment efficacy in patients with certain allergic eye conditions [1]. The result of this allergen stimulation causes multiple inflammatory mediators—histamine, eosinophil chemotactic factor, platelet activating factor (PAF), tryptase, chymase, cytokines (interleukin [IL]-4, IL-5, IL-6, IL-8, and tumor necrosis factor [TNF]-α), prostaglandin D2 (PGD2), cell adhesion molecules—to be released from conjunctival mast cells upon degranulation, resulting in a cascade of events of the allergic response. The conjunctival allergic response is a focal human model that has been accepted by the US Food and Drug Administration (FDA) for the approval of ocular allergy agents. It has also been used in animal models to demonstrate the presence of the early and late-phase response, as well as the extensive release of mediators during these phases; however, the clinical relevance in the development of specific signs and symptoms from each of the mediators in the late-phase response is not clear. These models have demonstrated that the early-phase exhibits the immediate development of increased vascular permeability, mucus secretion, and pruritus, whereas the late-phase response demonstrates similar signs and symptoms that might become more intense without treatment. The ocular late-phase response is also associated with cellular infiltration, (*eg*, eosinophils, lymphocytes) into the lamina propia and additional proinflammatory mediator release from these cells, leading to a protracted allergic response. Both azelastine and olopatadine are multiple action agents with antihistaminic/mast cell stabilizing effects and proinflammatory mediators, inhibiting properties that have been used to alleviate the symptoms of allergic conjunctivitis.

In this article, we examine the mechanisms of action, efficacy, and tolerability of these two agents on allergic ocular symptoms. By studying the various target sites of drug action, a better idea of clinical response to the use of topical pharmaceutical agents for the intervention, and possibly prevention, might be enhanced.

Azelastine Hydrochloride

Azelastine, FDA-approved in May 2000, is a phthalazinone derivative that functions as a topical ocular selective histamine H1-receptor antagonist, and an inhibitor of mast cell mediator release and other proinflammatory mediators. In the FDA standard conjunctival allergen challenge model, it demonstrated its primary inhibition of pruritus with a duration of up to 8 hours. It is approved for use in adults and in children 3 years and older [2].

Antihistamine/anti-inflammatory effects

Azelastine demonstrates histamine H1 and H2 receptor antagonist activity (H1 $K_i \sim 6.8$ nM; H2 $K_i \sim 4{,}200$ nM. K_i is the dissociation constant based on the Cheng-Prussof equation, $K_i + IC_{50}/(1 + L/K_d)$, such that a lower value denotes higher affinity binding (Figs. 1 and 2) and also inhibits histamine release from mast cells following antigen and nonantigen stimuli. Azelastine antagonizes histamine and leukotriene (LT)-induced bronchospasm in animal studies and reduces airway responsiveness to inhaled antigen or distilled water, and exercise challenge [3]. Azelastine has also been shown to inhibit the release of histamine from both human and animal mast cells in response to various stimuli (anti-IgE serum antigen, calcium ionophores, compound 48/80). In vitro and

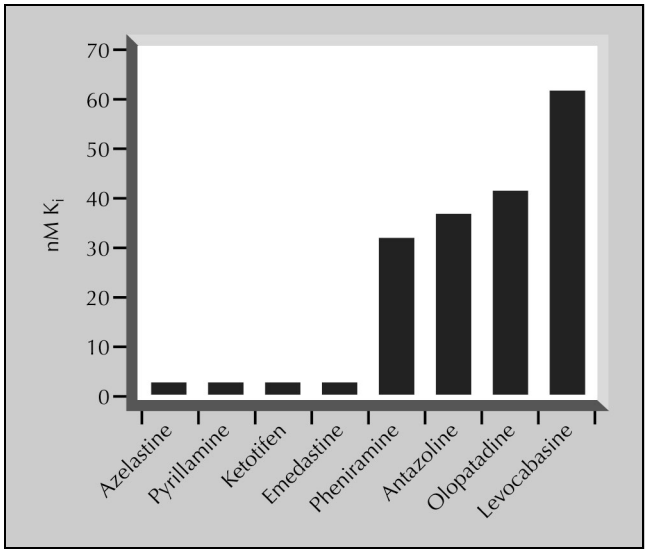

Figure 1. Relative H1 receptor affinity.

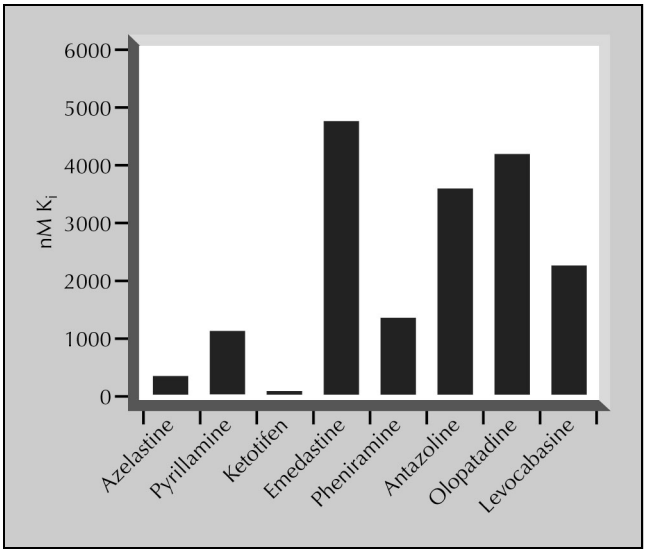

Figure 2. Relative H2 receptor affinity.

in vivo studies have demonstrated that azelastine prevents the activation of inflammatory cells and inhibits the synthesis or release of mediators, such as LTs, tosyl arginine methyl ester esterase, superoxide anion, oxygen free radicals, and PAF [4].

Azelastine's anti-inflammatory properties appear to stem from its ability to inhibit mast cell–mediator release, as well as inhibit LT production. Azelastine reduces antigen-induced production of LTs C_4 and D_4, and, therefore, it inhibits the 5-lipoxygenase pathway of arachidonic metabolism without much impact on the cyclooxygenase pathway.

Adhesion molecule expression is upregulated by cytokines and is important for the recruitment of eosinophils and Th_2 lymphocytes [5]. Intercellular adhesion molecule-1 (ICAM-1) is needed for both eosinophil and lymphocyte movement to the ocular surface [6]. Azelastine's ability to downregulate ICAM–1 in vivo expression on human conjunctival epithelial cells during the early-phase reaction might also be a component of its effect on the allergic response, especially the late-phase inflammation [7].

Clinical studies

Azelastine, in comparison with placebo, significantly reduced symptom scores, number of inflammatory cells, and ICAM-1 expression during the early and late-phase reaction [4]. In an in vitro study, azelastine and olopatadine were compared on the effects of release of histamine, IL-6, and tryptase release from cultured human mast cells (CHMCs) that were grown out of human umbilical cord–derived CD34+ cells. The results demonstrated that on an equimolar basis, azelastine was a five times more potent inhibitor than olopatadine of both CHMC and rat–skin mast cell activation [8,9••]. However, given the heterogeneity of mast cells throughout the human body [10], and the fact that IL-6 preferentially co-localizes to mast cell tryptase+ (MC_T) rather than MC_{TC} in human conjunctival tissue [11], these findings might represent a clinically relevant outcome for patients with the more chronic forms of ocular allergy, such as perennial allergic conjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis, and vernal keratoconjunctivitis [12].

A multicenter, randomized, double-blind placebo study of 99 patients was conducted to evaluate the efficacy of combined azelastine eye drops and a nasal spray in controlling the symptoms of allergic rhinoconjunctivitis [13]. The study concluded that the efficacy of azelastine was higher than placebo (49% vs 28%; $P = 0.04$). Adverse events were reported as burning sensation, "red eyes," nasal irritation, and bitter taste [13]. Azelastine has been shown to be statistically significantly more effective than placebo in inhibiting the primary complaint of ocular pruritus and the overall relief of allergic conjunctivitis [13,14,15••,16,17].

Comfort studies

Several studies have found that azelastine is not as comfortable as other topical ophthalmic solutions. A common adverse complaint has been transient eye burning and stinging (as discussed) [13]. This property of irritation likely stems from azelastine's moderate pH of 5.0 to 6.5, and perhaps intrinsic ocular membrane surface activity [2,14,18].

Olopatadine Hydrochloride

Olopatadine, FDA-approved in March 2000, is a dibenzoxepine derivative that has been shown to be a selective, noncompetitive inhibitor for the histaminic H1 and H2 receptors (Figs. 1 and 2), a mast cell stabilizer, and an inhibitor of proinflammatory mediators. Results of in vitro and in vivo tests have demonstrated that olopatadine is highly selective for MC_{TC} and that it has a relatively high affinity for histamine (H1) receptors [19,20].

The elimination half-life of olopatadine is approximately 8 hours [21]. Olopatadine is currently approved in Japan for treatment of symptoms of allergic rhinitis, chronic urticaria, at a total daily oral dose of 10 mg, and in the United States and Europe, it is approved only as an ophthalmic solution for the treatment of seasonal allergic conjunctivitis [22]. It is approved for use in adults and children aged 3 years and older [23].

Antihistamine/anti-inflammatory effects

Olopatadine is a selective histamine H1 and H2 receptor antagonist [24] (H1 $K_i \sim 31.6$ nM; H2 $K_i \sim 100{,}000$ nM) (Figs. 1 and 2) and moderate mast cell inhibitor that also possesses inhibitory effects on the release of inflammatory lipid mediators, such as LT and thromboxane from human polymorphonuclear leukocytes and eosinophils [25]. Olopatadine has been shown to suppress the release of LTs and thromboxane, and the formation of PAF by reducing arachidonic acid release from phospholipids in guinea pig eosinophils [26]. Olopatadine, as a mast cell stabilizer that is highly selective for MC_{TC} receptors [19,20], inhibits mast cell–mediator release of histamine, tryptase, TNF-α, and PGD2. Additionally, olopatadine inhibits proinflammatory mediators from another ocular tissue that might be important in the ocular allergic response, the human conjunctival epithelial cell. In vitro studies on this cell line demonstrated the inhibition of the release of IL-6 and IL-8 and the reduction of integrin lymphocyte function–associated antigen-1 (LFA-1) and CD11b/CD18 complement receptor 3 (Mac-1) expression on eosinophils [26]. One study done with rat peritoneal eosinophils suggested that olopatadine might inhibit antigen-induced eosinophil infiltration via repression of CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) expression, and, in the same study, it showed that it had no effect on IL-5–induced CD49d/CD29 (very late–appearing antigen [VLA]-4) expression [26].

Clinical studies

The conjunctival allergen challenge model is a standardized protocol accepted by the FDA for the induction of ocular and nasal signs and symptoms of allergic rhinoconjunctivitis. An in vitro conjunctival allergen challenge model evaluating the efficacy of olopatadine versus azelastine ophthalmic solutions versus placebo (artificial tears; $n = 111$ patients) demonstrated that olopatadine and azelastine were effective against ocular pruritus, with a shorter time of onset being recorded by olopatadine [14].

A study in the more chronic forms of ocular allergy, such as atopic keratoconjunctivitis, vernal keratoconjunctivitis, and ocular inflammation associated with contact lenses reflected that, even in the more chronic conditions, there is a trend toward relief, in 78% of patients studied, of itching/burning, tearing, hyperemia, and papillary reaction over the course of treatment (28 days), with some subjective improvement in symptom reduction (itching, burning, and tearing) 7 days after starting olopatadine treatment [15••]. Olopatadine is generally well-tolerated [8,14,27••,28].

Comfort studies

Several studies have found olopatadine to be more comfortable [14,29,30••,31,32]. This comfort likely is a consequence of olopatadine's more compatible pH[23] and possibly its low intrinsic ocular membrane surface activity [18]. The release of lactate dehydrogenase (LDH; an intracellular constituent of conjunctival mast cells) was used as an evaluation tool, although its clinical relevance is unclear. Measurement of intrinsic surface activity for all antihistaminic agents ranged from highly surface-active to weakly surface-active in the following sequence: desloratidine > clemastine > azelastine = ketotifen > diphenhydramine > pyrilamine > emedastine > epinastine > olopatadine.

Discussion

More than a decade ago, the treatment of ocular allergy was relegated to the use of oral agents and limited weak, nonspecific topical agents. Oral antihistamines have the advantage of controlling a variety of allergy symptoms affecting various organ systems and, thus, might be the preferred treatment when the symptoms are mild enough for monotherapy. However, the more direct approach of topical administration has been clearly more effective for the exclusive treatment of ocular symptoms. Many studies using the conjunctival antigen challenge model have demonstrated that topical agents are superior agents, particularly when used in conjunction with other modalities of treatment. With topical antihistaminic agents, there is a clear benefit in rapid relief of ocular symptoms over systemic antihistamines. In addition, the adverse effect profiles of topical antihistaminic agents are superior to those of systemic antihistamines because of the lower doses required for topical agents to penetrate the conjunctivae.

There have been several classes of topical ocular allergy agents, but only two classes have antihistaminic properties—the "pure" antihistamine group, and the "multiple-action" group—that combine antihistamine activity, mast cell stabilization, and proinflammatory mediator inhibitors, which includes azelastine and olopatadine. Other classes involved in the treatment of ocular allergies include vasoconstrictors, pure mast cell stabilizers, nonsteroidal anti-inflammatories, and corticosteroids. The vasoconstrictors are sympathomimetic agents that decrease vascular congestion and eyelid edema via alpha-receptor stimulation, but do not have any impact on the allergic inflammatory response.

The use of multiple-action agents, such as azelastine and olopatadine, is advancing our treatment options, particularly because we are now advancing into the realm of not only inhibiting the histamine binding and mast cell stabilization but also seeing an effect on other cell lines that might be involved in ocular allergy, such as the conjunctival epithelial cell, and on other phases of the ocular allergic response. The theoretic importance of the inhibition of the proinflammatory mediators released during the

late-phase response are obvious, but the direct correlation of any single inflammatory mediator to its clinical effect on the distinct signs and symptoms is hard to discern, because multiple mediators have complementary and overlapping synergistic effects. Late-phase phenomena are well known in other organ systems affected by the allergen–mast cell interaction, and, therefore, they demonstrate a similar allergic response in the eye during natural exposure to airborne allergens.

Although, pharmacologically, azelastine has a stronger binding affinity to the H1 receptor, in a single, direct, comparative study of olopatadine and azelastine performed with the conjunctival allergen challenge model, olopatadine appeared to have a quicker onset of effect on ocular itching [8,14]. The difference is in minutes, but might be due to the mild stinging sensation that some patients note with azelastine. In addition, azelastine and olopatadine were both initially approved for just ocular pruritus, but additional olopatadine studies have provided the FDA with additional information to expand the labeling to include a broader spectrum of ocular allergy signs and symptoms. In addition, azelastine and olopatadine both have rapid action (30 minutes after instillation), which might be attributable to their antihistaminic effects, which have the ability to decrease the inflammatory cascade. Consequently, the late-phase allergic reaction might be attributable to the inhibition of pro-inflammatory mediators that are comparable, such as IL-6 release by 83% and 74%, tryptase release by 55% and 79%, and histamine release by 41% and 45%, respectively [9••]. Azelastine might even provide some insight into the molecular control of allergic inflammation through the downregulation of ICAM-1 expression [4,24].

Conclusions

Topical ophthalmic agents with multiple actions provide excellent choices for therapeutic intervention in patients with predominant ocular symptoms. Topical agents, such as eye drops, typically provide faster relief of ocular symptoms than oral agents, and, logically, combination therapy with a topical and oral agent has been found to be superior to oral alone [33–35]. The topical ocular agents azelastine and olopatadine have exhibited both an early-phase symptomatic relief in patients with allergic conjunctivitis, using a multiple mechanistic approach of antihistamine/mast cell–stabilization, and an anti-inflammatory response.

Overall, in several studies of various in vitro models that include the ocular and other tissues, azelastine appears to have broad support for its inhibitory effect on the allergic response. Azelastine's anti-inflammatory properties appear to stem from its ability to inhibit mast cell–mediator release, including IL-6, TNF-α, and IL-8, as well as inhibiting LT production of LTC4, LTD4, and PAF [24].

Olopatadine appears to have more preliminary clinical studies, which examine its effect on the ocular allergic response. In addition to the mast cell, it has also shown effect on other ocular cells that might be related to the allergic response, the conjunctival epithelial cell, and eosinophil. It has been demonstrated to prevent release of histamine, tryptase, TNF-α, and PGD2 from mast cells; IL-6 and IL-8 from human conjunctival epithelial cells; and to reduce the in vitro expression of integrins LFA-1 and Mac-1 on eosinophils.

Clinical studies show both drugs to be highly effective at alleviating ocular redness and itching [36–39]. Azelastine has a higher binding coefficient for H1 and H2 receptor than olopatadine. Olopatadine appears to have an earlier onset of relief from ocular pruritus and to be somewhat more comfortable than azelastine, which might be due to the more neutral pH and, possibly, lower surface activity [40]. Clearly, the only way to truly discern differences between these agents would be to perform additional clinical studies between these two ocular agents, measuring different parameters (conjunctival redness, tear cytology for inflammatory cell counts, tear histamine, and ICAM-1 expression measurement) to provide more insight.

The treatment of allergic conjunctivitis has been focused in the past on symptomatic relief of symptoms [41,42,43••], but with a better understanding of conjunctival immunologic mechanisms and the inflammatory response the armamentarium of ocular agents will expand, on targeted therapeutic sites of action. This will enhance our opportunity to provide novel interventional therapeutic strategies, such as the development of topical immunophilin agents (*eg*, cyclosporine, tacrolimus), to further improve the symptomatic response in those patients who suffer from ocular allergies.

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