ORIGINAL ARTICLE

Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy

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ABSTRACT

Objective: To assess the efficacy and onset of action of azelastine nasal spray and desloratadine tablets in patients with pollen-induced seasonal allergic rhinitis (SAR).

Research design and methods: 46 adult patients with a history of SAR were exposed to a controlled grass pollen concentration for 6 h in the Vienna Challenge Chamber (VCC) in each treatment period according to a randomized, double-blind (double-dummy), three-period, three-sequence crossover design (wash-out period of 12 days). Single doses of study medication (one puff nasal spray into each nostril of azelastine, 0.28 mg, or placebo before swallowing one encapsulated tablet of desloratadine, 5 mg) were administered 2 h after the start of the allergen challenge. Results of subjective and objective assessments were recorded throughout the challenge.

Results: Efficacy of azelastine nasal spray was significantly superior compared to desloratadine tablets (p = 0.005) and placebo (p < 0.001). Desloratadine was significantly better than placebo (p < 0.001). Decrease both in Major Nasal Symptom Score (MNSS) and in Total Nasal Symptom Score (TNSS) was fastest after azelastine treatment. Improvement of nasal symptom severity was most pronounced after azelastine treatment for all nasal symptoms including nasal congestion. Onset of action was 15 min for azelastine compared to 150 min for desloratadine. Both active preparations were safe and well tolerated.

Conclusions: This study confirms the usefulness of azelastine nasal spray for the symptomatic treatment of seasonal allergic rhinitis. Concerning onset of action in particular, the results favour the topical treatment over systemic therapy.

Introduction

Allergic rhinitis is a common disorder world-wide causing considerable economic burden. It is mostly precipitated by seasonal or perennial allergens and presents with symptoms such as rhinorrhea, sneezing, itching of the nose and oropharyngeal palate and nasal congestion. Current thinking describes allergic rhinitis and asthma...
as a continuum of inflammation displacing historic understanding of both diseases as separate entities. Thus, treatment improves symptoms of seasonal allergic rhinitis (SAR) and might, in addition, reduce the prevalence of bronchial asthma. First approaches in prevention and treatment of allergic diseases are identification and avoidance of contact with the causative allergen. As these first steps often remain unsuccessful, physicians try to achieve improvement of symptoms with lavage-type products or nasal moisturisers and sympathomimetics/decongestants, and by prescribing anti-allergic and anti-inflammatory drugs (antihistamines, mast-cell stabilisers, corticosteroids). Antihistamines are selective antagonists of the H1-receptor, such as azelastine nasal spray and desloratadine tablets. Azelastine nasal spray has been marketed for many years in most European countries and in the United States. New compounds, sometimes called ‘third-generation antihistamines’, including desloratadine, are further pharmacological developments of second-generation antihistamines. In contrast to antihistamines of earlier generations they are believed to noticeably reduce nasal congestion, are non-sedating and do not cause cardiac side effects.

The present study was conducted to assess the efficacy and onset of action of azelastine nasal spray in the treatment of SAR compared to desloratadine tablets and placebo. Natural exposure to Aero-allergens is subject to extreme regional and chronological fluctuations. Ideally, patients need to be continuously exposed to a specific allergen over a period of several hours to quantify exactly the therapeutic response to an anti-allergic treatment or to assess its onset of action. The Vienna Challenge Chamber (VCC) is a self-contained, air-conditioned system, in which Aero-allergenic content is dispersed homogenously and is continuously controlled, allowing changes in the pathophysiology of the respiratory tract to be monitored during a more physiological type of exposure. In the current study, symptoms of SAR were induced by allergen challenge in the VCC with controlled pollen exposure over time. Environmental exposure units are widely used and are ethically accepted.

**Patients and methods**

**Patients.**

Suitable patients were 18-55 years old, had a documented SAR to grass pollen with a clinical history of at least 2 years, a positive response to cutaneous skin test (allergen induced wheal of a diameter at least 3 mm larger than that for diluent control), and to radioallergosorbent-test (RAST) at least class 2. Patients had to demonstrate a Major Nasal Symptom Score (MNSS) of at least 4 score points (for definition see Criteria for Evaluation) during the last three pre-treatment assessments of the allergen challenge during the first treatment period. Patients with allergy to one of the study medications or their ingredients, with relevant concomitant diseases or acute illnesses (within 7 days prior to screening) including polyposis nasi, sinusitis, any kind of non-allergic rhinitis or asthma, or malignancy within the last 5 years, neurological or psychiatric diseases including drug or alcohol abuse were excluded, as well as pregnant or lactating females. Prohibited therapies included decongestants or immunotherapy within 24 h, antihistamines, theophylline, or systemic antibiotics within 1 week, topical corticosteroids or anti-depressants within 2 weeks, inhaled, oral or intravenous corticosteroids within 4 weeks and intramuscular or intra-articular corticosteroids within 12 weeks prior to screening. Study protocol and informed consent were reviewed and approved by an independent ethics committee. Written informed consent was obtained from each patient prior to all screening procedures.

The study was conducted in accordance with the Declaration of Helsinki (Somerset West Amendment, 1996) and the ICH Guideline on Good Clinical Practice (Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95, 17 January 1997).

**Design/methodology of the study.**

This was a randomised, placebo-controlled, double-blind, single centre, three-period, three-sequence crossover study conducted in October–November. Patients received the following treatments: one puff azelastine into each nostril plus one placebo tablet; or one puff placebo into each nostril plus one desloratadine tablet (5 mg); or one puff placebo into each nostril plus one placebo tablet. Patients administered one puff of either azelastine nasal spray or placebo nasal spray before swallowing one desloratadine or placebo tablet. The desloratadine and the placebo tablets were encapsulated for blinding appearance (double-dummy). Earlier tests for release of the desloratadine tablet from the capsule showed a delay of 15-30 min (60% of the drug released at the 15 min time point, 100% at the 30 min time point). Each treatment period consisted of an allergen challenge followed by a wash-out period of at least 12 days. Patients were exposed to a stable and controlled concentration of grass pollen in the VCC for 6 h. Two hours after the start of the challenge, all eligible patients received a single dose of the randomised study medication. They were instructed to administer one puff of either azelastine (0.28 mg) or placebo nasal spray into each nostril before swallowing one encapsulated tablet desloratadine (5 mg) or placebo. The correct administration of the study medication was supervised by authorised study personnel. The allergen challenge
was then continued for another 4 h. Depending on the severity of symptoms, patients stayed in a pollen-free area for another hour after the end of the challenge for safety monitoring.

Assessments

Vital signs were taken before and after the allergen challenge. Urinary pregnancy tests were done at screening and repeated every 28 days after the previous test (for female patients of childbearing potential only). Patients recorded nasal (rhinorrhea, sneezing, nasal congestion, nasal itching) and non-nasal (eye itching, eye tearing, ear/palate itching) symptoms before the start of the allergen challenge and every 15 min during the challenge. For symptom assessments, a four-point rating scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) was used. Measurements of nasal secretion (weighting of paper tissues) were done every 30 min during the allergen challenge. An overall assessment of treatment efficacy (scores: very good/good, satisfactory, insufficient, not assessable) was completed by the investigator at the end of each treatment period. For safety reasons, lung function was monitored by measuring forced expiratory lung volume in 1 s (FEV1) before challenge and every 60 min during the challenge. Additionally, peak expiratory flow (PEF) rates were measured by the patients using peak flow metres (before the challenge, approximately 1 h after the challenge, and then every 2 h until approximately 8 h after the start of the challenge). Patients recorded measured PEF rates, occurrence of adverse events, and use of concomitant medication on provided diary cards. Procedures were identical for all three treatment periods. The investigator contacted the patients within 2 days after the last treatment period to assess occurrence or, if applicable, persistence of adverse events, which he then adequately treated and followed up.

Rescue medication

To alleviate asthma symptoms possibly occurring due to the allergen challenge, patients were provided with albuterol sulfate (Sultanol N, GlaxoSmithKline, GmbH & Co., Bad Oldesloe, Germany) as needed.

Criteria for evaluation

The main criterion for evaluation was the average MNSS during the last 2 h of the allergen challenge (4–6 h of challenge), defined as the sum of the scores of sneezing, rhinorrhea and nasal itching. A second sum score, the Total Nasal Symptom Score (TNSS), comprised additionally nasal congestion. All four symptoms were based on subjective assessment. Nasal congestion was evaluated separately to assess the specific efficacy of azelastine nasal spray on this symptom.

Vienna Challenge Chamber (VCC)

The VCC is a validated environmental exposure unit, allowing allergen challenges under reproducible conditions. Allergen concentration and physical conditions (temperature, relative humidity, CO₂-content) are closely monitored. Patients are under constant supervision by the study staff outside with communication being possible at any time. The chamber is charged with cleaned, cooled and dry indoor air and loaded with a defined amount of pollen. In the present study, pollen concentration was maintained stable at about 1500 pollen grains (equal amounts of Dactylis glomerata, Lolium perenne and Pletum pratense) per cubic metre of air. Relative humidity was kept constant at 35%, temperature at 24°C. These conditions resembled those found outdoors on a typical warm summer day.

Statistical analysis

Based on a previous publication, approximately 40 patients were needed for analysis. Sixty patients were planned to be randomised assuming a drop-out rate of 33%. P-values ≤ 0.05 were regarded as statistically significant.

All statistical analyses were performed using the programme SAS 8.2. The primary variable was the average MNSS change over the last 2 h of allergen challenge (4–6 h of challenge), calculated as the difference between the mean MNSS over the last 2 h of the challenge and the baseline MNSS (maximum of the last three pre-treatment assessments at 90, 105 and 120 min after the start of the challenge). For calculation of second variables, average TNSS and average nasal secretions change during the last 2 h of allergen challenge, the same approach as for calculation of MNSS was used (for nasal secretions, i.e. the baseline value was defined as the maximum of over the last two measurements before dosing at 90 and 120 min after the start of the challenge). For each time point, explorative tests were calculated for the MNSS versus placebo. The onset of action was defined as the first time point at which a statistically significant difference between azelastine (or desloratadine) and placebo was observed and maintained until the next consecutive time point. The primary variable was confirmatorily analysed by a paired t-test (two-sided, α = 0.05) and two-sided 95%-confidence intervals were calculated. As a sensitivity analysis, a Wilcoxon signed-rank test was calculated in addition. Descriptive statistics were calculated for the sum scores (MNSS, TNSS) for the total 6 h challenge period as well as for the last 2 h for TNSS and nasal
secretion. All symptoms were described for each time point with their frequency distribution as well as with a location parameter (mean).

Results

A total of 46 patients participated, 45 of these completed the study regularly (3 treatment sequences with 15 patients each) and were fully evaluated. One patient discontinued the study due to acute sinusitis. No statistically significant differences emerged between any of the randomised groups at baseline (Table 1).

The time course of MNSS is presented in Figure 1. During the first 2 h of allergen exposure, MNSS values increased comparably in all three groups. After administration of the study medication, MNSS values decreased in all groups with the most pronounced effect following azelastine treatment (Figure 2).

Confirmatory analysis of the MNSS 4–6 h mean change indicated that azelastine was significantly superior to placebo (p < 0.001) as well as to desloratadine (p = 0.005). Desloratadine was superior to placebo (p < 0.001) (Table 2).

The above mentioned results were consistent for all three treatment sequences and for each period. There was no evidence for carry-over effects.

The results for TNSS and nasal secretion 4–6 h mean change were consistent with those for MNSS. Onset of action was seen at 15 min after dosing for azelastine and at 150 min for desloratadine (Table 3).

The decrease of the sum scores MNSS and TNSS is explained by a decrease of all nasal symptoms. The largest improvement with azelastine was observed for nasal itching (1.46) followed by sneezing (1.41), rhinorhoea (1.05), and nasal congestion (0.74) (Figure 2).

Regarding non-nasal symptoms, the decrease of eye itching and eye tearing was comparable for azelastine and

<table>
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<tr>
<th>Variable</th>
<th>PLA/AZE/DES</th>
<th>AZE/DES/PLA</th>
<th>DES/PLA/AZE</th>
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<td>16</td>
<td>15</td>
<td>46</td>
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<td>Ethnic group, Caucasian n (%)</td>
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<td>16 (100)</td>
<td>15 (100)</td>
<td>46 (100)</td>
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<td>5 (31)</td>
<td>8 (52)</td>
<td>19 (41)</td>
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<td>7 (47)</td>
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<td>BMI (kg/m²) mean (range)</td>
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<td>23 (18–29)</td>
<td>22 (19–26)</td>
<td>22 (18–29)</td>
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PLA – placebo; AZE – azelastine; DES – desloratadine; BMI – body mass index

Figure 1. Major Nasal Symptom Scores averaged over treatment and time for the per protocol population (vertical line at 120 min marks the study drug administration)
desloratadine. Both substances were superior to placebo.

The effect of azelastine and desloratadine on ear/palate itching was comparable to that of placebo (data not presented). However, this symptom score was very low.

The overall assessment of efficacy also indicated a superiority of azelastine in comparison to placebo and desloratadine with at least ‘satisfactory’ results for 73.9% of patients compared to 55.6% for desloratadine and 24.4% for placebo.

As for safety results, a total of six adverse events occurred. Two of them (allergen-induced bronchospasm after treatment with desloratadine and decreased lung function after treatment with azelastine) were treatment emergent (i.e. occurred within 3 days after administration of the study medication). All adverse events were of mild intensity, short duration and patients recovered completely. None of the patients used rescue medication. Variables for monitoring of potential provocation effects such as vital signs and lung function measurements (FEV, and PEF) showed no clinically relevant findings.

**Discussion**

The present study was the first one to compare the efficacy and onset of action of the antihistaminic agent azelastine nasal spray to those of the so called ‘third generation’ antihistaminic agent desloratadine tablets. The results for the primary variable of efficacy (average MNSS during the last 2 h of allergen challenge, i.e. 4–6 h after the start of the challenge) indicated that azelastine nasal spray was significantly superior to placebo (p < 0.001) as well as to desloratadine tablets (p = 0.005) in reducing symptoms of SAR induced by allergen challenge in the VCC. Desloratadine tablets were superior to placebo (p < 0.001).

In order to exclude the effect of the mechanic action of nasal sprays (pollen causing symptoms of SAR are prone to be washed away shortly after dosing), the primary variable of efficacy (MNSS 4–6 h) was calculated for the last 2 h of the allergen challenge (i.e. 4–6 h after the start of the challenge). Thus, a break of 2 h was ensured between dosing and calculation of MNSS.
<table>
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<th>AZE-FLA</th>
<th>DES-FLA</th>
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<td>p-value paired t-test</td>
<td>Mean ± SD</td>
<td>p-value paired t-test</td>
</tr>
<tr>
<td>15</td>
<td>-0.5 ± 1.3</td>
<td>0.015**</td>
<td>0.02 ± 1.8</td>
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<tr>
<td>30</td>
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<td>&lt; 0.001***</td>
<td>-0.3 ± 2.2</td>
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<td>45</td>
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<td>&lt; 0.001***</td>
<td>-0.6 ± 2.3</td>
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<td>-0.4 ± 2.4</td>
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<td>75</td>
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<td>&lt; 0.001***</td>
<td>-0.3 ± 2.4</td>
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<td>90</td>
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<td>&lt; 0.001***</td>
<td>-0.3 ± 3.0</td>
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<td>105</td>
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<td>&lt; 0.001***</td>
<td>-0.5 ± 2.5</td>
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<tr>
<td>120</td>
<td>-1.8 ± 2.3</td>
<td>&lt; 0.001***</td>
<td>-0.4 ± 2.8</td>
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<tr>
<td>135</td>
<td>-1.7 ± 2.0</td>
<td>&lt; 0.001***</td>
<td>-0.4 ± 2.9</td>
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<td>&lt; 0.001***</td>
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<tr>
<td>240</td>
<td>-2.3 ± 2.5</td>
<td>&lt; 0.001***</td>
<td>-1.6 ± 2.6</td>
</tr>
</tbody>
</table>

PLA = placebo; AZE = azelastine; DES = desloratadine; PP = per protocol; MNSS = Major Nasal Symptom Score

The method of controlled doses of pollen in an allergen challenge chamber (such as the VCC) to induce symptoms of SAR in previously sensitised patients is well explored and established for studies assessing treatment effects of anti-allergic medication. The advantage of such an artificial setting is the induction of an acute disease pattern with a well controllable allergic reaction. Symptom evaluation is possible by subjective and objective methods in short intervals. Symptoms are expected to suspend within hours after the end of the allergen challenge. Significant results can be obtained with limited exposure to medication and in smaller numbers of patients. The safety of the method in this study was emphasised by the small number of adverse events and the absence of the use of rescue medication.

Scores for all assessments taken after administration of the study medication for patients treated with azelastine were lower than scores for patients treated with placebo or desloratadine (time course of MNSS, Figure 1). Results for TNSS, the amount of nasal secretion and the analyses of all individual nasal and non-nasal symptoms were consistent with those obtained for the MNSS. The results of the overall assessment of efficacy supported the findings of subjective symptom scores (nasal and non-nasal symptoms) and objective measurements (nasal secretion).

Regarding the individual nasal symptom 'nasal congestion', azelastine was shown to be superior to desloratadine when comparing absolute scores at the end of the challenge (i.e. 4 h after dosing) to values at the time of dosing. Furthermore, results for TNSS which differed from MNSS only by inclusion of 'nasal congestion' were significantly superior for azelastine. These results were surprising since up to date second-generation antihistamines have been found to have little decongestant activity whereas reduction of nasal congestion is mentioned as one of the principal clinical advantages of third-generation antihistamines. For azelastine nasal spray, significant decongestant activity was seen in previous studies only when using higher doses of the medication (2 puffs per nostril, total dose 560 µg). It should be considered, however, that the effect of azelastine nasal spray on 'nasal congestion' observed in this study is based on subjective assessments (TNSS defined as the sum of the scores of all four nasal symptoms recorded by the patients). For objective confirmation, future studies should include measurements of nasal flow or nasal resistance.

Concerning the onset of action, the current results demonstrated an onset of action of 15 min for azelastine nasal spray and of 150 min for desloratadine tablets. They confirmed the well-known capability of azelastine nasal spray to quickly and efficiently treat symptoms of SAR. This capability constitutes a major reason for the drug being part of the recommendations for the stepwise approach to the management of SAR. The known onset of action of 15 min for azelastine nasal spray is well in line with a former investigation. However, this finding was influenced by the time intervals chosen between recordings of the symptom scores: in this study, MNSS served as the primary variable for the calculation of the onset of action. It was assessed by the patients every 15 min during the allergen challenge. An onset of action
faster than 15 min could thus not be detected. Regarding desloratadine tablets, the onset of action was notably later than described in other clinical studies. One explanation constitutes the encapsulation of desloratadine tablets for the purpose of blinding. However, the delay for release of the desloratadine tablet from the capsule (15-30 min) is small and not sufficient to adequately explain the late onset of action found in this study. Another explanation might be found in the different methodology of our study: in order to better reflect the natural situation, symptoms of SARS were allowed to develop for 2 h before the study medication was administered. Other investigators mostly started the allergen challenge at a particular time point after administration of the study medication. Finally, the pronounced placebo effect immediately after the use of the drug is probably due to the mechanic action of the placebo nasal spray and one more factor holding up the relative onset of action of an active drug.

Both active preparations showed an excellent safety and tolerability profile as supported by the small number of adverse events.

Conclusion

In conclusion, we have demonstrated that azelastine nasal spray is significantly better than desloratadine tablets and placebo in reducing symptoms of seasonal allergic rhinitis including "nasal congestion" induced by allergen challenge in the Vienna Challenge Chamber. Both active preparations were shown to be safe and well tolerated. Concerning onset of action in particular, the results favour the topical treatment over systemic therapy with H-1-antihistamines and confirm the clinical usefulness of azelastine nasal spray in the symptomatic treatment of seasonal allergic rhinitis.

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References