

Intranasal antihistamines for allergic rhinitis: Mechanism of action

Philip Lieberman, M.D.

ABSTRACT

Although antihistamines have been in common use for treatment of allergic diseases including rhinitis for >60 years and topical therapy of the respiratory tract has been common for centuries, it is only in the past few years that topical intranasal antihistamine therapy has been widely used for treatment of allergic rhinitis. Much research has been done over the past several years showing broad anti-inflammatory effects of these medications, involving many different pathways. Effects have been shown on mediators including histamine, leukotrienes, platelet-activating factor, and substance P, as well as on cytokines, adhesion molecules, and chemokines involved in chemotaxis. It is significant that these effects have been seen at clinically relevant concentrations of the topical drugs, as opposed to the situation with oral antihistamines where anti-inflammatory effects are generally found only at concentrations much higher than that achieved with routine dosing. Clinically, it appears that this delivery of high local concentrations allows for other pharmacologic activity to be expressed. These anti-inflammatory actions may be part of the reason why these drugs also are effective in relieving many symptoms of nonallergic rhinitis, where histamine has much less of a role and where oral antihistamines have traditionally been of minimal help.

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Inhaled therapy for respiratory tract ailments, including asthma, has been around for centuries with references to inhaled medications such as plants with anticholinergic effects being used for asthma in texts from ancient Egypt, from Ayurvedic medicine traditions in India, and from the middle ages.^{1,2} Although most medications for asthma are now given by the inhaled route to maximize efficacy and minimize systemic side effects, the treatment of allergic rhinitis has lagged behind somewhat in this respect. Certainly, the use of topical nasal steroids has gained wide acceptance as a first-line therapy for persistent rhinitis, and use of topical decongestants has proven very effective (for short periods of time when appropriate). Although

antihistamines have been extremely popular treatments for allergic rhinitis for >60 years, the large majority of antihistamines used for allergy treatment continue to be administered by the oral route.³ This is despite the increased risk of side effects such as drowsiness or impairment, and their limited efficacy, especially with regard to congestion. Allergic rhinitis continues to be a significant problem for many patients,⁴ and there is room for improved treatments

There are currently two antihistamines approved in the United States for intranasal use, azelastine and olopatadine. Both of these have been studied in both animal and human studies and have been shown to have a wide range of anti-inflammatory activities, in addition to their actions as inverse agonists of histamine, which may contribute to their clinical efficacy in allergic and nonallergic rhinitis. These anti-inflammatory activities include effects on mast cells, eosinophils, and neutrophils; ILs and cytokines; neural mechanisms; and cellular migration. These are all pathways that have been implicated in allergic rhinitis.⁵

MAST CELL STABILIZER EFFECT

As a first example of anti-inflammatory activity, olopatadine has also been shown to be an effective mast

From the Division of Allergy and Immunology, University of Tennessee, Memphis, Tennessee

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Address correspondence and reprint requests to Philip Lieberman, M.D., Division of Allergy and Immunology, University of Tennessee, 7205 Wolf River Boulevard, Suite 200, Germantown, TN 38138

E-mail address: aac@allergymemphis.com

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cell stabilizer, with concentration-dependent inhibition of not just histamine but also tryptase and prostaglandin D₂ from human conjunctival mast cells.⁶ Azelastine, after a single dose, has similarly been found to decrease cysteinyl leukotriene and kinin release in nasal lavage fluid after allergen challenge.⁷ In a longer-term *in vivo* study, azelastine has also been shown to decrease tryptase as well as myeloperoxidase and eosinophilic cationic protein in patients with nasal polyps and dust-mite allergy.⁸ This study also showed that levels of all three mediators continued to decrease over several weeks, consistent with some inhibition of eosinophilic and neutrophilic activation.

EFFECT ON ILS AND CYTOKINES

Effects of these molecules have also been seen on ILS and other cytokines. In a study on conjunctival epithelial cells, although addition of several antihistamines led to suppression of histamine-induced production of IL-8, olopatadine was significantly more inhibitory of the cytokine production than would be predicted by its H₁-histamine receptor binding affinity.⁹ In cultured umbilical cord-derived mast cells, both olopatadine and azelastine inhibited IL-6 and tryptase secretion induced by anti-IgE and seemed to prevent activation of the mast cells based on microscopic appearance.¹⁰ Both of these studies appear to indicate anti-inflammatory actions beyond what would be expected from an antihistamine alone. Azelastine, studied in seasonal allergic rhinitis, showed a reduction in IL-8 in nasal lavage fluid along with a decrease in nitric oxide (NO).¹¹

Another important cytokine that is secreted after stimulation of conjunctival mast cells by anti-IgE, TNF- α , is similarly suppressed by olopatadine.¹² Azelastine has been shown to suppress secretion of TNF- α as well as IL-6, IL-1 β , and others in a revealing study by Yoneda *et al.*¹³ This article reviews the role of the transcription factor NF- κ B, which is crucial in the stimulation of many proinflammatory mediators. In addition to showing azelastine suppression of the aforementioned cytokines, Yoneda's group also shows suppression of NO and of NO synthase RNA. Furthermore, they show that azelastine can directly inhibit the activation of the NF- κ B, which provides a plausible mechanism of action for these anti-inflammatory effects.

EFFECT ON NEURAL MECHANISMS

Neural mechanisms may also play a role in allergic rhinitis,^{14–16} and this appears to be another area where the effects of these topical medications may go beyond the effects of traditional antihistamines. Elevated levels of the neuropeptide substance P are found in nasal

secretions of patients with allergic rhinitis, and these levels were significantly decreased by azelastine.¹⁴ Another recent study confirmed elevated levels of substance P, as well as vasoactive intestinal peptide, in nasal mucosal smears of allergic rhinitis patients.¹⁷

In a murine model, olopatadine was also shown to suppress the production of nerve growth factor and vascular endothelial growth factor in response to toluene diisocyanate challenge in toluene diisocyanate-sensitized rats.¹⁸ Of note is that other traditional antihistamines did not suppress these factors, and histamine application did not stimulate their production, implying a mechanism of action of olopatadine distinct from the antihistamine effects. Also, in a murine model, Sugimoto has looked at capsaicin-induced nasal rubbing and sneezing in mice, looking at wild-type mice as well as mice deficient in H₁-receptors or mast cell-deficient mice. It was found that while cetirizine blocked the nasal response only in wild-type mice, olopatadine was able to block the response in H₁-receptor-deficient and mast cell-deficient mice as well, indicating a probable effect on the release of mediators from the peripheral nerve rather than just a histamine inverse agonist effect.^{19,20} Similarly, in a guinea pig model, Kaise *et al.* showed olopatadine inhibited capsaicin-induced sneezing where traditional antihistamines did not.²¹

With congestion being a major symptom of many rhinitis patients, it is also worth noting that hyperresponsiveness of congestive nasal reflexes has been shown in allergic rhinitis,²² using a bradykinin challenge model. Another study has shown that although bradykinin normally enhances the capsaicin-induced release of substance P from neurons, this is attenuated by olopatadine.²³

EFFECT ON CELLULAR MIGRATION

When looking at allergic inflammation, the processes of chemokine release, chemotaxis, and cellular migration and tissue infiltration are important components of the ongoing allergic reaction. Studies on human conjunctival epithelial cells have shown that olopatadine prevents MCP1 and RANTES production.²⁴ Another study showed that olopatadine suppresses macrophage migration.²⁵ Adhesion molecules are very important in allowing inflammatory cells to migrate into the tissues, and studies on intracellular adhesion molecule 1 have shown a decreased expression of this important adhesion molecule on human conjunctival epithelium cells exposed to azelastine at clinically relevant doses, both in cultured cells²⁶ and *in vivo* with allergen challenge.²⁷ In the latter study, they went a step further and showed that azelastine also suppressed the influx of inflammatory cells, including eosinophils and lymphocytes, into the conjunctiva.

ROLE IN NONALLERGIC RHINITIS

Another indication that these topical antihistamines have actions beyond those of oral antihistamines comes in an analysis of their role in nonallergic rhinitis. Although nonallergic rhinitis is clearly not a single disease process, it does not appear that histamine plays a major role in most phenotypes, and there has been little evidence of efficacy of oral antihistamines in this disease.²⁸ On the other hand, there have been several studies of the intranasal antihistamine azelastine in nonallergic rhinitis showing significant reductions in nasal symptom scores, including nasal congestion, rhinorrhea, postnasal drip, and sneezing. Even in studies excluding patients with nonallergic rhinitis with eosinophils by requiring a negative cytology for eosinophils before entry into the study, the intranasal antihistamine showed significant clinical efficacy.²⁹

SUMMARY

Although the intranasal antihistamines are potent antihistamines, the studies reviewed here and elsewhere reveal a wide variety of anti-inflammatory effects made possible by the high local concentrations achieved with these products. These effects include mast cell stabilization, inhibition of chemokines release and of inflammatory cell chemotaxis and migration, and decreased influx of inflammatory cells in the mucosa. Studies have also shown suppression of several cytokines including ILs and TNF- α , possibly through inhibiting the activation of NF- κ B, which is involved in several inflammatory pathways. Neurally mediated inflammation is also suppressed. These various effects well beyond what is seen with other oral antihistamines in clinically relevant doses may account for the increased efficacy of these products over oral antihistamines, especially with regard to congestion and non-allergic rhinitis.

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