Comparative Efficacy and Safety of Azelastine and Levocabastine Nasal Sprays in Patients with Seasonal Allergic Rhinitis

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Summary

The aim of the present investigation was to compare the efficacy and tolerability of azelastine (CAS 58581-89-8) (1.12 mg/day) and levocabastine (CAS 79547-78-7) (0.4 mg/day) nasal spray administered twice daily to patients with seasonal allergic rhinitis. A total of 180 patients participated in a 4-week, double-blind, parallel group (n = 90 each) study. Symptom severity of nasal, ocular and other symptoms were recorded, out of which a total symptom score (TSS) was calculated. Physicians assessed symptoms at baseline and at days 7, 14, and 28, patients and physicians evaluated the efficacy and tolerability. After 4 weeks of treatment with azelastine the mean overall TSS was reduced from a baseline score of 18.7 to 4.2, after levocabastine from 17.8 to 5.9. Patients morning scores for treatment days 1 to 28 gave a mean total score of 212.4 for the azelastine group and 230.6 for the levocabastine group; the equivalent evening scores yielded a mean total score of 115.5 and 175.6 respectively. Global efficacy was judged by physicians as either 'very good' or 'good' for 90 % of azelastine patients and for 74 % of the levocabastine group; 92 % of azelastine patients and 76 % of levocabastine patients judged treatment to be either 'very good' or 'good'. No serious adverse events were reported, all adverse events were related to nasal symptoms. Both azelastine and levocabastine administered twice daily as a nasal spray provide effective and well tolerated symptomatic treatment of seasonal allergic rhinitis. Azelastine, however, was statistically superior in efficacy as well as in safety (PWei-Lachin < 0.0001, combined results).

Key words

- **Azelastine, clinical study, nasal symptom score, safety**
- **CAS 58581-89-8**
- **CAS 79547-78-7**
- **Levocabastine, clinical study, nasal symptom score, safety**
- **Rhinitis, seasonal allergic**

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Zusammenfassung

Vergleich der Wirksamkeit und Verträglichkeit von Azelastin- und Levocabastin-Nasenspray bei Patienten mit saisonaler allergischer Rhinitis

Ziel der vorliegenden Untersuchung ... keit von Azelastin (CAS 58581-89-8) (1,12 mg/Tag) und Levocabastin (CAS 79547-78-7) (0,4 mg/Tag), jeweils in Form eines Nasensprays 2mal täglich appliziert, bei Patienten mit saisonaler allergischer Rhinitis zu vergleichen. Insgesamt 180 Pa-

doppelblinden Vergleichsstudie (parallele Gruppen zu je 90 Patienten) teil. Erfaßt wurde der Schweregrad von nasalen, okularen und anderen Symptomen, aus denen ein Symptomen-Score (Total Symptom Score, TSS) errechnet wurde. Von den Prüfärzten wurden an den Tagen 0, 7, 14 und 28 die Symptome, von Patienten und Ärzten die Wirksamkeit und Verträglichkeit beurteilt. Nach der 4-wöchigen Therapie mit Azelastin war der TSS im Mittei von ursprünglich 18,7 auf 4,2 gefallen, unter der Levocabastin-Behandlung von 17,8 auf 5,9. Die morgendlichen Patienten-Werte über die gesamten 28 Tage der Studie ergaben einen mittleren Score von 212,4 für die Azelastin-Gruppe respektive 230,6 für die Levocabastin-Gruppe; die entsprechenden Abend-Scores erreichten mittlere Werte von 115,5 bzw. 175,6. Die globale Wirksamkeit wurde von den Prüfärzten entweder mit „sehr gut" oder „gut" bei 90 % der Azelastin- und bei 74 % der Levocabastin-Patienten beurteilt; 92 % der Azelastin-Patienten und 76 % der Levocabastin-Patienten beurteilten ihre jeweilige Therapie mit „sehr gut" oder „gut". Schwerwiegende unerwünschte Ereignisse wurden nicht berichtet, alle unerwünschten Ereignisse bezogen sich auf nasale Symptome. Sowohl Azelastin als auch Levocabastin, jeweils zweimal täglich als Nasenspray appliziert, stellen eine wirksame und gut verträgliche Behandlung der saisonalen allergischen Rhinitis dar. Dabei zeigte sich Azelastin in bezug auf Wirksamkeit und Verträglichkeit statistisch überlegen (PWei-Lachin < 0.0001, combined results).

1. Introduction

Azelastine (CAS 58581-89-8) being an antiallergic agent has potent activity at a number of sites associated with the allergic reaction; these include potent and selective H_1 receptor antagonism [1], blockade of histamine release from mast cells [2], and antagonism of leukotriene and platelet activating factor [3]. These activities combine to make azelastine an extremely effective treatment in patients with seasonal and perennial allergic rhinitis.

The efficacy of azelastine nasal spray in controlling the symptoms associated with seasonal allergic rhinitis is well established and has been confirmed in a series of large controlled clinical trials comparing azelastine 0.56 mg/day with oral agents such as terfenadine 120 mg/day [4] and cetirizine 10 mg/day [5].

In addition, these studies confirmed the favourable safety profile of azelastine. Sedation, commonly associated with first generation antihistamines, is not evident with nasally administered azelastine, even in children.

Levocabastine (CAS 79547-78-7) is a selective H_1 receptor antagonist which is marketed in many European countries and is waiting for marketing approval in the United States. Levocabastine can be administered by nasal spray and provides a rapid onset of action [6]. Previous clinical studies have demonstrated that levocabastine nasal spray administered twice daily is an effective and well tolerated treatment of ragweed-induced seasonal allergic rhinitis [7].

The present investigation was performed as a controlled double blind randomized study in order to determine the equivalence or superiority of azelastine in efficacy and tolerability in comparison to levocabastine in the treatment of seasonal allergic rhinitis [8].

2. Patients and methods

2.1. Patients

A total of 180 outpatients were recruited at two ENT (Ear Nose Throat) centres in Austria during the 1996 hay fever season. Consenting male and female patients were to be between 18 and 65 years of age and were to be suffering from seasonal allergic rhinitis, as confirmed by a positive prick-test (vs. histamine-positive control 10 HEP). Prior to admission to the study, patients underwent an allergy test, physical examination, and rhinoscopy.

The symptom rating scale (total symptom score, or TSS) on entry to the study was to be at least 8 out of a maximum of 30. Patients excluded from the study were those with asthma in need of treatment, those with non-allergic rhinitis, perennial allergic rhinitis, obstructive nasal adenoids or acute infection of the upper respiratory tract. Prior to the start of the study patients were not to have received anti-allergic therapy or psychopharmacologic agents for 14 days, topical steroids for 15 days and systemic corticosteroids for 4 weeks.

The following concomitant medications were not permitted during the trial period: oral or topical steroids, antihistamines, sympathicomimetics, selfmedication with any drug influencing nasal respiration or any drug which might influence the judgement about the efficacy or safety of the test compounds. After verbal instruction, a written explanation of the study was provided to each patient and informed written consent was obtained. Patients were allocated to treatment groups by a predetermined, computer-generated blockrandom code.

The severity of symptoms was documented by each patient in diary cards each morning before drug application and each evening 15 min after drug application by means of a four-point scale (0 = not present; 1 = mild, symptoms noticeable; 2 = moderate, detrimental to daily activities; 3 = severe, permanent detraction). The following ten symptoms were assessed:

Nasal symptoms:	sneezing
	itching of the nose
	rhinorrhoea
	stuffy nose
	disorded or defective sense of smell
Ocular symptoms	itching of eyes
	lacrimation
	photophobia
Other symptoms	itching of the throat
	cough.

Patients returned to the clinic for assessment after 7, 14, and 28 days. At the end of the study patients and physicians separately judged both the efficacy and the tolerability of the treatment according to a five-point scale (1 = very good; 2 = good; 3 = satisfactory; 4 = insufficient; 5 = not assessable).

As to safety and tolerability patients were questioned about the occurrence of any adverse events at each visit. Tolerance was rated as either 'very good', 'good', 'satisfacory', or 'insufficient'.

2.2. Methods

2.2.1. Study design

The parallel group randomized, double-blind, bicentric study compared azelastine nasal spray (azelastine) with levocabastine nasal spray (levocabastine). The attending physician, the principal investigator, the study coordinator and the statistician were blinded until the code was broken after double data entry. The study was conducted in compliance with the ICH/GCP guidelines and the Declaration of Helsinki and its revisions (Hong Kong 1989). Written approval of the International Freiburger Ethical Committee was obtained prior to the start of the study.

2.2.2. Treatment

Study medications were labelled according to the German Drug Law. Azelastine (batch number: 015042; supplied by ASTA Medica[1]) was administered using a nasal spray which delivered 0.14 mg/actuation. Levocabastine nasal spray (purchased in a local pharmacy) delivered 0.05 mg/actuation. Patients were requested to administer 2 puffs of study drug into each nostril in the morning and evening. Thus, the daily dose of levocabastine was 0.4 mg and that of azelastine was 1.12 mg. Patients were asked to return used containers so that an assessment of compliance could be made.

2.2.3. Primary end points

Five primary efficacy variables were defined in the protocol: the nasal symptom sum-score calculated out of 3 nasal symptoms (sneezing, itching of the nose, and rhinorrhea) as well as the sum of all 10 symptom scores (total symptom score, TSS) as recorded in the patient diaries, each at morning and evening. In addition, the global judgement of efficacy by the investigator was also a primary variable.

2.2.4. Secondary end points

Secondary efficacy criteria were changes of the individual symptoms as recorded both in the patient diaries and by the investigators on the case report forms from baseline through days 7, 14, and 28. Also included were changes in rhinoscopic findings (anterior rhinoscopy) from baseline through days 7, 14, and 28, as manifested by macroscopic assessment of inflammation, edema and secretion (0 = absent, 1 = slight, 2 = moderate, 3 = severe).

2.2.5. Sample size determination and statistical evaluation

The hypothesis to be tested was the one-sided test for equivalence within the framework of the Wilcoxon-Mann-Whitney test. The sample size calculation was based on a test for equivalence (one-sided) with the lower bound of the equivalence region defined as MW = 0.36, a medium-sized difference of two distributions. Alpha was defined as 0.025 (one-sided), beta as 0.1. The resulting sample size was N1 = N2 = 91, thus a total of 180 seemed to be an adequate number.

All five primary efficacy variables, the two indices for the time periods and the global judgement of the efficacy, were planned to be tested as an ensemble with the highly efficient directional test (test for stochastic ordered alternatives) of the generalized multivariate Wilcoxon-Mann-Whitney Test of Wei and Lachin [8]. A one-sided test for non-inferiority was performed. Equivalence was tested for an equivalence bound of MW = 0.4. In addition the degree of equivalence was described by means of a one-sided confidence interval (LB-CI) [9]. If equivalence was accepted a test for superiority was to be performed in addition, with the same alpha in a confirmatory manner according to the closed testing principle [10]. The Mann-Whitney estimator for the so called stochastic superiority of the test group in comparison to the reference group is a useful statistic with a range from 0 to 1 (0.5 indicating equivalence, > 0.5 indicating superiority of azelastine, < 0.5 indicating inferiority of azelastine). It denotes the probability, that a randomly selected patient of the test group achieves a better result than a randomly selected patient of the reference group. For all Mann-Whitney estimators the one sided 95 % confidence intervals have been calculated. Demographic and historical data were summarized for descriptive purposes and analysed for differences by means of the Mann-Whitney statistic and its confidence intervals.

The first line analysis of efficacy was the intention-to-treat (ITT) data set.

3. Results

3.1. Patients

Validated data were obtained for a total of 180 patients (90 each group). The ITT data set comprised n = 179 patients, the safety data set n = 180 patients. The two treatment groups were comparable with respect to the following demographic parameters: age, weight, height, and sex; no significant differences were found for any of these parameters. Demographic details and baseline characteristics are given in Table 1.

Table 1: Patients demographic and baseline characteristics.

	Azelastine	Levocabastine
Sex		
male	64 (27 %)	57 (63 %)
female	25 (28 %)	33 (37 %)
Age (years		
mean	30	29
median	25	25
Weight (kg)		
mean	79	77
median	81	80
Hieght (cm)		
mean	178	176
median	179	179
Duration of acute phase (days)		
mean	12	12
median	10	10

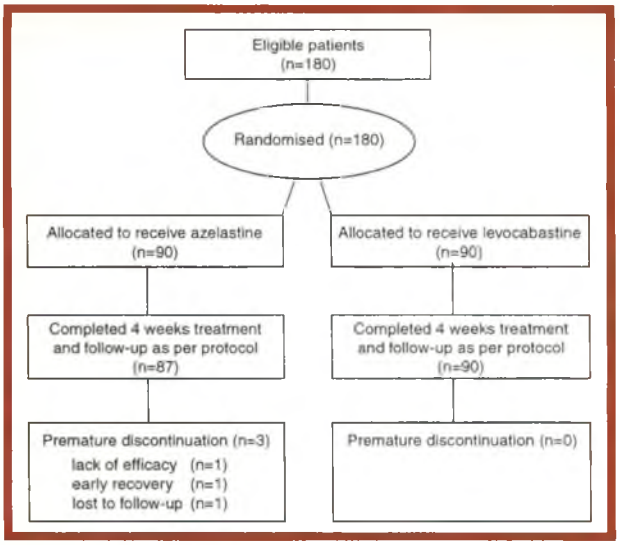

Fig. 1: Disposition of patients throughout the study.

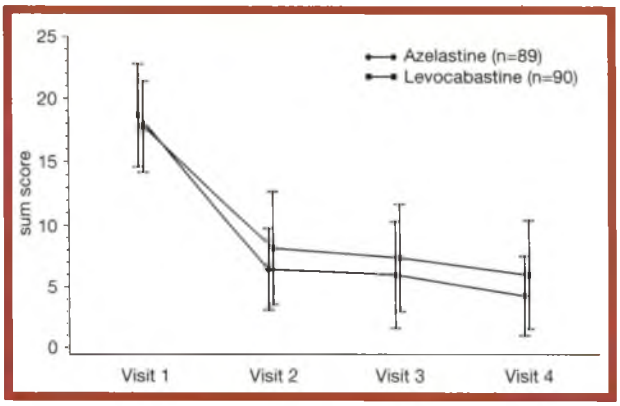

Fig. 2: Total Symptom Score (TSS) (means and standard deviations) at clinical assessments (N = 179).

Compliance with the medication regimen was assessed by checking the returned medication bottles. All patients were considered compliant (data were incomplete for only 2 patients). One hundred and seventy-seven of the 180 patients completed the 4-week treatment period according to the study protocol. Three patients (all receiving azelastine) did not complete the treatment period. This was due to early recovery in one patient, lack of efficacy in another, and a third patient was lost to follow-up. Only one patient was excluded from the intention-to-treat efficacy analysis as there were no data for the primary criteria for visit 2. There were no other major protocol violations. Disposition of patients is shown in Fig. 1. All patients who received at least one dose of study medication were included in the safety analysis.

The first patient was included in the study on April 20, 1996 and the last visit of the last patient took place on August 7, 1996. During this time period airborne pollen counts were regularly recorded [11]. Most widely found pollen during the the study-period were Betula, Platanus, Quercus, Pinus, Poaceae, and Urtica.

3.2. Efficacy

3.2.1. Primary end points

With regard to baseline pre-treatment efficacy criteria, the azelastine group showed more severe symptoms ($p = 0.0441$) compared with the levocabastine group. In both groups, there was a marked reduction in TSS as recorded at the visits. At all three follow-up visits, the reduction of TSS is more pronounced in the azelastine group than in the levocabastine group (Fig. 2). After 4 weeks of treatment with azelastine, the mean overall TSS was reduced from a baseline score of 18.7 to 4.2 at the final visit. In the levocabastine group the mean TSS was reduced from a baseline score of 17.8 to 5.9 at the

When considering morning diary card symptoms recorded by patients from treatment day 1 to 28, there was a mean TSS of 212.4 for the azelastine group and 230.6 for the levocabastine group. For the equivalent evening scores, there was a mean total score of 115.5 for the azelastine group and 175.6 for the levocabastine group (Fig 3). Thus, the evening patient diary data showed lower total scores (and hence milder symptoms) in the azelastine group.

The nasal symptom sum-score was defined as the sum of three symptoms: sneezing, itching of the nose, and rhinorrhoea. Fig. 4. shows a mean nasal symptom score for each of the clinical visits. In both treatment groups, the nasal symptom sum-score initially was at a moderate to severe level with a mean of 7.3 for the azelastine group and 7.1 for the levocabastine group. After 4 weeks of treatment with azelastine, the nasal symptom sum-score was reduced by a mean of 6.1 to 1.2; in the levocabastine group the mean nasal symptom score was reduced to 2.1, equivalent to a reduction by a mean of 5.0.

Efficacy was judged globally by physicians at the end of the study as either 'very good' or 'good' in 80/89

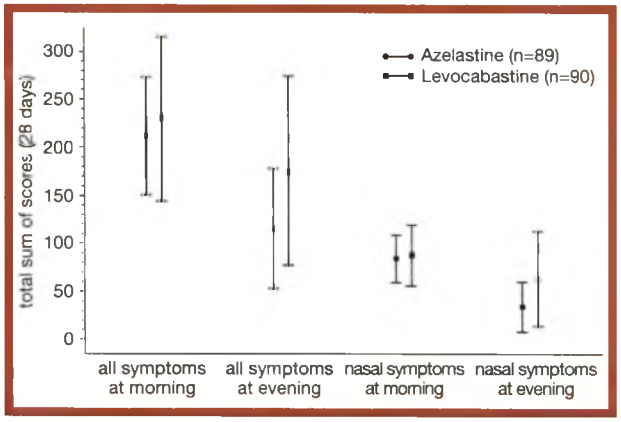

Fig. 3: Total Symptom Score (TSS) and nasal symptom sum-score

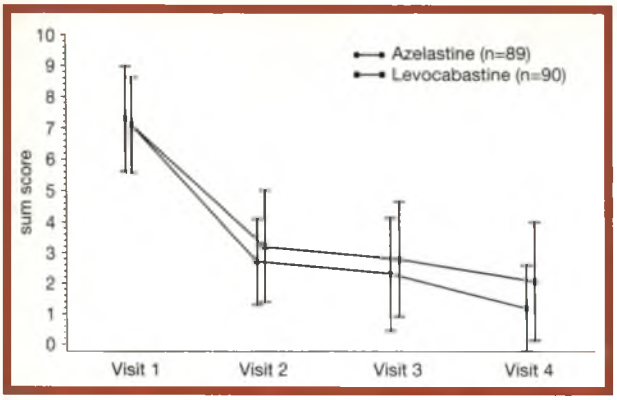

Fig. 4: Nasal Symptom Sum-Score (means and standard deviations) at clinical assessments (N = 179).

(90 %) of azelastine patients and as either 'very good' or 'good' in 67/90 (74 %) patients in the levocabastine group.

3.2.1.1. Confirmatory analysis of primary end points

Equivalence ('equal' or 'better') of the two treatments with respect to the combined criteria of efficacy (TSS and nasal sum-score morning and evening as well as global efficacy judgement by the investigator) was confirmed: the Mann-Whitney estimator being 0.6180 and the lower bound of the confidence interval of the Mann-Whitney estimator LB-CI being 0.5679, well above the critical level of 0.4. Since equivalence was accepted a test for superiority of azelastine with regard to the combined efficacy criteria was performed. This test demonstrated a statistically significant result ($p < 0.0001$).

When the individual efficacy criteria were tested for superiority, the Mann-Whitney estimators denoted a superiority of azelastine for 3 of the 5 criteria, namely: The TSS recorded in the evening ($p < 0.0001$) and the nasal symptom sum-score recorded in the evening ($p < 0.0001$), the lower bounds of the confidence interval LB-CI being 0.6385 and 0.6214, respectively, again well above the line of equivalence of 0.5. The global judgement of efficacy by the investigator showed also significant group differences ($p = 0.0007$, LB-CI = 0.5574).

3.2.2. Secondary end points

When looking at the reduction in scores for individual symptoms, it was seen that the morning values of the azelastine group showed superiority (MW > 0.5); the most responsive symptoms with regard to change from baseline at the end of the study were lacrimation, rhinorrhoea, and itching of the nose. For the evening values, azelastine showed superiority for seven symptoms (MW = 0.5622). The most responsive symptoms were itching of the nose, rhinorrhoea, and disordered or defective sense of smell.

Efficacy was judged globally by patients at the end of the study as either 'very good' or 'good' in 92 % of azelastine patients and as either 'very good' or 'good'

The results of anterior rhinoscopy showed greater improvements from baseline with azelastine for all three criteria (inflammation, edema, nasal secretion). The lower bounds of the univariate one-sided 95 %-confidence intervals were above the 0.5-line of equivalence for all three single criteria. The most responsive criteria was nasal secretion (MW > 0.64).

3.2.3. Drug tolerability

Adverse events were reported by two patients in the azelastine group and by 20 patients in the levocabastine group. All events were related to nasal symptoms. Seventy-eight percent of levocabastine adverse events were deterioration of nasal symptoms, the remainder were stuffy nose. Azelastine events were cough at night, itching, and sneezing attacks after administration. All but two of the adverse events (one in each group) were classified as severe. None of the adverse events was considered serious.

Tolerance was rated as either 'very good' or 'good' by 87/89 (98 %) of azelastine patients and by 63/90 (70 %) of levocabastine patients. 'Insufficient' tolerance was reported by one patient in the azelastine group and by 17 patients in the Levocabastine group. Investigators rated tolerance as either 'very good' or 'good' in 88/89 (99 %) of cases in the azelastine group and in 70/90 (78 %) of cases in the levocabastine group. There was a clear superiority in the azelastine group with regard to judgements of tolerance by patients and investigators ($p < 0001$).

3.2.4. Benefit risk analysis

In addition to the analyses of the primary and secondary as well as the safety parameters a special benefit risk analysis has been performed using the global judgments of efficacy and tolerance by the patient and the investigator as criteria for 'benefit' and 'risk'; all test results have to be interpreted in an explorative manner. This analysis shows a clear superiority of azelastine with respect to the four criteria mentioned and to all criteria combined. Fig. 5 shows Mann-Whitney statistics and confidence intervals for this benefit-risk analysis.

4. Discussion

The results indicate that both azelastine and levocabastine administered nasally provide effective relief of the symptoms of seasonal allergic rhinitis as demonstrated by significant reductions in symptom scores recorded on patient diary cards and by physicians at clinic assessments. When comparing efficacy, i.e. symptom scores between the two treatment groups, consistent advantages were seen for the azelastine group which obtained a significantly greater relief of symptoms during the course of the study.

This is particularly true for the total symptom score as well as for the nasal sum-score: patients in the azela-

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