Antihistamine treatment for allergic rhinitis: Different routes, different outcomes?

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ABSTRACT

Allergic rhinitis is one of the most common chronic disorders in the United States, causing patients significant discomfort and interfering with quality of life and functioning. Histamine is the primary mediator in the development of allergic rhinitis symptoms and is a primary therapeutic target. Guidelines, both in the United States and globally, recommend antihistamines as first-line therapy of allergic rhinitis. This article discusses the outcomes associated with intranasal versus oral administration of antihistamines. Both oral and intranasal antihistamines are approved for the first-line treatment of allergic rhinitis and both formulations result in a reduction in symptoms and an improvement in quality of life. Intranasal agents may be preferred in patients in whom nasal congestion is particularly bothersome or in cases where a more rapid onset of action is desired. Oral agents would be a better choice in young children (especially children who are at risk of developing asthma), in cases of poor medication compliance, and in patients who are bothered most by histamine-associated symptoms, such as itching or red and watery eyes. Both oral and intranasal antihistamines are safe and well tolerated and meet the needs of patients with allergic rhinitis, especially those with mild to moderate disease.

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Key words: Allergic rhinitis, azelastine, intranasal antihistamines, nasal congestion, olopatadine, onset of action, oral antihistamines, quality of life, safety, second-generation antihistamines

Allergic rhinitis is recognized as one of the most common chronic disorders in the United States. It has been estimated that 65 million persons nationwide suffer from the disease.[1] In a recent telephone survey of 31,470 households, 1 in 7 adults reported having been diagnosed with nasal allergies. Survey responders reported nasal congestion as the most bothersome symptom, followed by headache and postnasal drip. The discomfort caused by allergic rhinitis was described by two of five patients as intolerable without relief.[2] Furthermore, patients are frequently dissatisfied with the effectiveness of medications used to treat allergic rhinitis, and many simply stop taking them as a result.[2,3]

Allergic rhinitis also has documented effects on quality of life and functioning. The symptoms associated with allergic rhinitis interfere with sleep, such that patients often feel tired during the day. Work productivity is reduced and many patients miss work altogether when symptoms are at their worst. Psychomotor functioning, decision making, and psychosocial well being are also adversely effected. In children, complications of nasal allergies include sleep disturbances, poor school performance, and hyperactivity.[4] Thus, although often downplayed by both patients and health care providers, the impact of allergic rhinitis is substantial.[2,5]

Histamine is the primary mediator in the development of symptoms of allergic rhinitis in both the early and the late-phase reactions. In the early phase, presensitized mast cells exposed to an allergen release histamine to cause acute symptoms. In the late phase, inflammatory mediators lead to the activation of basophils and eosinophils, resulting in further histamine release and inflammation. Symptoms directly attributed to early and late-phase histamine release include sneezing, itchiness, rhinorrhea, and nasal congestion.[6] Blocking the actions of histamine results in relief from allergic rhinitis symptoms and is one of the primary therapeutic targets. The U.S. Rhinitis Practice Parameters, updated in 2008, promote a stepwise approach to rhinitis care and recommend either an oral or an intra-

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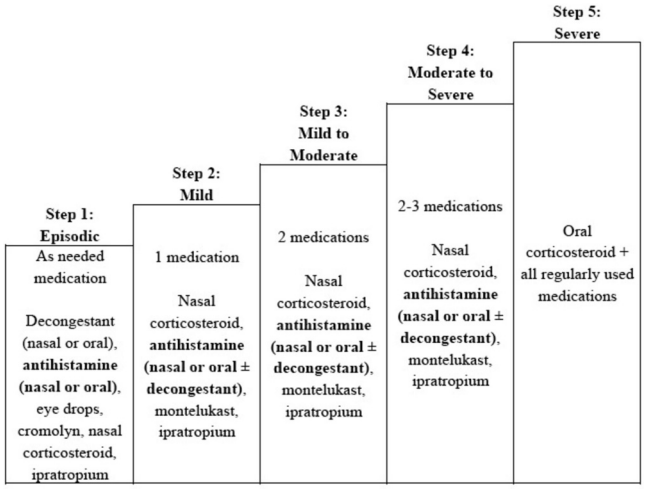

Figure 1. *U.S. Rhinitis Practice Parameters update 2008. (Adapted from the Rhinitis Action Plan included in Ref. 5.)*

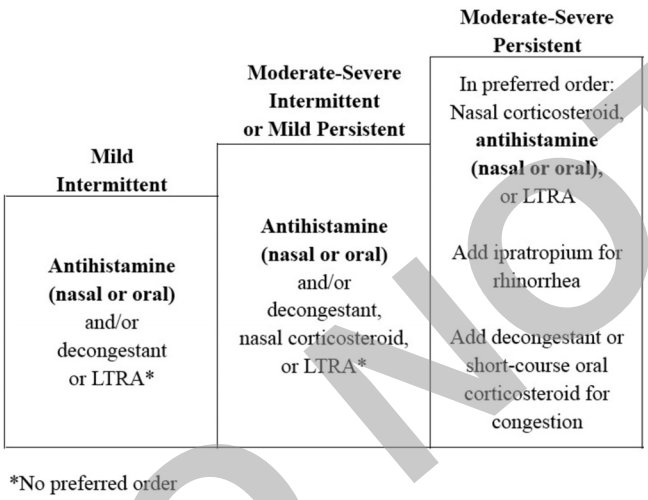

Figure 2. *ARIA/WHO Allergic Rhinitis Guidelines update 2008. ARIA = Allergic Rhinitis and its Impact on Asthma; LTRA = leukotriene receptor antagonist; WHO = World Health Organization. (Adapted from Ref. 6.)*

nasal antihistamine in every step of treatment (Fig. 1).[7] Global Allergic Rhinitis and its Impact on Asthma guidelines, in collaboration with the World Health Organization, similarly endorse the use of antihistamines in all stages of disease severity (Fig. 2).[8] The goal of this article is to discuss the outcomes associated with intranasal versus oral administration of antihistamines.

INTRANASAL ANTIHISTAMINES

There are a number of advantages to intranasal administration. Medication is more effectively delivered to the nasal mucosa, directly onto the target tissue harboring histamine-filled mast cells and inflammatory mediators. Intranasal administration is also associated with a faster onset of action and lower incidence of unwanted systemic side effects.[3] According to both U.S. and global rhinitis management guidelines, intranasal antihistamines may be considered for use as first-line treatment, especially in patients with milder symptoms (Figs. 1 and 2).[7,8]

Approved intranasal antihistamines available in the United States include azelastine hydrochloride with either a saline diluent (Astelin; Meda Pharmaceuticals, Somerset, NJ) or with sucralose/sorbitol (Astepro; Meda Pharmaceuticals) and olopatadine hydrochloride 0.6% (Patanase; Alcon Laboratories, Sinking Spring, PA). Azelastine with sucralose/sorbitol and olopatadine are approved for the treatment of seasonal allergic rhinitis in patients ≥12 years of age, and azelastine with saline is approved for use in patients ≥5 years of age. All available formulations are dosed twice daily (azelastine, 1–2 sprays/nostril; olopatadine, 2 sprays/nostril).

Intranasal antihistamines have been found to be especially effective in the treatment of seasonal allergic rhinitis. In a multicenter, randomized, double-blind study comparing 0.4 or 0.6% intranasal olopatadine to placebo, olopatadine (2 sprays/nostril twice daily) provided statistically significant improvements in allergic rhinitis symptoms (as reflected by a reduction in total nasal symptom score [TNSS]) and in quality-of-life variables, while exhibiting a safety profile comparable with placebo.[9] Olopatadine therapy has also been associated with improvements in functions such as work and activities.[10] Similarly, in two trials comparing intranasal azelastine (1 spray/nostril twice daily) to placebo, azelastine significantly improved the reflective TNSS (−16.5% versus −7.6% and $p = 0.012$, and −22.1% versus −14.9% and $p = 0.017$).[11,12] Azelastine nasal spray has also been shown to be efficacious in patients with an unsatisfactory response to loratadine. In a study of 428 patients with seasonal allergic rhinitis who had previously failed loratadine, both the azelastine and the azelastine/loratadine arms had a statistically significant reduction in TNSS compared with the placebo arm (−21.9 and −21.5% versus −11.1%; $p = 0.001$).[13]

Because of their targeted action on the nasal mucosa, intranasal antihistamines significantly reduce the nasal symptoms associated with allergic rhinitis, including nasal congestion, the symptom reported as most bothersome by patients. In a study of 151 patients with moderate to severe seasonal allergic rhinitis, olopatadine 0.6% reduced all nasal symptom scores when compared with placebo, including stuffy nose (−21.7% versus −13.2%; $p = 0.002$), runny nose (−30.0% versus −18.4%; $p < 0.001$), itchy nose (−32.4% versus −19.4%; $p < 0.001$), and sneezing (−35.7% versus −18.8%; $p < 0.001$).[14] When compared with oral antihistamines, intranasal antihistamines may more effectively target nasal symptoms. In a head-to-head study comparing

azelastine nasal spray with oral cetirizine, statistically significant improvements in favor of azelastine were observed for nasal congestion ($p = 0.049$) and sneezing ($p = 0.01$). Azelastine also improved all aspects of rhinoconjunctivitis quality of life to a greater extent than cetirizine.[15]

Although additional comparative studies are needed, limited data suggest that intranasal antihistamines may be equivalent to intranasal corticosteroids at reducing nasal symptoms, including congestion. In a recent study comparing olopatadine and fluticasone nasal sprays over a 2-week period, there were no significant between-treatment differences in effects on congestion, runny nose, sneezing, itchy nose, or ocular symptoms, and olopatadine had a faster onset of action for reducing all symptoms.[16] Furthermore, intranasal antihistamines can be used in combination with intranasal corticosteroids to achieve added benefit. In a study comparing azelastine nasal spray, fluticasone nasal spray, and the combination in the treatment of moderate to severe seasonal allergic rhinitis, fluticasone showed a slightly greater reduction in nasal congestion score than azelastine (−21.1% versus −19.2%; p value not reported), and in the combination group, the nasal congestion score was reduced by 31.2% ($p < 0.05$). Similarly, the TNSS was reduced by 24.8% in the azelastine group, 27.1% in the fluticasone group, and 37.9% in the combination group, showing an added improvement, relative to fluticasone alone, of almost 11%.[17]

One of the advantages of intranasal antihistamines is their onset of action, which can be as rapid as 30 minutes. Onset of action is defined by the Federal Drug Administration as the first time point at which a drug shows a statistically significant improvement over placebo that is sustained for the length of the observation period. In a study that resulted in the drug's approval, Astepro (azelastine hydrochloride) showed a statistically significant improvement in the TNSS compared with placebo at the 30-minute time point and this improvement was sustained throughout the 4-hour observation period.[18] According to the package insert, in dose-ranging trials, administration of Astelin (2 sprays/nostril twice daily) resulted in a statistically significant decrease in symptoms compared with placebo within 3 hours of initial dosing.[11] In a study comparing olopatadine 0.6% nasal spray to placebo, olopatadine was significantly more effective at all time points starting at 90 minutes postdose and continuing over 12 hours. Notably, there was a statistically significant difference in favor of olopatadine at 30 minutes, but this difference was not sustained at 60 minutes.[19] The Patanase package insert claims an onset of action of 30 minutes.[20] In a study comparing olopatadine and mometasone, olopatadine had a more rapid onset of action (30 minutes versus 150 minutes).[21]

Table 1 **Benefits of intranasal antihistamines**

First-line, guideline-recommended treatment
Efficacious
Clinically significant effect on nasal congestion
Rapid onset of action
Added benefit in combination therapy
Improve quality of life
Safe and well-tolerated
Meet patient needs

Finally, intranasal antihistamines are safe and well tolerated. The available agents are similar in terms of overall safety, with the primary side effects including headache and nosebleed. They differ, however, in sensory attributes such as taste and odor, which can directly impact patients' acceptance of a prescribed medication and, ultimately, affect treatment success. In a recent study, 110 patients were asked to evaluate the sensory attributes of olopatadine 0.6% nasal spray and azelastine 0.1% nasal spray in a double-blinded, crossover fashion. Olopatadine was superior to azelastine in overall aftertaste (60.6% versus 30.3%; $p = 0.0005$), patient preference (62.4% versus 33.9%; $p = 0.0001$), and likelihood of extended use (60.9% versus 34.5%; $p = 0.0004$). Both treatments were well tolerated.[22] The taste of azelastine has been improved by the addition of sucralose/sorbitol to the formulation, with a statistically significant 71% reduction ($p < 0.05$) in bitterness reported with Astepro (azelastine with sucralose/sorbitol) when compared with Astelin (azelastine without sucralose) as analyzed by professional taste panelists.[23] Azelastine with sucralose/sorbitol still has not been compared with olopatadine in a head-to-head trial.

Overall, intranasal antihistamines meet the needs of patients with allergic rhinitis very well. In a 2005 survey conducted by the Asthma and Allergy Foundation of America, 1214 patients reported that the ideal allergic rhinitis medication would (1) be safe, (2) have a long duration of action, (3) have a rapid onset, (4) cause few adverse effects, and (5) not cause drowsiness.[24] Intranasal antihistamines have been shown to be very well tolerated, causing only mild side effects with a low incidence of drowsiness. Their local delivery and favorable pharmacokinetics lead to a rapid onset of action and duration of action that extends throughout the dosing interval. They also effectively target nasal congestion, the symptom that causes patients the most discomfort (Table 1).

ORAL ANTIHISTAMINES

Like intranasal antihistamines, oral antihistamines are also recommended as first-line therapy in the treatment of allergic rhinitis, both in the United States and globally.[7,8] Second-generation agents are generally pre-

ferred because they are less likely to cause sedation (cetirizine is the most sedating of the available agents, with an incidence of 11%), performance impairment, and anticholinergic side effects, in both adults and children.[25] Second-generation oral antihistamines currently available in the United States include loratadine (Claritin, Schering-Plough Healthcare Products, Memphis, TN), desloratadine (Clarinex, Schering-Plough), fexofenadine (Allegra, Sanofi-Aventis, Bridgewater, NJ), cetirizine (Zyrtec, Pfizer Pharmaceuticals, New York, NY) levocetirizine (Xyzal, Sanofi-Aventis), and acrivastine (only available in combination with pseudoephedrine as Semprex-D, UCB Pharma, Smyrna, GA). Both loratadine and cetirizine can be acquired over the counter; generic formulations of loratadine, cetirizine, and fexofenadine are available.

Controlled studies have shown the efficacy of oral antihistamines in the treatment of adults and children with allergic rhinitis. Unlike intranasal antihistamines, which mainly target nasal symptoms, oral antihistamines primarily target symptoms associated with histamine, such as sneezing, rhinorrhea, itchiness, watery eyes, and eye redness. Oral antihistamines have some effect on nasal congestion, although less than intranasal agents.[7] In a study of 331 patients comparing desloratine, 5 mg daily, to placebo, desloratadine significantly reduced the total symptom score (−32% versus −19%; $p < 0.001$), total asthma symptom score (−27% versus −18%; $p < 0.023$), and nasal congestion score (−24% versus −16%; $p < 0.006$) over days 1–15.[26] Similarly, in a study of patients with seasonal allergic rhinitis, fexofenadine (120 and 180 mg daily) and cetirizine (10 mg daily) both had a statistically significant effect compared with placebo on sneezing; rhinorrhea; itchy nose, palate, and throat; itchy, watery and red eyes; and nasal congestion. There were no differences between the treatment arms.[27] Finally, in a study of 421 adults with persistent allergic rhinitis, levocetirizine, 5 mg daily, improved all domains of rhinoconjunctivitis quality of life compared with placebo. This same study showed the cost-effectiveness of levocetirizine, showing a 32.5% reduction in total costs ($p = 0.01$) associated with persistent allergic rhinitis in the levocetirizine group compared with placebo.[28]

An advantage of oral antihistamines is that they are approved for young children (desloratadine and cetirizine, age 6 months and up; loratadine and fexofenadine, age 2 years and up; levocetirizine, age 6 years and up). Additionally, a 2001 study indicated that oral antihistamines may delay or prevent the development of asthma in a subgroup of infants with atopic dermatitis. In this study assessing the effects of cetirizine on the development of asthma, 795 infants, aged 12–24 months, were treated with either cetirizine or placebo for 18 months, and then followed for an additional 18 months. Although there was no difference in cumulative prevalence of asthma between cetirizine and placebo, those infants with evidence of sensitivity to house-dust mites or grass pollen who were treated with cetirizine were significantly less likely to develop asthma compared with those treated with placebo over the 18 months of treatment ($p = 0.005$ and 0.002, respectively), and this effect was sustained for the grass pollen–sensitized infants over the full 36 months ($p = 0.008$).[29]

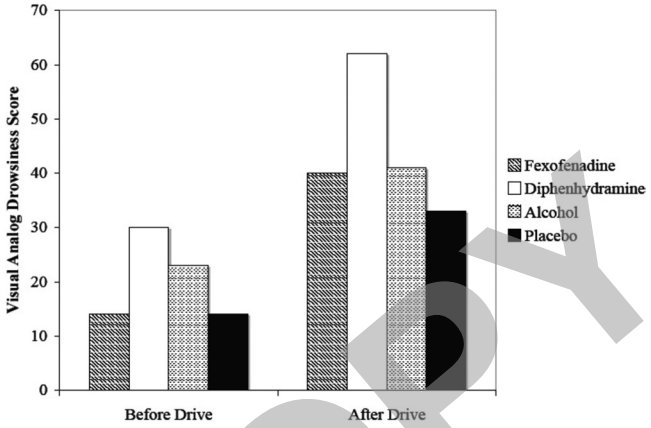

Figure 3. *Change from baseline in visual analog drowsiness scores. Participants rated drowsiness on a scale from 1 (wide awake) to 100 (extremely drowsy). (Adapted from Ref. 26.)*

Although not as rapid as intranasal antihistamines, oral antihistamines have a relatively rapid onset of action. A review of the literature from 1985 to 2002 found the following data regarding onset of action after a single oral dose: cetirizine, 59–126 minutes; loratadine, 102 minutes; fexofenadine, 60 minutes.[30] In a study comparing onset of action of loratadine and cetirizine (based on half-hourly assessment of symptoms after a single oral dose in comparison with placebo), cetirizine had a more rapid onset of action than loratadine (1 hour versus 3 hours; $p < 0.01$).[31] Second-generation antihistamines also have a long duration of action that allows them to be dosed once daily, a characteristic that promotes patient compliance.

Like intranasal antihistamines, second-generation oral antihistamines are well tolerated and cause little to no sedation or performance impairment. This was shown in a study of driving performance, in which 40 patients were randomized to either fexofenadine, 60 mg × 1 dose; diphenhydramine, 50 mg × 1 dose; alcohol (to achieve an ~0.1% blood alcohol concentration); or placebo and then asked to self-assess their level of drowsiness both before and after a 45-minute drive. Before the drive, participants were most drowsy after taking diphenhydramine and least drowsy after taking fexofenadine or placebo (Fig. 3). In terms of driving, participants had the best performance when treated with fexofenadine or placebo. Driving performance was poorer after alcohol use and poorest after

Table 2 **Benefits of oral antihistamines**

First-line, guideline-recommended treatment (second-generation agents preferred)
Efficacious
Target symptoms such as sneezing, rhinorrhea, itchiness, and watery eyes
Approved in children as young as 6 mo
May delay or prevent development of asthma
Available in combination with decongestants
Dosed once daily
Improve quality of life
Safe and well tolerated
Meet patient needs

diphenhydramine.[32] Studies suggest that cetirizine may be more sedating than other second-generation antihistamines or placebo, but that the drug is less sedating than first-generation antihistamines.[33,34]

In summary, oral antihistamines are efficacious in the treatment of the histamine-associated symptoms of allergic rhinitis, but less effective at treating nasal congestion. However, many are available in fixed-dose formulations in combination with a decongestant to enhance their effect on nasal congestion. Oral antihistamines improve rhinoconjunctivitis quality of life and are a cost-effective treatment modality, especially given the availability of over-the-counter and generic formulations. Although the onset of action with oral agents is not as rapid as with intranasal administration, the oral antihistamines have the advantage of being dosed once daily. Furthermore, they meet the needs of patients with allergic rhinitis by causing little to no sedation (Table 2).

CONCLUSIONS

Both oral and intranasal antihistamines are approved for the first-line treatment of allergic rhinitis and both formulations result in a reduction in symptoms and an improvement in quality of life. Intranasal agents may be preferred in patients in whom nasal congestion is particularly bothersome or in cases where a more rapid onset of action is desired. Oral agents would be a better choice in young children (especially children who are at risk of developing asthma), in cases of poor medication compliance, and in patients who are bothered most by histamine-associated symptoms, such as itching or red and watery eyes. Both oral and intranasal antihistamines are safe and well tolerated and meet the needs of patients with allergic rhinitis, especially those with mild to moderate disease.

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