Azelastine in Pollen-Induced Allergic Rhinitis
A Pharmacodynamic Study of Onset of Action and Efficacy

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Summary
The manifestation of rhinitic symptoms in 9 patients with grass pollen-induced rhinitis was studied during long term allergen exposure at physiological concentrations in the ‘Vienna Challenge Chamber’. Patients were pretreated with a single dose of azelastine (either 2.2mg orally or 0.28mg intranasally) or placebo. Nasal resistance was estimated by active anterior rhinomanometry every 15 minutes. Analysis of changes in nasal Airways resistance demonstrated significant protection against allergen-induced nasal obstruction (p<0.01) for azelastine administered by either route. The onset of action of treatment in relation to nasal obstruction was significantly more rapid for the nasal spray (135 minutes) than for the tablet (205 minutes) [p<0.01] formulation. Similarly, the onset of effect derived from subjective assessment of symptom severity was markedly more rapid (60 minutes) after intranasal azelastine than after administration of the oral form (120 minutes). Tolerability of azelastine was good, with no side effects reported with either oral or intranasal therapy.

Azelastine is a phthalazinone derivative that not only possesses potent histamine H1-receptor blocking activity (Casale 1989; Zechel et al. 1981), but also inhibits the release of several mediators involved in the pathogenesis of allergic respiratory disease (Achternath-Tuckermann et al. 1988; Chand et al. 1985). Oral azelastine 1.1 to 2.2mg twice daily has been found to be effective in the treatment of both seasonal (Weiler et al. 1988) and perennial (Meltzer et al. 1988) allergic rhinitis, with an onset of action as early as 2 hours after dosing. Indeed, when compared with terfenadine 60mg twice daily, azelastine 1.1mg twice daily for 6 weeks has been shown to be equivalent, and a dose of 2.2mg twice daily was superior in terms of both efficacy and safety (Lenhard & Gerhardt 1988).

Because allergic rhinitis is predominantly associated with nasal symptoms, it is logical to administer treatment intranasally for a rapid and localised effect. A nasal spray delivering azelastine 0.14mg in aqueous solution per actuation has been developed, and is currently being used in both seasonal and perennial rhinitis. The aim of the present study was to evaluate and compare the onset of effect and protective efficacy of orally administered azelastine, intranasal azelastine and placebo against rhinitis symptoms experienced during continuous exposure to physiological concentrations of inhalant allergens.

Methods
Patients

Nine patients, 4 females and 5 males, with a mean age of 24.8 (range 21 to 31) years and with a 2-year or more history of seasonal allergic rhinitis caused by grass pollen, were studied. The diagno-
sis of grass pollen allergy was confirmed in all cases by positive skin prick testing, nasal challenge and radioallergosorbent test (RAST) class 3 or 4 to grass pollen allergen (g3). The study was performed prior to the onset of the grass pollen season, when all patients were asymptomatic. Patients with perennial rhinitis, polyposis, vasomotor rhinitis or asthma were excluded from the study, as were those currently undergoing hyposensitisation. No concomitant medication other than the contraceptive pill was allowed throughout the study period.

All patients were required to give written, informed consent to participate in the study. The study was approved by the Ethics Committee associated with the Medical Faculty of the University of Vienna and was carried out in accordance with the requirements of the Declaration of Helsinki.

Study Design

The study was conducted as a randomised double-blind/open crossover trial. The double-blindness was in relation to the comparison of azelastine nasal spray and placebo nasal spray only because the topically used formulation was of primary interest. The comparison between azelastine nasal spray and tablets was conducted in an open manner only. Each patient was randomly allocated to receive a single dose of one of each of the test medications within the 3 different study days, separated by a washout period of 2 weeks. Nasal spray preparations were presented as pump aerosol sprays releasing 0.14ml per actuation and containing either azelastine HCl 0.1% aqueous solution (i.e. 0.14mg per spray) or placebo. The dose of azelastine was 1 spray per nostril (0.28mg total). Azelastine and placebo aerosols were visually indistinguishable to ensure blind comparison. Azelastine tablets contained 2.2mg azelastine HCl. All medications were administered 15 minutes prior to allergen exposure.

Allergen Exposure

Natural exposure to aeroallergens is subject to extreme regional and chronological fluctuations. Experimentally, challenge tests usually consist of short exposures to allergen solutions, or aerosols, in concentrations often in excess of those normally experienced. As a result, many challenges make it difficult to quantify exactly the therapeutic response to an antiallergic treatment or to calculate the onset of action of a medication under natural conditions. Ideally, patients need to be continuously exposed to a specific allergen over a period of several hours at concentrations mimicking natural exposure. The Vienna Challenge Chamber (VCC) [Horak & Jüger 1987] is a self-contained, air-conditioned system where aeroallergenic content is dispersed homogeneously and continuously controlled, allowing changes in the pathophysiology of the respiratory tract to be monitored during a more physiological type of exposure.

On each of the 3 investigative days all 9 patients were exposed simultaneously to continuous challenge with grass pollen (1000 pollen grains per m³ air) in the VCC for a period of 4 hours. Measures of efficacy (see below) were recorded in the morning, just prior to medication, and 15 minutes after administration of medication, at which point allergen exposure was commenced. Further measurements were conducted every 15 minutes throughout the 4-hour exposure (i.e. for a total of 255 minutes after administration of study treatment). The only exception to this schedule was the measurement of nasal secretion, which was estimated every 30 minutes during the study period.

![Graph](image)

**Fig. 1.** Change in total airway resistance (ΔṘaw) at 150Pa (Pa/s/ml) during long term challenge, following premedication with placebo, oral azelastine 2.2mg or intranasal azelastine 0.28mg.
Assessment of Efficacy/Onset of Effect

Objective Measurements

Nasal resistance, $R_{nas}$ (cm H$_2$O/ml · sec), and nasal flow, $F_{nas}$ (ml/sec) were measured by computerised active anterior rhinomanometry. Recordings were obtained at several pressure differences (75, 150, 300Pa) between anterior and posterior nares. The target variable was the change from baseline in total nasal airways resistance at a pressure difference of 150Pa. The weight of nasal secretions produced over the previous 30 minutes was recorded at 9 time-points during the study period. In addition to the above, the effect of allergen exposure on the lower respiratory tract was monitored by recordings of peak expiratory flow rates (PEFR).

Subjective Symptom Scores

At each time-point patients were asked to score respiratory and ocular symptoms according to a 4-point scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Symptoms scored were sneezing, rhinorhoea, nasal itching, nasal obstruction, itching of the eyes, lacrimation and bronchial obstruction. An overall assessment of rhinitic symptoms was also recorded by means of a 10cm visual analogue scale (VAS).

Assessment of Tolerability

Patients were interviewed regarding adverse events during each of the 3 trial sessions. Adverse events were monitored by recording all complaints, including intercurrent diseases and accidents (but excluding pre-existing conditions) occurring on each study day.

Statistical Analysis

A baseline correction was conducted for the target variable, $R_{nas}$, at 150Pa. To obtain a far-reaching, unlimited measure of the total changes during pollen exposure and hence of the therapeutic efficacy of azelastine, the areas under the time curves (0 to 255 minutes and 180 to 255 minutes) were calculated using linear trapezoidal rules. The earliest point in time after commencement of the challenge period at which a 20% difference in nasal resistance occurred between the study drug and the placebo was generously considered to be the point of ‘onset of effect’. This judgement was necessarily designed under the auspices of no available existing precise definition of ‘onset of effect’ of an active drug.

Statistical comparison of objective data ($R_{nas}$, $F_{nas}$) was by means of crossover analysis of variance and the Wilcoxon pairs test. The significance level required for rejection of the null hypothesis was $\alpha = 0.05$. Because of the small number of patients studied, statistical analyses of subjective symptoms must be considered as descriptive only. Significance levels of subjective symptoms may therefore be misleading and have not been quoted.

Results

Objective Measurements

Changes in total nasal airways resistance from baseline are shown in figure 1. A statistical comparison of baseline and final values as well as a comparison of AUCs (0 to 255 minutes and 180 to 255 minutes) show a significant difference between the study drug and placebo ($p < 0.01$; crossover analysis of variance, Wilcoxon test).
though the nasal spray was numerically superior to the oral formulation, no significant difference in efficacy between the 2 formulations could be identified.

Table I shows the time to onset of effect after administration of medication, which was significantly more rapid (135 minutes) for azelastine nasal spray than for azelastine tablets (205 minutes) [p < 0.01; Wilcoxon test]. There was no measurable onset of effect following premedication with placebo, as the nasal resistance curve showed a continual deterioration throughout the period of allergen exposure. Results at other pressure differences between anterior and posterior nasal cavities showed a similar pattern of results to that obtained for the target variable, as did recordings of nasal flow rates.

Mean weights of nasal secretions produced at 30-minute intervals during allergen exposure are recorded in Table II. There was a trend towards decreased amounts of secretion produced following premedication with both intranasal and oral azelastine, which was especially marked in the later stages of pollen exposure (195 to 255 minutes) after drug administration. However, no significant difference between treatments could be identified at any time-point.

There were no significant mean changes in PEFRs during the study in any of the 3 treatment groups. Only 1 patient consistently reported a subjective sensation of bronchial constriction, which occurred during all allergen exposures irrespective of pretreatment. This was confirmed by PEFR recordings, which showed a fall of 29%, from 580 L/min to a minimum of 410 L/min following placebo pretreatment, a fall of 15% (620 to 530 L/min) with azelastine nasal spray and 17% (600 to 500 L/min) following oral azelastine.

Subjective Symptom Scores

Figure 2 shows the results of subjective symptom scores throughout the period of allergen exposure. Scores are presented as means of the sum of the totals for combined nasal and ocular symptoms. The onset of effect of azelastine with respect to symptom control appears to occur earlier than the recorded effect on nasal patency, being 60 minutes for the nasal spray and 120 minutes for the orally administered drug. Again, no ‘onset of effect’ could be identified following placebo. This is also true when ‘sneezing’ is considered as an isolated symptom, when the onset of effect is even more rapid, being 30 minutes for intranasal application and 60 minutes for azelastine tablets (fig. 3).

Results of VAS scales of overall rhinitic symptoms (not illustrated) followed a pattern that was almost identical to that for the sum of scores of the individual symptoms.

<table>
<thead>
<tr>
<th>Time after drug administration (min)</th>
<th>Placebo</th>
<th>Weight of nasal secretions (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>azelastine nasal spray</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>0.02 ± 0.03</td>
</tr>
<tr>
<td>45</td>
<td></td>
<td>1.58 ± 0.79</td>
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<tr>
<td>75</td>
<td></td>
<td>1.81 ± 0.58</td>
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<tr>
<td>105</td>
<td></td>
<td>1.32 ± 0.39</td>
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<tr>
<td>135</td>
<td></td>
<td>1.19 ± 0.34</td>
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<tr>
<td>165</td>
<td></td>
<td>0.89 ± 0.29</td>
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<tr>
<td>195</td>
<td></td>
<td>2.04 ± 0.70</td>
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<tr>
<td>225</td>
<td></td>
<td>1.73 ± 0.62</td>
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<tr>
<td>255</td>
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<td>1.43 ± 0.44</td>
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</table>
There were no significant differences in efficacy between intranasally and orally administered azelastine. Both formulations inhibited the pollen-induced rise in nasal airways resistance and the expression of rhinitic symptoms.

The finding that the allergen-induced rise in total nasal airways resistance could be inhibited by azelastine is of particular interest. There are controversial findings in other compounds (Corrado et al. 1987; Dockhorn et al. 1987; Holmber et al. 1989; Kemp et al. 1985). It therefore seems unlikely that the efficacy of intranasal azelastine against nasal obstruction is a result solely of its potent H1-receptor antagonism, but may derive from additional 'anti-allergic' activity.

The time to onset of effect for both the oral and intranasal formulations of azelastine differed depending on the variable measured. However, and not surprisingly, intranasal azelastine was always significantly more rapid in its effect. Onset of effect of both formulations in relation to expression of subjectively experienced symptoms occurred well before noticeable effects on objective tests of nasal patency. The most rapid onset of effect was related to protection against pollen-induced sneezing attacks, occurring within 30 minutes of instillation of intranasal azelastine and within 60 minutes of oral administration.

**Discussion**

Seasonal allergic rhinitis caused by aeroallergens such as pollens and fungal spores is a difficult condition in which to research the therapeutic efficacy of new drugs. Spontaneous variations in atmospheric allergen levels, and consequently in the intensity of symptoms, complicate the design and interpretation of clinical trials.

In the present study the use of the VCC allowed all patients to simultaneously undergo a standardised long term challenge at physiological concentrations of allergen. Symptoms of rhinitis provoked during carefully controlled conditions similar to natural pollen exposure could therefore be studied. As a result, the protective effect of azelastine in comparison with placebo was clearly apparent, despite the small number of patients investigated. However, the sophisticated method used allowed a considerable amount of scaled data to be obtained from each single patient and this led to statistically calculable results.
Sneezing and nasal hypersecretion result from the interaction of the preformed mediator, histamine, which is released from mast cells on contact with allergen, with H1-receptors on sensory nerve endings (Cauna et al. 1969). This has been confirmed by the fact that specific H1-receptor antagonists are very effective in relieving these symptoms (Holmber et al. 1989; Howarth & Holgate 1984). However, it is generally accepted that, in addition to histamine, other newly generated metabolites of arachidonic acid, such as prostaglandin D2 (PGD2) and leukotrienes C4 and D4 (LTC4 and LTD4) contribute to allergen-induced nasal blockage (Bisgaard et al. 1986; Miadonna et al. 1987; Walsh et al. 1990). This may explain the much more rapid effect of azelastine, a potent and fast acting H1-receptor antagonist (Casale 1989; Spector et al. 1987), on pollen-induced sneezing compared with nasal obstruction.

The mechanism through which azelastine inhibits nasal blockage is unclear. In vitro, it has been shown to inhibit the release of LTC4 and LTD4 (Achternath-Tuckermann et al. 1988; Katayama et al. 1987) and to antagonise their effect on guinea-pig ileum (Chand et al. 1986a; Katayama et al. 1987). In vivo, orally administered azelastine has a potent and long-lasting inhibitory effect on leukotriene-mediated bronchoconstriction in guinea-pigs (Chand et al. 1986b), but the same inhibition is not reproduced in man (Albazzaz & Patel 1988). It therefore seems unlikely that the clinical effect of azelastine on nasal obstruction is mediated via inhibition of the release or actions of leukotrienes.

In addition to arachidonate derivatives, potent vasoactive peptides such as bradykinin have also been shown to induce nasal blockage (Rajakulasingam et al. 1990), as has the sensory neuropeptide, substance P (Devillier et al. 1988). The obstruction caused by vasoactive peptides has been shown to be receptor specific, in common with arachidonic acid metabolites, as the bradykinin metabolite, [des-arg9]-bradykinin, has no effect on nasal airflow, nor does the PGD2 metabolite 9α,11βPGF2 (Rajakulasingam et al. 1990). The effect of the β2-agonist, [des-arg9]-bradykinin, is indicative of a direct effect of kinins on the vascular β2-receptor. Azelastine, however, does not appear to interact with β-receptors (Casale 1989), although it has been shown to block the activity of bradykinin (Inoue 1983).

Middleton et al. (1989) have suggested that probable diverse pharmacological activities do not all derive from direct receptor antagonism since it is unlikely that a single molecule could act as a receptor antagonist to such a structurally diverse group of agonists, postulating instead that azelastine most probably acts on a post-agonist-receptor interaction event such as an interaction with calmodulin, the ubiquitous Ca2+-dependent enzyme system.

Although the mechanism of action by which azelastine affects nasal patency is yet to be explained, its efficacy against pollen-induced nasal blockage in addition to symptomatic control typical of other antihistaminic compounds make it potentially extremely valuable in the treatment of allergic rhinitis.

The onset of action of azelastine in controlling symptoms occurs less than 1 hour after administration by either the oral or the intranasal route, offering rapid relief for rhinitis sufferers. Intranasal azelastine may prove useful for patients with rhinitis only where its proven efficacy when applied topically at low doses suggest it to be a useful alternative to oral therapy with no anticipated systemic effects.

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References

Albazzaz MK, Patel KR. Effect of azelastine on bronchoconstriction induced by histamine and leukotriene C4 in patients with extrinsic asthma. Thorax 43: 300, 1988

Casale TB. The interaction of azelastine with human lung histamine H1, beta and muscarinic receptor sites. Journal of Allergy and Clinical Immunology 83: 771-776, 1989


Chand N, Pillar J, Diamantis W, Sofia RD. Inhibition of IgE-mediated allergic histamine release from rat peritoneal mast cells by azelastine and selected antihistamine drugs. Agents and Actions 16: 318-322, 1985

Corrado OJ, Gomez E, Baldwin DL, Clague JE, Daviss RL. The effect of nedocromil sodium on nasal provocation with allergen. Journal of Allergy and Clinical Immunology 90: 218-222, 1992


Holmber B, Bake B, Blychert LO, Pijlorn E. Effects of topical H1 and 2 receptor antagonists on symptoms and local vascular reactions induced by nasal allergen challenge. Allergy 44: 281-287, 1989


Howard PH, Holgate ST. Comparative trial of two non-sedative H1 antihistamines, terfenadine and astemizole, for hayfever. Thorax 39: 668-672, 1984


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