

A Nasally Applied Cellulose Powder in Seasonal Allergic Rhinitis in Adults with Grass Pollen Allergy: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study

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Key Words

Allergic rhinitis · Barrier protection · Cellulose powder · Clinical trial · Grass pollen

Abstract

Background: A nasally applied cellulose powder is increasingly used in many countries as a remedy for allergic rhinitis. In 2009, a 4-week study in birch pollen-allergic children showed a reduction in nasal symptoms. The best effect occurred on days with lower pollen counts. The present study in grass pollen-allergic adults used the same basic design. **Methods:** In May 2013, a double-blind, placebo-controlled study was conducted in 108 patients with allergic rhinitis due to grass pollen (18–40 years of age). SMS on mobile phones were used as reminders of treatment and reporting of symptom scores. **Results:** We found significant reductions in severity scores for sneezing, runny nose, stuffy nose and symptoms from eyes and lower airways, both separately and together (all $p < 0.001$). Reflective opinion of effect and guess on treatment at follow-up visits (both $p < 0.001$) confirmed a high efficacy. No clinically significant adverse effects were reported. **Conclusions:** The product provided significant protection against all seasonal allergic rhinitis symptoms

from both upper and lower airways during the grass pollen season in an adult population. The magnitude and scope of efficacy support the use of the product as an early choice in the treatment of allergic rhinitis.

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Introduction

Allergic rhinitis is a very common chronic condition. In the United States alone, it affects 65 million people [1]. The prevalence of allergic rhinitis increases with age [2], peaking in teenagers and young adults, and allergy to pollen is a predominant cause [3]. The adverse consequences for the individuals include impacts on their educational career [4] and substantial suffering [5]. A range of remedies and treatments is available on prescription and over the counter. Nasal steroid sprays are considered most efficacious but many sufferers are reluctant to take them due to fear of adverse effects.

An inert cellulose powder (Nasaleze®) has been on sale as a medical device against hay fever in Europe since 1994. It is applied in the nostrils by a simple puffer device. The mechanism of action of the cellulose is through a reaction

with moisture on the mucous membrane, which forms a gel layer. This protective barrier on the nasal mucosa helps to prevent the contact between inhaled allergen and mucosal cells [6].

A double-blind, placebo-controlled study of birch pollen-allergic children in Sweden showed a significant alleviation of runny nose and total nasal symptoms [7]. The best effect was seen on days with pollen counts defined as low or moderate. Our hypothesis was that the trial product in the given dosage should be even more efficacious in grass pollen allergy, a more common problem in a global perspective. In contrast to birch pollen, which is dispersed during a limited period of often intense flowering, grass pollen is often present in the air for several months, and days with low-moderate values generally predominate [7, 8]. The present study aimed to assess the efficacy of the powder in grass pollen rhinitis in young adults on the European continent using the same basic design as the Swedish study in children.

Methods

Research Design

The study was performed at the University Clinics of Kharkov and Dnepropetrovsk, Ukraine, in May 2013, which are urban areas situated in a region dominated by semiarid grassland, which is to a large degree converted into agricultural land. The growing season starts in April, and grass flowering mainly occurs in May and June. A power calculation based on the study in children [7] corresponded to the number of subjects obtained. Subjects 18–40 years of age ($n = 108$) were recruited locally among the patients already followed at respective clinics. All of them had a history of typical nasal symptoms of seasonal allergic rhinitis (SAR) during late spring to early summer. At the first appointment, patient history was scrutinized and severity was assessed. To exclude severe disease, we did not accept patients with previous use of nasal steroids or an assessed current need for nasal steroids. Subjects should not have perennial symptoms or a history of asthma. They were tested with a blood sample for ImmunoCAP specific IgE for timothy grass pollen and birch pollen, with >0.35 kU/ml counted as positive. A positive test for timothy grass pollen was required for inclusion.

The patients were randomly assigned to active or placebo groups using an identical device to be puffed in each nostril 3 times daily. The nasal powders were supplied in plastic containers, which deliver the powder from a nozzle when squeezed. The exact amount delivered is not standardized and the variation in the patterns of deposition in the nose is not known. The placebo was a lactose powder with the same particle size, appearance and the same tinge of mint taste as the cellulose powder.

After emergency contacts with the investigators, rescue medication could be obtained. It consisted of oral antihistamine, loratadine (10-mg tablets) and sodium cromoglycate eye drops. Each subject obtained oral and written instructions about the SMS. The SMS reporting of symptoms started with a 3-day run-in period

before the treatment and continued during the 4-week treatment period during the grass pollen season.

Three times a day the patients were reminded by SMS to take their nasal puffs and were asked to confirm the intake by a response SMS. In the evening, they were asked about the severity of symptoms during the preceding day from the nose, eyes and lower airways and to answer with a figure from 1 to 6, corresponding to (1) *no trouble at all*; (2) *little trouble*; (3) *moderate trouble*; (4) *rather much trouble*; (5) *much trouble* and (6) *very much trouble*. For the nose, scoring of sneezing, running nose and blocked nose were reported. For the eyes and lower airways, only a concluding figure was used.

In the registration, a question on the use of rescue medication was added daily.

At a concluding appointment after the treatment period, the subjects were asked about their global opinion of the efficacy: *no effect*, *good effect* or *very good effect*. They were also asked whether they believed they had obtained the active substance or placebo. Adverse events including discomfort related to the treatment were affirmed or denied.

Pollen Counts

Daily average grass pollen concentration was recorded with a nonstandard volumetric spore trap, which was situated on a balcony in an urban environment near the center of Kharkov.

Statistical Methods

For each question, the mean score was calculated for the whole 28-day period for every subject. Mean values for the sum of all scores as well as the sum of the nasal scores were also calculated. The scores from the two treatment groups were then compared using t tests. The group comparison of reflective opinions and the guess on obtained medication at the follow-up visit were assessed using the χ^2 test.

The study was approved by the local ethics committees at the respective hospitals.

Results

For the study, 108 patients were recruited. One subject in the placebo group withdrew during the 1st day of treatment because of nasal irritation and was the only patient not included in the full analysis set. One further subject in each group was tainted with protocol violations but analyses with exclusion of these did not cause discernible changes of the results. Therefore, all analyses presented were based on the full analysis set of the population. The group characteristics (table 1) were equivalent except for a slightly higher age in the active group. Less than half of the participants in both groups had a positive test for birch pollen in addition to the grass pollen allergy. There were more female than male subjects.

An excellent compliance was obtained in that the subjects had a very good adherence to the requirements of the study, such as reporting their symptoms. Missing replies

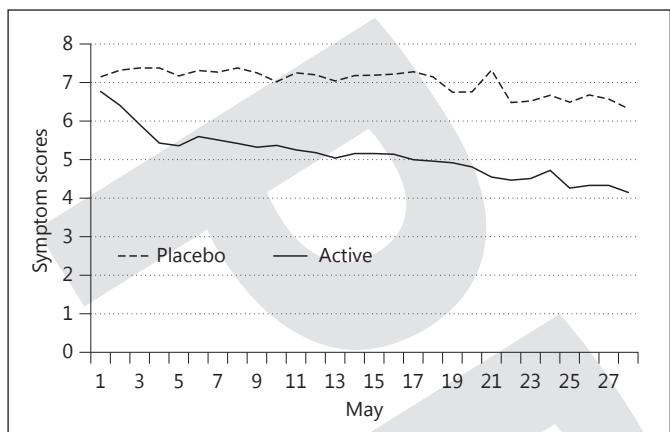


Fig. 1. Sum of nasal symptoms day by day in the respective groups (full analysis set, n = 107). Significance of daily group differences: May 1, nonsignificant, May 2, p < 0.05, May 3–28, p < 0.001.

were not replaced but just omitted. Still, no analysis was based on less than 50 answers from the placebo group and 51 from the active group. The severity scoring during May 1–28 is shown in table 2. The mean scores were generally in the low range. Over the entire 4 weeks, there was a highly significant reduction in all symptoms from the nose, eyes and lower airways in the active group compared to the placebo group both for separate symptoms, total nasal symptoms, and all symptoms from upper and lower airways taken together.

Total nasal scores each day are shown in figure 1. The fluctuations in severity were relatively small. A 3-day run-in served as a technical adjustment period and no more than 66 subjects participated any day; the scores were virtually identical in the two groups. The following 3 days, the difference between the groups increased markedly, followed by a slightly increasing divergence between the groups with duration of treatment. Except for the 1st day, the group differences were significant (day 3 and later, all p < 0.001).

At the follow-up visit, the global appreciation of treatment was in strong and significant favor of the active treatment (table 3). The subjects also guessed which treatment they had received; guessing that the active treatment was received was 10 times more common in the active group than in the placebo group (table 4).

There were only a few signs of adverse events reported during the treatment period (active group 1) or at the follow-up visit (placebo group 4, active group 5); almost all of these concerned nasal irritation and none was severe or serious. Correspondingly, only 1 patient in each group

Table 1. Group characteristics for the full analysis set

Characteristics	Placebo	Active	Total
Mean age, years	24.5	29.3	26.9
Positive test for pollen, n			
Birch	24 (45.3%)	23 (42.6%)	47 (43.9%)
Timothy grass	53 (100%)	54 (100%)	107 (100%)
Gender, n			
Female	34 (64.2%)	34 (63%)	68 (63.6%)
Male	19 (35.8%)	20 (37%)	39 (36.4%)

Table 2. Total of symptoms scored retrospectively at night for 4 weeks

Question	Placebo (n = 53)	Active (n = 54)	p value
Sneezing	2.31	1.65	<0.001
Runny nose	2.37	1.75	<0.001
Blocked nose	2.32	1.76	<0.001
Eye symptoms	2.18	1.59	<0.001
Lower airways	1.92	1.44	<0.001
Sum of nasal symptoms	6.99	5.16	<0.001
Sum of all symptoms	11.1	8.19	<0.001

Table 3. Global opinion about the effect of treatment reported at follow-up

Opinion	Placebo, n	Active, n
No effect	28 (52.8%)	4 (7.4%)
Good effect	12 (22.6%)	32 (59.3%)
Very good effect	1 (1.9%)	15 (27.8%)
Don't know	12 (22.6%)	3 (5.6%)

Group differences, p < 0.001.

Table 4. Patient's guess about treatment received reported at follow-up

Guess	Placebo, n	Active, n
Active	4 (7.5%)	44 (81.5%)
Placebo	26 (49.1%)	4 (7.4%)
Don't know	23 (43.4%)	6 (11.1%)

Group differences, p < 0.001.

received emergency medication in terms of antihistamine tablets, and none received eye drops.

Pollen Counts

The daily average grass counts were low and never exceeded 25 grass pollen grains/m³. The situation of the trap was not optimal to monitor the regional pollen load adequately, but the results confirm the presence of grass pollen in the air throughout the study period.

Discussion

Since 1994, this British remedy for hay fever has been on sale as a medical device and it has been increasingly used in many parts of the world. In various previous studies, the inert cellulose powder has been free from clinically significant adverse effects [7, 9, 10], making the product particularly attractive for over-the-counter use and self-medication. A previous double-blind, placebo-controlled study of birch pollen-allergic children in Sweden showed a significant alleviation of runny nose and total nasal symptoms [7]. In a previous study on adults with grass pollen rhinitis, there was a reduction in rescue medication but no decrease in symptom scores [9]. The dosage of the trial product in this study varied, however, and was generally lower than in the Swedish study in children as well as in the present study.

The use of SMS on mobile phones for reminders and reporting of symptom scores was an original feature in the Swedish children's study that we wanted to test in another clinical context. The continuous and instantaneous reporting of symptom scores into a database speeds up the study procedure and allows a continuous supervision of the study progress on an individual level. This use of mobile phones implies a further development of e-diaries, a methodology with clear benefits compared to paper records in terms of compliance and data safety [11]. The high response rate in symptom reporting and other aspects of the study may be due to both the interactive design and, as we were told, a strong historical tradition of compliance in the area.

Population

The study population was drawn from patients presenting to university hospital clinics. All subjects in the study had a laboratory-confirmed allergy to grass pollen of mild/moderate severity; exclusion criteria were a history of asthmatic or perennial symptoms at inclusion or previous use or assessed need of nasal steroids.

Dosage

The fixed dose of 3 times daily was the same as in the Swedish children's study and is based mainly on clinical experience. For the period of most intense pollen exposure, it may have been somewhat insufficient, but for the more moderate exposure that is most common during grass pollen seasons in many temperate areas [7, 8] it may be more adequate. Another reflection is whether the evening dose really was necessary when the daily pollen exposure was finished; morning and afternoon dosage may have been sufficient. On the other hand, the inert nature of the product allows for considerable dosage increase on demand.

Efficacy

There was a strong and highly statistically significant reduction in all symptom scores analyzed both separately and together. The scoring was also relatively low in the placebo group, which might depend both on the severity of the disease and the pollen exposure. The relief of ocular and bronchial symptoms is considered secondary to the nasal effects in line with the concepts of 'united airways' [12] and naso-ocular reflex [13]. It might be that a certain threshold of nasal disease is necessary in order to elicit the secondary organ effect and that the very low level of nasal symptoms in the active group largely remained below this hypothetical threshold.

The reflective opinion on the effect and guess on treatment obtained was similarly convincing and corroborates the picture of a pronounced clinical effect.

The symptom reduction was larger than in the corresponding study in Swedish children with birch pollen allergy both in terms of absolute scores and relative reduction [7]. One apparent difference between the studies was the pollen seasons. The Swedish birch pollen season in 2009 was intense [7] and the grass pollen load in Kharkov during the present study was light, a fact that probably also explains the small day-by-day fluctuation in mean symptom scores in the present study compared to those reported in other studies [7, 14, 15].

In the study of children in 2009, there was an increased efficacy in periods with lower pollen counts, which can be interpreted in support of the opinion that the product is most appropriate for mild/moderate disease. Maintaining relative freedom from nasal symptoms may be of particular importance for this kind of treatment. Any breakthrough of nasal symptoms may readily reduce the potential action of the product; a blocked nose may obstruct the deposition, a sneezing and runny nose may throw it out. There are no restrictions other than convenience in the

concurrent use of other remedies [7]. Such combinations may in certain severity grades be necessary to maintain the wanted and optimal freedom from symptoms.

Another aspect of the efficacy is demonstrated in the day-by-day view of nasal symptom scores. There is an apparent long-term increase in efficacy, which may support the general advice to start the treatment early, sometimes even before the pollen season has begun.

Nasal steroid sprays are recommended as the first choice in the international ARIA (Allergic Rhinitis and Its Impact on Asthma) guidelines [16]. These guidelines, however, do not discuss non-pharmacological products, probably due to the scarcity of studies of acceptable scientific quality in this context. The degree of symptom reduction in the present study is comparable with a usual result in placebo-controlled studies of nasal steroids and oral antihistamines [17, 18]. Hence, considering the complete absence of significant adverse effects and, with a reservation for the huge imbalance in the number of studies performed compared with intranasal steroid treatment, we suggest that this kind of barrier protection may be tried as an early choice in the treatment of SAR, particularly in the mild/moderate stages of the disease, corresponding to the selected contingent in the present study; our inclusion criteria selected cases with mild/moderate disease, and the degree of severity also comprised the majority of patients with allergic rhinitis [4].

Furthermore, the ARIA guidelines state that allergen avoidance should be part of the management strategy [16]. From a biomedical point of view, the use of cellulose powder is an avoidance measure acting locally on a crucial point of the pathogenetic chain. For many sufferers, a number of psychosocial adverse effects are related to general environmental measures. If this can be averted by the use of a handy spray it may be very valuable. There are other effects of allergen exposure which are related to natural tolerance induction or protection from sensitization [19]. Reduction of the amount of environmental allergen exposure may reduce such a potentially beneficial development. The use of this product implies a targeted avoidance measure for the intranasal route, but it allows all other mucosal allergen exposure. Therefore, theoretically, it may disturb a natural tolerance induction less than gross environmental measures would.

Other Non-Pharmacologic Treatments

There are other local nasal treatments acting physically. The best known is intranasal irrigation with saline [20]. A gel formulation from seawater using a barrier concept was efficacious against allergic rhinitis in an experi-

mental setting [21]. Another product based on the barrier principle, an oil emulsion, has shown a protective effect in a pollen challenge study but with a mode of treatment not feasible for clinical conditions [22]. The magnitude and scope of efficacy in the present study, however, prevails in comparison.

Pollen Exposure

The choice of grass pollen in this study was partly because it is probably the most common allergen in SAR in Europe and globally. Based on the profile in children with a better effect of the product in periods of lower birch pollen exposure and the many days with low/moderate pollen counts that are common during the generally long grass pollen seasons [7], we also expected a high efficacy in grass pollen SAR. The pollen counts from the non-standard volumetric spore trap were low and never exceeded 25 grass pollen grains/m³. The construction of the trap and its location, however, were not optimal to register the regional pollen load adequately, but the counts confirmed the presence of grass pollen in the air throughout the study period.

Conclusions

We could demonstrate that the efficacy of a cellulose powder in the treatment of birch pollen SAR proven in children was even more pronounced in grass pollen SAR in adults, both in terms of magnitude and scope of symptom reduction. All nose, eye and lower airway symptoms were substantially alleviated. As grass pollen allergy is a very common condition all over the world, we believe that this product will provide an increasingly significant contribution to the scope of treatments available today.

Acknowledgments

Nasaleze Ltd, UK, sponsored the study and supplied test products. The Clinical Trial Management Organization workup was diligently performed by the staff at Russian Clinical Research. We are grateful to the staff at the Department of Internal Medicine, Kharkiv National Medical University, and Dr Svitlana Kharkivska and the staff at the Mechnikov Dnipropetrovsk Regional Clinical Hospital, Ukraine, for their skill in performing the clinical work and logistics related to the patient contacts.

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