Ophthalmic Antihistamines

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Ophthalmic Antihistamines

Overview

Conjunctivitis or inflammation of the conjunctiva may be infectious or non-infectious. Seasonal and perennial allergic conjunctivitis are non-infectious types of conjunctivitis and are among the most common ophthalmic problems. Seasonal allergic conjunctivitis has an estimated prevalence of 15 percent and can occur in adults and children.[1] The signs and symptoms may cause extreme discomfort. Seasonal allergic conjunctivitis usually presents with bilateral involvement and occurs during seasonal exposure to allergens such as ragweed. Perennial allergic conjunctivitis presents similarly to seasonal allergic conjunctivitis; however, symptoms do not have seasonal variation. The range of symptoms varies from itching and redness to swelling, excessive lacrimation, and mucous discharge.

As with allergic rhinitis, avoidance of allergens, when known, is a part of overall therapy for allergic conjunctivitis. In addition to the topical antihistamines included in this review, other topical agents, such as NSAIDs, mast cell stabilizers, and, for severe cases, corticosteroids, are effective in reducing these symptoms of allergic conjunctivitis.

Pharmacology

The ophthalmic antihistamines are relatively selective histamine H_1 antagonists and inhibitors of the release of histamine and other mediators from cells (e.g. mast cells) involved in the allergic response. Ketotifen, epinastine, and olopatadine also have mast cell-stabilizing properties.[2,3,4]

FDA-Approved Indications

Drug	Manufacturer	Age of Use	Indication
azelastine 0.05% solution (Optivar®)	MedPointe	≥3 yrs	Treatment of itching of the eye associated with allergic conjunctivitis
emedastine 0.05% solution (Emadine®)	Alcon	≥3 yrs	Temporary relief of the signs and symptoms of allergic conjunctivitis
epinastine 0.05% solution (Elestat™)	Allergan	≥3 yrs	Prevention of itching of the eye due to allergic conjunctivitis
ketotifen 0.025% solution (Zaditor™)	generic	≥3 yrs	Temporary prevention of itching of the eye due to allergic conjunctivitis
olopatadine 0.1% solution (Patanol™)	Alcon	≥3 yrs	Treatment of the signs and symptoms of allergic conjunctivitis
olopatadine 0.2% solution (Pataday™)	Alcon	≥3 yrs	Treatment of ocular itching associated with allergic conjunctivitis

Ketotifen 0.025% (Zaditor) by Novartis is approved by the FDA for over-the-counter (OTC) use for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.[5] Ketotifen 0.025% (Alaway™) is also now available over-the-counter.

Pharmacokinetics

Drug	Systemic absorption	Preservative	Metabolism and Excretion
azelastine 0.05% solution (Optivar)[6]	low systemic exposure Systemic absorption does occur with plasma concentrations of 0.02 to 0.25 ng/mL after 56 days of treatment.	benzalkonium chloride	Major metabolite - N-desmethylazelastine Feces: 75 percent
emedastine 0.05% solution (Emadine)[7]	below level of detection	benzalkonium chloride	Multiple metabolites Excreted in the urine
epinastine 0.05% solution (Elestat)[8]	low systemic exposure Average maximum plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about two hours.	benzalkonium chloride	Predominantly renal excretion
ketotifen 0.025% solution (Zaditor)[9]	below level of detection	benzalkonium chloride	No data
olopatadine 0.1% solution (Patanol)[10]	below level of detection A small percentage of patients with measurable levels within two hours of dosing ranged from 0.5 to 1.3 ng/mL.	benzalkonium chloride	Predominantly renal
olopatadine 0.2% solution (Pataday)[11]	No data	benzalkonium chloride	Predominantly renal

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials with multiple doses for ophthalmic FDA-approved indications are considered the most relevant in this category. Criteria for study inclusion in this review are the following: English language, human studies, analyze the data consistently with the study question, randomly allocate participants to comparison groups, include follow-up (endpoint assessment) of at least 80 percent of those entering the investigation, and have clearly stated, predetermined outcome measure of known or probable clinical importance. Unbiased studies were then reviewed for validity and importance. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers.

While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

Many of the studies of the ophthalmic agents for the treatment of allergic conjunctivitis are performed as single-dose studies. These studies give very little information regarding efficacy and safety in chronic use of these agents. Additionally, many of the studies are done with the conjunctival allergen challenge (CAC) model in an effort to induce an allergic response and evaluate drug efficacy in a short-term model. Generally, the number of patients in the studies was less than 100. Several comparisons to levocabastine appear in the literature; levocabastine is no longer available in the United States.

emedastine (Emadine) and ketotifen (Zaditor)

A total of 45 subjects were enrolled in this single-center, double-masked study to compare the efficacy of two agents and placebo for the temporary relief of ocular itching related to allergic conjunctivitis.[12] Patients were randomized to treatment in one of three groups: emedastine 0.05% in one eye and placebo in the other; ketotifen 0.025% in one eye and placebo in the other; or emedastine in one eye and ketotifen in the other. Patients eliciting a positive allergic response were identified. In 25 subjects, bilateral CAC was performed five minutes after study medication instillation. In a second group of 20 subjects, CAC was performed 15 minutes after medication instillation. Both emedastine and ketotifen significantly inhibited itching ($p<0.05$) compared with placebo at all time points after the five- and 15-minute CAC. Itching scores were similar in the two active treatment groups. No adverse events were reported.

epinastine (Elestat) and olopatadine (Patanol)

Olopatadine 0.1% and epinastine 0.05% were compared for efficacy and safety in the prevention of itching and conjunctival redness in a CAC model in a prospective, randomized, double-blind study.[13] Screening for response to the allergen challenge (n=96) occurred prior to randomization. A total of 66 evaluable patients with allergic conjunctivitis were randomized to olopatadine in one eye with epinastine in the other eye, olopatadine in one eye with placebo in the other or epinastine in one eye with placebo in the other eye. Allergen was applied to both eyes five minutes after treatment administration. Olopatadine was associated with significantly less itching and conjunctival redness than contralateral epinastine-treated eyes ($p=0.003$, $p<0.001$, respectively). Olopatadine-treated eyes also had less chemosis ($p<0.001$), ciliary redness ($p<0.001$), and episcleral redness ($p<0.001$) than epinastine-treated eyes in this single-dose CAC model.

ketotifen (Zaditor) and olopatadine (Patanol)

A randomized, double-masked, single-center, CAC study comparing ketotifen 0.025% and olopatadine 0.1% was conducted in 53 patients.[14] Primary efficacy variables were ocular itching and subject satisfaction. Itching was graded on a five-point scale at three, five, and ten minutes post-challenge. After the screening, there were 32 patients who were randomized to two groups. The first group instilled olopatadine one drop in the right eye and ketotifen one drop in the left eye. The second group instilled ketotifen one drop in the right eye and olopatadine one drop in the left eye. Twelve hours after instillation, subjects were challenged with the antigen concentration. Efficacy scores for olopatadine were significantly higher than those for ketotifen at three and five minutes post-challenge ($p<0.05$). Olopatadine-treated eyes were rated significantly more comfortable than those treated with ketotifen both immediately after drug instillation and 12 hours later ($p<0.05$).

In a double-masked study, 66 patients with seasonal allergic conjunctivitis were randomized to treatment with ketotifen 0.025% or olopatadine 0.1% instilled twice daily.[15] Patients were assessed on days five and 21. Responder rate was higher on day five for ketotifen (72 and 54 percent for patient assessment; 88 and 55 percent for investigator assessment). Likewise, the responder rates on day 21 were 91 percent versus 55 percent for patient assessment and 94 versus 42 percent for investigator assessment. Severity scores for hyperemia and itching were significantly lower for the ketotifen group. In both groups, the most common adverse effects were burning/stinging and headache; however, patients rated both drugs similarly for comfort.

A comparison of olopatadine 0.1% and ketotifen 0.025% on patient preference was performed in 100 patients with allergic conjunctivitis.[16] In this European double-blind study, patients administered olopatadine and ketotifen to a single eye on an as-needed basis up to two drops daily per eye over four weeks. After four weeks, patients' preference was assessed using five questions regarding comfort, preference, and efficacy in reducing signs and symptoms. Olopatadine was preferred by 81 percent of patients based on comfort and efficacy in reducing symptoms; these patients would select olopatadine at their next doctor's visit ($p<0.0001$). Most patients (76 percent) based their preference on efficacy and comfort ($p<0.0001$).

In a randomized, double-blind trial, ketotifen 0.025% and olopatadine 0.1% ophthalmic solutions were compared in patients with seasonal allergic conjunctivitis.[17] A total of 49 patients were randomized to ketotifen, olopatadine, or artificial tears administered two drops twice daily to both eyes for 30 days. Thirty-nine patients completed the trial. At baseline, day 15, and the end of the trial, clinical sign and symptom scores for itching, tearing, physician's assessment of eyelid swelling, redness and chemosis, conjunctival cytology specimens, and reports of adverse events were reported. For clinical sign and symptom scores, both active treatment groups reported significant improvement in tearing and itching at day 15 and 30 compared to baseline. The artificial tears group experienced a significant reduction in tearing at both days 15 and 30. The inflammatory markers were significantly lower with the active treatment groups at both day 15 and 30 compared to artificial tears. Adverse events were not reported during the one-month trial.

olopatadine (Patanol) and azelastine (Optivar)

In a prospective, multicenter, double-masked, allergen challenge study, 180 patients were randomized to one of three treatment groups: olopatadine 0.1% solution in one eye and azelastine 0.05% solution in the other eye; olopatadine in one eye and placebo in the other eye; or azelastine in one eye and placebo in the other eye.[18] The placebo was artificial tears. Two screening phases were performed to define the elicited allergic response. Five minutes after the drops were instilled, subjects (n=111) were bilaterally challenged with an allergen concentration that had previously elicited a positive conjunctival allergic response. Subjects rated itching every 30 seconds for a total of 20 minutes. Both treatments were significantly more effective than placebo at reducing itching postchallenge. Olopatadine was significantly more effective than azelastine in reducing itching at 3.5 minutes through 20 minutes post-challenge (average mean unit difference of -0.31; $p<0.05$) in the CAC model. Single-dose administration did not result in any serious adverse events.

olopatadine 0.2% (Pataday)

Olopatadine 0.2% (Pataday) has only been compared to placebo in published literature at this time.

Two randomized, double-masked, placebo-controlled studies evaluated the efficacy and safety of olopatadine 0.2% ophthalmic solution once daily in a combined total of 500 patients including 44 children.[19,20] In the 10-week (during April-August 2003) and 12-week study (during July-December 2001), patients (n=260) assessed their ocular signs and symptoms for frequency (score of 0 to 5) and severity (score of 0 to 4). With high grass pollen counts, ocular itching and redness were scored for frequency >2 in 21 and 14 percent of patients receiving olopatadine 0.2% and 47 and 31 percent of patients receiving placebo ($p<0.001$ for ocular itching; $p<0.003$ for redness). Similar findings were evident for the severity based analysis. Olopatadine 0.2% was associated with lower mean scores for ocular itching and redness by pollen level. Effects on the nasal symptoms associated with olopatadine 0.2% ophthalmic solution were also investigated. In the 10-week study, patients also recorded the frequency of their nasal symptoms whereas in the 12-week study, patients reported both the frequency and severity of their nasal symptoms. Pollen counts for grass and ragweed were recorded at the investigative center during the study periods. In the 12-week fall study, olopatadine 0.2% significantly reduced the frequency of sneezing ($p=0.0355$) and itchy nose ($p=0.0032$) compared to placebo. The severity of symptoms were also significantly reduced with olopatadine 0.2% compared to placebo for sneezing ($p=0.0451$), itchy nose ($p=0.0178$) and runny nose ($p=0.0327$). Olopatadine 0.2% was also associated with reduced frequency of pollen effects on sneezing ($p=0.0017$) and runny nose ($p=0.0031$) compared to placebo in the springtime study. Two patients discontinued treatment due to adverse effects of dry eye and tachycardia.

Pediatrics

The agents in this class have been proven to be safe and effective in children as young as three years of age.

ketotifen (Zaditor) in children

The efficacy and safety of ketotifen 0.025% was evaluated in a double-blind, multicenter, placebo-controlled trial.[21] The study was a CAC design using both single and multiple doses. Patients (n=133) were eight to 16 years old who produced an allergic response to allergen. Patients were given one drop of ketotifen to one eye and placebo to the other eye. CAC was administered 15 minutes and eight hours after the dose. Patients who had a reaction to the allergen in both eyes then were randomized to multiple dose treatment (n=60). Patients administered ketotifen to one eye and placebo to the other eye twice daily for four weeks. CAC was performed eight hours after the last dose. Of the 55 evaluable patients, ketotifen significantly reduced ocular itching compared to placebo after CAC ($p<0.001$). Hyperemia, chemosis, and lid swelling were also significantly reduced with ketotifen ($p=0.031$). Adverse effects were similar to placebo.

Precautions[22,23,24,25,26,27]

Emedastine (Emadine) is pregnancy category B; all other ophthalmic antihistamines are pregnancy category C.

Contraindications[28,29,30,31,32,33]

For the class, if a patient has a hypersensitivity to a product or its excipients, the patient should not receive the product.

Drug Interactions

Due to the topical instillation of these products, clinically significant systemic drug interactions are not well identified.

Adverse Effects

Drug	Stinging/ Burning	Headache	Eyelid edema	Rash	Rhinitis	Conjunctival injection	Blurred vision
azelastine 0.05% solution (Optivar)[34]	30	15	--	--	--	--	1-10
emedastine 0.05% solution (Emadine)[35]	<5	11	--	--	<5	--	<5
epinastine 0.05% solution (Elestat)[36]	1-10	1-3	--	--	--	--	--
ketotifen 0.025% solution (Zaditor)[37]	<5	10-25	<5	<5	10-25	10-25	
olopatadine 0.1% solution (Patanol)[38]	<5	7	<5	--	<5	--	--
olopatadine 0.2% solution (Pataday)[39]	<5	<5	<5	--	<5	--	<5

Adverse effects are reported as a percentage. Data are taken from product package information and should not be considered comparative.

FDA-Approved Dosages

Drug	Dosage (in affected eye(s))	Bottle Size
azelastine 0.05% solution (Optivar)	1 drop twice daily	6 mL
emedastine 0.05% solution (Emadine)	1 drop up to four times daily	5 mL
epinastine 0.05% solution (Elestat)	1 drop twice daily	5 mL
ketotifen 0.025% solution (Zaditor)	1 drop twice daily every 8 to 12 hours	5 mL
olopatadine 0.1% solution (Patanol)	1 drop twice daily at an interval of 6 to 8 hours	5 mL
olopatadine 0.2% solution (Pataday)	1 drop once daily	2.5 mL

Summary

Although there have been numerous comparative trials with the ophthalmic antihistamines, these trials have used single administration of one drop in the eye and evaluated effects based on a

CAC model. From the results of these trials, it is difficult to select the one best agent. Olopatadine 0.2% (Pataday) has not been directly compared to other agents within this class.

Another factor used to evaluate these drugs is ocular comfort. Unfortunately, this measure has also been based on the single administration of one drop studies. It appears that these agents currently have more similarities than differences. There may be individualized patient preference for certain agents based on ocular comfort of the drops. Emedastine has the disadvantage of being dosed up to four times daily while the other agents are administered twice daily. Olopatadine 0.2% is administered once daily.

A British systematic review and meta-analysis evaluated the currently published double-blind, randomized, controlled trials of agents which are used in the management of seasonal allergic conjunctivitis.[40] The authors concluded that no one agent is clinically superior to others in this class. Selection should be dependent on frequency of administration, patient preference, and cost.

The American Academy of Ophthalmology recommends the step-wise approach to the patient with allergic conjunctivitis.[41] The recommendations do not recommend any particular ophthalmic antihistamine; any of the ophthalmic antihistamines may be used as therapy for allergic conjunctivitis. . For persistent symptoms or frequent symptoms, an agent with mast cell stabilizer activity may be utilized. Short courses of corticosteroids may be used to treat flares or severe symptoms.

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