

EFFECTS ON SYMPTOMS AND QUALITY OF LIFE OF HYPERTONIC SALINE NASAL SPRAY ADDED TO ANTIHISTAMINE IN PERSISTENT ALLERGIC RHINITIS - A RANDOMIZED CONTROLLED STUDY

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INTRODUCTION

Allergic rhinitis (AR) is an high-prevalence disease, characterized by the typical symptoms of rhinorrhea, sneezing, nasal congestion and itching, possibly associated with conjunctivitis. These symptoms are caused by the release of mediators (mainly histamine) in the nasal mucosa following the specific IgE-allergen interaction. When the exposure to allergen persists, an inflammatory reaction with cell infiltration, which is largely responsible for nasal obstruction, also takes place. Allergic rhinitis has a measurable impact on the quality of life (QoL) of patients, and is responsible for significant costs (1, 2). According to current guidelines (3), allergic rhinitis is classified based on the duration of symptoms (intermittent or persistent) and on the impact on everyday activities (mild or moderate/severe). Oral antihistamines are presently considered the first-line therapy of allergic rhinoconjunctivitis (4-6), although in severe and/or persistent disease, nasal corticosteroids may be necessary. Second generation antihistamines are preferred because of their low incidence of sedative and anticholinergic side effects (7). These agents are effective in suppressing histamine-mediated symptoms of rhinitis such as sneezing and nasal discharge and, in addition, can exert also anti-inflammatory actions (8).

Several clinical trials reported favourable results using nasal lavages (NL) as adjunctive treatment, in many nasosinus diseases including allergic rhinitis (9-13). Nasal irrigation seems to be a simple approach to clear allergens from nasal cavities, and to remove nasal secretions. Moreover, nasal lavage is safe also in patients with concomitant asthma. In this regard, the tonicity of the solution used seems to be

crucial, and it was suggested that hypertonic saline is more effective than normal saline in controlling allergic rhinitis-related symptoms (9, 14).

In the present study we evaluated the effects of hypertonic saline nasal spray (HSNS) associated to regular antihistamine therapy in patients with persistent allergic rhinitis. In addition to clinical evaluation, nasal patency was objectively measured by acoustic rhinometry, and QoL was assessed as well over a 4-week period of treatment.

METHODS

This is a randomized, parallel-group, open controlled prospective study. Adult patients with a consistent clinical history of persistent rhinitis were enrolled after signing an informed consent. Daytime and nighttime symptoms, QoL and acoustic rhinometry were assessed during a 1-week run-in period. Afterwards, patients were randomized through a computer-generated list, to receive oral cetirizine 10 mg/day alone (group CZ), or cetirizine plus NL with hypertonic saline (Iperclean® UCB Pharma) four times a day (group CZ+HSNS), for 4 weeks. Symptoms were recorded daily throughout the whole study, whereas QoL and acoustic rhinometry were reassessed at the end of the treatment period. The study was approved by the inner Ethical Committee.

■ **Patients:** Outpatient of both sexes, aged between 18 and 65 years were enrolled. They had to have a clinical history of persistent allergic rhinitis (symptoms present 4 days or more a week) since at least 1 year, and a positive skin prick test (mean wheal diameter > 3mm) or RAST (at least class II) for house dust mites or/and Parietaria. In addition they had to be symptomatic during the run-in period (total symptom score >6) as detailed below. Patients with anatomical abnor-

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malities of the nasal cavity or relevant associated diseases (i.e. vasomotor rhinitis, glaucoma, uveitis, infections, malignancies) were not admitted. Patients with asthma requiring continuous inhaled steroids and pregnant women were excluded as well.

■ **Symptom score:** Patients had to record their symptoms on a proper diary card throughout the study. Daytime symptoms included rhinorrhea, itching, sneezing, stuffy nose, watery eyes, itching, conjunctival hyperemia, palpebral oedema. Nighttime symptoms were stuffy nose, insomnia, nocturnal awakenings, palpebral oedema in the morning. Each symptom was graded from 0 (none) to 3 (severe). The sum of symptom scores for each week of the study was calculated and used for statistical analysis.

■ **Quality of life:** This aspect was quantified during the run-in and at the end of the study by means of the Rhinasthma® questionnaire (15). This instrument is designed for patients with respiratory allergy, independent of the disease (rhinitis or asthma). It is a 30 items questionnaire evaluating the impact of respiratory allergy on physical, psychological and practical aspects of life. Each item is scored on a five point Likert scale (1=not at all, 5= very much). Analytic scores for Lower Airways (LA), Upper Airways (UA) and Respiratory Allergy Impact (RAI) can be extracted. A synthetic score covering the entire questionnaire (so-called Global Impact, GI) is also calculated. The highest score, indicating the heaviest impact of respiratory allergy on QoL is 100 (15).

■ **Acoustic rhinometry:** An Ecovision Acoustic Rhinometry System (Sensormedics Italia s.r.l., Milan, Italy) with an external nasal adapter and nose-pieces of adaptable different diameters was used. Each measurement was repeated three times in each nasal cavity, in order to obtain reproducible readings, and the test was performed at least one hour after nasal lavage. From each measurement, the minimal cross-sectional area (A-min) and the total volume of the nasal cavity (VOL) were calculated (16).

■ **Statistical analysis:** The nonparametric tests of Wilcoxon and Mann-Whitney were used for intragroup and between group comparisons respectively. Demographic data were compared by means of the chi-square test. P values < 0.05 were considered significant.

RESULTS

Fourteen patients (mean age 32.5 ± 4.2 , age range 18-60) participated in the trial. After the random allocation the two groups resulted to be homogeneous

at baseline (run-in week) for all parameters as shown in table 1.

The daytime symptoms improved significantly in both groups versus baseline (figure 1). Nevertheless, in the 3rd and 4th weeks, the symptoms were significantly lower in the CZ+HSNS group ($p=0.02$ and $p=0.01$ respectively) than in the CZ group. The same occurred for nighttime symptom scores, with a greater improvement in the CZ+HSNS group starting from the 2nd week ($p=0.05$) (figure 2). Concerning acoustic rhinometry, no intra-group or between-group difference in the minimum sectional area was found. The total volume of the nasal cavities displayed a significant and equal increase versus baseline in both groups (figure 3).

A significant improvement in all domains (GI, UA, LA, RAI) of the Rhinasthma questionnaire was achieved in both groups with respect of the baseline values (table 2), but in the CZ+HSNS group the UA, RAI and GI scores were better than in the CZ group at the end of the study ($p=0.02$, $p=0.02$ e $p=.007$ respectively).

	CZ+HSNS (n=7)	CZ (n=7)
Age (range)	18-56	18-60
Sex (M/F)	4/3	2/5
Daytime symptoms (mean, SEM)	129 ± 18	110 ± 16
Nighttime symptoms (mean, SEM)	65 ± 13	57 ± 14
Rhinasthma UA	73.3	67.8
Rhinasthma LA	46.13	36.2
Rhinasthma RAI	46.4	35.4
Rhinasthma GI	55.1	45.7
A-min (cm ²)	0.41 ± 0.1	0.47 ± 0.15
VOL (cm ³)	6.6 ± 2.5	6.4 ± 1.6

Table 1: Baseline (run-in) characteristics of patients.

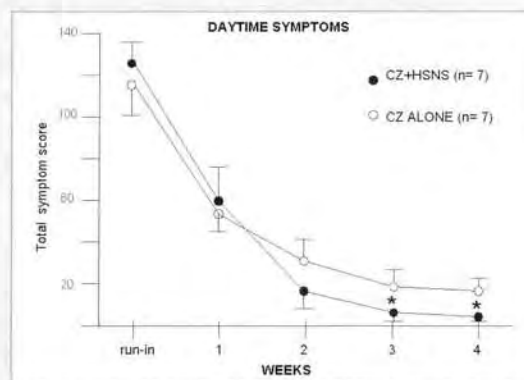


Figure 1: Daytime symptoms (total weekly mean ± SEM) in the two groups at the different time points (the asterisks indicates $p < 0.05$).

DISCUSSION

Allergic rhinitis has a high prevalence and non negligible direct and indirect costs. Moreover it has been clearly shown that the disease, although non life-threatening, affects the QoL of patients and can limit everyday activities (1, 17). The current therapeutic approach is stepwise, according to duration and severity of the disease and involves antihistamines as first line therapy. In persistent disease, usually a chronic

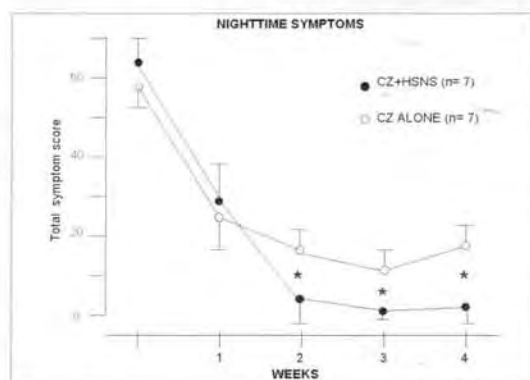


Figure 2: Nighttime symptoms (total weekly mean $\pm$ SEM) in the two groups at the different time points (the asterisks indicates $p < 0.05$).

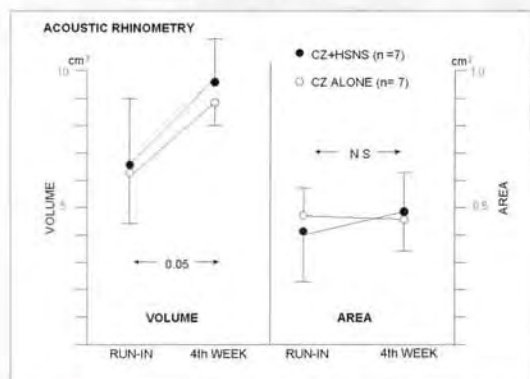


Figure 3: Volume of the nasal cavity (left) and sectional area (right) expressed as mean $\pm$ SEM in the two groups at baseline and after 4 weeks of treatment.

CZ+HSNS	LA	UA	RAI	GI
Run-in	46,1	73,4	46,4	55,1
End study	6,6	5,6	12,1	7,7
p	0,0008	0,0001	0,0008	<0,0001
CZ				
Run in	36,3	67,9	35,6	45,5
End study	10,2	16,7	22,8	15,5
p	<0,0001	0,0001	0,0363	<0,0001
CZ+HSNS vs CZ				
end study	p= 0,2845	p= 0,0188	p= 0,02	p= 0,0076

Table 2: Rhinasthma scores of the four domains: Lower Airways (LA), Upper Airways (UA), Respiratory Allergy Impact (RAI), Global Impact (GI) in the two groups at the two time points.

inflammatory process takes place, being inflammatory infiltration responsible for the troublesome nasal obstruction. This can explain at least in part, for instance, the significant impact that persistent disease may have on sleep and its quality (18). Thus, when evaluating a treatment for AR, the measurement of symptom scores only may not fully represent the impact of disease and therapy, and additional parameters such as QoL and nighttime symptoms should be considered (19). In the present study we evaluated the effect of a nasal spray with hypertonic saline added to standard treatment, and assessed all the possible parameters related to AR. As expected, both treatments (cetirizine alone and cetirizine plus HSNS) significantly improved nighttime and daytime symptoms and QoL of the patients. Nevertheless, the addition of HSNS to antihistamine therapy provided a significant additional benefit on all the evaluated parameters, and this may be due to the mechanical effect of the hypertonic solution that removes allergens, secretions and mediators from the nasal cavity. One possible drawback of this study is the open design, but this was partly imposed by the technical difficulty to have a placebo nasal lavage. On the other hand, the homogeneity of the two groups at baseline and the measurable effects seen also in the control group grant the methodological correctness. Finally, the nasal lavage was well tolerated and no side effect was reported. In conclusion, hypertonic saline (Iperclean®) nasal spray can represent an effective and useful therapeutic option, in association with drug therapy, in persistent allergic rhinitis.

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Article MEDEC EZETROL

EZETROL NAMED "DRUG OF THE YEAR" IN FRANCE

"Which medicine would you call the "Drug of the Year"? This year more than 10,000 French doctors responded, "EZETROL."*

The question was submitted through a vote earlier this year during the annual meeting of MEDEC (Medicine and Communication), the largest congress for general practitioners organized in France. "Doctors were asked to name the drug that represents the biggest therapeutic advance in their daily practice experience". Thanks to their vote, EZETROL won the 2005 MEDEC PRIZE for International Research.

The prize was presented during a ceremony in the French Senate in Paris, on September 27th, 2005 to Jean-Marie Zacharie, Managing Director for MSD France, and Pierre Verstraete, Managing Director for Schering-Plough France. "This prize rewards a successful partnership between our two companies and their teams", said Jean-Marie Zacharie at the ceremony, "and the powerful partnership of EZETROL



Photo : from right to left, Jean-Marie Zacharie and Pierre Verstraete receiving the prize.

together with any statin, providing patients with superior efficacy only offered by Dual Inhibition of two sources of cholesterol".

Representatives from the French Government, including the French Minister of Health, leaders from the pharmaceutical industry and journalists attended the event where four other companies received awards in the areas of Health Education Campaign, OTC product, Medical Information, and Laboratory of the Year.

EZETROL was launched on January 10, 2005, and is on track to achieve its objective in market sales for 2005 and to be a successful launch.

*EZETROL is sold under the name ZETIA in the US (check if any other markets).