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Olopatadine 0.2% ophthalmic solution: the first ophthalmic antiallergy agent with once-daily dosing

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Background: Olopatadine 0.2% is the first topical ophthalmic antihistamine/mast cell stabilizer indicated for once-daily dosing. *Objective*: This review provides a comprehensive description of the pharmacology of the olopatadine molecule, as well as of the clinical efficacy, tolerability, and safety of olopatadine 0.2% ophthalmic solution. *Methods*: References cited in this review were obtained from the PubMed biomedical literature database. Also included were several posters presented at nationally renowned ophthalmology-related conferences. *Results/conclusion*: Olopatadine 0.2% was found to be a safe and effective medication for the reduction of itching with a duration of action of up to 24 h. The added convenience of a once-a-day dosing regimen is a major advancement in this drug class.

Keywords: antiallergy, antihistamine, olopatadine, ophthalmic

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1. Introduction

Approximately 20% of Americans have ocular allergies [1], and this prevalence is increasing worldwide [2]. The most common forms of ocular allergy include acute seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), in which the primary sign and symptom is redness and itching, respectively. Rhinoconjunctivitis involves the manifestation of both ocular and nasal allergy symptoms. Ocular allergies can have a negative impact on sufferers, due to intense bouts of ocular itching and effects on their appearance (red and puffy eyes). Patients seek potent medications that will alleviate their allergies in a rapid, effective, and comfortable manner [3]. Olopatadine is the most commonly prescribed topical antihistamine/mast cell stabilizer, and provides relief from SAC and PAC. Multitudes of patients have used olopatadine, supporting its strong safety and efficacy profile, which spans more than a decade. Olopatadine 0.1% ophthalmic solution was developed for twice-daily dosing, and is indicated for the treatment of the signs and symptoms of allergic conjunctivitis. A new formulation – olopatadine 0.2% ophthalmic solution – has been recently developed and marketed. The double-strength formulation allows for once-a-day dosing and a duration of action of up to 24 h. As olopatadine 0.2% is relatively new to the ocular allergy market, a review of the pharmacology, clinical studies, and therapeutic use of the drug is warranted to highlight its efficacy, tolerability, and safety.

2. Overview of market

First-generation topical antihistamines include antazoline and pheniramine, which have been formulated with naphazoline, a vasoconstrictor that reduces redness. These over-the-counter (OTC) medications are available for q.i.d. dosing. The presently available mast cell stabilizers include nedocromil sodium and pemirolast, which are both indicated for itching due to ocular allergies. Topical antihistamine/mast cell stabilizers comprise of olopatadine, ketotifen, epinastine, and azelastine. Ketotifen has recently been introduced to the OTC market as the first non-prescription topical antihistamine/mast cell stabilizer. Olopatadine 0.1% is indicated for signs and symptoms of allergic conjunctivitis, whereas the other members of this drug class are indicated for itching only. Olopatadine 0.2% is the first topical antiallergy agent approved for once-daily dosing.

3. Chemistry

Olopatadine hydrochloride is a selective histamine (H_1) receptor antagonist and mast cell stabilizer. It inhibits the activity of released histamine on its receptors and suppresses further release of histamine and other allergic and proinflammatory mediators. The chemical name for olopatadine is 11-[(Z)-3-(dimethylamino)propylidene]-6-11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride. It is a white, crystalline, water-soluble powder and has a molecular weight of 373.88.

Olopatadine hydrochloride is the active ingredient in olopatadine hydrochloride 0.2% ophthalmic solution, which contains 2.22 mg of olopatadine hydrochloride, equivalent to olopatadine 2 mg. Olopatadine hydrochloride also contains the preservative benzalkonium chloride 0.01% and excipients povidone, dibasic sodium phosphate, sodium chloride, edetate disodium, hydrochloric acid/sodium hydroxide, and purified water [4].

4. Ocular allergy: pathophysiology

Ocular allergies are type I hypersensitivity reactions that first commence with allergic sensitization. The allergen binds to an antigen-presenting cell, such as a macrophage, which internalizes the allergen, processes it, and presents it as part of a MHC complex. The binding of T helper (T_H) cells to the MHC complex triggers IL production, secretion of T_H2-specific cytokines, and proliferation of B cells into plasma cells. Plasma cells then produce IgE molecules specific to the allergen, which bind to Fc receptors on conjunctival mast cells. The mast cells are thus sensitized, and subsequent exposure to the allergen will provoke the allergic response to specific IgE receptors [1].

When a sensitized individual is exposed to allergen again, the allergen degrades into antigens upon entry into the conjunctiva. Antigen then binds to IgE receptors on mast cells, causing IgE cross-linkage. This leads to mast cell degranulation, and within seconds the inflammatory mediator histamine is released. Histamine is the only mediator that reproduces all of the clinical signs and symptoms of the ocular allergic reaction, which include itching, redness, chemosis, tearing, and lid swelling. Of the four histamine receptors that have been identified in humans, only H_1 and H_2 have been detected in the eye. Histamine binding to H_1 receptors on nerve endings causes itching, while histamine binding to H_1 and H_2 receptors on endothelial vascular smooth muscle tissue leads to vasodilation and increased vascular permeability (redness), as well as endothelial gaping (swelling). Selective antagonists block these receptors, which results in diminished itching and redness [1].

During mast cell degranulation, *de novo* proinflammatory mediators are generated and released. These include cytokines, chemokines, and growth factor. TNF-α, a cytokine, increases the expression of intercellular adhesion molecule-1 (ICAM-1) and triggers histamine release. The arachidonic acid cascade is also activated upon mast cell degranulation; this mechanism ultimately leads to the recruitment of inflammatory cells and the formation of prostaglandins and leukotrienes, whose combined effects contribute to redness, chemosis, and mucous discharge [1]. Since the mechanism of the ocular allergic reaction is so complex and involves a variety of mediators, antihistamine/mast cell stabilizer medications such as olopatadine provide a dual action that is valuable in the treatment of allergies.

5. Pharmacology of olopatadine

The specificity and strong binding affinity of olopatadine to H_1 receptors distinguishes this molecule from other antihistamines. One study demonstrated that olopatadine blocks the binding of histamine to receptors and has a stronger affinity for H_1 receptors than for H_2 and H_3 receptors [5]. A unique binding pocket containing an aspartate residue within the H_1 receptor might be the reason for olopatadine's high selectivity for H_1 receptors [6].

The capacity of olopatadine to effectively suppress allergen- and histamine-induced conjunctivitis was displayed in the oral and topical administration of the compound in rats and guinea-pigs [7]. Olopatadine also exhibited its antiallergic effect – namely, the inhibition of mast cell and basophil degranulation – in an *in vitro* study of human conjunctival mast cells and rat basophilic leukemia cells. This study specifically showed the dose-dependent inhibition of histamine release. Olopatadine, when tested at 10 times the maximally effective dose, successfully inhibited more than 90% of histamine release without demonstrating any mast cell cytotoxicity [8]. Olopatadine has also been shown to counteract histamine-induced phosphoinositide turnover in cultured human conjunctival epithelial cells,

human corneal fibroblasts, and transformed human trabecular meshwork cells [5]. Furthermore, olopatadine inhibited the release of leukotrienes and thromboxanes (TX), as well as the formation of platelet-activating factors, which are all lipid mediators that contribute to the allergic reaction [9].

The functional consequences of the interaction of olopatadine and various antihistamines with natural cell membranes were investigated in various comparative studies. Olopatadine, in comparison to other antihistamines, displayed restricted membrane perturbation and subsequent limited release of hemoglobin, lactate dehydrogenase, and histamine; these effects might contribute to the ocular comfort of the drug [10,11]. High concentrations of olopatadine have also demonstrated superiority over nedocromil, pemirolast, and cromolyn sodium in the reduction of histamine release from human conjunctival mast cells [12]. Olopatadine's ability to maintain its stabilizing effect at high concentrations implicates its efficacy in a stronger concentration formulation.

Several *in vitro* studies demonstrated that olopatadine also successfully blocks the release of other inflammatory mediators. The drug was more potent than pheniramine and antazoline in the inhibition of IL-6 and -8 (proinflammatory mediators) secretion from human conjunctival epithelial cells [13]. When human conjunctival mast cells were incubated with olopatadine and then challenged with anti-IgE antibody, olopatadine inhibited the release of TNF-α in a dose-respondent fashion [14]. A subsequent study indicated that olopatadine can also inhibit the upregulation of ICAM-1, whose expression is elevated by TNF-α. In this study, olopatadine significantly blocked the anti-IgE mast cell supernate-mediated upregulation of ICAM-1 on human conjunctival epithelial cells [15]. Another study similarly demonstrated that olopatadine inhibits IgE-activated human conjunctival mast cell supernates from stimulating eosinophil-derived neurotoxin release [16]. The abilities of olopatadine to suppress the release of inflammatory mediators and to inhibit inflammatory cell recruitment are thought to contribute to the drug's long duration of action.

Olopatadine has also demonstrated its ability to affect allergic mechanisms other than those of the eye. Studies showed that the nasal lavage fluid of guinea-pigs with allergic rhinitis had high concentrations of histamine, peptide leukotrienes, and TXB_2. The oral administration of olopatadine decreased the levels of these inflammatory mediators [17,18]. Olopatadine also inhibited the early phase reaction and the late phase reaction of antigen-induced nasal obstruction (blockage) [19]. These results represent the suppressive effect olopatadine can have on nasal obstruction.

6. The conjunctival allergen challenge model in olopatadine studies

The conjunctival allergen challenge (CAC) model is a validated clinical method that has been accepted for the evaluation of ocular antiallergic medications, including olopatadine, in the US, Europe, and Japan. The CAC design involves two screening visits, during which patients who have positive skin tests for specific environmental or perennial allergens receive bilateral ocular challenges. At the first visit, increasing doses of allergen are administered to each eye until a moderate ocular allergic reaction occurs. The second visit challenges subjects with the final dose determined at the first visit. Onset and duration of action, as well as comfort, of the test medication can be evaluated at subsequent visits. This methodology provides a controlled, safe, reproducible, and standardized way to evaluate ocular itching, redness, chemosis, tearing, and eyelid swelling. In the CAC model, the contralateral eye can also be used as an internal control to limit variability within an individual [20].

7. Clinical efficacy of olopatadine hydrochloride 0.1% ophthalmic solution

The clinical efficacy and safety of olopatadine hydrochloride 0.1% ophthalmic solution was first established by several double-masked, placebo-controlled, contralateral eye, CAC studies that compared solutions of different olopatadine concentrations. Results revealed that olopatadine concentrations of 0.05% and 0.1% effectively diminished itching and redness with an onset of 27 min and an 8-h duration of action [21]. Another similar study confirmed the 27-min onset and 8-h duration and found that olopatadine 0.1% was the most effective concentration (in comparison to 0.01%, 0.05%, 0.1%, and 0.15% formulations) for the reduction of itching and redness [22].

Olopatadine has also effectively and safely reduced eyelid swelling and chemosis associated with allergic conjunctivitis. In one CAC study, eyelid swelling was evaluated by assessments provided by the participants and three-dimensional objective scanning and imaging technology. Analysis of both the subjective and objective assessments revealed that olopatadine significantly reduced eyelid swelling [23]. Another CAC study revealed that olopatadine significantly decreased chemosis, which was assessed by the investigator at 3, 10 and 20 min postchallenge [24].

In a CAC study that included clinical assessments and tear cytology, olopatadine 0.1% significantly reduced itching and redness at 30 min and 5 h postchallenge. Olopatadine reduced ICAM-1 expression, tear histamine levels, and numbers of leukocytes at 30 min and 5 h postchallenge, suggesting that the drug inhibited the release of mast cell-derived mediators [25].

7.1 Comparative studies

Several comparative studies of olopatadine with other anti-allergy agents indicated olopatadine's superior efficacy and tolerability. Olopatadine significantly reduced ocular itching more effectively than nedocromil [26] and diminished both

itching and redness more effectively than cromolyn sodium and levocabastine [27,28]. In a comparative study of olopatadine, cromolyn, and levocabastine, olopatadine was the most effective agent to inhibit ocular allergy symptoms in children as young as 4 years of age [29]. Various studies comparing olopatadine to the combination antihistamine/mast cell stabilizers ketotifen fumarate and azelastine indicated the superiority of olopatadine in terms of comfort and the reduction of itching [30-34]. Olopatadine was significantly more effective than the anti-allergy agent epinastine in the relief of itching, conjunctival and episcleral redness, and chemosis [35,36]. Olopatadine also demonstrated superior efficacy and tolerability over the corticosteroid loteprednol in the treatment of seasonal allergic conjunctivitis [37]. Finally, in comparison to non-steroidal anti-inflammatory drug ketorolac, olopatadine yielded significantly less ocular itching and redness [38]. These results support olopatadine as a preferable treatment for ocular allergy over other topical antiallergy medications.

7.2 Olopatadine and other ocular conditions: contact lenses and dry eye

Contact lens wearers can safely treat ocular allergy with olopatadine, as long as they ensure that their eyes are not red before using the solution and that they wait 10 min after drug instillation before inserting their lenses [4,39]. Several studies have demonstrated the advantages olopatadine 0.1% can have for contact lens wearers who follow the dosing directions. Olopatadine successfully inhibited the symptoms of allergic conjunctivitis in contact lens wearers to the same degree that it did in non-contact lens wearers [40], and the drug is also more effective and comfortable than placebo in suppressing ocular allergy [41]. Contact lens use can induce signs and symptoms of dry eye such as tear deficiency and rapid tear film break-up time (TBUT) [42]; however, a study indicating that olopatadine 0.1% improves tear function and maintains the strength of the tear film barrier suggested that the medication is suitable for contact lens wearers as well as dry eye patients [43]. Indeed, a study comparing the effects of olopatadine 0.2% to those of saline solution showed that both agents yielded comparable changes in dry eye signs and symptoms, as well as similar tolerability ratings among patients suffering from ocular allergy and dry eye [44]. Another study also demonstrated that the incidence of dry eye after the use of either olopatadine 0.1% and olopatadine 0.2% was less than or equal to that of placebo [45].

7.3 Olopatadine and systemic drugs

Systemic oral antihistamines, through nonspecific interactions with G protein–coupled receptors (GPCR), have been shown to induce ocular drying. Histamine and muscarinic receptors are both GPCRs, and M_3 receptors are involved in regulation of lacrimal gland function. Antagonists to the M_3 receptor – such as nonselective antihistamines – cause diminished lacrimal gland secretion, which in turn leads to ocular surface drying. This desiccated tear film means decreased barrier protection: allergens can more easily penetrate the ocular surface [46-48], which may in turn exacerbate the allergic reaction. The antiallergic effects of olopatadine were replicated with the concomitant treatment of oral antihistamines. Olopatadine, in comparison to loratadine, significantly reduced ocular itching [46,49], and has not been shown to elicit significant ocular drying [48]. These findings suggest that the combined use of oral antihistamines (for rhinitis) and olopatadine (for ocular allergies) is safe and effectively decreases allergic signs and symptoms without drying the ocular surface.

7.4 Olopatadine and rhinitis/rhinoconjunctivitis

The comorbidity of seasonal allergic conjunctivitis and rhinitis manifests itself as allergic rhinoconjunctivitis, of which the primary symptoms include nasal itching, irritation, sneezing, rhinorrhea, and congestion, as well as the ocular characteristics of itching, tearing, and swelling. When inhaled, airborne allergens can result in the development of a nasal allergic response; they can also enter the eye and leak through the nasolacrimal duct into the nose, leading to the presentation of ocular and nasal allergy signs and symptoms. Likewise, topically administered ophthalmic solutions can also drain into the nasal cavity, and olopatadine can have an effect on nasal allergic symptoms [50]. Studies have shown that olopatadine is significantly more effective than placebo in the reduction of nasal allergic symptoms. The combined therapy of olopatadine and a nasal spray reduced ocular itching and redness significantly more than the combined use of the nasal spray and a systemic antihistamine [49]. Another study indicated that among olopatadine, a nasal spray, and a systemic antihistamine, the former was the most effective in the reduction of ocular allergic signs and symptoms [50]. Furthermore, the added treatment of olopatadine in allergic rhinitis patients who were already using a nasal spray or systemic drug significantly improved their quality of life scores [51]. These studies demonstrate that the local treatment of site-specific allergies is important and that olopatadine can even contribute to the reduction of nasal allergy symptoms.

8. Increased concentration of olopatadine

As reviewed, many studies have established the efficacy and safety of the twice-daily treatment of olopatadine 0.1% ophthalmic solution. A preclinical study provided evidence of detectable drug levels of a single 30-µl drop of olopatadine 0.2% ophthalmic solution that had been instilled in the conjunctiva 24 h earlier. It has also been shown that after a single 1-mg/kg bilateral dose of olopatadine, 50% H_1-receptor occupancy remained for 24 h. These findings collectively suggested that a higher-concentration formulation of olopatadine could be developed for a once-daily dosing

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