

LEVOCETIRIZINE IMPROVES NASAL SYMPTOMS AND AIRFLOW IN PATIENTS WITH PERSISTENT ALLERGIC RHINITIS: A PILOT STUDY

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SUMMARY:

■ **Background:** Nasal obstruction is the main symptom in patients with persistent allergic rhinitis. Some antihistamines have been demonstrated to be capable of improving this symptom.

The aim of this pilot study was to evaluate nasal symptoms, nasal airflow, and decongestant activity in patients with persistent allergic rhinitis, before and after treatment with levocetirizine or placebo.

■ **Methods:** Forty patients with persistent allergic rhinitis were evaluated, 35 males and 5 females (mean age 23.3 ± 5.9 years). All of them received levocetirizine (5 mg/daily) or placebo for 4 weeks. The study was double-blind, parallel-group, placebo-controlled, and randomized.

Total symptom score (including: nasal itching, sneezing, rhinorrhea, and nasal obstruction) was assessed before and after treatment. Rhinomanometry and decongestion test were performed in all subjects before and after treatment.

■ **Results:** Levocetirizine treatment induced: significant symptom relief ($p < 0.001$), improved nasal airflow ($p < 0.001$), reduction of reversibility percentage ($p < 0.05$), and increase of total airflow after decongestion test ($p < 0.03$). Placebo did not improve nasal symptoms and airflow.

■ **Conclusions:** This pilot study demonstrates the effectiveness of levocetirizine in: i) relieving nasal symptoms, including obstruction, ii) improving nasal airflow, and iii) exerting decongestant activity. Thus, these findings are the first evidence of the impact on airflow and the decongestant activity exerted by levocetirizine in persistent allergic rhinitis.

Key-words: Persistent allergic rhinitis - Nasal obstruction - Nasal airflow - Rhinomanometry - Decongestion test - Levocetirizine.

List of abbreviations: AMP Adenosine Monophosphate ; TSS Total symptom score ; IR Index of Reactivity.

Allergic rhinitis is a common chronic condition that affects up to 21% of the general population in the U.S.A. (1, 2). Its prevalence is also progressively increasing (3).

Experimental evidence supports a direct relationship between the IgE-mediated reaction and the resulting inflammatory process in allergic rhinitis (4). Allergen exposure activates mast cells with consequent release of preformed mediators, mainly histamine, and cytokines capable of inducing inflammatory cell recruitment (including eosinophils, neutrophils, and Th2 cells) and activation (4).

Nasal obstruction constitutes the leading symptom in rhinitis sensitized to perennial allergens; moreover, this symptom may be objectively measured by rhinomanometry. Allergic inflammation, mucosal congestion, and mucus hypersecretion contribute to cause nasal obstruction, as allergic inflammation induces a swollen mucosa, vasodilation causes engorgement of

sinusoidal capacitance vessels, and increased mucus production contribute to impair nasal airflow (5).

Antihistamines have been accepted as highly effective therapy for allergic rhinitis because of their symptomatic activity (6). It is well known that antihistamines have efficacy in controlling nasal itching, sneezing, and rhinorrhea, but many of them, have poor activity against nasal obstruction (7). However, some recent studies showed that the newer antihistamines are capable of reducing also nasal obstruction (8, 9, 10, 11). This decongestant effect might suggest that this property should be due to an additional anti-inflammatory activity, even though it is still under investigation (12).

Levocetirizine, the active enantiomer of cetirizine, is a potent antihistamine as demonstrated by inhibition of histamine-induced wheal and flare reactions [13] and in clinical studies (14). In addition, levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration (15) and improves airway hyperresponsiveness to AMP [16]. Very recently, a study provided evidence that levocetirizine is effective for symptom

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relief, including nasal congestion, in patients with perennial allergic rhinitis (17).

Nevertheless, no data are still available concerning the levocetirizine's effects on nasal airflow in patients with persistent allergic rhinitis. Thus, the aim of this pilot study was to evaluate the effects of levocetirizine, compared with placebo, on nasal symptoms, nasal airflow, and the decongestant effect in patients with persistent allergic rhinitis.

METHODS

■ **Patients:** Forty-three patients with persistent allergic rhinitis were screened. A detailed clinical history and a complete physical examination, including anterior rhinoscopy, were carried out for each patient.

The diagnosis of persistent allergic rhinitis was made, according to international guidelines [18], on the basis of history and skin prick test positivity for perennial allergens. In our geographic area, the most important perennial allergens include *Dermatophagoides farinae* and *pteronyssinus*, cat, and dog (11).

■ **Study design:** The study was conducted as double-blind, placebo-controlled, parallel group, and randomised, when patients were symptomatic and outside the pollen season.

Subjects participated in the study for 28 days and they attended two visits: at baseline, and after 28 days.

Only patients who met all the following criteria were eligible for inclusion into the study: males and females aged >18 years, history of allergic rhinitis due to perennial allergen exposure for the previous 2 years, rhinitis symptoms for the 2 previous weeks with total symptom score (TSS) minimum value > 6 at baseline, particularly with nasal obstruction moderate-severe (see below), and an informed consent obtained prior to study entry. Exclusion criteria were: pollen allergy, acute and chronic upper respiratory infections within 30 days before the study, anatomic nasal disorders (i.e. septum deviation), nasal polyps, use of antibiotics, intranasal or oral corticosteroids within the previous 4 weeks, and use of antihistamines within the previous week. Women of child-bearing potential could not be pregnant, lactating or likely to become pregnant and had to be using a medically accepted, adequate form of birth control.

All patients were randomly subdivided in two parallel groups (10 patients/each) and treated with levocetirizine (5 mg/daily in the morning) or placebo (one tablet/daily in the morning) for 4 weeks. Thus, this was the only pharmacological treatment allowed during the study. Nasal lavage with saline solution was allowed as rescue medication.

Symptom assessment, rhinomanometry, and decongestion test were performed in all subjects immediately before and after treatment. The study was approved by the Navy Hospital Institutional Review Board.

■ **Skin prick test:** Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing skin prick test. It was performed as stated by the Italian Society of Allergy and Clinical Immunology (19). The allergen panel consisted of the following: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel tree, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix; the concentration of allergen extracts was 100 I.R./mL (Stallergenes, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations as negative control. Each patient was skin tested on the volar surface of the forearm using 1 mm prick lancets (Stallergenes, Milan, Italy). The skin reaction was recorded after 15 minutes by evaluating the skin response rate to the inoculation of each allergen extract in comparison with the wheal given by the positive and the negative control. A wheal diameter equal or greater than 3 mm was considered a positive reaction. Antihistamines were stopped 1 week before skin prick test.

■ **Nasal symptoms:** The following symptoms were assessed by the patient, answering the questions made by the investigator, before and after treatment: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated on the following scale: 0= absent, 1= mild (symptom was present but was not annoying or troublesome), 2= moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3= severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep). Total symptom score (TSS) being the sum of each individual symptom was also considered.

■ **Rhinomanometry:** Nasal airflow was measured by active anterior rhinomanometry. Patients wore a tight-fitting facemask, and with the mouth closed, breathed through one nostril. A sensor, placed in the contralateral nostril, recorded data on pre- and post-nasal pressures via airflow and pressure transducers. The instrument (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete GmbH, Germany) was connected to a personal computer. The signals of transnasal airflow and pressure were amplified, digitized, and saved for statistical analysis.

Nasal airflow was reported as the sum of recorded airflow through right and left nostrils in milliliter per

second at a pressure difference of 150 Pa across the nasal passage.

Four or more airflow measurements were performed for each patient and the mean was recorded when reproducible values were achieved.

■ **Decongestion test:** After baseline rhinomanometry, two sprays of naphazoline (0.1%) were then applied per nostril. This drug is a potent α -adrenostimulator inducing quick vasoconstriction. Rhinomanometry was performed 5 and 10 minutes after. The best result was considered. Total nasal airflow volume and percentage of reversibility were evaluated.

■ **Statistical analysis:** The primary outcome variable was considered the TSS. Differences on evaluated parameters at baseline and after treatment were assessed within groups by Wilcoxon Signed Rank test, and between groups by Mann-Whitney U test. P values <0.05 were considered statistically significant. Data are presented as means $\pm$ SD.

RESULTS

■ **Subjects:** Forty allergic patients with seasonal allergic rhinitis were studied, 35 males and 5 females, with an average age of 23.3 ± 5.9 years (range 18-43). Four patients were excluded because of septal deviation and nasal polyps.

All of them were sensitized to perennial allergens only. General physical examination was normal, apart from rhinitis symptoms, in all patients before and after treatment. All subjects tolerated the prescribed therapy without significant side effects.

■ **Nasal symptoms:** At baseline, total nasal symptom scores were not different among the two groups (figure 1).

After treatment, TSS significantly decreased in levocetirizine group ($p<0.001$), whereas placebo-treated patients showed slight increase of TSS.

The intergroup analysis revealed significant differences between levocetirizine and placebo group ($p<0.0001$).

The analysis of single symptoms (figure 2) showed that levocetirizine was effective in significantly relieving all nasal symptoms, such as: itching ($p<0.01$), sneezing ($p<0.04$), rhinorrhea ($p<0.02$), and obstruction ($p<0.03$).

Placebo did not improve any symptom.

Levocetirizine was more effective than placebo in relieving each single nasal symptom ($p<0.001$).

■ **Rhinomanometry:** At baseline, nasal airflow values were not different among the two groups (figure 3).

After treatment, levocetirizine increased (+31%) nasal airflow ($p<0.001$). Placebo induced slight reduction (-13.4%) of nasal airflow.

The intergroup analysis showed that levocetirizine was more effective than placebo ($p<0.0001$).

■ **Decongestion test:** at baseline the percentages of reversibility of nasal airflow were not different in the 2 groups (figure 4).

After treatment, levocetirizine induced lower reversibility ($28.8\% \pm 6.7$) in comparison with pre-treatment values ($44.3\% \pm 6.8$) with statistical significance ($p<0.03$). Placebo induced a slight increase ($p<0.05$) of the percentage of reversibility (before treatment $45.8\% \pm 6.9$; after treatment $56.1\% \pm 10.5$).

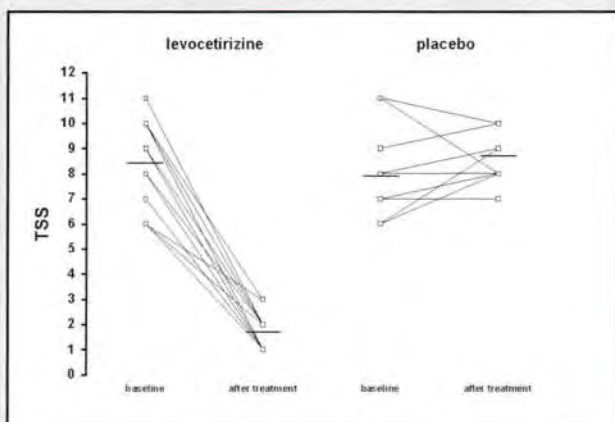


Figure 1: Total symptom score evaluation before and after treatment with levocetirizine or placebo.

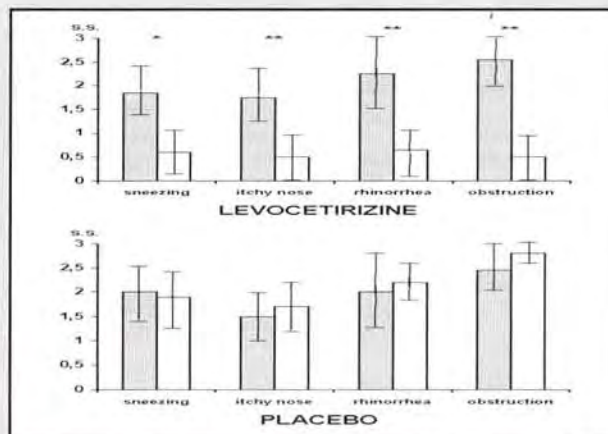


Figure 2: Symptom score for sneezing, itching, rhinorrhea, and obstruction before (grey bars) and after (white bars) levocetirizine treatment upper quadrant or placebo treatment lower quadrant. Data are expressed as means $\pm$ SD.

■ **Total nasal airflow:** considering the total airflow volume after decongestion, levocetirizine treatment induced significant increase (before therapy 649.1 ± 66.4 mL/sec; after therapy 772 ± 76.4 mL/sec) ($p < 0.03$). Placebo treatment induced significant reduction of total nasal airflow (before treatment 668.7 ± 64.8 mL/sec; after treatment 645 ± 84.2 mL/sec) ($p < 0.02$). The intergroup analysis showed that levocetirizine induced a significant increase of total nasal airflow in comparison with placebo ($p < 0.0001$).

DISCUSSION

The present pilot study aimed at investigating the effects of levocetirizine and placebo on symptom relief, nasal airflow, and decongestant activity in patients with persistent allergic rhinitis.

Allergic rhinitis is characterized by inflammation that accounts for occurring nasal symptoms, mainly concerning nasal obstruction. Nasal obstruction constitutes a crucial symptom as it may affect quality of life, bronchial hyperreactivity, and ostiomeatal complex and Eustachian tube patency, thus allowing the occurrence of several sequelae, including rhinosinusitis, otitis media, and asthma (20).

The pathogenesis of nasal obstruction is very complex and consists of three main events: inflammatory mucosal edema, vascular congestion, and mucus hypersecretion (20).

Therapeutic intervention in allergic rhinitis has often focused on blocking the effects of histamine as it represents a major contributor to the nasal symptom appearance. The second-generation antihistamines possess major advantages over the earlier drugs and

some of the newer molecules have additional anti-inflammatory properties (21). In this regard, nasal obstruction constitutes the nasal symptom more representative of allergic inflammation. However, antihistamines are classically considered to be less effective against nasal obstruction than against other nasal symptoms (22). Thus, nasal obstruction relief might express an additional anti-inflammatory property exerted by an antihistamine. Numerous studies showed that some antihistamines are capable of affecting nasal obstruction (7, 8, 9, 10). In addition, several in vitro and in vivo studies showed the impact on inflammatory parameters exerted by some antihistamines (22). The question of whether these additional properties are clinically relevant is however still controversial.

In this study, we have demonstrated that levocetirizine significantly relieves nasal symptoms, including nasal obstruction, and increases nasal airflow. It is noteworthy that this last effect was objectively measured by rhinomanometry. Thus, this functional effect might account for an anti-inflammatory effect by the light of pathophysiologic mechanisms causing nasal obstruction. In support of this hypothesis, levocetirizine affects both the percentage of reversibility and total nasal airflow volume after decongestion. After levocetirizine treatment, the percentage of airflow reversibility significantly diminished: it could mean that nasal congestion may be reduced by levocetirizine. On the other hand, the significant increase of total nasal airflow after decongestion let foresee that other pathogenetic factors, such as inflammatory edema and mucus hypersecretion, as provided by reduced rhinorrhea, may be affected by levocetirizine. These findings are consistent with previous report showing

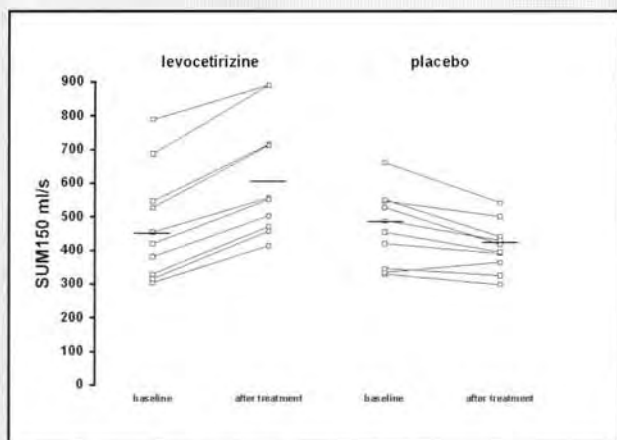


Figure 3: Nasal airflow evaluation before and after treatment with levocetirizine or placebo.

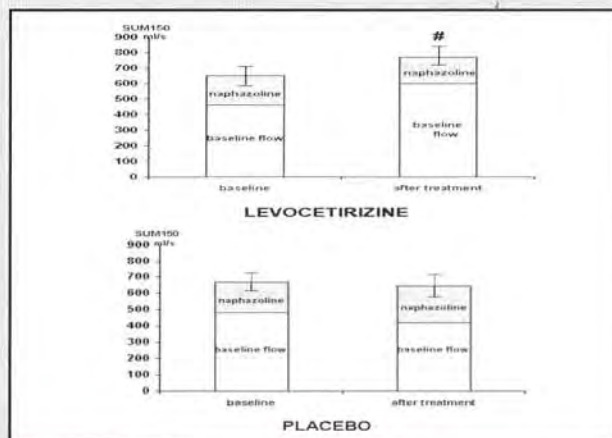


Figure 4: Nasal airflow after decongestion (grey) before and after levocetirizine treatment upper quadrant or placebo treatment lower quadrant. Data are expressed as means $\pm$ SD.

the capability of levocetirizine of relieving nasal obstruction [17]. Moreover, the decongestant activity played by levocetirizine attains a clinical relevance as evidenced by the contestual symptom relief. However, we do not know the exact mechanism of action of this activity exerted by levocetirizine. It might be hypothesized that the decongestant activity may be related to an anti-inflammatory activity as preliminarily reported [15,16]. Moreover, it has been recently provided evidence that levocetirizine is capable of improving nasal airflow and controlling allergic inflammation in patients with seasonal allergic rhinitis (23). It is noteworthy to underline that placebo worsened both symptoms and nasal airflow as expected.

CONCLUSIONS

This pilot study provides the first evidence of the capability of levocetirizine of improving nasal airflow in patients with persistent allergic rhinitis. Therefore, we retain that, taken together, these data may be considered proof of the decongestant activity exerted by levocetirizine in persistent allergic rhinitis. Further studies should be addressed to this issue enrolling more numerous patients.

Competing interests: none declared - Authors' contribution : GC conceived of the study, and participated in its design and coordination, IC participated in the design of the study and performed the statistical analysis, MAT revised the manuscript, and AV participated in the clinical study. All authors read and approved the final manuscript.

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