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A Multicenter Randomized Double-Blind 2-Week Comparison Study of Azelastine Nasal Spray 0.1% versus Levocabastine Nasal Spray 0.05% in Patients with Moderate-to-Severe Allergic Rhinitis

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Key Words
Allergic rhinitis · Antihistamine · Azelastine · Chinese · Levocabastine

Abstract
Objective: To compare the onset of action, efficacy, and safety of azelastine and levocabastine in the treatment of allergic rhinitis. ***Subjects and Methods:*** In a multicenter, randomized, double-blind, parallel-group trial, 244 patients with moderate-to-severe allergic rhinitis were randomized to receive either azelastine hydrochloride nasal spray (ANS) 0.1% or levocabastine hydrochloride nasal spray (LNS) 0.05% for 14 consecutive days. A visual analog scale was used to record total nasal symptom score (TNSS) changes. Indexes for further assessment included onset of action, total effective rate, and evaluation of therapeutic effect. ***Results:*** Statistically significant changes from baseline in TNSS were seen in both the LNS group and the ANS group. No significant differences were seen between the two groups in terms of evaluation of therapeutic effect, total effective rate, and onset of action, except for a higher symptom relief rate in the LNS group than in the ANS group within 30 min of administering the first dose. Adverse reactions were mild to moderate, with an incidence of 0.9% for LNS and 2.5% for ANS. ***Conclusion:*** Both ANS and LNS were effective and safe in the treatment of moderate-to-severe persistent allergic rhinitis. Moreover, LNS reached a higher symptom relief rate within 30 min of administering the first dose.

Introduction

Allergic rhinitis (AR) is a highly prevalent and worrisome inflammatory disease affecting about 10–40% of the global population [1]. Surveys suggest that AR affects about 23–30% of the population in Europe [2, 3], and ac-

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cording to data from the USA about 20–40 million people (10–30% of adults and up to 40% of children) are affected each year [4], while a Chinese study demonstrated that the prevalence of self-reported AR in 11 cities across mainland China has wide variations, ranging from 10 to 20% [5]. However, it is likely that the prevalence of AR is actually higher because the disease is often underdiagnosed or unconfirmed by allergy testing in about 45–50% of AR sufferers in the general population [2, 6]. Although AR is not a life-threatening condition, it is a major cause of suffering, associated with impairments of quality of life, work and school productivity [7], and substantial impact on the health and the economic burden of individuals and society alike [8].

AR is characterized by inflammation of the nasal mucosa. Sneezing, rhinorrhea, nasal itching as well as itching of the palate and eyes occur as a result of the release of mediators of inflammation, such as histamine, leukotrienes, prostaglandin D_2, tryptase, and kinins. Histamine plays an important role in the pathophysiology of AR through its neural and vascular effects, resulting in nasal itching, rhinorrhea and nasal obstruction [9].

Treatment strategies for AR include topical corticosteroids, oral or topical antihistamines, allergen-specific immunotherapy, and other methods, among which antihistamines are an essential cornerstone, although the nasal steroid spray should be most effective among several types of nasal sprays. Compared with oral antihistamines that are currently widely used, topical administration of antihistamines directly to the nasal passages has several advantages including lower risk of systemic side effects and drug interactions.

Azelastine nasal spray (ANS) and levocabastine nasal spray (LNS) are currently the most widely used topical antihistamine products in the treatment of seasonal AR. Both agents are potential and selective H_1 receptor antagonists with no appreciable affinity in vitro for H_2, dopaminergic, adrenergic, serotoninergic, or cholinergic receptors. When administered nasally, ANS and LNS have been demonstrated to be effective against nasal itching, sneezing, and rhinorrhea. There are two direct, prospective studies comparing the efficacy and tolerability of these two agents [10, 11]. It is not surprising that both ANS and LNS provided effective and well-tolerated symptomatic treatment of seasonal AR [1, 2]. ANS was reported to be statistically superior in efficacy as well as in safety in a 4-week treatment of 180 patients [11], while LNS was found to be at least as effective as, but better tolerated than, ANS in a 1-week treatment of 123 patients [10]. As no direct comparison of these two topical antihistamines for the treatment of persistent AR has been undertaken to date, the present study was initiated to compare the onset of action, efficacy, and tolerability of either ANS or LNS as monotherapy for moderate-to-severe persistent AR.

Subjects and Methods

Subjects

A total of 244 patients aged 18–65 years met the criteria for enrolment in this study. All subjects were required to have a history of at least 2 years of moderate or severe symptoms of perennial AR, according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1]. Each subject needed to have a positive skin prick test and had to be in good general health as indicated by physical examination (heart rate, breathing, systolic blood pressure, and diastolic blood pressure) and clinical laboratory values.

Exclusion criteria included: (1) seasonal AR; (2) non-allergic rhinitis; (3) other nasal diseases that might interfere with the results; (4) upper respiratory tract inflammation; (5) severe rhinostenosis resulting from deflection of the nasal septum; (6) severe asthma; (7) treatment with other nasal drops, nasal or oral antihistamine medications, or vasoconstrictors within the previous 7 days; (8) severe cardiac disease, liver or renal function failure; (9) pregnancy or lactation; (10) hypersensitivity to levocabastine or azelastine; (11) AIDS, venereal disease, alcohol abuse or alcohol dependence, and (12) operation scheduled during the study period.

Study Design

This was a multi-center, randomized, double-blind, parallel-group study, conducted in five hospitals in four cities across China. The study was performed from December 2008 to October 2009. Written informed consent was obtained from each patient. This study was approved by the Ethic Committees of all centers involved in the study and performed in accordance with the ICH and Good Clinical Practice regulations and the principles of the Declaration of Helsinki.

During the 1-week screening period before final enrolment, the patients' general information and medical history were recorded, and a nasal symptom assessment and general physical examination were undertaken, including measurements of vital signs, such as heart rate, breathing, and blood pressure, and a urine pregnancy test for female participants.

In this study, 244 patients, aged 18–65 years, passed screening and were finally enrolled and randomized to one of the two treatment groups, which either undertook 2 weeks of treatment with two sprays of LNS in each nostril twice daily (equal to a daily dose of 0.40 mg) or one spray of ANS in each nostril twice daily (equal to a daily dose 0.56 mg), as a positive control. Three follow-ups were conducted in both groups, including visits on day 0 (baseline) and day 14, and one telephone follow-up on day 7. On day 0, all eligible patients were asked to complete a visual analog scale (VAS) evaluation of their nasal symptoms and were then provided with the study medications and a diary card to record nasal symptom changes, onset of action after first dose, and adverse events (AEs). The second follow-up was via telephone and focused on patients' compliance with treatment and any AEs. During the fi-

nal visit, patients were again required to complete a VAS assessment in addition to compliance and AE reports as on day 0. At the end of the study, the patients and investigators were asked to give a general evaluation of the treatment they had received or administered, respectively.

Efficacy Analysis

A total nasal symptom score (TNSS) based on a scale from 0 ('nasal symptoms, not at all bothersome') to 10 ('nasal symptoms, extremely bothersome') VAS was the main data source required for primary efficacy analysis. TNSS indicated a combination status of a patient's nasal symptoms, including sneezing, running nose (rhinorrhea), nasal itching, and nasal blockage. Secondary efficacy indexes included onset of action, total effective rate, and evaluation of clinical therapeutic effects by patients and investigators, respectively.

Onset of Action

The first dose was given on day 1. The onset of action after the first dose and symptom relief were recorded at different time points (5, 15, and 30 min, 1, 1.5 and 2 h after first application) for each patient.

Evaluation of Clinical Therapeutic Effect

At the end of the 14-day study, patients and investigators, respectively, gave a general evaluation of therapeutic effects for each patient's treatment. Evaluations were rated as not good, general, good, excellent or ideal. The last 4 evaluations were considered as a clinical therapeutic effect for analysis.

Total Effective Rate

We defined a no-effect case as a patient having no change or even worsening of TNSS after the 2-week treatment. Total effective rate was calculated according to the following formula: (the number of total cases – the number of no-effect cases)/the number of total cases × 100%.

Compliance

Compliance with the treatments was assessed by checking the returned medication bottles and diary cards. Those patients who did not use the study medications or complete the cards according to our protocol were considered non-compliant.

Safety Evaluation

Heart rate, respiration, blood pressure, and AEs were recorded during each visit. Severity of each AE as well as whether or not it was related to the study medication was documented carefully. AE rate = (the number of cases of AEs/total number of patients) × 100%.

Population Samples and Statistical Analysis

Three population samples were introduced for statistical analysis: (1) FAS, the full population, which included all patients with diary data for at least 1 efficacy evaluation during a scheduled visit; (2) PPS, the per-protocol population (or efficacy population), which included all patients who completed the study without major protocol violation and patients who withdrew within 2 weeks because of being cured or finding no therapeutic effect at all, and (3) SS, the safety population, comprising all patients who were randomized and received at least 1 dose of study medication with diary data for at least 1 efficacy evaluation during a scheduled visit. Data from the PPS and SS populations are further discussed in this paper.

For measurement data, a t test or Wilcoxon rank sum test was used to compare groups. For count data, the Fisher exact probability test was used.

Results

Of the 298 patients entering the screening period of the study, 244 patients (FAS) were finally enrolled and randomized to either the LNS group (122 patients, 60 males and 62 females) or the ANS group (122 patients, 63 males and 59 females) for the 2-week treatment period. Among them, 224 patients (PPS) completed the efficacy evaluation (112 patients in the LNS group, 112 patients in the ANS group) and 238 patients (SS) completed the safety evaluation (117 patients in the LNS group, 121 patients in the ANS group).

Reasons for cases withdrawing during the study included 11 with poor compliance (6 patients in the LNS group, 5 patients in the ANS group), 4 who were lost to follow-up (2 patients in the LNS group, 2 patients in the ANS group), and 5 who withdrew due to other reasons (2 patients in the LNS group, 3 patients in the ANS group). Patients randomized to the two medication groups were well matched in terms of age, sex, and severity of symptoms.

Nasal Symptom Control

Individual TNSSs were seen to be significantly reduced in both the LNS group (reduced by a value of 2.90 $\pm$1.98, $p < 0.01$) and the ANS group (reduced by a value of 3.21 $\pm$2.13, $p < 0.01$) from baseline, respectively. No significant differences were seen between the two groups (fig. 1).

Onset of Action

More cases in the LNS group than in the ANS group reported onset of action within 15 and 30 min after administration of the first dose of study medication (15 min: LNS 59% vs. ANS 41%, $p < 0.05$; 30 min: LNS 80% vs. ANS 65%, $p < 0.05$). At 2 h after the first dose, the two groups were comparable (LNS: 90%, ANS: 92%; fig. 2).

Evaluation of Therapeutic Effect

At the end of the 2-week treatment period, overall evaluations were made by both the investigators and the patients. The investigators gave a positive assessment of the treatment for 95% of patients in the LNS group versus 92% of patients in the ANS group, while 88% of patients

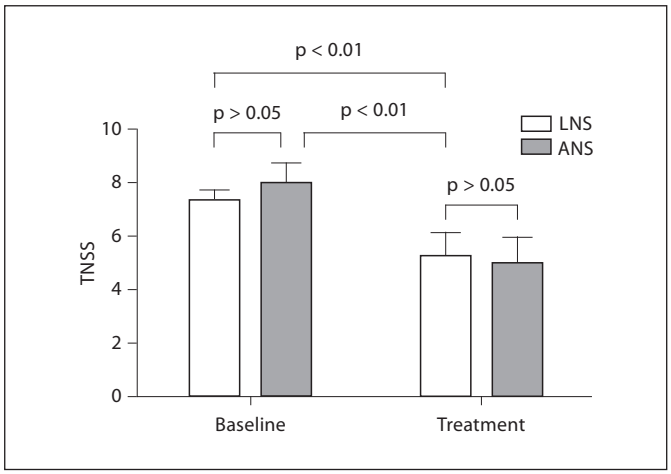

Fig. 1. Comparison of TNSSs in the LNS and ANS groups. Significant reductions were seen in both the LNS group (reduced by a value of 2.90 ± 1.98, $p < 0.01$) and the ANS group (reduced by a value of 3.21 ± 2.13, $p < 0.01$), respectively. No significant differences were seen between the two groups.

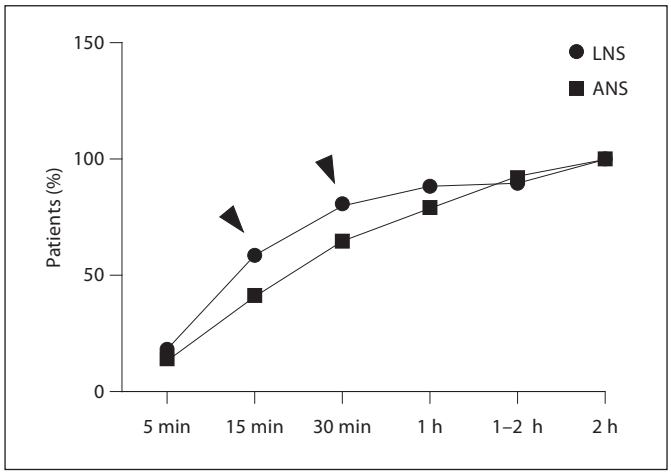

Fig. 2. Comparison of symptom control by LNS and ANS at different time points. Ratio of cases with improved TNSS at scheduled time points (from 5 min to 2 h) are shown. LNS was more effective than ANS at 15 and 30 min after the first dosage ($p < 0.05$), but both sprays were similar after 1 h.

in the LNS group versus 91% of patients in the ANS group assessed themselves positively. No significant difference was seen between the groups. Overall, both the investigators and the patients were satisfied with each of the two treatments (fig. 3).

Total Effective Rate

Clinical effectiveness was recorded for 103 patients out of 112 in the LNS group and 104 patients out of 112 in the ANS group (92 vs. 93%) with no significant difference between groups in terms of symptom control.

Compliance

Patient compliance was similar in both the LNS (6 incompliant cases) and ANS (5 incompliant cases) treatment groups in this study.

Adverse Events

Of the 238 patients randomized to either treatment, 2.6% from the LNS group and 3.3% from the ANS group experienced an AE, among which 0.9% (1 case, mycteroxerosis) of LNS-treated patients' AEs and 2.5% (3 cases, 1 each of nasal obstruction, epistaxis, and nasal burning) of ANS-treated patients' AEs were medication related. None of the AEs was serious, and there were no cases of early withdrawal due to AEs in either group. No clinically significant differences in vital signs were seen within the groups and between groups.

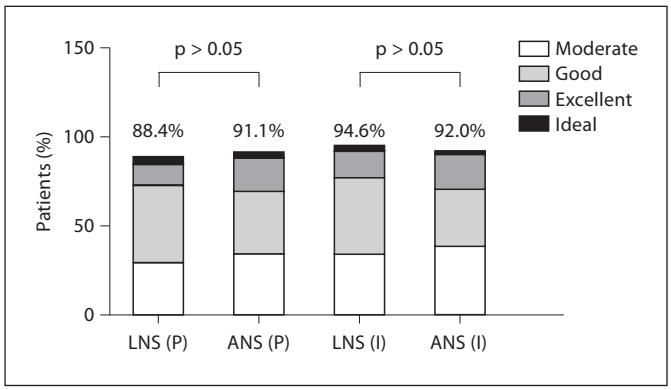

Fig. 3. Comparison of overall therapeutic effects in the LNS and ANS groups at the end of the 2-week treatment period evaluated by the investigators (I) or the patients (P). The investigators gave a positive assessment of the treatment for 95% of patients in the LNS group versus 92% of patients in the ANS group, while 88% of patients in the LNS group versus 91% of patients in the ANS group assessed themselves positively. No significant difference was seen between the groups.

Discussion

AR is a common health problem globally. The short-term expectation of pharmacotherapy for AR is symptom control with minimal impact on daily functioning, and little or no sedation and associated cognitive impairment.

Administration of antihistamines directly to the nasal passages has several advantages over oral administration. Given the fact that the potential for systemic adverse effects is lowered when a drug is delivered directly to the target organ, higher concentrations of the drug can be used for better symptom control. Azelastine and levocabastine are the only two nasal antihistamines currently available in China. ANS (0.1%) [12] and LNS (0.05%) [13] are selective histamine H1 receptor antagonists with no appreciable affinity in vitro for H_2, dopaminergic, adrenergic, serotoninergic, or cholinergic receptors. Although in general, nasal antihistamines are less effective at relieving total nasal symptoms than topical steroids, current treatment guidelines for AR recommend nasal antihistamines as a first-line treatment, probably due to rapid onset of action and safety.

Noble and McTavish [13] reported that topical levocabastine could provide a rapid onset of action, a marked effect on nasal symptoms, and fewer side effects. This is consistent with the results we have obtained in this study. Recently, 335 patients with moderate-to-severe perennial AR in Japan were treated with 2 doses of levocabastine (0.025 or 0.05%) or placebo for 2 weeks, respectively. Significant improvement of nasal symptoms was observed in the levocabastine groups, while there were no significant differences of efficacy between the high-dose and low-dose levocabastine groups. On the other hand, there was no significant difference in the occurrence of adverse effects among the three groups (16, 17, and 20%) [14].

The safety profiles of both ANS and LNS have been extensively evaluated in clinical trials. Nasal irritation, headache, somnolence, and fatigue were the most frequently reported AEs of LNS [13, 15–17], but these were mostly mild or moderate. In our study, only a few mild side effects such as nasal cavity dryness, epistaxis, nasal obstruction, and nasal cavity irritation were reported, indicating that both LNS and ANS were well tolerated. A review of the AEs reported by 1,758 patients undertaking levocabastine treatment identified the following most common AEs: headache (4%), nasal irritation (3%), somnolence (3%), and fatigue (2%) [18]. In another post-marketing survey of 4,002 patients treated with azelastine for 1 month, the most common adverse effects reported were rhinitis (4%), taste disturbance (2.5%), and nasal irritation (1.2%) [19].

In our multicenter study, both nasal sprays provided rapid and effective symptomatic relief. Total nasal symptom control was similar in both the LNS and ANS group (LNS 92% and ANS 93%). These results are consistent with those of other investigators [10, 11]. In terms of onset of action, both LNS [10, 13] and ANS [12, 13] for treatment of AR had a rapid onset of effect. Generally, more than 50% of patients reported symptom relief within 30 min of administration of LNS [10]. In our study, onset of action favored LNS over ANS within 30 min of receiving the first dose of medication. The rapid onset of action indicated a potential for administration on an as-needed basis for relief and control of AR symptoms. In addition, both the investigators and patients involved in this study were highly satisfied with the treatments, indicating a potential for wider use of these two nasal antihistamines in the treatment of persistent AR.

In conclusion, both nasal antihistamines employed in this study are effective and safe for the treatment of moderate-to-severe perennial AR. LNS is superior in terms of onset of action compared with ANS. Further studies are required to assess the effectiveness of symptom control and the safety of long-term administration of these agents.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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