

Management of allergic rhinitis with a combination antihistamine/anti-inflammatory agent

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Azelastine nasal spray is a topical antihistamine treatment for the symptoms of seasonal allergic rhinitis. Besides histamine antagonism, azelastine affects other chemical mediators of the inflammatory response including leukotrienes and kinins. This article reviews and discusses the antihistaminic and anti-inflammatory properties of azelastine and the results of pharmacokinetic studies and controlled clinical trials. (J Allergy Clin Immunol 1999;103:S400-4)

Azelastine nasal spray (Astelin® Nasal Spray) is an effective topical management for the symptoms of seasonal allergic rhinitis. The active ingredient, azelastine hydrochloride, is a selective, high-affinity, histamine H₁-receptor antagonist with structural and chemical differences (it is a phthalazinone derivative) that distinguish it from currently available antihistamines. On a milligram-per-milligram basis, azelastine is approximately 10 times more potent than chlorpheniramine at the H₁-receptor site.¹

In addition to histamine antagonism,² azelastine has demonstrated inhibitory effects on cells and chemical mediators of the inflammatory response over a range of concentrations in laboratory animals and in *in vitro* tests. Azelastine prevented leukotriene generation^{3,4} from mast cells and basophils and demonstrated inhibitory effects on bradykinin-induced smooth muscle contraction in isolated rat uterine tissue⁵ and the production of oxygen free radicals from polymorphonuclear leukocytes.⁶ Azelastine has been shown to modulate the activity of eosinophils and neutrophils,⁷ platelets,⁸ macrophages,⁹ monocytes, and cytokines¹⁰ and to inhibit calcium influx² and intracellular calcium release.⁹

The anti-inflammatory effects of azelastine have also been shown in studies in patients with seasonal allergic rhinitis. Single 2-mg doses of orally administered azelastine significantly reduced levels of leukotrienes and kinins in nasal lavage fluid after allergen challenge,¹¹ and single 0.14-mg doses of intranasally administered azelastine significantly decreased eosinophil and neutrophil counts in nasal washings and downregulated intercellular adhesion molecule-1 expression on nasal epithelial cells after allergen challenge.¹²

Abbreviation used

TSC: Total rhinitis symptom complex score

In clinical efficacy trials¹³⁻¹⁷ azelastine nasal spray was effective in treating the symptoms of allergic rhinitis including both nasal and non-nasal symptoms at a dosage of 2 sprays per nostril twice daily. Onset and duration of action assessments in these studies^{13,14} showed that azelastine nasal spray improved baseline symptom scores within 1 hour in most patients. These improvements reached statistical significance versus placebo saline spray within 2 to 3 hours and were sustained for 12 hours after a single dose. In an open-label evaluation many patients treated with azelastine nasal spray reported having an effect within 30 minutes (Wallace Laboratories, data on file). Azelastine nasal spray is well tolerated, with a relatively low incidence of somnolence reported in long-term studies. Bitter taste is the most often reported adverse effect.

PHARMACOKINETICS

The systemic bioavailability of azelastine after intranasal administration is approximately 40%. At the manufacturer's recommended dosage of 2 sprays per nostril twice daily (1.1 mg/d), steady-state plasma concentrations ranged from 0.72 (± 0.47) to 1.09 (± 0.56) ng/mL. Azelastine mean maximal plasma concentrations ($C_{\max}$) occur in 2 to 3 hours, and both $C_{\max}$ and trough plasma concentrations (C_{trough}) are proportional to the dose.

Orally administered azelastine undergoes oxidative metabolism through the cytochrome P450 enzyme system to an active metabolite, desmethylazelastine, and 2 inactive carboxylic acid metabolites. Although the specific P450 isoforms responsible for the metabolism of azelastine have not yet been identified, *in vitro* experiments to measure P450 activity indicated that azelastine did not inhibit P450 isoforms 1A2, 2A6, 2C9, or 2E1 but did inhibit 2C19 and 2D6 at concentrations at least 100-fold greater than would be achieved therapeutically at recommended dosages.¹⁸ Protein binding averaged 88% and 97% for azelastine and desmethylazelastine, respectively. The plasma clearance of azelastine is approximately 0.5 L/h/kg, and the elimination half-lives of azelastine and desmethylazelastine are approximately 22 and 54 hours, respectively.

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Azelastine steady-state pharmacokinetic estimates in the elderly are similar to those in individuals less than 60 years of age. The elimination of azelastine was not altered in patients with hepatic dysfunction; however, the renal elimination of azelastine was somewhat lower in patients with renal impairment than in healthy subjects.

In a 2-week, double-blind, placebo-controlled study,¹⁹ a single dose of azelastine nasal spray had no effect on histamine skin test reactivity when measured 5 hours after the first dose of study medication. Based on the time for histamine skin test reactivity to 20% of baseline values after discontinuation after 14 days of therapy at a dosage of 2 sprays per nostril twice daily (1.1 mg/d), it was concluded that azelastine nasal spray should be discontinued for 48 hours before allergy skin testing is begun.

DRUG INTERACTIONS

There was no evidence of clinically significant electrocardiographic effects (QTc prolongation) when oral azelastine 8 mg/d (approximately 8 times the recommended daily nasal spray dosage of 1.1 mg/d) was administered with either ketoconazole¹⁸ or erythromycin.²⁰ The coadministration of azelastine and erythromycin did not influence the pharmacokinetic parameters of either drug, indicating that azelastine is not metabolized by the cytochrome P450 isoenzyme CYP3A4.

Azelastine had no significant effect on the blood levels of theophylline, and theophylline did not affect azelastine plasma levels. Azelastine plasma concentrations increased by 65% when coadministered with cimetidine; however, these values appeared to be within the normal range of variability for the administered dose (Wallace Laboratories, data on file).

Adverse experience reports among patients taking pseudoephedrine concomitantly with oral azelastine indicated no evidence of a drug/drug interaction.^{21,22} The concomitant use of azelastine and inhaled beclomethasone was well tolerated in a clinical trial in 193 patients with bronchial asthma.²³ At the recommended dosage of 1.1 mg/d, azelastine nasal spray is unlikely to be associated with significant central nervous system depressant effects; however, its use with alcohol or other central nervous system depressants might produce additive effects.²⁴

ANTI-INFLAMMATORY EFFECTS

In vitro studies

Azelastine has demonstrated inhibitory effects on cells and chemical mediators of the inflammatory response in a variety of in vitro studies. Azelastine (10 µg/mL) inhibited the production of leukotrienes B₄ and C₄ by inhibition of phospholipase A₂ and leukotriene synthase,⁴ and it inhibited the synthesis and release of leukotriene C₄ in a dose-related manner at concentrations of 10⁻⁸ and 10⁻⁴ mol/L and of leukotriene B₄ at 10⁻⁶ mol/L in cultured human eosinophils.²⁵ In dose-response experiments azelastine significantly inhibited anti-IgE-stimulated hista-

mine release from human basophils at concentrations ≥10 µmol/L.²⁶ At concentrations ranging from 10⁻⁹ to 10⁻⁷ mol/L, azelastine inhibited calcium ion influx induced by platelet activating factor and inhibited the secretion of eosinophil cationic protein in a human leukemic cell line.²⁷

Azelastine inhibited the reduced nicotinamide adenine dinucleotide phosphate oxidase generation of superoxide free radicals in human neutrophils with IC₅₀s of 0.7 µmol/L in whole cells and 0.5 µmol/L in a cell-free system.²⁸ In human neutrophils and eosinophils, azelastine significantly inhibited the generation of superoxide in a dose-dependent manner over a concentration range of 10⁻⁷ to 10⁻⁵ mol/L.⁷

In vivo studies

Similar types of anti-inflammatory effects seen with azelastine in the in vitro studies have been observed in animal models. Orally administered azelastine inhibited leukotriene-mediated allergic bronchospasm in guinea pigs at ID₅₀s of 0.063 and 0.12 mg/kg administered 2 and 24 hours, respectively, before allergen challenge.²⁹ Azelastine (ED₅₀ of 1.55 mg/kg) administered 2 hours before challenge inhibited aeroallergen-induced bronchial eosinophilia in guinea pigs by 44%.³⁰ At a dose of 0.05 mg/kg, azelastine significantly inhibited lipopolysaccharide-induced increases in cytokines (interleukin-1β and tumor necrosis factor-α) in mice.³¹

Clinical studies

Anti-inflammatory effects with both orally and intranasally administered azelastine have been reported in clinical studies in patients with seasonal allergic rhinitis. In a double-blind, placebo-controlled trial, pretreatment with a single 2-mg oral dose of azelastine significantly reduced the levels of leukotrienes and kinins in nasal washings from patients with seasonal allergic rhinitis.¹¹ In a randomized, double-blind, single-dose study,¹² pretreatment with azelastine nasal spray 0.137 mg (1 spray) resulted in statistically significant decreases in eosinophil and neutrophil counts and intercellular adhesion molecule-1 expression on nasal epithelial cells during both the early-phase response and late-phase response of the allergic reaction. Serum eosinophil cationic protein levels were also significantly decreased with azelastine during the late-phase response.

CLINICAL EFFICACY STUDIES

United States clinical trials

Azelastine nasal spray was effective in the treatment of patients with symptomatic seasonal allergic rhinitis in 5 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials conducted in the United States. Two of these trials were 2-day outdoor studies that also evaluated onset of action, whereas the remaining 3 trials were long-term studies (2 to 4 weeks) in which patients were treated in their everyday environment. Efficacy was assessed by a total rhinitis symptom complex score (TSC),

which consisted of symptoms of runny nose/sniffles, sneezing, itchy nose, nose blows, watery eyes, postnasal drip, cough, and itchy eyes/ears/throat/palate. Physician and patient global evaluations of treatment efficacy were secondary efficacy variables. Azelastine nasal spray was administered at dosages of 1 spray per nostril twice daily (0.55 mg/d), 2 sprays per nostril daily (0.55 mg/d), or 2 sprays per nostril twice daily (1.1 mg/d). Placebo treatment consisted of a saline solution that contained the same components as azelastine nasal spray with the exception of the active ingredient.

In the first outdoor trial,¹³ conducted during the height of the fall pollen season in 264 patients, the overall mean percent improvements in the TSC severity score for azelastine 2 sprays per nostril every day and 2 sprays per nostril twice daily were statistically significant ($P = .003$ and $P = .006$, respectively) versus placebo. Although the percent improvements with 1 spray per nostril twice daily were numerically superior to placebo, the difference from placebo was not statistically significant. Eighty-nine percent of the patients treated with 2 sprays per nostril every day ($P < .001$), 83% of the patients treated with 2 sprays per nostril twice daily ($P < .001$), and 75% of the patients treated with 1 spray per nostril twice daily ($P = .023$) rated their therapeutic response improved compared with 49% of the patients who received placebo.

In the second outdoor trial,¹⁴ conducted during the spring pollen season in 294 patients, treatment with azelastine 2 sprays per nostril every day and 2 sprays per nostril twice daily resulted in statistically significant improvements over placebo in the TSC ($P = .009$ and $P = .0007$, respectively), with 73% of the patients treated with azelastine nasal spray reporting overall symptom improvement on global evaluation compared with 65% of the patients treated with placebo.

In these studies azelastine nasal spray resulted in improvements over baseline in rhinitis symptoms at the first assessment point (1 hour after dose). These improvements reached statistical significance compared with placebo within 2 to 3 hours and were sustained for 12 hours after a single dose. There is, however, evidence that a clinical effect with azelastine nasal spray may be more rapid than reported in the previous trials. In a small, double-blind, placebo-controlled crossover study in patients with seasonal allergic rhinitis, azelastine nasal spray significantly reduced the number of sneezes compared with placebo within 15 minutes after initial administration.³² In an open-label evaluation of 106 patients with seasonal rhinitis, approximately 80% of the patients treated with azelastine nasal spray reported having an effect within 30 minutes (Wallace Laboratories, data on file).

The first long-term study was a 2-week trial¹⁵ conducted during the height of the Texas mountain cedar pollen season and included 251 patients. The overall mean percent improvement versus placebo in the TSC severity score was statistically significant in favor of azelastine nasal spray 2 sprays per nostril every day ($P =$

.04) and 2 sprays per nostril twice daily ($P = .003$). For both weeks of treatment, physician ratings showed a significantly ($P \leq .05$) greater percentage of patients treated with azelastine (84% for 2 sprays per nostril twice daily and 73% for 2 sprays per nostril every day) as therapeutically improved versus those treated with placebo (66%).

In the second 2-week trial,¹⁶ conducted in 247 patients during the spring and summer pollen seasons at 5 investigational sites in 5 different states, the overall improvements versus placebo in the TSC score in patients treated with 2 sprays per nostril twice daily were significantly ($P = .0008$) greater than with placebo. The improvements in the 2 sprays per nostril every day group were twofold greater than with placebo; however, the differences were not statistically significant. Physicians rated 84% of the patients treated with 2 sprays per nostril twice daily and 80% of the patients treated with 2 sprays per nostril every day as therapeutically improved compared with 66% of the patients treated with placebo ($P \leq .01$). In addition, more patients favored ($\leq .01$) azelastine nasal spray (86% and 80%) over placebo (59%) when rating their therapeutic response.

The third long-term trial was a 4-week study¹⁷ conducted with 264 patients at 5 investigational sites during the spring pollen season. During the 4 weeks of the study, patients treated with azelastine nasal spray showed greater improvements in the TSC than patients treated with placebo. The mean percent improvement in the TSC severity score approached statistical significance ($P = .06$). Physician and patient assessments significantly ($P \leq .024$) favored treatment with azelastine 2 sprays per nostril twice daily over placebo.

In addition, 3 multicenter, randomized, double-blind studies were conducted to determine whether patients with seasonal allergic rhinitis who had responded inadequately to therapy with either an oral antihistamine or an intranasal steroid and who would be candidates for combination therapy with an oral antihistamine and an intranasal steroid could be effectively treated with azelastine nasal spray monotherapy. A physician global assessment of therapeutic effectiveness demonstrated azelastine nasal spray monotherapy to be as effective as loratadine and beclomethasone in combination in controlling seasonal allergic rhinitis symptoms based on the percentage of patients in each treatment group who responded to therapy. No statistically significant differences were seen in the percentage (32% to 45%) of patients who responded to azelastine nasal spray monotherapy versus the percentage (39% to 46%) of patients who responded to a combination of loratadine and beclomethasone. A patient global evaluation indicated that 77% to 84% of the patients treated with azelastine nasal spray had symptomatic improvement versus 85% to 90% of the patients treated with loratadine and beclomethasone (Berger 1998, submitted to Ann Allergy Asthma Immunol).

European studies

Azelastine nasal spray is currently marketed in Europe at a dosage of 1 spray per nostril twice daily (0.55 mg/d), which is one half the recommended United States dosage. Several European studies compared azelastine nasal spray with commonly used oral antihistamines or nasal steroids in patients with seasonal allergic rhinitis and evaluated its effects on nasal airway obstruction.

Azelastine nasal spray and terfenadine were studied in a randomized double-blind trial in 167 patients during a 6-week treatment period.³³ Statistically significant ($P < .001$) improvements were seen at day 8 and at the end of the 6-week treatment period for the total symptom score in both treatment groups. The mean total symptom score decreased by 45% at day 8 and by 70% at the end of treatment with azelastine and by 43% at day 8 and 72% at the end of treatment with terfenadine. Efficacy was judged by physicians as "very good" for 59% of the patients treated with azelastine and for 46% of the patients treated with terfenadine.

In a randomized double-blind trial 32 patients were treated with azelastine nasal spray or astemizole 10 mg/d during a 2-week study period.³⁴ Physician assessments of efficacy indicated significant improvement with astemizole at week 1 but not week 2, whereas improvement with azelastine was significant at both weeks.

Azelastine nasal spray and loratadine 10 mg/d were compared in 30 patients in a 6-week, randomized, double-blind trial.³⁵ Compared with baseline, the mean total symptom scores for azelastine and loratadine were significantly ($P < .05$) reduced at each of the evaluation periods during treatment. All patients had improvement in their symptoms. The physician global assessment resulted in "good" or "very good" classifications of treatment in 11 of 15 patients in the azelastine group and in 10 of 15 patients in the loratadine group.

Azelastine nasal spray and cetirizine 10 mg/d were compared in a randomized, double-blind, multicenter study in 136 patients during a 2-week study period.³⁶ The total symptom scores improved 47% and 61% for azelastine and 55% and 67% for cetirizine on days 7 and 14, respectively. No statistically significant differences were seen between the 2 treatments.

In 2 well-controlled studies versus nasal steroids, azelastine nasal spray demonstrated positive effects on nasal airway resistance objectively assessed by passive posterior rhinomanometry. In a randomized parallel-group study,³⁷ azelastine nasal spray 2 sprays per nostril twice daily (1.12 mg/d) was studied with budesonide 2 sprays per nostril twice daily (400 µg/d) in 14 patients with seasonal allergic rhinitis. After 2 weeks of treatment both azelastine and budesonide significantly decreased total nasal airway resistance and significantly increased nasal airflow. At the end of a 2-week placebo-controlled study,³⁸ azelastine nasal spray was comparable to beclomethasone in relieving symptoms of seasonal allergic rhinitis including congestion and ocular

symptoms, and both drugs were statistically superior to placebo. In addition, in a placebo-controlled, allergen-provocation study³⁹ in 36 patients with seasonal allergic rhinitis, a single dose of azelastine nasal spray (0.56 mg) significantly inhibited the nasal airway obstruction in response to histamine at 1 and 2 hours after administration.

SAFETY

The most frequently reported adverse events in the clinical trials were headache, somnolence, bitter taste, and nasal burning. These adverse experiences were mostly mild or moderate in severity and did not limit the long-term use of the drug. Most (approximately 75%) of the taste effects were of short duration and were caused by the physical passage of the drug into the oropharynx after intranasal administration. The incidence of somnolence with azelastine nasal spray was 11.5% versus 5.4% with placebo; however, somnolence was reported in 7.7% of patients treated with azelastine compared with 2.6% of patients treated with placebo in the long-term studies, and none of the patients reporting somnolence in the clinical trials dropped out of the study because of that adverse effect. In 3 well-controlled studies (Wallace Laboratories, data on file) to determine to what extent azelastine affects central nervous system performance, oral dosages 2 to 8 times higher than the recommended dosage of azelastine nasal spray caused no significant effects on motor function and performance capacity.

A safety profile similar to that seen in the clinical trials has been observed during the postmarketing period (Wallace Laboratories, data on file).

CONCLUSIONS

Azelastine nasal spray is an effective topical treatment for the symptoms of seasonal allergic rhinitis including nasal congestion and ocular symptoms. Azelastine affects early- and late-phase allergic reactions through interrelated effects on histamine and other mediators of the inflammatory response. Symptomatic improvement was fast and was sustained for 12 hours after a single dose. Azelastine demonstrated anti-inflammatory effects in laboratory animals and in clinical studies in patients with seasonal allergic rhinitis including significant reductions in inflammatory cell migration, mediator levels, and intercellular adhesion molecule-1 expression. Azelastine nasal spray had a relatively low incidence of somnolence (7.7%) associated with its use in long-term studies and did not demonstrate psychomotor impairment even at oral dosages 4 to 8 times the recommended daily dosage of azelastine nasal spray. Azelastine is not associated with drug interactions and the types of adverse cardiac effects that have been reported with terfenadine and astemizole. Azelastine nasal spray can be used as an alternative to oral antihistamines or can be administered concomitantly with topical corticosteroids.

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