

Comparative efficacy of azelastine nasal spray and terfenadine in seasonal and perennial rhinitis

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The efficacy and tolerability of intranasal azelastine (0.14 mg/nostril twice daily) and oral terfenadine (60 mg twice daily) were compared under double-blind conditions in two 6-week, multicenter, parallel-group studies, including 167 patients suffering from seasonal and 52 patients suffering from perennial allergic rhinitis. In both studies, patients were symptomatic on entry and showed significant improvement on both treatments within the first 8 d of therapy, showing little further improvement with continued treatment. Symptoms most pronounced on entry – nasal itching, rhinorrhea, sneezing, and nasal obstruction – responded best to treatment (response rates 80–90%). Objective signs such as mucosal swelling and conjunctivitis improved in a manner parallel to symptoms. In perennial rhinitis, azelastine showed a trend to a superior relief of rhinorrhea and nasal obstruction, whereas terfenadine showed a trend toward better control of sneezing and nasal itchiness. No clinically relevant or statistically significant differences between treatments could be identified. The incidence of adverse effects of possible causal relationship to therapy was low. The most frequent effects in azelastine-treated patients were related to application site disorders, e.g., nasal irritation. Results indicate that with the dose used azelastine nasal spray is an effective treatment for both seasonal and perennial allergic rhinitis.

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Azelastine, a phthalazinone derivative, is a chemically unique, orally effective drug whose pharmacologic profile includes interaction with a wide variety of chemical mediators relevant to the pathogenesis of respiratory allergy. Azelastine exhibits potent H_1 -receptor-blocking activity, which, *in vitro* and *in vivo* in animal models, also inhibits the release of several mediators implicated in the pathogenesis of airway hyperresponsiveness and allergic reactions (1–8, 11, 17, 25). This activity has been extensively confirmed in man, where the compound has a long duration of action (16, 22). After both single and multiple dose administration, it has been shown to be a powerful inhibitor of histamine-induced bronchoconstriction (1, 11, 15, 21).

In *in vivo* animal and *in vitro* models, azelastine also appears to have "antiallergic" activity which is distinct from and additional to its proven antihistaminic properties. This activity involves interaction with the synthesis/release of the products of the

lipooxygenase/leukotriene synthetase pathway (3, 12), and inhibition of the activity of leukotrienes (2, 4). Furthermore, azelastine inhibits more potently the release of mediators from rat mast cells than do sodium cromoglycate (SCG), theophylline, and astemizole (7–9); modulates *in vitro* anaphylaxis (3, 6); and demonstrates a long duration of action against IgE-mediated passive cutaneous anaphylaxis in the rat (5).

Histamine released locally from mast cells has long been acknowledged as the primary mediator in allergic rhinitis (19), many of the symptoms resulting from the effects of this inflammatory, vasoactive mediator. For this reason, orally administered, second-generation antihistamines such as terfenadine, cetirizine, and astemizole, which are devoid of anticholinergic and central sedative effects, have become the standard treatment for seasonal allergic rhinitis.

Azelastine administered in oral doses of 1.1–

2.2 mg twice daily has been shown to be effective in the treatment of both seasonal (14, 23) and perennial (18) allergic rhinitis. Onset of action is as early as 2 h after dosing (20).

Following confirmation of the therapeutic benefit of orally administered azelastine in allergic rhinitis, a nasal spray formulation has been developed. This formulation offers various advantages since topical preparations are often effective at much lower doses than those required systemically and are frequently better tolerated. Topical application of azelastine also offers the opportunity of achieving high local concentrations of the drug.

The present multicenter studies were designed to assess the efficacy and tolerability of a 6-week treatment with azelastine nasal spray, as compared with an orally administered standard H_1 -receptor antagonist, terfenadine, in both seasonal (Study I) and perennial rhinitis (Study II).

Material and methods

Patients

Study I. A total of 167 patients, 108 men and 59 women, mean age 29.5 years (range 16–64 years), were studied from April to October 1987 (Table 1). All had a history of seasonal allergic rhinitis of at least 3 years' duration. In all cases the diagnosis was confirmed by skin prick testing. Symptoms were mainly due to grass or cereal pollen, although allergies to early flowering trees and to herbaceous plants were identified in a few cases. An acute total rhinitis symptom complex score (see below) of ≥ 8 was required to confirm allergen exposure at the time of study entry. All antiasthmatic, antiallergic, neuroleptic, antidepressant, psychotherapeutic, or sedating treatments were prohibited during the study. Most patients were free of all medication on entry to the

study, with the exception of 25 patients who received antiallergic medication (mainly antihistamines) at the time of enrolment. Patients with asthma were excluded from participation.

Study II. A total of 52 patients, 19 women and 33 men, with a mean age of 30.5 years (range 17–55 years) with perennial allergic rhinitis were studied from May 1987 to January 1988 (Table 1). The duration of symptoms was required to be at least 3 years before study entry. The diagnosis was again confirmed by skin prick testing. Symptoms were mainly due to house dust or house-dust mite. As for Study I, an acute total rhinitis symptom complex score of ≥ 8 was required to confirm allergen exposure on enrolment. Medication restrictions during the study were as detailed above, and asthmatic patients were again excluded. Most patients were free of all medication on entry to the study, but 12 patients had been treated (80% of them with antihistamines) before the beginning of the trial.

In all cases, patients were required to give written, informed consent to their participation. Both studies were conducted in accordance with the requirements of the Declaration of Helsinki and German drug law, and were approved by the ethics committee of the medical faculty of the University of Heidelberg.

Study design

Studies I and II. With the exception of the indication for treatment, either seasonal or perennial allergic rhinitis, the design of both studies undertaken was identical.

Patients were randomized to treatment with either azelastine nasal spray, one puff (0.14 mg per nostril), or terfenadine 60 mg, morning and evening, over a

Table 1. Demographic data

	Study I (Seasonal)		Study II (Perennial)	
	Azelastine <i>n</i> =81	Terfenadine <i>n</i> =86	Azelastine <i>n</i> =25	Terfenadine <i>n</i> =27
Male	47 (58.0%)	61 (70.9%)	13 (52.0%)	20 (74.1%)
Female	34	25	12	7
Age in years*	29.9±10.5 16–64	29.1±9.1 18–62	30.2±7.4 18–49	30.9±8.9 17–55
Weight (kg)*	69.4±11.1 50–98	68.4±9.9 47–100	68.2±7.8 52–80	71.2±8.3 58–100
Duration of disease in years*	9.5±7.4 2–50	8.8±5.6 3–40	6.2±2.4 3–12	9.5±7.8 3–40
Days since onset of current symptoms*	12.6±17.7 0–75	15.7±23.7 1–120	5.1±4.0 1–12; <i>n</i> =19	4.9±4.2 1–12; <i>n</i> =20

* Means ± standard deviation; ranges.

Table 2. Reasons for discontinuation of patients

	Study I (Seasonal)		Study II (Perennial)	
	Azelastine n=80	Terfenadine n=82	Azelastine n=25	Terfenadine n=27
Inefficacy	4	7	—	—
Intolerance	1	—	—	—
Intercurrent disease	1	—	—	—
Noncompliance	2	8	2	—
End of pollen season	4	2	—	—
Inefficacy and noncompliance	—	1	—	—
Intolerance and noncompliance	—	1	—	—
Total	12	19	2	0

6-week period in a multicenter, double-blind, parallel-group fashion. As a means to ensure the double-blind character of the studies, a "double-dummy" method was employed. Study treatments were supplied in identical packages containing one bottle (30 ml) of aqueous solution with a pump action spray and a tube containing 50 gelatin capsules, representing supplies sufficient for a 3-week treatment. Bottles contained either azelastine HCl (azelastine) 0.1% or placebo and delivered 0.14 ml of solution per actuation. Capsules contained either terfenadine tablets, 60 mg (Teldane®), or placebo.

Efficacy, assessed in terms of 13 signs and symptoms, and tolerability, assessed on the basis of responses to a "nonleading" question and spontaneously reported effects, were recorded on day 0 (before treatment), day 8, day 22, and day 43 (at the end of treatment). In addition, laboratory investigations including hematology and serum biochemistry were

performed on screening and on completion of the study. Clinical symptoms used to assess efficacy were the following: rhinorrhea, sneezing, itchy nose, itchy eyes, lacrimation, stuffy nose, lost sense of smell, tickling in the throat, cough, and photophobia. In addition, three signs of rhinitis were assessed: conjunctival inflammation (redness), erythema of pharyngeal mucosa, and swelling of the nasal mucosa.

Each sign or symptom was graded according to a 4-point scale: 0 = absent; 1 = slight; 2 = moderate; 3 = severe. A total rhinitis symptom complex (TSC) score with a range of 0–30 was derived from symptom grading as the target index for both trials. As described above, a score of at least 8 on screening was an inclusion criterion. On day 43, at the end of treatment, the physician's overall assessment of efficacy in each patient was recorded, again using a 4-point scale (1 = very good; 2 = good; 3 = sufficient; 4 = not satisfactory). Global tolerability was also assessed according to the same scale.

Results

Study I

Of the 167 patients who entered the study, 81 were randomized to receive azelastine treatment, and 86 to terfenadine. Although the two treatment groups did not differ in age, time since diagnosis, duration of acute seasonal rhinitis, and initial rhinitis score, there were differences in sex distribution (Table 1). The azelastine group consisted of 47 men (58.0%) and 34 women, as compared with 61 men (70.9%) and 25 women randomized to take terfenadine ($P = 0.055$; one-sided Fisher test).

Table 3. Number of patients (%) showing improvement at day 8*

Symptom/sign	Study I (Seasonal)		Study II (Perennial)	
	Azelastine n=80	Terfenadine n=82	Azelastine n=22	Terfenadine n=27
Itchy nose	68/77 (88.3%)	71/80 (88.8%)	19/22 (86.4%)	26/27 (96.3%)
Sneezing	63/79 (79.7%)	58/73 (79.5%)	18/22 (81.8%)	23/24 (95.8%)
Stuffy nose	52/60 (86.7%)	54/68 (79.4%)	20/20 (100.0%)	21/22 (95.5%)
Rhinorrhea	63/71 (88.7%)	65/72 (90.3%)	20/22 (90.9%)	24/27 (88.9%)
Itchy eyes	58/63 (92.1%)	43/50 (86.0%)	12/12 (100.0%)	12/12 (100.0%)
Lost sense of smell	37/40 (92.5%)	39/41 (95.1%)	16/17 (94.1%)	21/22 (95.5%)
Lacrimation	41/46 (89.1%)	33/41 (80.5%)	10/10 (100.0%)	5/5 (100.0%)
Tickling in throat	13/17 (76.5%)	13/14 (92.9%)	—** —	—** —
Photophobia	11/14 (78.6%)	8/10 (80.0%)	—** —	—** —
Cough	7/8 (87.5%)	3/4 (75.0%)	—** —	—** —
Swollen nasal mucosa	67/75 (89.3%)	62/73 (84.9%)	20/22 (90.9%)	26/27 (96.3%)
Conjunct. inflammation	42/44 (95.5%)	38/40 (95.0%)	12/12 (100.0%)	9/10 (90.0%)
Redn. pharyngeal mucosa	16/17 (94.1%)	16/18 (88.9%)	2/2 —**	8/9 (88.9%)

* Figures relate to number of patients experiencing respective symptom on entry to study.

** Because of the very low number of patients affected by these symptoms, values are not listed.

Five patients were excluded from assessments of efficacy. One of those receiving azelastine was excluded for poor cooperation and understanding of the study requirements. Of the other four terfenadine patients excluded, three failed to return after their initial consultation and, retrospectively, one was unable to satisfy the inclusion criteria. Therefore, data from a total of 162 patients were available for assessment of efficacy. An additional 19 terfenadine-treated patients and 12 azelastine-patients discontinued the study prematurely (Table 2), but they were included in the main analysis of the "intent to treat" type.

The fact that the mean total rhinitis symptom complex (TSC) score on entry to the study was approximately 16 points of a maximum of 30 confirms the existence of a substantial symptomatology before therapeutic intervention.

Symptoms which were most pronounced on entry – nasal itching, rhinorrhea, sneezing, and nasal obstruction – responded best to treatment. Of patients who reported these symptoms to be of at least "moderate" severity on entry to the trial, 80–90% showed improvement (Table 3). The time course for severity for the most pronounced symptom, nasal itching, is shown in Fig. 1; it confirms the changes seen in total rhinitis symptom complex scores. It can be demonstrated for both treatments that the greatest change occurred during the first week, continued treatment producing only slight further improvement. Changes in total rhinitis symptom complex scores (Table 4) showed a significant decrease by day 8, with a further slight improvement by day 43. No clinically relevant or statistically significant differences between the two treatments were identified,

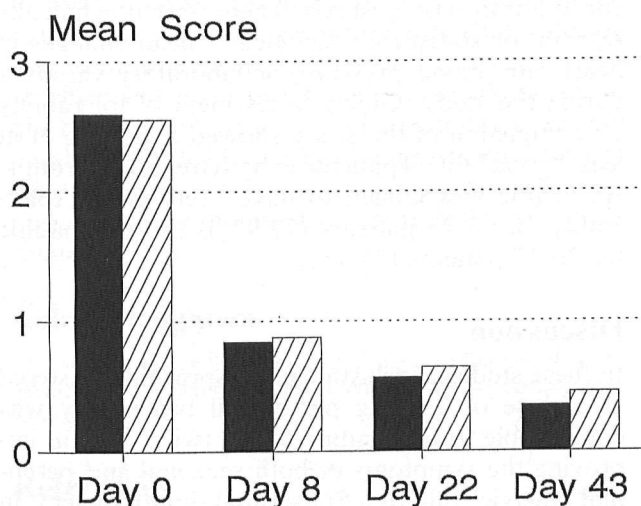


Fig. 1. Mean scores for nasal itching in seasonal rhinitis patients (at days 0, 8, 22, 43) treated with intranasal azelastine (■) or terfenadine tablets (▨).

Table 4. Total rhinitis symptom complex (TSC) scores (means $\pm$ standard deviation)

	Day 0	Day 8	Day 22	Day 43
Study I (seasonal)				
Azelastine (n=80)	16.92 $\pm$ 4.00	5.09 $\pm$ 5.35*	2.89 $\pm$ 3.38*	2.09 $\pm$ 3.70*
Terfenadine (n=82)	16.20 $\pm$ 4.00	5.49 $\pm$ 5.32*	3.67 $\pm$ 4.78*	2.45 $\pm$ 3.15*
Study II (perennial)				
Azelastine (n=22)	16.05 $\pm$ 4.03	4.09 $\pm$ 3.37	2.23 $\pm$ 3.18	1.59 $\pm$ 3.07
Terfenadine (n=27)	14.81 $\pm$ 3.56	4.07 $\pm$ 3.05	2.48 $\pm$ 2.81	1.88 $\pm$ 2.67

* Significant difference from initial values; $P < 0.001$ one-sample t-test. Statistical comparisons were not undertaken for Study II because all patients in the two groups showed improvement.

although azelastine did show a trend towards better control of nasal obstruction (Fig. 2).

Objective signs improved parallel to symptoms, improvement rates varying 90–95%. Again, azelastine showed a beneficial effect on nasal obstruction by limiting swelling of the nasal mucosa. However, this effect did not reach statistical significance, as compared with terfenadine.

In terms of global assessment of efficacy (day 43), results were reported as "very good" for 58.8% of azelastine patients, as compared with 45.7% of ter-

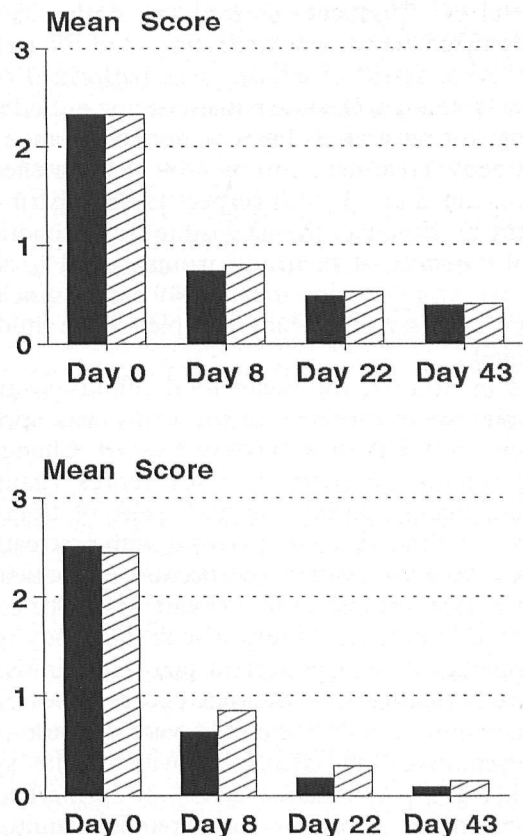


Fig. 2. Mean scores for severity of nasal obstruction during 6-week treatment with intranasal azelastine (■) and terfenadine (▨) in seasonal (upper panel) and perennial allergic rhinitis (lower panel).

fenadine patients. This difference did not reach statistical significance ($P = 0.115$, Fisher test). An efficacy of at least "good" was found in about 80.0% of patients, irrespective of treatment.

Adverse effects judged by physicians to be probably or possibly drug-related were reported by eight patients (9.9%) in the azelastine-treated group (acne, sweating, headaches, sore throat, nasal irritation, dry nose, and tiredness) and four patients (4.7%) in the terfenadine group (urticaria, gastric disorders, kidney pain, mucus in the throat, and tiredness). Two patients, both in the azelastine group, withdrew from the study because of adverse effects; one because of a variety of unrelated symptoms (ascribed by the doctor to the patient's psychologic state rather than to the trial medication), and one because of headache. Global assessment of tolerability was "very good" for 70.0% of azelastine patients and 76.3% of terfenadine patients. There was no significant difference in tolerability between the two therapies. No clinically relevant or statistically significant mean changes in heart rate, blood pressure, or laboratory investigation were seen during the study.

Study II

A total of 52 patients entered the study; 25 were randomized to receive azelastine, and 27 terfenadine. Assessment of efficacy was performed on 49 patients, three azelastine patients being excluded for failing to return after day 0 or noncompliance with treatment. Treatment groups were well matched except, as in Study I, with respect to sex distribution (Table 1). Whereas the azelastine group contained equal numbers of men and women, 74.1% of the terfenadine group were men. All 49 patients included in the analysis of efficacy completed the study as planned.

As in Study I, the mean total rhinitis symptom complex score on entry to the study was approximately 16 points of a maximum of 30. Changes in total rhinitis symptom complex scores again occurred, mainly during the first week of treatment (Table 4). Statistical comparisons with pretreatment values were not undertaken because all patients in both groups showed improvement. It can be clearly shown that patterns of response in this study reflect the significant changes seen in seasonal rhinitis. The effects of treatment on the time course of severity of nasal itching, initially the most severe symptom, were representative of the effects seen with all other symptoms (Fig. 3). As in seasonal rhinitis, a marked improvement in symptoms of perennial rhinitis occurred during the first week of the study, further therapy only slightly influencing symptoms.

Patients with at least "moderate" symptoms on entry to the study showed improvements in 80–

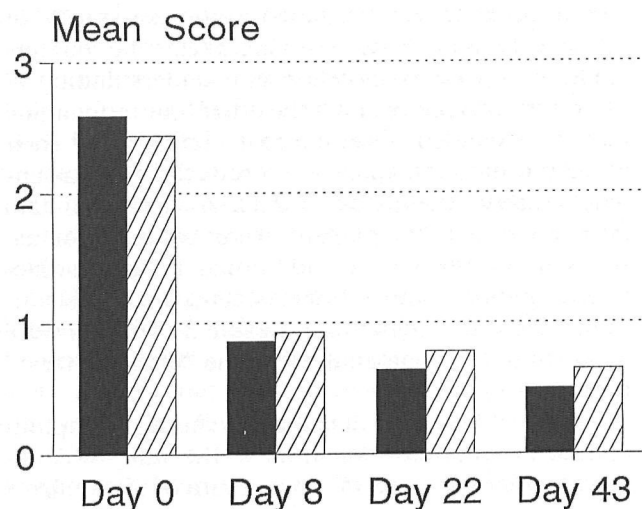


Fig. 3. Mean scores for nasal itching at days 0, 8, 22, and 43 in patients with perennial allergic rhinitis treated with intranasal azelastine (■) or terfenadine tablets (▨).

100% of cases from day 0 to day 8 (Table 3). Numerically, azelastine showed a slight advantage in relieving nasal obstruction (Fig. 2), and terfenadine showed a slight advantage in improving sneezing. However, no statistically significant differences were seen.

Objectively assessed signs of rhinitis, mucosal swelling, conjunctivitis, and pharyngeal inflammation also showed improvement rates of 90–100% between days 0 and 8. Global assessment of efficacy (day 43) was reported as "very good" for 10/22 (45.5%) of azelastine patients and 10/27 (37.0%) in the terfenadine group. Efficacy was judged as being at least "good" in 90.9% of azelastine- and in 85.2% of terfenadine-treated patients.

The only adverse effect during the study was reported by an azelastine-treated patient who experienced a transient epistaxis. There were no clinically relevant or statistically significant mean changes in heart rate, blood pressure, or laboratory variables during the study. Global assessment of tolerability on completion of the study showed a grading of at least "good" for all patients in both treatment groups. Azelastine was judged to have "very good" tolerability for 17/23 patients (73.9%), and terfenadine for 20/27 patients (74.1%).

Discussion

In these studies, azelastine nasal spray administered at a dose of 0.14 mg per nostril twice daily was comparable to terfenadine 60 mg twice daily in improving the symptoms of both seasonal and perennial allergic rhinitis. Substantial improvement in signs and symptoms was evident in the first evaluation made on day 8 of treatment, and was maintained for the duration of each 6-week study. The

continued efficacy of both medications suggests that the patients did not develop tolerance for either terfenadine or azelastine over the course of therapy.

In both studies, symptoms which were originally most pronounced – nasal itching, sneezing, rhinorrhea, and nasal blockage – responded best to treatment. Although there were no significant differences between treatments, there was a trend in perennial rhinitis toward a better influence of azelastine in controlling rhinorrhea and nasal blockage, whereas terfenadine was numerically superior in sneezing and nasal itching. In seasonal rhinitis, azelastine showed a trend toward superiority in controlling nasal obstruction, which was paralleled in a similar trend toward reduction in swelling of the nasal mucosa.

The relief of nasal obstruction by both therapies is of interest since, classically, H_1 -receptor antagonists, including terfenadine, have been shown to relieve nasal congestion much less than the other symptoms of allergic rhinitis (9, 13, 24). Our results differ both from previous reports of terfenadine (24) and from the previous experience of Meltzer et al. (18), who reported that orally administered azelastine appeared to function similarly to other H_1 -antihistamines in exerting less effect on nasal congestion than on sneezing or rhinorrhea. Interpretation of the latter finding is, however, confounded by the fact that the use of decongestant "escape" medication decreased in azelastine-treated patients but increased in placebo controls. Further work is indicated to clarify the role of azelastine nasal spray in the treatment of nasal obstruction, a particularly important feature of perennial rhinitis.

Azelastine nasal spray was generally well tolerated. The incidence of adverse effects of possible causal relationship to therapy was low. The most frequent events in azelastine-treated patients related to application site disorders such as nasal irritation.

In conclusion, the results of this study indicate that azelastine nasal spray with the dosage used is an effective treatment for both seasonal and perennial rhinitis. Both efficacy and tolerability were comparable to those of a systemic antihistamine, terfenadine. Therefore, azelastine nasal spray is a potentially important new therapy for the treatment of allergic rhinitis.

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