Nasaleze & Nasaleze Cold Safety Study

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Angotoyeva IB, Sukhovetchenk o YV

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Study of the Effects of Inert Cellulose Powder on Nasal Mucosa

I.B. Angotoyeva, Ye.V. Sukhovetchenko
Russian Medical Academy of Postgraduate Education

Key Words: inert cellulose powder, allergic rhinitis, study of the efficacy and safety of Nasaleze and Nasaleze Cold, mucociliary clearance.

This article describes the results of the study of therapeutic efficacy of inert cellulose powder in allergic rhinitis (AR), its safety and effect on the nasal mucosa.

The purpose of this open-label prospective trial was to study new treatment options able to reduce clinical symptoms of AR.

Materials and Methods Two groups were enrolled in the study (30 healthy volunteers and 30 patients with AR). Quality of Life assessment using a questionnaire, evaluation of nasal mucosa, mucociliary clearance rate, ciliary movement frequency of columnar epithelium cells, inflammation signs in mucosal smears prior to and after the treatment with inert cellulose powder (Nasaleze and Nasaleze Cold) were performed.

Results. After administration of the medication, quality of life significantly improved in patients with AR, rhinoscopy and endoscopy as well as cytological findings showed attenuation in inflammation signs in the nasal mucosa. It was shown that the medication had no ciliotoxic effect on nasal mucosa. During the whole study period, there were no allergic reactions or significant side effects associated with the medication which demonstrates its safety.

Conclusion. Inert cellulose powder is a therapeutically effective and safe agent for AR treatment and has no negative effect on nasal mucosa.

Introduction

Allergic rhinitis (AR) is a widespread disease with steadily rising prevalence. This leads to increasing social and economic costs. Various prescription and non-prescription medications and treatments are currently available; however, many of these agents have side effects, and patients are reluctant to use them [2]. The existing medications cannot guarantee 100% safety during their administration, especially in such populations as children, pregnant and breast-feeding women. Therefore there is still a significant unmet need for a safe and effective agent for AR prevention and treatment in the urban environment.

Cellulose powder is used as a filler in a variety of liquid nasal sprays and is very safe. There is a patented method for grinding fine-dispersed (micronized) cellulose particles, which provides delivery of an optimal dose of substance to the nasal cavity. As opposed to liquid nasal sprays, in which preservatives are used, cellulose powder suppresses bacterial growth. Not being a drug, cellulose powder, nevertheless, is classified as a medical device, which can be safely used for a year. Ground cellulose directly prevents the cause rather than the consequences of allergic reactions, since it acts as a face mask and prevents dust, pollutants and allergens from getting into the lungs. Respiratory mucosa is characterized by a low surface tension and can readily adsorb allergens from air flowing to lungs [3]. Every day up 20 billion particles enter the nasal passage, deposit on the posterior nasal wall, are swallowed and finally destroyed by gastric fluid. This process is completed by the wave activity of nasal ciliary cells [4]. Properly functioning mucociliary clearance is the first barrier on the way of infectious agents and allergenic particles to the lower respiratory tract, playing a key role in the protective function of the nose [2, 5]. Consequently, the absence of ciliotoxic effect of the drug is the most important criterion of its safety.

The purpose of this study was to assess new treatment options able to reduce clinical symptoms of AR.

The main trial objectives were: to assess the ciliotoxic effect of inert cellulose powder, to determine the mucociliary transport rate prior to and after inert cellulose powder administration, and to assess safety of inert cellulose powder administration.

Materials and methods

This prospective open-label study was performed in healthy volunteers (urban residents) and patients with AR. 30 volunteers in general good health and 30 patients with perennial or seasonal AR were enrolled in the study. The inclusion criteria were: age 15 to 70 years; males and non-pregnant, non-breast feeding females; patients with perennial and seasonal AR, earlier diagnosed in an allergy clinic.

The exclusion criteria were: patients with chronic sinusitis; patients on systemic antibacterial therapy; patients with severe nasal septum deviation; patients involved in other clinical studies. The exclusion of a patient from the study could occur on patient's or the investigator's decision. The reasons for exclusion were documented the Patient's Case Report Form (CRF).

The inert cellulose powder Nasaleze Cold (group of healthy volunteers) and the inert cellulose powder Nasaleze (group of patients with AR) were used in the study. Group I (healthy volunteers) were recommended to receive the medication twice a day for 7 days. Group II (patients with AR) were recommended to receive the medication prior to the contact with an allergen, if possible, but not less than twice a day for 40 days.

To evaluate patients' condition the following tests were performed:

1. Physician's assessment of nasal mucosa condition according to the results of anterior rhinoscopy and endoscopic examination (colour and moisture level of nasal mucosa, severity of turbinate oedema, amount of discharge, severity of nasal obstruction) using visual analogue scale.
2. Measurement of mucociliary clearance time using polymer films with methylene blue and saccharin.
3. Determination of ciliary beat rate (CBR) of nasal ciliated epithelium.
4. Cytological analysis - nasal mucosa smears.
5. Patient's subjective assessment of life quality (filling in the modified Quality of Life Questionnaire for Rhinological Patients followed by the statistic processing of data).

CBR and mucociliary transport rate as well as nasal mucosa smears prior to and after the drug administration were evaluated in group I (healthy volunteers). The quality of life was also assessed by the subjects (filling in the modified Quality of Life Questionnaire for Rhinologic Patients followed by the statistic processing of data); side effects occurring during the administration of this medicinal product were registered.

In group II consisting of patients with AR, the investigator evaluated the intensity of clinical symptoms of AR, assessed the nasal mucosa with the use of anterior rhinoscopy and endoscopic examination (colour and moisture level of nasal mucosa, severity of turbinate edema, discharge properties) using a visual analogue scale. The patients assessed their quality of life (filling in the modified Quality of Life Questionnaire for Rhinological Patients followed by the statistic processing of data) and recorded side effects occurring during the administration of this medicinal product.

Allergic reactions and side effects were assessed for the safety profile. Adverse events (allergic reactions, anaphylaxis) were also recorded. If any side effects associated with the study drug arose, it was documented in CRF. The details concerning adverse events (nature, severity, actions taken and their outcomes) were recorded in Adverse Event Report Forms. A subject was asked to discontinue taking the investigational product if any clinical adverse event, or if another medicinal condition or complication occurred making their ongoing participation in the study not in best interests of the subject. The study drug was stopped if any exclusion criterion became apparent.

Monitoring regimen:

On day 1 of the study the following procedures were performed in groups 1 and 2:

1. Assessment of inclusion/exclusion criteria.
2. Physician's assessment of nasal mucosa using anterior rhinoscopy and endoscopic examination (colour and moisture level of nasal mucosa, severity of middle and lower turbinate edema, amount of discharge and severity of nasal obstruction). The data were recorded in the form of a table using quantitative

values (0, 1, 2), reflecting sign intensity prior to and after the drug administration with the subsequent statistical analysis of the data.

3. Measurement of mucociliary clearance time using polymer films with methylene blue and saccharin.
4. Measurement of CBR of nasal ciliated epithelium prior to and after the administration of inert cellulose powder. CBR was assessed without drug administration and 10 min after its administraton.
5. Cytological analysis - nasal mucosa smears, in which epithelium composition and the presence of inflammation elements were assessed. Percentages of cells with cilia (functional activity of cells) and without cilia (loss of functional activity) in cell composition of columnar epithelium were estimated, as well as the presence of metaplastic epithelium (manifestation of the reaction to inflammation) was registered as «+», «++» and «+++». Inflammation elements were assessed semi-quantitatively («+» – few, «++» – moderately, «+++» – many) and according to the contents (in percentage): neutrophilic leukocytes (manifestation of acute inflammation) and lymphoid-histiocytic elements (monocytes, lymphocytes, histiocytes) - manifestation of productive inflammation.
6. Subjective assessment of the drug effects by a patient. The modified Quality of Life Questionnaire for Rhinological Patients with a maximum score of 140 and a possibility of separate assessment of nasal breath, olfaction, nasal secretion, pain, attitude to treatment, productivity etc. was used for this purpose.

On day 7 in group I (healthy volunteers) all the above parameters were re-evaluated and documented in the patient's Case Report Form. Determination of CBR of nasal ciliated epithelium prior to and after the administration of Nasaleze Cold. At this stage CBR was determined in nasal cavity without drug administration and 30 min after its administration.

Patients in group II (patients with AR) were re-examined on day 40 of the study. All the above listed parameters were re-evaluated. CBR was determined prior to and 30 min after its administration.

Statistical analysis was carried out using program Microsoft Excel and STATISTICA Computer Software (version 6.0). The level of significance was 0.05.

Study Results

The parameters (CBRs, questionnaire scores, mucociliary clearance times, the physician's subjective assessment of nasal cavity) prior to and after the treatment in all the groups were compared using the Wilcoxon test for normal distribution (the number of subjects in each group was 30) with Yates' continuity correction and the threshold value of 1.96 for normal distribution according to the corresponding table at significance level of 5%.

When study parameters were evaluated in group I, the following results were obtained:

1. There was no deterioration in quality of life measurements in volunteers treated with Nasaleze Cold, since the differences in scores were not statistically significant.
2. The physician's endoscopic examination prior to and after Nasaleze Cold administration showed no negative nasal mucosal alterations, which was confirmed by the statistical processing of the scores.
3. Nasaleze Cold did not inhibit mucociliary transport. The difference in mucociliary clearance rates in healthy volunteers prior to and after Nasaleze Cold usage was not statistically significant.
4. Nasaleze Cold did not show ciliotoxic effect. CBR did not change significantly 10 and 30 minutes after a single dose of the drug or on day 7 after its repeated twice-daily dosing.
5. Nasaleze Cold did not affect cell composition of nasal mucosa. Cytological analysis of smears from nasal mucosa prior to and one week after the drug administration revealed no statistically significant reduction in the number of functionally active cells (cells with cilia) relative to the total number of columnar epithelial cells. No changes in the numbers of metaplastic epithelial cells, inflammation elements, percentages of neutrophilic leukocytes and lymphoid-histiocytic elements were observed either.
6. No allergic reactions or significant side effects were observed. 20% of patients complained of a garlic smell, 8% of a tickling sensation in the nose for the first 10-15 minutes after dosing.

When study parameters were evaluated in group II (patients with AR), the following results were obtained:

1. Nasaleze-treated patients with AR reported an improvement in their quality of life. Analysis of the data of the modified Quality of Life Questionnaire for Rhinologic Patients prior to and 40 days after Nasaleze administration showed statistically significant [standard deviation 2.072>1.96 (threshold t value on 5% significance level)] increase in the patients' quality of life scores after the treatment (by a mean of 13.5 points).
2. Comparing mucosa condition scores as assessed by the physician prior to and after 40-day treatment, revealed a statistically significant positive therapeutic effect, by a mean of 2 points. Standard deviation was 2.32>1.96 (threshold t value on 5% significance level).
3. Nasaleze did not slow mucociliary transport even after 40-day continuous usage. The saccharin test showed no statistically significant changes in mucociliary clearance rates for this period.
4. Nasaleze did not exert ciliotoxic effect during its 40-day continuous usage, which was confirmed by the absence of statistically significant changes in CBRs 10 and 30 min after the drug dosing or after 40 days of its twice-daily dosing.
5. Nasaleze administration caused a reduction in inflammation elements in nasal mucosa. Cytological analysis of nasal mucosa smears prior to and 40 days after the drug administration revealed no statistically significant reduction in the number of functionally active cells (cells with cilia) relative to the total number of columnar epithelial cells. No changes in the numbers of metaplastic epithelial cells were observed either. A statistically significant decrease in inflammation elements (standard deviation 2.13>1.96 on 5% significance level) owing to neutrophilic leukocytes was noted in smears with a concomitant increase in the relative counts of lymphoid-histiocytic elements to neutrophilic leukocytes (standard deviation 1.99>1.96 on 5% significance level).
6. There were no drug-related allergic reactions or side effects in this group. 80% of patients estimated the effect of the drug administration as "good", 5% - as "excellent", 15% - as "insufficiently pronounced". 25% of patients reported slight irritation of nasal mucosa ("tickling") within first few minutes after drug dosing.

The results of the study suggest that Nasaleze and Nasaleze Cold did not slow mucociliary clearance neither in healthy volunteers, nor in patients with AR, i.e. both medications have no ciliotoxic effect. They also do not affect CBR which was demonstrated in both groups of subjects during the whole period of monitoring.

The attenuation of inflammation signs in the cellular composition of nasal mucosa smears owing to the reduction in the relative counts of neutrophilic leukocytes was observed in patients with AR after 40-day usage of inert cellulose powder At the same time there was no reduction in the number of ciliary epithelial cells. In healthy volunteers, drug administration did not influence the cellular composition of nasal mucosa smears.

Forty-day Nasal administration in patients with AR was accompanied by an improvement in quality of life (based on the data of the modified Quality of Life Questionnaire for Rhinologic Patients) and the positive therapeutic effect confirmed by the results of the physician's assessment of nasal mucosa. For the whole period of study no allergic reactions or side effects associated with the medications were reported, showing their safety.

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