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Intranasal Azelastine

A Review of its Efficacy in the Management of Allergic Rhinitis

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Data Selection

Sources: Medical literature published in any language since 1966 on azelastine, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase, Medline and EMBASE search terms were 'azelastine' and 'allergic rhinitis'. Searches were last updated 13th May 1998.

Selection: Studies in patients with allergic rhinitis who received intranasal azelastine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Azelastine, allergic rhinitis, pharmacokinetics, pharmacodynamics, therapeutic use.

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Summary

Abstract

Azelastine, a phthalazinone compound, is a second generation histamine H_1 receptor antagonist which has shown clinical efficacy in relieving the symptoms of allergic rhinitis when administered as either an oral or intranasal formulation. It is thought to improve both the early and late phase symptoms of rhinitis through a combination of antihistaminic, antiallergic and anti-inflammatory mechanisms. Symptom improvements are evident as early as 30 minutes after intranasal administration of azelastine [2 puffs per nostril (0.56mg)] and are apparent for up to 12 hours in patients with seasonal allergic rhinitis (SAR). The effect on nasal blockage is variable: in some studies objective and/or subjective assessment showed a reduction in blockage, whereas in other studies there was no improvement.

Intranasal azelastine 1 puff per nostril twice daily is generally as effective as standard doses of other antihistamine agents including intranasal levocabastine and oral cetirizine, ebastine, loratadine and terfenadine at reducing the overall symptoms of rhinitis. The relative efficacies of azelastine and intranasal corticosteroids (beclomethasone and budesonide) remain unclear. However, overall, the corticosteroids tended to improve rhinitis symptoms to a greater extent than the antihistamine.

Azelastine was well tolerated in clinical trials and postmarketing surveys. The most frequently reported adverse events were bitter taste, application site irritation and rhinitis. The incidence of sedation did not differ significantly between azelastine and placebo recipients and a preliminary report showed cardiovascular parameters were not significantly altered in patients with perennial allergic rhinitis (PAR).

Conclusion: Twice-daily intranasal azelastine offers an effective and well tolerated alternative to other antihistamine agents currently recommended for the symptomatic relief of mild to severe SAR and PAR in adults and children (aged ≥12 years in the US; aged ≥6 years in some European countries including the UK). The rapid onset, confined topical activity and reduced sedation demonstrated by the intranasal formulation of azelastine may offer an advantage over other antihistamine agents, although this has yet to be confirmed.

Rationale for the Development of Intranasal Azelastine

Antihistamine compounds have been in use for the management of allergic rhinitis since the 1940s. The clinical value of the first generation histamine H_1 receptor antagonists, however, was marred by their ability to cross the blood-brain barrier and cause, among other adverse events, sedation. The second generation histamine H_1 receptor antagonists, which include ketotifen, cetirizine, terfenadine, loratadine, ebastine and azelastine, are generally less sedative and have fewer nonspecific effects.

Azelastine is a phthalazinone derivative which binds preferentially to peripheral rather than central receptors; the drug has been used orally to manage the symptoms of bronchial and allergic asthma and allergic rhinitis. Local adminis-

tration via intranasal inhalation serves to further confine the activity of the drug and reduce possible adverse effects brought about by systemic exposure.

Pharmacodynamic Properties

Sneezing caused by histamine nasal challenge was significantly reduced within 1 hour after initial application of azelastine 0.56mg (2 puffs per nostril) in patients and volunteers and it remained so for 10 to 12 hours thereafter. However, the effects of the drug on nasal blockage were varied: some studies showed improvements in either subjectively or objectively assessed nasal blockage, whereas others failed to show any improvements.

After allergen-specific nasal challenge, compared with baseline, single or repeated (twice daily for 2 weeks) administration of azelastine 1 puff per nostril significantly reduced objectively assessed nasal airway resistance (NAR) and increased nasal inspiration peak flowmeter values in patients with seasonal allergic rhinitis (SAR). The effects of azelastine compared with placebo on NAR, however, were varied. In a study which showed single-dose azelastine to have a significant effect compared with placebo, the mean time to onset of this effect was 135 minutes. Both the early (EPR) and late phase reaction (LPR) symptoms of allergen-induced rhinitis were significantly reduced (by up to 30%) in azelastine compared with placebo recipients. Azelastine significantly reduced allergen-induced sneezing within 15 minutes and was active for up to 10 hours.

In addition to its antihistamine and antiallergic effects, azelastine also has anti-inflammatory properties. It reduces EPR and LPR nasal mucosal infiltration of eosinophils and neutrophils by up to 49% after allergen-specific nasal challenge. Levels of a variety of inflammatory mediators were also reduced by azelastine, including nasal eosinophil cationic protein, myeloperoxidase, tryptase and intercellular adhesion molecule-1.

In vitro in human neutrophils, azelastine significantly and concentration-dependently inhibited arachidonic acid release and leukotriene B_4 production. In neutrophils or eosinophils from nonallergic volunteers, stimulated generation of superoxide, a reactive oxygen species, was decreased. Furthermore, azelastine significantly reduced the mobilisation of intracellular calcium in *N*-formyl-methionyl-leucyl-phenylalanine (FMLP)-stimulated neutrophils, a process that precedes superoxide generation.

Results from trials in rodent mast cell preparations suggest that azelastine may also interfere with protein kinase C activity and the release of tumour necrosis factor-α.

In animal models, azelastine has poor access to the CNS. In addition, studies in patients with SAR found that intranasal azelastine generally increased vigilance during the medication period. Intranasal but not oral azelastine reduced the circadian variation in vigilance.

Pharmacokinetic Properties

Pharmacokinetic data for intranasal azelastine are scarce. Maximum plasma concentrations of azelastine were achieved approximately 2.5 hours after intranasal administration. After daily intranasal azelastine 0.56mg, mean steady-state plasma concentrations of the drug were about 0.26 μg/L in healthy volunteers and about 0.65 μg/L in patients; the estimated systemic exposure to the drug was 6- to 8-fold lower than that with oral azelastine 4.4mg. The systemic bioavailability after intranasal administration was approximately 40%. Azelastine is metabolised by the cytochrome P450 enzyme system to its major active metabolite desmethylazelastine. At steady state, the plasma metabolite concentration accounted for 20 to 50% of the azelastine concentration.

Therapeutic Efficacy

In adults and children aged ≥5 years with SAR or perennial allergic rhinitis (PAR), azelastine 1 or 2 puffs per nostril (0.28 or 0.56mg) twice daily over periods of 30 hours to ≥6 months, compared with baseline or placebo, significantly improved rhinitis symptoms including rhinorrhoea, itchy nose, sneezing, watery eyes, itchy eyes, ears or throat and postnasal drip. Compared with placebo, azelastine (2 puffs per nostril) significantly improved baseline rhinitis symptoms as early as 3 hours after drug administration in patients with SAR; significant improvement was apparent for up to 12 hours after initial use. Patient and physician global assessment of treatment with azelastine (1 or 2 puffs per nostril twice daily) of at least 'good' was similar and ranged from 75 to 86%.

Azelastine had varied effects on nasal blockage in clinical trials; some studies showed a significant improvement in azelastine compared with placebo recipients, whereas others found no significant effects.

In children (aged ≤12 years) with allergic rhinitis, azelastine 1 puff per nostril twice daily compared with placebo for up to 6 weeks significantly improved rhinitis symptoms. In a postmarketing survey in children aged 3 to 12 years, 85% of physicians evaluated the efficacy of azelastine as 'good'/'very good'. Rhinoscopic evaluation in children (aged 7 to 16 years) with PAR revealed significant improvement in nasal secretion, oedema and inflammation after 6 weeks' therapy with intranasal azelastine (0.6 mg/day); these symptoms were further improved in the 62 children who completed 6 months' treatment.

Intranasal azelastine as an adjunct to oral azelastine therapy further improves rhinitis symptoms compared with the effects of oral therapy alone in patients with SAR.

In comparative studies, azelastine 1 puff per nostril twice daily was generally as effective at reducing the overall symptoms of rhinitis as the standard doses of other antihistamine agents including intranasal levocabastine and oral cetirizine, ebastine, loratadine and terfenadine.

Symptom relief within 30 minutes of initial drug administration occurred in similar numbers of patients receiving azelastine (1 puff per nostril) or levocabastine (2 puffs per nostril); the effect was maintained for up to 8 hours after initial drug administration in both groups. Each drug improved nasal congestion by about 48% and ocular symptoms by about 66% from baseline after 1 week of twice-daily administration.

Results from studies that compared the effects of azelastine 1 puff per nostril twice daily and intranasal corticosteroids on the symptoms of rhinitis were varied, but overall, the corticosteroids appeared more effective. A significantly more rapid overall symptom relief was achieved in azelastine compared with beclomethasone recipients in 1 study, but after 2 weeks' therapy, improvements in overall symptom scores were significantly greater in the beclomethasone recipients. Both beclomethasone and budesonide were superior to azelastine at reducing the nasal symptoms of rhinitis in some studies, whereas others found no statistically significant difference between treatments. Budesonide was associated with greater improvements in nasal blockage than azelastine, although these did not reach statistical significance. In addition, patients' global assessments of 'substantial' or 'total' control of symptoms were significantly more common with budesonide (0.256mg once daily) than with azelastine (0.28mg twice daily) in a double-blind study (70.4 *vs* 44.7%).

Tolerability

Results from postmarketing surveys in 7682 patients aged 3 to 85 years with

allergic rhinitis who received azelastine 1 puff per nostril twice daily for up to 1 month showed the drug to be generally well tolerated. When azelastine was given alone, approximately 8% of patients reported adverse events; when it was given in combination with other antihistamines and/or topical corticosteroids the incidence of adverse events was approximately 20%. Bitter taste and rhinitis were the most frequently reported adverse events.

Where stated in clinical trials, physician and/or patient global assessment of tolerability was at least 'good' in more than 70% of patients (adults and children aged ≥7 years) receiving azelastine (typically 1 puff per nostril twice daily). Indeed, >90% of 35 azelastine recipients assessed tolerability as at least 'good' during a 21-month period of medication.

The most frequently reported adverse events were mild, transient bitter taste (associated with the taste of the drug) and application site irritation. Sedation did not differ significantly in azelastine or placebo recipients. Indeed, some study reports remarked on its absence and 1 trial reported an improvement in overall vigilance during a 2-week medication period.

Treatment withdrawal because of drug-related adverse events was rare (1 to 3 patients per study; ≤7%); reasons for withdrawal included mild increased nasal pruritus, nasal congestion, nausea and vomiting, dizziness and increased blood pressure.

No significant changes in PR, QS, QT or QT_c intervals were observed in patients with PAR who were randomised to receive azelastine (2 puffs per nostril) or placebo twice daily for 8 weeks. In addition, there were no changes in mean heart rate or blood pressure in any patient.

Dosage and Administration

The US prescribing recommendations specify 2 puffs per nostril of azelastine nasal spray twice daily for adults and children aged ≥12 years; each puff delivers approximately 0.14mg of the drug. In the UK and a number of other European countries, azelastine is approved as 1 puff per nostril twice daily for adults and children aged ≥6 years.

Although somnolence is rare, the US prescribing information carries a caution regarding use of the medication and driving or operating potentially dangerous machinery. Concurrent use of alcohol and/or other CNS suppressants should be avoided.

1. Rationale for the Development of Intranasal Azelastine

The use of antihistamine compounds in the management of allergic rhinitis is not new; they have been in use since the 1940s. However, the clinical value of the classical or first generation histamine H_1 receptor antagonists was marred by their ability to cross the blood-brain barrier and cause sedation (resulting from CNS depression) and a number of nonspecific events (resulting from blockade of muscarinic-cholinergic, α-adrenergic and serotonergic receptors).[1] The newer, or second generation histamine H_1 receptor antagonists, which include ketotifen, cetirizine, terfenadine, loratadine, ebastine and azelastine, are generally less sedative and have fewer nonspecific effects.

Azelastine is a phthalazinone derivative which, like many of the second generation H_1-receptor antagonists, binds preferentially to peripheral rather than central receptors.[2] Local administration via intranasal inhalation serves to further confine the activity of the drug and reduce possible adverse effects brought about by systemic exposure.

Oral azelastine has been extensively used to manage the symptoms of bronchial and allergic asthma and allergic rhinitis.[3] This review focuses

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