

Azelastine eye-drops in seasonal allergic conjunctivitis or rhinoconjunctivitis

A double-blind, randomized, placebo-controlled study

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This study was carried out to assess the efficacy of 0.025% and 0.05% azelastine eye-drops in patients with seasonal allergic conjunctivitis of ≥ 1 year's duration. A total of 151 patients received 0.025% or 0.05% azelastine eye-drops or placebo b.i.d. for 14 days according to a double-blind, randomized, placebo-controlled, parallel-dosing design; 129 patients completed the study as planned. The three target symptoms, scored on 4-point scales, were itching, lacrimation, and redness of the eyes; responders were patients whose symptom sum score decreased by ≥ 3 from a baseline score of ≥ 6 by day 3. Mean scores of these and five other symptoms were recorded also on days 7 and 14, and patients kept daily diaries of the three main symptoms and swollen eyelids. Responder rates were 73% for 0.025% ($P=0.115$ vs placebo) and 82% for 0.05% azelastine eye-drops ($P=0.011$ vs placebo) and 56% for placebo. The time courses of the mean (investigators' and patients') scores for the three main symptoms reflected the dose-dependent effect of azelastine eye-drops. One patient each from the two azelastine groups and three from the placebo group withdrew because of inefficacy. Adverse drug reactions were reported by 14 and 24 patients receiving 0.025% and 0.05% azelastine eye-drops, respectively, and by eight placebo patients. These reactions were mainly slight application site reactions and taste perversion (bitter or unpleasant taste). Azelastine eye-drops are effective and well tolerated at a dose of 0.05% for the treatment of seasonal allergic conjunctivitis.

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Seasonal allergic conjunctivitis is a very common disorder characterized by marked bilateral itching, watery discharge, and conjunctival redness. Burning, conjunctival edema, swollen eyelids, and photophobia may also be seen, and patients frequently experience associated nasal symptoms; hence the term "rhinoconjunctivitis" (1). The condition results from an IgE-mediated mast-cell reaction to airborne allergens and varies considerably in severity (2). The severest form can lead to vision impairment.

Drug therapy of allergic conjunctivitis is heterogeneous (3). Prophylaxis with sodium cromoglycate or nedocromil is effective but is associated with compliance problems. Oral histamine antagonists are widely effective in the treatment of acute symptoms but first-generation agents are inadequate when administered locally. Topical cortico-

steroids may be used for short-term treatment of severe cases. For the more rapid relief of itching and inflammatory symptoms, levocabastine is currently the only second-generation H_1 -receptor antagonist which is available as eye-drops, which can be administered as the sole local therapeutic alternative (3, 4).

Azelastine is another antiallergic agent with histamine H_1 -receptor antagonist activity which also inhibits mast-cell histamine release, has some leukotriene and platelet-aggregating factor (PAF) antagonistic activity, and inhibits IgE-mediated inflammation *in vivo* (5). It is widely used by intranasal administration for the treatment of allergic rhinitis. Given intranasally, azelastine has a fast onset and a long duration of action, inhibiting both nasal and optical symptoms in patients with seasonal or perennial allergic rhinitis (6). A formula-

tion as azelastine hydrochloride eye-drops has now been developed which permits its use for the local therapy of allergic conjunctivitis.

The present study was carried out to compare the efficacy and safety of two different concentrations of azelastine eye-drops in patients suffering from seasonal conjunctivitis or rhinoconjunctivitis.

Material and methods

Subjects

One hundred and fifty-one subjects (66 male and 85 female), aged 17–64 years (mean 35.5 years), suffering from seasonal allergic conjunctivitis or rhinoconjunctivitis (confirmed in all cases by at least one of the following methods: slit lamp test [$n=64$], skin testing [$n=84$], or RAST antibody test [$n=87$]) for at least 1 year, participated in the study, which was carried out in March–September 1994. The subjects all had a score of at least 6 points for the main eye symptoms “itching of the eyes”, “conjunctival redness”, and “lacrimation” on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). None had perennial allergic conjunctivitis, conjunctivitis sicca, keratitis, glaucoma, any other eye disease, perennial allergic rhinitis, bronchial asthma, or allergic skin disease. Pregnant women, women with inadequate contraception, subjects wearing contact lenses, subjects with eyelid or lacrimal defects, subjects with hypersensitivity to test preparations, or subjects taking other ophthalmologic or antiallergic agents were not included in the study. The protocol was approved by both the regional ethical committee and the local ethical committees of the centers involved. The study was carried out in accordance with the principles of the Declaration of Helsinki and the European Guidelines for Good Clinical Practice. All subjects provided their written, informed consent to inclusion in the study.

The subjects had not received astemizole within the 4 weeks before the study. Antiswelling nose-drops and intranasal corticosteroids were permitted.

Study design

The investigation was performed as a double-blind, randomized, placebo-controlled study with parallel therapy groups in 18 centers in Germany. Assuming a responder rate of 50% for the placebo group, 67 patients per treatment group ($\alpha=0.025$, $\beta=0.10$) were considered necessary to show a superior effect of azelastine, based on a responder proportion of at least 80%. Allowing for dropouts, the

study was planned with a total of 225 patients, but only 151 could be enrolled because of recruitment difficulties during the wet spring. Subjects were randomly allocated to treatment with either 0.025% or 0.05% azelastine eye-drops or placebo for a 14-day treatment period. Efficacy and safety variables were assessed at baseline and after 3, 7, and 14 days' treatment, during visits to the physician.

Drugs

Azelastine eye-drops (ASTA Medica, Frankfurt/Main, Germany) containing 0.008 mg (0.025%) or 0.015 mg (0.05%) azelastine HCl/drop and the corresponding placebo were used (all containing benzalkonium chloride and sodium edetate). The placebo was identical to the azelastine eye-drops except for the active drug. The drops were applied, one drop to each eye, twice daily at intervals of 10–12 h in the morning and evening.

Efficacy variables

The primary target variable was the responder rate. Therapy responders were defined as patients whose sum score of the three main symptoms decreased by at least 3 score points between baseline (day 0) and day 3, taking into account a baseline score of at least 6. Patients who withdrew prematurely due to lack of efficacy were considered nonresponders. The three target symptoms, scored by the physician, were eye itching, lacrimation, and conjunctival redness. In addition, a further five symptoms were assessed by the physician: burning sensation, foreign-body sensation, photophobia, swollen eyelids, and discharge/eyelids sticking together. Each symptom was assessed at baseline and on days 3, 7, and 14 on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). The physician provided a global assessment of efficacy on a 4-point scale (1=very good/good, 2=satisfactory, 3=insufficient, 4=not assessable) at the end of the treatment or on discontinuation.

Patients assessed their conjunctival symptoms daily (in the evening) in a diary on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe) using the following symptoms: itching, lacrimation, conjunctival redness, and swollen eyelids.

Patients also documented the number of eye-drop applications, the duration of the effect, the weather conditions (sunny, rainy, cloudy) and their individual whereabouts (in a room – window open/closed; outside – city/countryside), the physicians recording the number of applications and duration of action on days 3 and 14.

Table 1. Characteristics of patient population at baseline

	Azelastine 0.025% (n=47)	Azelastine 0.05% (n=52)	Placebo (n=52)
Sex M	22	18	26
F	25	34	26
Age (years), mean±SD	35.4±11.4	35.2±10.7	35.9±11.5
Height (cm), mean±SD	172±9	169±8	173±10
Weight (kg), mean±SD	69.6±11.9	71.0±16.5	71.8±15.1
Duration of disease (years), mean SD	8.3±8.9	7.0±7.3	7.4±7.6
Allergy confirmed by			
Prick test (n)	24	28	32
RAST test (n)	28	29	30
Intracutaneous test (n)	1	1	—
IgE (kU/l), mean±SD	151±129 (n=15)	169±127 (n=13)	160±108 (n=18)
Slit lamp test, chemosis (n)			
Slight (L/R)	3/3	2/3	1/2
Moderate (L/R)	13/13	17/15	16/15
Severe (L/R)	4/4	3/4	4/5
Concomitant disease (n)	7	8	10
Concomitant medication (n)	25	27	32

L: left eye; R: right eye.

Safety

Vital signs were recorded at each visit to the physician. Adverse events were documented in their diaries by the patients, who were questioned about these at each visit. At the end of the treatment, physicians provided a global assessment of safety, using the same 4-point scale as for efficacy.

Statistical analyses

Efficacy data were analyzed both on an intention-to-treat and on a per protocol basis, and the latter are presented here. Safety data were assessed for all patients who received medication and for whom documentation was available. Response rates to 0.025% and 0.05% azelastine vs placebo were compared confirmatively with the two-sided Fisher exact test ($\alpha=0.025$, α -adjustment due to multiple tests). Patients who discontinued the study due to lack of efficacy or had taken disallowed medication (prior to day 3) were regarded as nonresponders. Values for these patients were replaced by baseline data, except when baseline values were lower than the values for day 3.

Results

Patient disposition and demography

Of the 151 patients recruited, 129 completed the study as planned and were evaluable per protocol. A total of 41 patients in the 0.025% azelastine

Table 2. Responder rates for three main eye symptoms itching, lacrimation, and conjunctival redness by day 3 of treatment

	Azelastine 0.025% (n=41)		Azelastine 0.05% (n=45)		Placebo (n=43)	
Response ^{a)}	n	%	n	%	n	%
No	11	27	8	18	19	44
Yes	30	73	37	82	24	56
P vs placebo (Fisher's two-tailed test)	0.115		0.011			

^{a)} Decrease by day 3 of ≥ 3 in sum of scores for three main eye symptoms.

group, 45 in the 0.05% azelastine group, and 43 in the placebo group were evaluated for efficacy. Among 11 patients (7%) who withdrew prematurely from the study, one subject in each azelastine group and three in the placebo group withdrew because of inefficacy. No patient withdrew from the azelastine treatment because of adverse events; other reasons for withdrawal included noncompliance and intercurrent diseases.

All patients who participated in the study suffered from symptoms of allergic conjunctivitis or rhinoconjunctivitis, as confirmed by prick and/or RAST tests and in some cases by intracutaneous tests or IgE determinations (Table 1). Apart from 16 patients who received disallowed concurrent medication, the most frequent classes of concomitant medication were sex hormones and modulators of the genital tract (35 patients), nasal preparations (34 patients), and analgesics (10 patients). All treatment groups were homogeneous with regard to demographic characteristics and baseline values for the three target symptoms. The climate and environment were comparable for all three treatment groups, with the exception of days 3 (environment) and 9 (climate) (data not shown).

Investigators' assessment of efficacy

The number of patients in each treatment group who responded with a decrease between days 0 and 3 of at least 3 points in the sum of the scores for the main symptoms, itching, lacrimation, and conjunctival redness, are shown in Table 2. Only in the 0.05% azelastine group was the responder rate significantly higher than that in the placebo group.

The time courses of the mean scores for the three main symptoms in the three treatment groups are shown in Fig. 1. Dose dependency was observed in the response to azelastine, the mean symptom score decreasing significantly between day 0 and day 3 with the 0.025% eye-drops, and showing a highly significant decrease between baseline and both days 3 and 7 at the 0.05% dose. Similar

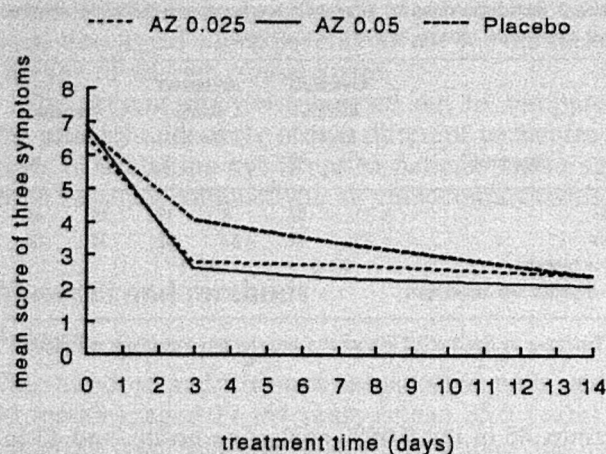


Fig. 1. Decrease with treatment time in investigators' assessment of three main eye symptoms, itching, lacrimation, and redness, in response to three different treatments. Values are mean scores of 41 (0.025% azelastine), 45 (0.05% azelastine), and 43 (placebo) patients. Significance of differences from placebo: day 3, AZ 0.025 ($P=0.020$); AZ 0.05 ($P=0.001$); day 7, AZ 0.05 ($P=0.015$).

changes were observed in the mean scores for all eight eye symptoms (data not shown).

From the information provided by the patients after 3 days, the duration of action of the treatment was assessed as 7.8 ± 0.6 h (mean $\pm$ SEM), 7.3 ± 0.5 h, and 5.8 ± 0.6 h in the 0.025% and 0.05% azelastine and placebo groups, respectively. The global assessment of efficacy on day 14 was satisfactory to very good in 86% and 89% of patients on 0.025% and 0.05% azelastine, respectively, and in 75% of patients on placebo.

Patients' assessment of efficacy

The changes in the mean scores of the three main eye symptoms, itching, lacrimation, and conjunctival redness, as recorded daily by the patients in their diaries, are shown in Fig. 2A–C. Symptoms decreased rapidly in both azelastine groups, being continuously suppressed most effectively at the 0.05% dose. Of the three symptoms, lacrimation was the most sensitive to treatment with azelastine, being suppressed rapidly at both doses within 1–2 days. Eyelid swelling was very slight at baseline and was not included in the analysis.

Safety

The total numbers of patients with adverse events at all four visits were 21 (40.4%) in the placebo group, 20 (42.6%) in the 0.025% azelastine group, and 35 (67.3%) in the 0.05% azelastine group. No serious adverse events occurred.

In a total of 46/151 patients (30.5%), the adverse events were considered to be probably related to

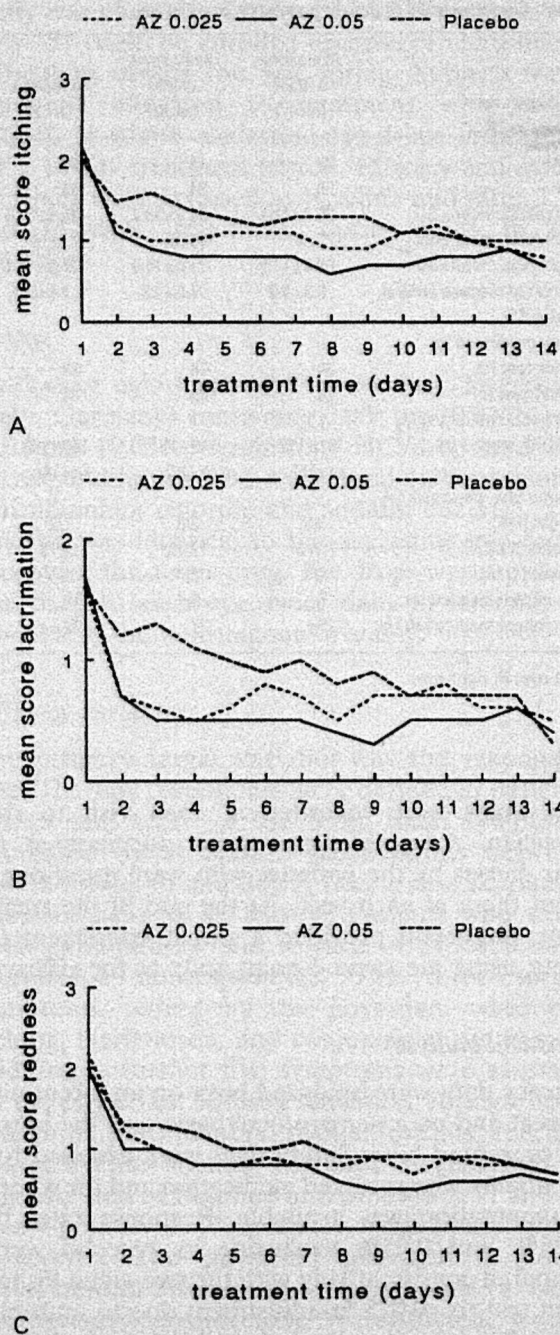


Fig. 2. Decrease with treatment time in patients' daily assessment of (A) itching, (B) lacrimation, and (C) redness in response to three different treatments. Values as in legend to Fig. 1.

treatment (Table 3). The most frequent adverse drug reaction was an application site reaction which was reported as a burning sensation and was dependent on the dose of azelastine. "Taste perversion" also occurred in a dose-dependent manner. This was the preferred term to describe the bitter taste of the active medication which entered the mouth via the nasal cavity.

Table 3. Adverse events, expressed as WHO preferred terms, considered to be probably related to treatment

Event	Azelastine 0.025% (n=47)		Azelastine 0.05% (n=52)		Placebo (n=52)	
	n	%	n	%	n	%
Application site reaction	10	21	20	39	6	12
Conjunctivitis	2	4	1	2	3	6
Eye pain	2	4	1	2	—	—
Vision abnormal ^{a)}	2	4	—	—	—	—
Mouth dry	—	—	1	2	—	—
Taste perversion	4	9	6	12	—	—
Rhinitis	1	2	1	2	—	—
Influenza-like symptoms	1	2	—	—	—	—
Dysphagia	—	—	1	2	—	—
Epistaxis	—	—	1	2	—	—
Total ^{b)}	14	30	24	46	8	15

^{a)} Blurred vision, transient. ^{b)} Includes multiple reports.

Apart from a slight decrease in mean diastolic blood pressure from 80 ± 11 mmHg (mean $\pm$ SD) on day 0 to 76 ± 11 mmHg on day 14 in the 0.05% azelastine group, there were no differences in mean vital signs between the treatment groups.

The investigators' global assessment of safety on day 14 was satisfactory to very good in 95% and 98% of patients on 0.025% and 0.05% azelastine, respectively, and in 97% of patients on placebo.

Discussion

The results of this double-blind study show that azelastine eye-drops provide rapid, dose-dependent relief from ocular symptoms in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis.

The primary target variable, the responder rate after 3 days of treatment, was only significantly higher than placebo at the dose of 0.05% azelastine. The more pronounced inhibitory effect of 0.05%, as opposed to 0.025% azelastine, was also observed in the time courses of the mean scores for the three main ocular symptoms, and this trend was maintained across all eight symptoms assessed. The daily assessment of symptoms by the patients themselves confirmed the greater efficacy of the 0.05% dose and indicated that the onset of the therapeutic effect is more rapid. These findings confirm the results of a previous, smaller, double-blind study in 24 patients with grass-pollen allergy, in which 0.05% azelastine eye-drops were significantly better than placebo in protecting against allergen-induced itching and conjunctival redness measured by digital imaging of the vascular response (7).

Individual assessment of the three most distressing symptoms of allergic conjunctivitis, itching, lacrimation, and conjunctival redness, indicated

that all three were rapidly relieved within 1–2 days at both doses of azelastine eye-drops, although lacrimation appeared to be most rapidly reduced in comparison to the effect of placebo. Itching is generally the only symptom to be inhibited by first-generation antihistamines, and it is strongly subject to a placebo effect (3, 4), as confirmed in the present study. A high placebo response to eye-drops is generally associated with changes in atmospheric and environmental conditions (8) and can also arise as a result of a washout effect of the eye-drops, or through the protective effect of the viscous solution. The fact that external conditions did not differ notably between treatment groups in the present study contributed to the clarity of the response. Nevertheless, a placebo response of up to 70% for some individual symptoms, as seen by other authors (8), was also observed here. Permitted intranasal medication was used by 34/151 (22.5%) of patients, distributed homogeneously across the three groups. The specific therapy used was not indicated, but where topical corticosteroids were given, these may have contributed to the placebo response through effects on the eye.

Levocabastine eye-drops until now have been the only topical, second-generation antihistamine preparation available for allergic conjunctivitis, inhibiting itching, exudation, and vasodilation in comparison to placebo (4). These actions can now also be extended to azelastine eye-drops. Comparison of the symptom scores recorded daily by the patients suggests that azelastine eye-drops may act more rapidly than do levocabastine eye-drops, as reported in a study on seasonal allergic conjunctivitis (9).

A recent double-blind, placebo-controlled study in 20 patients with allergic rhinoconjunctivitis found that 0.05% azelastine eye-drops cause a significant reduction in total symptom score within 10–20 min and inhibit inflammatory cell infiltration and adhesion molecule (ICAM-1) expression after treatment for 7 days (10). This indicates that azelastine eye-drops are as effective in inhibiting allergic inflammation of the eye as azelastine nasal spray in inhibiting similar inflammation of the nose (11).

The most frequent adverse reaction to azelastine eye-drops was a burning sensation immediately after application, which occurred in 21–39% of patients, depending on the dose. Such transient, local irritant effects reflect the generally increased sensitivity to instilled medications of inflamed eyes, since similar effects are observed with other eye-drop preparations (12, 13). "Taste perversion" is a recognized complaint after treatment with azelastine hydrochloride and corresponds to a substance-specific bitter or unpleasant taste. "Taste pervers-

sion" after instillation of azelastine eye-drops is the result of the transport of the compound through the nasolacrimal duct into the pharynx with subsequent action on the posterior part of the tongue.

The results of this investigation show that azelastine eye-drops are well-tolerated and effective in the treatment of seasonal allergic conjunctivitis. The 0.05% dose is more effective than the concentration of 0.025% and should be studied in larger trials.

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