Clinical Trial Data

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ALLERGY Nasaleze®

ALLERGY Nasaleze®
natural hayfever and allergy prevention

Contents

An introduction to Nasaleze

Nasaleze has performed over 19 trials on nearly 1000 participants for the past decade in England, Sweden, Russia, Greece, China, Bulgaria and Ukraine. Participants have been both male and female with an age range from 1.5 years old to 62 years old. These numerous studies have looked into the benefits Nasaleze products can give to people suffering from allergic rhinitis.

These clinical trials have all been held to the highest standards and have been published and presented all over the world. Each trial has looked into a different problem that allergy patients suffer from. There have been trials focused on the effect Nasaleze has on children, on different allergens and on persistent allergic rhinitis sufferers.

Each trial has used Nasaleze Allergy; an inert cellulose powder which on contact with moisture, found in the nasal tract, forms a gel-like barrier. This stops all air-borne allergens such as pollen, dust mites and animal dander contacting the mucosa. By stopping the allergens reaching the mucosa an allergic reaction is prevented and so are its symptoms. Relief from symptoms can occur in minutes for many patients.

Nasaleze Allergy is a unique product that contains natural cellulose powder of vegetable origin and peppermint powder. There are no antihistamines, steroids, drugs or medicines present in this product. Due to the absence of any medicine Nasaleze is a Class 1 medical device.

Clinical research on Nasaleze

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Number	Study	Description	Population	Measurements and Results	Page
1	**Use of Cellulose Powder for the Treatment of Seasonal Allergic Rhinitis** **Advances in Therapy. 2003; 20(4): p213-219.**	Josling, Steadman. Participants were instructed to have one puff in each nostril of Nasaleze. Drug treatment was allowed if a full hay fever attack occurred. Participants kept a diary documenting the effectiveness of the powder (a score of 5 represents no symptoms and complete control) and average time to relieve symptoms.	102 participants 66 female and 36 male Mean age: 44	Overall average daily score was reported as 3.85 (on the 5 point scale) for men and women indicating a minimum 77% success rate, in chronic hay fever sufferers. Only 12% of volunteers recorded a daily average score under 2.9 revealing a higher score than all pharmaceutical alternatives that were comparatively referred to. Relief was obtained within 0.1-3 hours.	**8**
2	**Clinical study of Nasaleze for relief of allergy symptoms including sneezing, runny nose, itchy and watery eyes** **Presented at the Pan-Hellenic Conference of ENT Specialists in 2004.**	Vlahtis, K. The product was used once a day, usually in the morning or shortly before the known time of day when symptoms usually appear. One application per nostril. Evaluation at time 0, 3 weeks and 6 weeks. Trial took place from December 2003 till March 2004 so that participants were perennial or chronic allergy sufferers rather than seasonal sufferers.	40 participants 24 female and 16 male	All participants were using a pharmaceutical treatment (Decongestant 35% corticosteroids 42.5%, antihistamines 2.5%, corticosteroid/antihistamine combination 20%) at the beginning of the study. Participants were asked to discontinue use of this medication during the study. After 3 weeks of use, 85% of participants realized improvement in their allergy symptoms. After 6 weeks of use, 90% of participants realized improvement in their symptoms. No reported side effects.	**16**
3	**Measure of improvement in nasal mucociliary clearance and PNIFR (peak nasal inspiratory flow rate) in children with allergic rhinitis** **Presented at World Allergy Congress in 2005.** **Nea Pediatrica Chronica. 2005; 5(2)**	Aivazis, Bourli, Maratou et al. Conducted at the University of Thessaloniki, Greece. The mucociliary clearance was determined with use of a non-invasive dye (Edicol Orange 3% + CaHPO42H20 97%) in vivo. The participant's mucociliary clearance was measured prior to using Nasaleze and then 2 days after finishing the 6 week treatment.	100 participants Mean age: 8.2 Age range: 1.5 – 8.2	There was significant improvement in Nasal Mucociliary Clearance (reduced from 39 minutes to 18.15 minutes) and PNIFR values. The mean clearance time was reduced from 55.23 minutes to 21.2 minutes. Out of the 51 children who started the trial with abnormally prolonged clearance all but 5 children had improved nasal mucous clearance times. No adverse effects were reported.	**18**
4	**A double blind placebo controlled trial of inert cellulose powder for the relief of symptoms of hay fever in adults** **Poster presented at World Allergy Congress, 2005** **Current Medical Research and Opinion. 2006; 22(2): p275-285**	Emberlin, Lewis. A double blind, placebo controlled trial in 2004. Participants could take any other medication along with Nasaleze or the placebo.	97 participants 40 male and 57 female Age range: 18+	The amount of rescue medication used by the placebo group (overall and in individual categories e.g antihistamines, nasal sprays and eye drops) was significantly greater than that used by the active (Nasaleze) group. No significant difference found in the symptom scores for the two groups. Nasaleze significantly reduced the need for rescue medication. No adverse effects were reported.	**20**
5	**Double blind placebo controlled cross over trial of inert cellulose powder, by nasal provocation with grass pollen to assess efficacy of the product in controlling symptoms of hay fever** **Poster presented at EAACI, 2006**	Emberlin, Lewis. A trial of Nasaleze by nasal provocation with grass pollen (350 grains per cubic metre). At baseline and at regular intervals after challenge scores were taken for 6 symptom categories, measures were taken of nasal peak inspiratory and expiratory flow and ECP was tested for in nasal secretions.	11 participants Age range: 18+	Nasaleze had significant effects in reducing symptoms of sneezing and itchy eyes ($p<0.01$) due to grass pollen allergy. It can also have significant effects in reducing nasal inflammations, as measured as nasal PEF, PIF and as ECP in secretions ($p<0.05$). Results indicate that use of Nasaleze can help to alleviate symptoms of hay fever.	**34**
6	**Double blind placebo controlled trial of cellulose powder as a remedy for persistent allergic rhinitis, by nasal provocation with Der p1 and Der f1** **Poster presented at EAACI, 2007** **Current Medical Research and Opinion. 2007; 23(10); p2423-2431**	Emberlin, Lewis. A trial of Nasaleze by nasal provocation tests with Der p1 and Der f1. Base line measurements were taken before the challenge of 0.01µg dose containing 5µg of Der p1 and 5µg of Der f1 per g. Measurements taken at 15 minute intervals for the first hour, then at 30 minutes until 4 hours, then at 6 hours and at 24 hours.	15 participants Age range: 18+	There was a significant difference in the results for sneezing, itchy nose, runny nose and ECPs in nasal secretions. The peak nasal expiratory and inspiratory flow were also significantly different but there was considerable variation. There was no significant difference between the other symptoms and there were no adverse reactions. The Nasaleze can have significant effects in reducing some symptoms of persistent rhinitis due to house dust mite allergy.	**36**

Clinical research on Nasaleze (continued)

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Number	Study	Description	Population	Measurements and Results	Page
7	**Nasaleze cellulose powder delays house dust mite allergen (Der p1) diffusion in vitro** **Poster presented at EAACI, 2008** **Natural Science. 2010; 2(2): p79-84**	Diethart and Emberlin of University of Worcester and Lewis of Worcestershire Royal Hospital. The amount of Der p1 (house dust mite allergen) that diffused through the cellulose and agar gel was compared to the baseline allergen content at 15, 30, 45, 60, 180 and 300 minutes after the application of the allergen solution.	In Vitro	There was a significant reduction in the amount of Der p1 that diffused through the Nasaleze compared to the control at all points of time. Only 0.76% of the allergen passed through the cellulose layer after 15 minutes. After 360 minutes only 14% of the baseline Der p1 had crossed the cellulose gel while 100% had passed through the agar layer.	**48**
8	**A meta-analysis of the Efficacy and Safety of Nasaleze in the Prevention and Management of Allergic Rhinitis** **The Open Allergy Journal. 2008; 1(1): p1-4**	A meta-analysis paper by Professor Patrick JD Bouic, Division of Medical Microbiology, Dept. of Pathology, University of Stellenbosch, South Africa. Published in The Open Allergy Journal, 2008, 1, 1-4.	N/A	This meta-analysis review the clinical data conducted on Nasaleze between 2004 and 2008. Presented under 3 categories: Study designs and patient population studied, Study outcome measures, safety and product acceptability and Possibilities of product development.	**56**
9	**Efficacy and safety of medical device Nasaleze in prevention and treatment of persistent allergic rhinitis in adults and children** **Presented at Moscow XVI Congress for Man and Drugs, 2009**	Zakharzhevskaya, Sidorenko, Treskunov and Karaulov at the Sechenov Medical Academy, Moscow. The paper describes the findings of an open non-comparative clinical study of efficacy and safety of Nasaleze in prevention and treatment of persistent allergic rhinitis (AR). Participants were administered Nasaleze 3 times per day over the course of 4 weeks.	48 total participants 25 adults and 23 children Age range: 2 - 62	The severity of AR symptoms and the tolerability of the product were assessed during each visit to the investigator. The results showed that Nasaleze reduces the severity of AR symptoms already in the first week of treatment and overall there was significant improvement in symptom reduction by week 4. A twofold improvement in the quality of life of the AR patients was recorded. Therefore proving Nasaleze is an effective and safe method of prevention and treatment of allergic rhinitis both in adults and children.	**62**
10	**A nasally applied cellulose powder in seasonal allergic rhinitis (SAR) in children and adolescents; reduction of symptoms and relation to pollen load** **Poster presented at EAACI, 2010** **Paediatric Allergy and Immunology. 2011; 22(1): p594-599**	Åberg and Benson. Conducted at the Queen Silvia Children's Hospital, Gothenburg, Sweden in 2009. A double blind, placebo controlled trial. All participants were on daily oral antihistamine appropriate for their age and Nasaleze 3 times daily. Reporting of symptoms and reminders was done by SMS.	53 participants Age range: 8 – 18	There was a significant reduction in total symptom scores for the nose ($p=0.033$) and specifically a running nose ($p=0.0017$). There was a tendency for all symptoms scores to be lower for the active group. During low or moderate pollen count there is a significant reduction in total nasal symptoms and running nose along with sneezing severity.	**72**
11	**Intranasal Inert Cellulose Powder in Prevention and Management of Seasonal Allergic Rhinitis (SAR) in children.**	Geppe, Snegotskaya, Kolosova, Konopelko. The study took place at the Clinic of Child Diseases at the I.M Sechenov Moscow Medical Academy in 2009. An open comparative randomized study. Participants divided into 4 groups depending on their current treatment. Each group received a different medication. Group 1: Nasaleze twice a day. Group 2: Montelukast 5 mg once a day. Group 3: 2 doses of 50mg Sodium Cromoglicate. Group 4: Budesonide 50mg 3-4 times a day.	50 participants Age range: 8 – 18	26 patients demonstrated positive results from the very first application of Nasaleze. After 6 weeks treatment, Group 1 demonstrated a significant decrease (all $p<0.001$) of all SAR symptoms: rhinorrhea, sneezing, nasal blockage, nasal itching, eye itching, nasopharyngeal itching. Children using Nasaleze decreased frequency of use of antihistamine, decongestants and topical steroids. Nasaleze has minimal side effects and is appropriate for children.	**80**
12	**Open non-comparative study to evaluate the effectiveness of Nasaleze preparation for patients with allergic rhinitis** **Russian allergy Journal. 2011.**	Chief clinical physician, N.I. Ilina. The study was conducted at the Russian Federal Medical Biological Agency. An open study over 3 months to determine the effectiveness of Nasaleze at treating allergic rhinitis by nasal provocation test with significantly causative aeroallergens.	30 participants 18 female and 12 male Mean age: 28.5	The therapy using Nasaleze was found to be effective in 28 (99.6%) of the patients, there is also a significant decrease in nasal reactivity due to a causative allergen. The best results were obtained in patients with isolated dust sensitivity and a mild period of rhinitis. No participants showed any adverse reactions.	**89**
13	**Nasal mucociliary clearance and mucoadhesion of hydroxypropyl-methylcellulose of powder used for alleviation of allergic rhinitis** **Poster presented at EAACI, 2010**	Diethart of School of Human and Health Sciences, Swansea Univeristy, Emberlin of National Pollen and Aerobiology Research Unit, University of Worcester and R. Lewis, Worcestershire Royal Hospital. 12 healthy volunteers were tested at the end of the grass pollen season in 2008. The mucociliary clearance time was tested in the absence and then presence of HPMC using a modified Andersen saccharine test.	12 participants 9 female and 3 male Mean female age: 32.8 Mean male age: 37.0	When the HPMC was applied to the nostril it significantly increased the mucociliary clearance time. The mean mucociliary clearance time at baseline was 11.14 minutes this significantly increased to 35.45 minutes when 10 mg of HPMC were applied to the nostril prior to the test ($p<0.0005$). Application of 20 mg resulted in a mean MCT of 50.37 this increase in MCT was statistically significant when compared to baseline and 10 mg HPMC ($p<0.0005$). The HPMC reduced the mesh spacing of the mucus to form a barrier slowing down MCT.	**95**
14	**Efficacy of cellulose powder as part of a complex therapy if patients with intermittent allergic rhinitis** **Russian Allergy Journal. 2011**	Penechko, Sizyakina. Participants were divided into 2 groups. Group one received standard therapy (second generation cetirizine antihistamine, sorbents and topical glucocorticosteroids). Group two received Nasaleze three times a day in addition to the basic therapy. The observation period was 4 weeks with the patients visiting the clinic once a week.	30 participants Age range: 18 - 33	Group one only saw significant improvement in symptoms such as runny and stuffy nose. Participants in group two condition improved by the end of the first week and at the end of the fourth week there was statistically significant reduction in symptoms: runny nose, sneezing, itchy nose and stuffy nose. Analysis of the questionnaire showed significant improvement in quality of life for the second group. Comparative analysis demonstrated that Nasaleze leads to faster alleviation of symptoms and improves quality of life.	**97**

Clinical research on Nasaleze (continued)

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Number	Study	Description	Population	Measurements and Results	Page
15	**Study of the effects of inert cellulose powder on the nasal mucosa** **Russian Allergological Journal. 2011. N6.**	Angotoyeva and Sukhovetchenko. The study took place at the Russian Medical Academy of Postgraduate Education. Two types of participants (healthy and diagnosed with allergic rhinitis) took part in the study. The participant's quality of life was assessed using a questionnaire before treatment with inert cellulose powder (Nasaleze and Nasaleze Cold) and after treatment.	30 participants in general good health. 30 participants with perennial or seasonal AR	Group one participants showed no deterioration in their quality of life after being treated with Nasaleze cold. The mucociliary rate was not statistically significant. Group two participants treated with Nasaleze reported an improved quality of life supported by the significantly improved life scores. Mucosa condition significantly improved by 2 points. There was no ciliotoxic effect for either group and there was no drug related allergic reactions. The mucociliary transport was unaffected in both groups.	**105**
16	**A Nasally Applied Cellulose Powder in Seasonal Allergic Rhinitis in Adults with Grass Pollen Allergy: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group study** **International Archives of Allergy and Immunology. 2014; 163(1): p313-318**	Åberg, Ospanova, Nikitin, Emberlin and Dahl. The study was performed at the University Clinics of Kharkov and Dnepropetrovsk, Ukraine, in May 2013. The patients were randomly assigned active or placebo and given identical devices to be puffed in each nostril 3 times daily. Three times a day the patients were reminded by SMS to take their nasal puffs and were asked to confirm the intake with a response SMS. In the evening, they were asked about the severity of symptoms during the day from the nose, eyes and lower airways and to answer with a figure from 1 (no symptoms) to 6 (strong symptoms).	108 participants Age range: 18 – 40	Significant reductions were found 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. There was a significant difference between the global opinions of the two groups. 87.1% of the active participants found the product had a good effect. The product provided significant protection against all seasonal allergic rhinitis symptoms. There were no severe adverse events.	**110**
17	**Effect of micronized cellulose powder on the efficacy of topical oxymetazoline in allergic rhinitis** **Poster presented at EAACI, 2014** **Allergy Asthma Proceedings. 2015; 36(1): p1-6**	Valerieva A, Popov T, Staevska M, Kralimarkova T, Petkova E, Valerieva E, Mustakov T, Lazarova T, Dimitrov V and Church MK. The study was conducted at the New Bulgarian University in 2012. A double-blind placebo-controlled study. Participants received puff of oxymetazoline followed by either active or placebo powder twice daily for 7 days. Followed by 7 days of just oxymetazoline.	40 participants 23 women and 17 men Mean age = 35	Nasaleze enhances oxymetazoline, PNIF was higher at day 1 and 8. Nasaleze reduces nasal congestion as PNIF is greater in the Nasaleze group than in the placebo. By day 8 both groups had relieved nasal symptoms but only the active group continued to see improvements until day 15.	**118**
18	**Real-Life Study on the Effect of Micronized Cellulose Powder as Add-On to Intranasal As-Needed Treatment of Subjects with Pollen Allergic Rhinitis** **Poster presented at AAAAI 2016**	Popov T, Valerieva A, Church M, Staevska M, Kralimarkova T, Petkova E, Valerieva E, Lazarova T, Dimitrov V. The study was performed Medical University of Sofia in 2015. Patients were given xylometazoline and/or azelastine and/or mometasone or, if symptoms persevered with oral bilastine or prednisolone. Patients were randomized with one puff of either HPMC or placebo (lactose powder). They completed diaries with symptom scores (0-3), and medication scores (1 score for any drug application);combined symptom and medical scores were calculated for 26 days at the peak of pollen season and outcomes analysed.	25 male participants Mean age: 31	Objective measurements of Peak Nasal Inspiratory Flow (PNIF), measure of the level of nasal congestion, and Exhaled Breath Temperature, surrogate marker of airway inflammation, were made before and after treatment. CSMS were significantly lower in the HPMC group. Following treatment PNIF increased in the HPMC arm by 60% vs. 31% in the placebo one. The before vs. after treatment differences were in favour of the HPMC for both PNIF ($P=0.01$) and EBT ($P=0.007$). In real life HPMC applied following rescue medication decreased symptoms and medication use and reduces nasal congestion and inflammation.	**126**
19	**Clinical efficacy of nasal cellulose powder for the treatment of allergic rhinitis.** **Journal of Clinical Otorhinolaryngology Head and Neck Surgery. 2015;15 p1340-1342**	Wan Lanlan Wan, Li Peizhong. The study was conducted at Department of Otorhinolaryngology Huai'an First People's Hospital, Nanjing Medical University Huai'an in China. Patients with allergic rhinitis were randomly divided into control group and experimental group. The control was treated with physiological sea water and the experimental group with HPMC. Nasal congestion, nasal itching, sneezing and runny nose were symptoms subjected to evaluation. The average score was measured after 14 and 28 days of treatment.	36 patients Control group: 8 male, 10 female average age: 32.5 Experimental group: 5 male, 13 female average age: 34.5	The experimental group and the control group of subjective symptoms and objective nasal function were improved, but the experimental group (HPMC) scores were significantly higher than control group. The difference was statistically significant ($P<0.05$); Two groups of patients had no adverse reaction occurred.	**128**
20	**A Double Blind Placebo Controlled Study Documenting the effect of Nasally Applied Cellulose-Derived Powder in Subject Sensitized to Grass Pollen** **Poster presented at AAAAI 2017**	Popov TA, Emberlin JC, Aberg N. A double blind placebo controlled study documenting the effect of nasally applied cellulose-derived powder in subjects sensitized to grass pollen. J Allergy Clin Immunology 2017; 139 (2, Suppl.): AB386.	107 patients Age range: 18-40	The number of subjects without nasal symptoms increased in the course of time (group difference $p<0.0001$) and the number of subjects without other symptoms was about twice as high as in the placebo group over the entire period. The mean of severity scores were roughly halved in the active group for both nasal ($p<0.0001$), ocular ($p<0.0001$) and bronchial symptoms ($p=0.0015$); the inter-group differences increased during the study period for nasal and bronchial symptoms (both $p<0.0001$).	**134**

Nasaleze patented delivery system

The nozzle delivers a fine mist of powder

The air and powder travel up the hollow delivery tube to the nozzle

When the bottle is squeezed, air forces Nasaleze powder up the hollow tube

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Nasaleze®
DRUG FREE • CLINICALLY PROVEN • FAST ACTING
Nasaleze®
ALLERGY BLOCKER
Relieves Sneezing, Runny Nose and Sinus Congestion
ALL DAY PROTECTION
ALL DAY PROTECTION
100% NATURAL
Nasaleze
Allergy Blocker

Use of Cellulose Powder for the Treatment of Seasonal Allergic Rhinitis.

Josling P. and Steadman S.

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Use of Cellulose Powder for the Treatment of Seasonal Allergic Rhinitis

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ABSTRACT

Our study was designed to determine whether a unique cellulose powder extract could prevent the classic hay fever attack from occurring among volunteers who have suffered for some years. Nasaleze enhances nasal mucus, which allows the filtration of allergens, to ensure that only clean air reaches the lungs. One hundred and two volunteers were recruited and, using a simple five-point scoring system to grade their general well-being and severity of any hay fever attacks, the overall average score was 3.85, indicating that Nasaleze was able to control hay fever very well. Rapid relief of symptoms was also demonstrated, sometimes within minutes after inhalation. Overall, 77% of volunteers reported a significant reduction in the number of challenges throughout the study period and most graded Nasaleze as more effective and reported fewer side effects than with a wide range of chemical treatments.

Keywords: cellulose; seasonal allergic rhinitis; allergen

INTRODUCTION

Approximately 12 million people in the United Kingdom[1] and more than 60 million in the United States[2] have seasonal allergic rhinitis. Symptoms vary from mild discomfort to activity-limiting.

Seasonal allergic rhinitis is characterized by a relatively dry nasal tract, without adequate mucus to absorb airborne dust, animal dander, pollens, and spores and prevent these irritants from reaching the lungs. Each day, up to 20 billion particles enter the nasal passages[3] and are swept to the back of the throat, swallowed, and ultimately destroyed by stomach acid. This process, accomplished by the on going wave action of the nasal hair cells.

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The rising prevalence of seasonal allergic rhinitis parallels the increase in environmental allergens whose presence in the nose trigger the release of histamine and other compounds into the bloodstream.

CAUSES AND SYMPTOMS

An allergic reaction may result when the immune system mistakenly identifies a normally harmless substance as a threat, the filtration system of the nasal tract becomes overloaded from excessive pollution, or the nasal tract dries out. The precise mechanism is unknown but may be genetic.

An allergic reaction is triggered when mast cells found in or near the nose, lungs, skin, eyes, and blood vessels release high concentrations of histamine in response to stimulation by the body's immune defenses.

Histamine, in turn, induces the classic symptoms of seasonal allergic rhinitis, including nasal congestion and itching; runny nose; itchy, watery eyes; swollen, itchy eyelids; difficulty breathing; loss of taste and hearing; dry cough; and headache.

The severity of symptoms varies among individuals and in response to pollen counts and local weather conditions.

TREATMENTS

In the United Kingdom, the allergy market is currently worth about £67.9 million sterling and is growing by about 5.5% each year according to the OTC Bulletin published in June 2003.

Antihistamines

Antihistamines prevent the release of histamine from mast cells or diminish its effect after release. Oral antihistamines are probably the most convenient chemical treatment for most people, although a number of natural alternatives are available.

Older antihistamines cause substantial drowsiness because they can cross the blood-brain barrier; newer, nonsedating antihistamines are longer-acting and better tolerated but still elicit adverse effects.

Topical Agents

The effectiveness of eyedrops and nasal sprays depends, to a considerable degree, on frequent application. Sodium cromoglycate, the most widely used topical treatment, acts by preventing the release of histamine. Instillation is not recommended in the presence of contact lenses or glaucoma.

Nasal sprays, like beclomethasone, reduce inflammation and mucus production. These products are not used in cases of nasal infection and are not licensed for sale over the counter to patients younger than 18 years of age, in the UK.

A number of herbal or plant-based compounds, including garlic, goldenseal, and feverfew, are also available for oral use.

Cellulose powder is used as a thickener in many liquid nasal sprays and is generally regarded as safe. The special proprietary grade of micronized cellulose in this study* used a patented method that ensures delivery into the nose of a suitable amount of material drawn from the container. Compared with liquid nasal sprays, which require preservatives, powdered cellulose inhibits bacterial growth. While not a medicine, it is classified as a medical device that is safe to use throughout the year. The powdered cellulose product addresses the cause of allergic reactions, rather than the symptoms, because it works as a facial mask in preventing inhaled pollen, dirt, and allergens from reaching the lungs. In a healthy individual, the nose and nasal tract extract these materials from the inhaled air, including air that has been exposed to mucus membranes and therefore been stripped of allergens. Mucus has a low surface tension and can easily absorb allergens from air as it passes down into the lungs.

Uniquely, the cellulose powder described herein turns into a gel on contact with the moisture always present in the nasal cavity. This gel is similar to normal mucus and helps to maintain delivery of a supply of clean air to the lungs.

METHODS

Following recruitment through local and national press releases, 102 volunteers (66 female, 36 male; mean age, 44 years), who had previously used products for seasonal allergic rhinitis, were enrolled in the early spring of 2003. Each participant completed a pretrial questionnaire designed to assess the severity and range of symptoms experienced and the months when they were most distressing (Table 1). Pharmaceutical treatments used in the past were identified, and their effectiveness was rated on a five-point scale (1 = not effective at all to 5 = very effective). General well-being during the study was recorded daily in a take-home diary and graded on a five-point scale (5 = well, no problems; 4 = quite well with occasional sneeze; 3 = can feel an attack coming on, some minor symptoms; 2 = feeling low and definitely suffering; 1 = full hay fever attack with symptoms listed). Also listed were the number and variety of symptoms, the day or time elapsed when recovery began, and the time until symptoms resolved. A global assessment of the cellular powder was provided at the end of the 6-week study.

Participants were instructed to place one puff of the inert cellulose powder into each nostril according to the manufacturer's recommendations. If a full-scale hay fever attack occurred, drug treatment was allowed but was to be recorded in the diary.

The pollen count, obtained from both local and national sources, was monitored and recorded every day throughout the study. A large number of volunteers rode horses and admitted to symptoms throughout the year mainly as a result of daily exposure to hay and horse hair.

The average time to symptom relief in minutes, hours, or days and the total number of days when symptoms occurred were recorded and compared with the predicted onset of action of previously used pharmaceutical alternatives[4] and with the volunteer's own subjective assessment of the efficacy of these products. Data were analyzed by means of a Student's *t* test to gain a probability coefficient that allowed for the calculated number of degrees of freedom.

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*Nasaleze, a registered trademark of Kisska International Ltd, Keighley, West Yorkshire BD21 3ND UK
www.nasaleze.com

Table 1. Time of Hay Fever Symptoms

Month	Volunteers, no.	
	Male	Female
January	6	18
February	14	19
March	24	45
April	36	66
May	36	66
June	36	66
July	34	66
August	26	58
September	12	27
October	6	14
November	5	13
December	7	19

RESULTS

A wide range of pharmaceutical treatments had been used in the past to alleviate hay fever symptoms, but most of these products were rated as not very effective (Table 2). When exceptions were noted (as with beclomethasone), side effects were often recorded. In contrast, the natural cellulose powder earned, on average, a higher score than all the pharmaceutical alternatives. The scores of 3.8 for men and 3.9 for women represent a minimum 77% success rate, because a rating of 5 equals no symptoms and complete control. The average daily score with the cellulose powder was in excess of 4.0 in over 35% of volunteers and above 3.0 in over 70%, indicating an occasional sneeze but no hay fever symptoms. In only 12% of volunteers was the average daily score less than 2.9. A total symptom-control score of nearly 88% with the cellulose product is therefore warranted. At the end of 6 weeks, more than 70% of volunteers rated the cellulose powder as good or excellent (Table 3). Either of these ratings was more likely in women than in men.

Volunteers were statistically likely ($P<0.005$) to gain relief from symptoms within 0.1 to 3 hours of using the cellulose powder—a rapid onset of action suggesting value in the relief of the most chronic hay fever symptoms.[5]

A comparison of the weekly average scores for volunteers and the reported pollen count in the United Kingdom indicates a small reduction in quality-of-life scores as pollen increased in weeks 3 and 4 of this study (Figure 1); however, high scores throughout the 6-week trial indicated considerable benefit from the test substance.

The single treatment failure occurred in a woman who could not record a score above 1 at any time throughout the study. She reported a wide range of symptoms and a number of concomitant diseases. Her removal from the calculations would result in a slightly higher average score for women.

Table 2. Use of Pharmaceutical Treatments

Treatment	Average Efficacy Score: Male Volunteers	Average Efficacy Score: Female Volunteers
Beconase®(steroid nasal inhaler) Glaxo Smith Kline, UK	3.0	3.1
Sodium cromoglycate (antihistamine nasal inhaler) - Various generic manufacturers	1.3	2.1
Opticrom® (eyedrops) Aventis Pharma, UK	1.5	2.0
Clarityn® (oral tablets) Schering Plough, UK	2.0	2.2
Zirtek® (oral tablets) Glazo Smith Kline, UK	1.1	1.8
Piriton® (oral tablets and liquid) Stafford Miller, UK	1.3	1.8
Telfast® (oral caplet) HMR, UK	2.0	1.8
Natural cellulose powder	**3.8**	**3.9**

Scale from 1 (not effective at all) to 5 (very effective).

Other products used regularly in the past by volunteers included Benadryl, Otrivine, Flixonase, Triludan, Sudafed, New Era, Rhinocourt, Atarax, Phenergan, Vallergan, Semprex, and Zaditen.

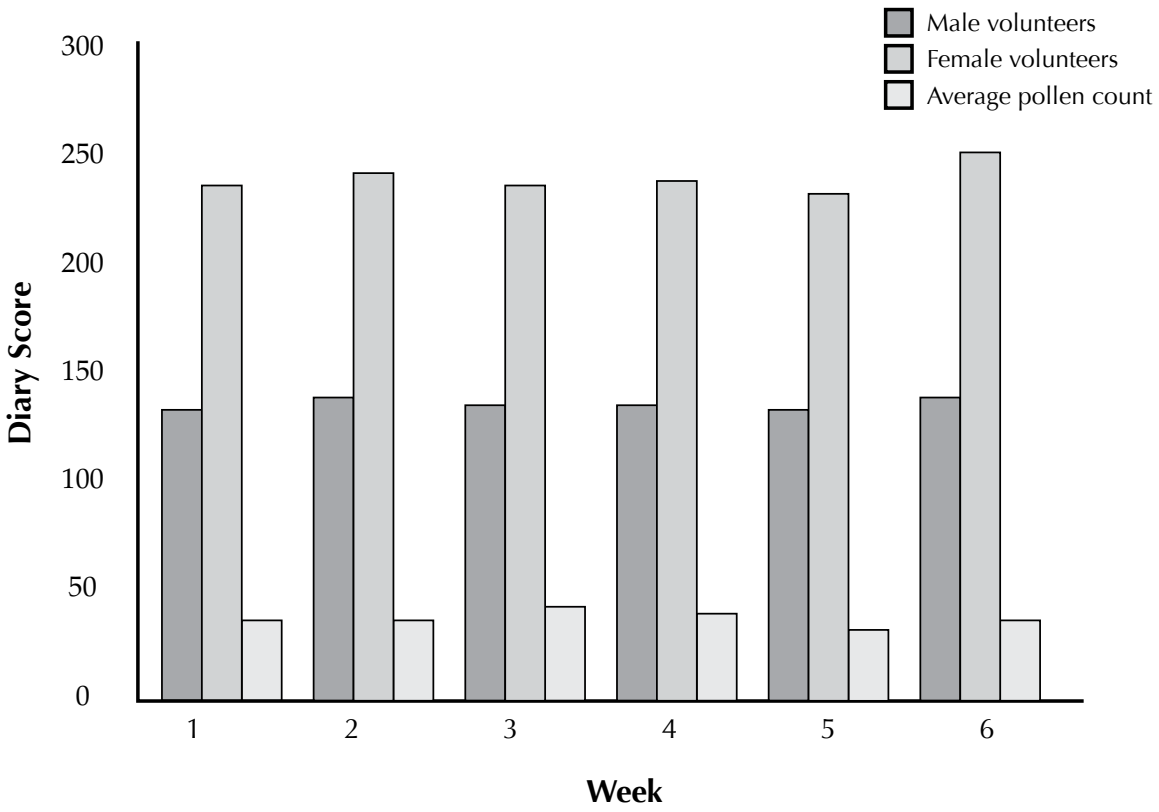
Table 3. Global Assessment of Efficacy of Cellulose Powder

Volunteers	Overall Impression, %: Good	Overall Impression, %: Excellent
Male	76	69
Female	80	75
Total	78	72

Side effects were infrequently reported, but in week 1, 10% of volunteers noted that it was easy to inhale a large amount of powder, which caused an uncomfortable sensation at the back of the throat. One person reported itchy eyes, and another mentioned a sore throat; both symptoms may have been related to hay fever. Difficulty gauging how much powder remained in the bottle (opaque white plastic) was a common complaint, and in one case when the powder ran out, serious hay fever symptoms occurred immediately. Nine volunteers reported being able to smell the powder on inhalation, but this was not regarded as a problem.

Six women and two men required additional treatment with pharmaceutical products; however, volunteers who took more than the recommended one puff in each nostril per day could derive increased and accelerated relief of symptoms.

Figure 1 Average Weekly diary scores*



* Maximum score: 180 for men, 330 for women

DISCUSSION

In this pilot investigation, an inert cellulose powder placed into a novel, patented delivery system relieved classic hay fever symptoms, sometimes within minutes but usually within 3 hours of inhalation. The volunteers selected had a long history of multiple symptoms requiring chemical treatments that were, at best, only moderately effective. Of the 102 volunteers, 78 volunteers reported no hay fever episode during the study and experienced their first season free of sore throat, runny nose, sneezing, and watery eyes. The cellulose powder was easy to take and effective; the overall success rate exceeded 77%.

Although a short period of experimentation appears to be necessary before effective use of the product, adequate instructions are provided in patient leaflets supplied by the manufacturer (not used in this study). A metered-dose delivery system is under consideration that would allow more frequent use of the product (when the pollen count is especially high) and easier identification of the need for a new supply. The ability to filter air in the nasal passages appears to be superior to air purifiers and room air-conditioning filters.

Most volunteers observed that previous drug treatment had never alleviated all symptoms, whereas resolution of symptoms was complete with the cellulose powder.

This pilot investigation demonstrated that inert cellulose powder, delivered into the nasal cavity, prevents allergic reaction to pollen and other irritants and represents a safe and natural alternative to pharmaceutical preparations. Treatment with cellulose powder should be started as early as possible and continued throughout the pollen season, with the number of applications per day increased as appropriate. This product is suitable for use by individuals with diabetes and asthma, pregnant women, and children.

Further work should be done to ascertain the exact degree of efficacy, perhaps by adopting a double-blind placebo-controlled design for future evaluations, but in the meantime, Nasaleze treatment represents a real opportunity to significantly improve the quality of life for hay fever sufferers everywhere.

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Clinical study of Nasaleze for relief of allergy symptoms including sneezing, runny nose, itchy and watery eyes.

Vlahtis K.

Poster presented: The Pan-Hellenic Conference of ENT Specialists on 19th March 2004 in Thessaloniki, Greece.

ALLERGY Nasaleze®
natural hayfever and allergy prevention

Clinical Study Results Summary

Dr. Konstantinos Vlahtsis
External Co-operator American Hellenic Educational Progressive Association (AHEPA) Hospital, Aristotelian University of Thessaloniki, Greece

Product Use:

- Used once daily, mainly in the morning or shortly before the known time of day when symptoms usually appear.
- One application per each nostril.
- Symptoms measured were sneezing, runny nose, itchy and watery eyes.
- Scale used to measure symptoms
- 5 – complete relief, without symptoms
- 4 – major relief, casual sneezing
- 3 – light, but noticeable allergy symptoms
- 2 – allergy symptoms apparent with periodic flare ups
- 1 – allergic rhinitis with complete symptoms

Time period:

- December 2003 through March 2004; this time period does not represent seasonal sufferers, but rather perennial or chronic allergy sufferers. This means they could suffer from a variety of triggers including but not limited to dust mites, pet dander, and/or smoke in addition to pollen.
- Duration of 6 weeks with evaluation at time zero, 3 weeks (21st day after start of treatment), and 6 weeks (42nd day after start of treatment).

Study participants:

- Suffer from diagnosed allergic rhinitis as diagnosed by a radioallergosorbent test (RAST) which is an allergy test that involves collecting blood or by traditional dermal skin tests.
- Currently use a pharmaceutical treatment (either over-the-counter or prescription); participants were asked to discontinue use of their current medications during the study.
- Total of 40 participants (16 men, 24 women)
- Summary of previous treatments used by participants:
- Decongestant – 35%
- Corticosteroids – 42.5%
- Antihistamines – 2.5%
- Corticosteroid/Antihistamine combination – 20%

Table 1

	Scale 1	Scale 2	Scale 3	Scale 4	Scale 5	% scoring complete or major relief (4,5)
Baseline - before treatment	4 (10%)	16 (40%)	14 (35%)	6 (15%)	0 (0%)	15%
3 weeks	1 (2.5%)	5 (12.5%)	16 (40%)	13 (32.5%)	5 (12.5%)	45%
6 weeks	1 (2.5%)	2 (5%)	6 (15%)	20 (50%)	11 (27.5%)	77.5%

Table 1 shows number of patients during each time period and their reported score (percent of total participants in parenthesis).

Table 2

	3 scale improvement	2 scale improvement	1 scale improvement	0 scale improvement	Mean improvement
3 weeks	0%	5%	80%	15%	0.9 scales
6 weeks	7.5%	35%	47.5%	10%	1.4 scales

Table 2 shows the percent of participants that experienced improvement. After 3 weeks of use, 85% of participants realized improvement in their allergy symptoms. After 6 weeks of use, 90% of participants realized improvement in their symptoms.

Side Effects

- There were no reported side effects from any participants.
- Participants reported that the product was simple and easy to use.

Presented at the Pan-Hellenic Conference of ENT Specialists on 19th March 2004 in Thessaloniki, Greece.
Open Clinical Trial

Study of mucociliary clearance in children with allergic rhinitis, before and after a six week therapy with natural cellulose powder.

Aivazis V, Bourli E, Maratou E, Mavroudi A, Aivazi D, Foutzila E, and Ilonidis G.

Poster presented: World Allergy Congress in Munich, Germany June 2005.

Published: *Nea Pediatrica Chronica*. 2005; 5(2).

Clinical Study Results Summary

Aivazis V, Bourli E, Maratou E, Mavroudi A, Aivazi D, Foutzila E and Ilonidis G
1st Paediatric Department of Aristotle University of Thessaloniki, Greece

Study of mucocilary clearance in children with allergic rhinitis, before and after a six week therapy with natural cellulose powder

Background: The aim of the study was to estimate the nasal mucus clearance before and after monotherapy with natural cellulose administrated in the form of inhaled powder in children with allergic rhinitis.

Method: One hundred (100) children: 53 boys and 47 girls were selected. Mean age of the study group was 7.96 years (range 1.5 - 8 years). All children had a positive medical history for allergic rhinitis. Seventy eight out of 93 children (83.8%) who were subjected to allergological investigation had high serum total IgE immunoglobulin, specific IgE antibodies or positive skin prick tests. Mucocilialy clearance was determined in vivo by means of a simple non invasive dye method (Edicol Orange 3%+ $CaHPO_4 2H_20$ 97%). Mucociliary clearance was measured once before starting therapy and one more time 2 days after the child had received a six week therapy.

Results: The clearance reduced from 39 minutes measured before therapy to 18.15 minutes after therapy. The reduction was statistically significant ($p<0.001$). In the beginning of the clinical trail 51 out of 100 children had abnormally prolonged clearance with a mean value 55.23 min (range 31-80 min) which became 21.1 min after treatment. Only 5 children did not improve and mucociliary clearance remained abnormally long above 37 minutes.

Conclusion: The significant decrease of clearance observed in children of our study after treatment, especially in those with mean value above 31 minutes is due to the effect of cellulose, since the children received no other therapy. It is apparent that the improvement in clearance may be attributed to regeneration and normalization of the ciliary epithelium. Mucociliary clearance is the first line of defense of ciliated nasal epithelium against inhaled particles such as allergens, pollutants and viruses. Cellulose enhances nasal mucus, which allows the filtration of allergens, to ensure that only clean air reaches the lungs.

Poster was presented at 6th Pan-Hellenic Conference of Allergiology and Clinical Immunology as a poster at 7th, 8th and 9th of April 2005 in Athens, Greece. Published in Nea Pediatrica Chronica, June 2005, Vol 5 no 2. Open Clinical Trial.

A double blind, placebo controlled trial of inert cellulose powder for the relief of symptoms of hay fever in adults.

Emberlin JC, and Lewis RA.

Poster presented: *World Allergy Congress* in Munich 2005.

Published: *Current Medical Research and Opinion*. 2006; 22(2): p275-285.

ALLERGY Nasaleze®
natural hayfever and allergy prevention

A double blind placebo controlled trial of inert cellulose powder for the relief of symptoms of hayfever in adults

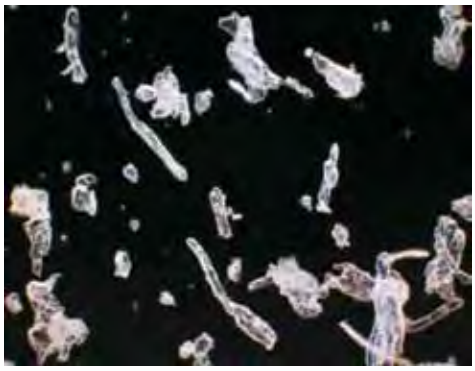
JC Emberlin* and RA Lewis++

*Director, National Pollen and Aerobiology Research Unit, Institute of Health, University College Worcester WR2 6AJ UK
++Consultant in Respiratory & General Medicine, Worcestershire Royal Hospital, Charles Hastings Way, Worcester WR5 1DD UK

Background

Seasonal allergic rhinitis due to pollen allergy occurs in 15 to 37% of the population of Europe depending on age group and region resulting in notable social and economic costs.

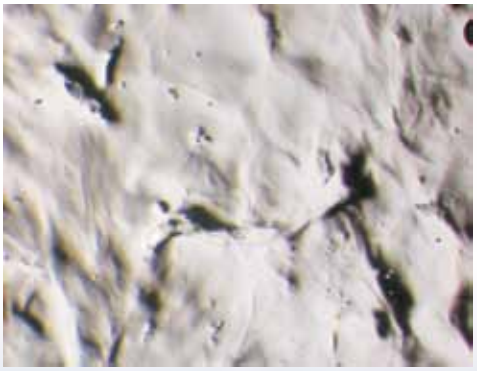
An inert cellulose powder (Nasaleze) has been on sale in the UK since 1994 as a remedy for hay fever but no scientific trials have been conducted previously. The principal aim was to determine if there is a significant difference in the amount and type of rescue medication required for adult hay fever sufferers to control their symptoms in the grass pollen season while using either Nasaleze or a placebo. The second objective was to see whether Nasaleze resulted in an improvement in symptom control.



Nasaleze powder dry (taken from 100 x magnification)

Methods

A double blind placebo controlled study was conducted of 106 adult hay fever sufferers, over the grass pollen season of 2004. Participants were allowed to take any medications they wished in addition to the Nasaleze or placebo.



Nasaleze powder after exposure to damp surface (taken from 100 x magnification)

Results

No significant differences were found ($p<0.01$) between the active and placebo groups in Likert scores for any of the rhinitis nasal symptoms or in the total Likert symptom daily scores (Fig 1). Significant differences were found in the amounts of rescue medication taken by the active and placebo groups ($p<0.05$) (Fig 2). More people in the placebo group took rescue treatments than those in the active group.

Conclusion

The amount of rescue medication taken by the placebo group was significantly more than that taken by the active group both overall, considering all types of medication, and also in the individual cases of antihistamines (Fig 3), nasal sprays and eye drops. These results provide strong evidence that Nasaleze reduces the need to take rescue medication for the symptoms of hay fever.

Fig 1

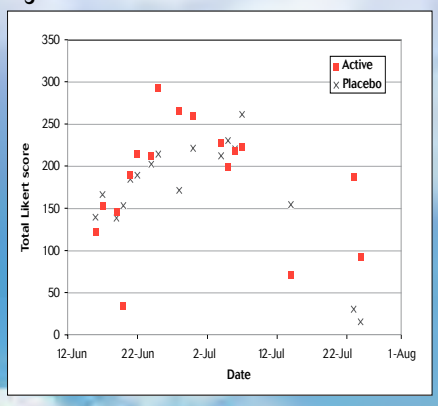


Fig 2

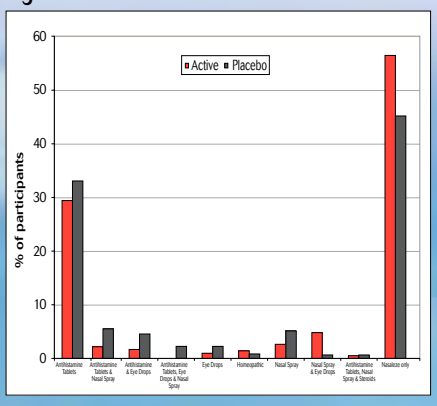
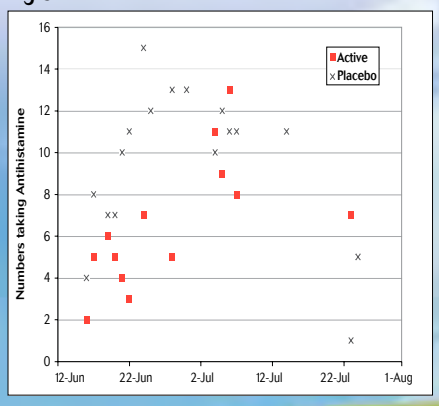


Fig 3



Grass pollen grain from SEM. Actual size c. 35 microns diameter

Nettle (Urtica spp.) pollen grain from SEM. Actual size c. 14 microns diameter

Plantain (Plantago spp) pollen grain from SEM Actual size c. 20 microns diameter

NPARU National Pollen and Aerobiology Research Unit

University College Worcester

Acknowledgement - This study was funded by Kisska International Ltd makers of Nasaleze

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ORIGINAL ARTICLE

A double blind, placebo controlled trial of inert cellulose powder for the relief of symptoms of hay fever in adults*

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Key words: **Hay fever – Inert cellulose powder – Seasonal allergic rhinitis**

ABSTRACT

Objective: An inert cellulose powder has been on sale in the UK since 1994 as a remedy for hay fever but no scientific trials have been conducted previously. It is applied to the inside of the nose where it forms a gelatinous coating. The principal aim was to determine if there is a significant difference in the amount and type of rescue medication required for adult hay fever sufferers to control their symptoms while using either the inert cellulose powder or a placebo. The second objective was to see whether the cellulose powder resulted in an improvement in symptom control.

Research design: A double blind, placebo controlled study was conducted of 97 adult hay fever sufferers, over the grass pollen season of 2004. Participants (selectively recruited to be living within the catchment area of a 50-km radius from Worcester, UK) were assigned randomly to two groups (A, Active and B, Placebo) matched by age by decades and gender. Of those completing the trial, group A had 19 males and 28 females and group B had 21 males and 29 females. There were no significant differences between the groups in age distributions, severity of symptoms over the last 2 years or in medication taken. They completed daily symptom diary score cards and were allowed to take any medications they wished in addition to the inert cellulose powder or placebo because medication use was taken as an outcome measure. Results were analysed in relation to pollen counts.

Results: Significant differences were found in the amounts of rescue medication taken by the active and placebo groups ($p < 0.05$). More people in the placebo group took rescue treatments than those in the active group.

No significant differences were found ($p < 0.01$) between the active and placebo groups in Likert scores for any of the rhinitis nasal symptoms or in the total Likert symptom daily scores. No adverse events were reported during the study.

Conclusions: The amount of rescue medication taken by the placebo group was significantly more than that taken by the active group both overall, considering all types of medication, and also in the individual cases of antihistamines, nasal sprays and eye drops. These results provide evidence that the inert cellulose powder reduces the need to take rescue medication for the symptoms of hay fever.

Introduction

Seasonal allergic rhinitis due to pollen allergy occurs in 15–35% of the population of Europe depending on age group and region[1–3]. In the UK hay fever affects at least 10% of the general population[4] and in teenagers (12–14 year olds) lifetime prevalence increased from 34.8% in 1995 to 37.4% in 2002[5], resulting in notable

* Selected material from this paper was presented as a poster at the World Allergy Congress, Munich, 26th June–1st July 2005

social and economic costs. A wide range of remedies and treatments is available both on prescription and for sale over the counter but many of these can have side effects and some sufferers are reluctant to take them. An inert cellulose powder (Nasaleze†) has been registered as a class one medical device with the Medical Devices Agency (MDA) since 1994 and is on sale in many countries, including the UK, as a remedy for hay fever. It is applied to the inside of the nose by a simple puffer device. The mechanism of action of the cellulose is unclear although it is likely that the cellulose reacts with moisture within the airway to produce a protective barrier over the nasal mucosa, preventing binding of inhaled allergen with receptors. Evidence for the efficacy of this device in the management of rhinitis has been almost entirely anecdotal as no scientific trials have been conducted previously. The popularity of the product has been increasing steadily over the last 10 years with numerous unsolicited testimonials being cited by the manufacturers.

In the UK, and the majority of Europe, the most important allergenic pollen type is grass, with approximately 95% of hay fever sufferers being allergic to this taxon, whereas only about 25% are allergic to tree pollen and about 20% to weed pollen[6].

The UK grass pollen season typically starts in late May and continues through to mid-August, with the main peak occurring in June and a second smaller peak typically occurring in early July. This period overlaps with the flowering times for some weeds, such as Nettle (*Urtica* spp.), certain trees such as Lime (*Tilia* spp.) and pollen from some crops (such as Oil seed rape, *Brassica napus*).

A trial was conducted with the principal objective of determining if there is a significant difference in the amount of and type of rescue medication required for adult hay fever sufferers to control their symptoms in the main grass pollen season while using either the inert cellulose powder or a placebo. The secondary objective was to establish whether the inert cellulose powder has a significant effect in the control of the symptoms of hay fever in adults during the grass pollen season.

Patients and methods

Patients and their selection

Subjects were recruited via local general practitioners, leaflets in libraries and other public places and via the National Pollen and Aerobiology Research Unit (NPARU) web site. Informed consent was obtained from potential volunteers who then completed a baseline questionnaire which supplied the following types of information: age range, name and address of doctor, occurrence and timing of hay fever in the previous two summers, qualitative assessment of symptoms (as none, slight, moderate or severe for frequent sneezing, itchy eyes, blocked nose, running eyes, headache/tiredness, itchy throat/mouth). Subjects were also asked if they took medication or other treatments (if so, were these bought over the counter or on prescription) and the generic types e.g. eye drops (choices to tick plus 'other'). They were also asked about asthma in the summer months and whether this required treatment with steroids.

The criteria for inclusion were as follows:

1. Subjects must be 18 years or over.
2. Subjects must have had symptoms of seasonal allergic rhinitis during June and July for at least the previous 2 years.
3. Subjects must have had symptoms sufficiently severe to need treatment by medication either from a pharmacy or on prescription.
4. Subjects must be residing and spending the majority of time within 50 km of Worcester during the trial period.

Criteria for exclusion were as follows:

1. Subjects who did not understand English clearly. This was because the relevant documents need to be completed in English.
2. Subjects with a history of severe grass pollen associated asthma who were likely to require steroid treatment for asthma symptoms during the hay fever season.
3. Subjects who were likely to be spending more than 2 weeks at a time away from the region during June and July.
4. Subjects who had rhinitis outside of the grass pollen season.

These criteria ensured that recruits were highly likely to suffer symptoms of seasonal allergic rhinitis due to grass pollen allergy. The baseline questionnaire specifically asked about the occurrence of symptoms in relation to calendar month. Only those people who had clear seasonal rhinitis during the grass pollen season were included. People who had symptoms at other times of the year were excluded. If people were sensitized to other allergens such as dogs, cats, house dust mites or mould, it is highly likely that they would have symptoms outside of the grass pollen season.

The catchment area was a 50-km radius from Worcester so that symptoms could be related to pollen count data at the National Network pollen-monitoring site at the National Pollen and Aerobiology Research

† Nasaleze is a registered trade mark, Kisska International Ltd, Keighley, UK

Unit, Worcester. Previous research has demonstrated that it is acceptable to use the results from a standard roof top pollen monitoring site to indicate the pollen counts prevailing in a region of about 50 km radius from the site[7–9]. Throughout the duration of the trial the daily average pollen counts for all allergenic pollen types were taken from the Worcester site which uses the standard techniques of the British Aerobiology Federation[10].

Study design

A double blind, placebo controlled study was conducted on adult hay fever sufferers (aged 18 years and over) who had experienced symptoms of hay fever in June and July in the previous 2 years that were sufficiently severe to require treatment. A pilot study was conducted in the summer of 2003 in one GP practice in Worcester, which indicated a high efficacy for the inert cellulose powder. This indicated the power of the study and the sample size required. The pilot indicated that with 100 patients in this two treatment study, the probability is 90% that the study will detect a treatment difference at a two-sided 1.000% significance level, if the true difference between the treatments is 0.555 units. This is based on the assumption that the within patient standard deviation of the response variable is 1.000.

The trial was planned for the main grass pollen season (June and July) in 2004 with the intention of recruiting 120 hay fever sufferers (sample size of 100, plus 20% over-recruitment to allow for 'dropout').

Suitable volunteers were assigned randomly to two groups matched by gender and age within decades from 18 to 57 years, then to the groups as people 58 years and over to give stratified random samples (Table 1). Recruits were given a participant number and were grouped by gender and age range. Within these categories they were assigned to group A or B by alternate random draw of sealed shuffled envelopes. There were no significant differences at the 95% level in the occurrence or severity of symptoms experienced by the people in the two groups over the previous 2 years (Table 2). Similarly there were no significant differences at the 95% level in the numbers taking different types of medication (Table 3). Participants who were recruited but did not complete the trial are not included in the tables.

Ethical considerations

Ethical approval was obtained from the Hereford and Worcestershire NHS Local Research Ethics Committee. The study complies with the Declaration of Helsinki.

Collection and analysis of data

In early June those recruited were given daily diary cards to cover 4 weeks together with detailed instructions, prepaid envelopes for returns and nasal powder type A or B. They were given the opportunity to discuss the project and to ask any questions. They were also given a phone number to contact if they had any questions during the trial period. The diary cards included reports on symptoms as Likert scores. These are widely used as a qualitative assessment of the severity of symptoms. The Likert technique presents a set of statements. Subjects are asked to express agreement or disagreement of a five-point scale (in relation to having symptoms). Each degree of agreement is

Table 1. *The age and gender of participants completing the trial*

Age range	Active group		Placebo group	
	Male	Female	Male	Female
18–27 years	3	6	2	7
28–37 years	7	8	8	7
38–47 years	3	9	3	9
48–57 years	5	3	6	3
58+ years	1	2	2	3
Totals for analysis	19	28	21	29

Table 2. *Results from the baseline questionnaire. Occurrence and severity of symptoms over the last 2 years*

	Sneezing	Itchy eyes	Blocked nose	Running nose	Running eyes	Headaches/ tiredness	Itchy throat/ mouth
Active group							
Severe	19	21	15	23	14	11	10
Moderate	25	19	16	15	15	16	17
Slight	3	7	10	5	10	10	10
None			5	4	8	8	8
Placebo group							
Severe	20	27	18	24	17	15	10
Moderate	26	17	17	16	13	16	16
Slight	4	6	8	9	11	9	13
None			5	1	9	10	9

Table 3. *Results from the baseline questionnaire. Medication taken regularly during grass pollen season over the last 2 years*

	Active group	Placebo group
Antihistamines only	20	21
Antihistamines with nasal spray	4	4
Antihistamines with eye drops	4	5
Antihistamines with eye drops and nasal spray	9	10
Antihistamines with eye drops, nasal spray and steroids	1	1
Nasal spray only	1	2
Nasal spray and eye drops	2	3
Eye drops only	1	1
Eye drops and herbal	1	0
Eye drops, nasal spray and herbal	1	0
Steroids only	1	0
Herbal only	2	0
Antihistamines with nasal spray and herbal	0	1
Antihistamines with eye drops, nasal spray and herbal	0	1
Antihistamines with eye drops, nasal spray, herbal and steroids	0	1

given a numerical value from one to five. Thus a total numerical value can be calculated from all the responses.

The daily diary cards requested the following information:

- Likert scores for each of four individual categories of symptoms of hay fever over the last 24 h.
- How many times the nasal powder was used that day.
- Whether they had taken any hay fever medication or treatment today, if so what type and how much.
- Visits to GP or nurse related to allergy.
- Whether they had cold or flu like symptoms. If so what were these?
- If they had been away from the Worcester area (more than 50 km radius) during the day.

Subjects were told that they could use any hay fever treatments or remedies they felt they needed during the trial. This was done because use of medication was to be taken as an outcome measure. Also if it was overtly allowed and monitored it could be taken into account. Restrictions on the use of rescue remedies and medication in a field trial could have resulted in non-compliance. If this was not recorded it could have distorted the results considerably.

One group was given the active product and the other the placebo, which was a lactose powder with the same particle size and appearance as the inert cellulose powder and supplied in an identical container (the containers were labelled A and B). The codes for the active and placebo products were not revealed until the data had been analysed at the end of the study. The nasal powders were supplied in plastic containers which delivered the powder from a nozzle when squeezed. The exact amount delivered is not standardized and the variation of patterns of deposition in the nose are not known. These are topics of ongoing product development and research.

In total 116 subjects were recruited to the study, but 19 did not complete the 4 weeks. The analysis of results has been based only on those subjects who completed the whole trial. Analysis was done anonymously and in accordance with the data protection act. After the study was completed all participants were informed whether they had taken the active or placebo product and they were sent a summary of the results.

Statistical methodology

Diary card data have been analysed for differences between the active and placebo groups both for individual aspects and combinations taking only those days with grass pollen counts at moderate, high or very high levels. Non-parametric tests have been used as follows: Chi^2 to test for differences in the distributions of the actual frequencies of scores, Mann–Whitney U-test of medians and correlations. Statistical significance was applied at the 95% level or above.

Results

Features of the two sample groups at the start of the study

The demographic features of age and gender showed no significant differences between the active and placebo groups at the start of the trial (Table 1). Similarly the occurrence and severity of individual hay fever symptoms (Table 2) reported from the previous 2 years also showed no significant differences between the groups. With 2 degrees of freedom, no values were within 1%, or 5% of significance levels. No significant differences were found between the active and placebo

groups in the use of different types of medication for hay fever in the previous two summers (at 1% significance level) (Table 3). Based on these results the two groups can be taken as being drawn from the same population for the study.

Diary card results

No significant differences were found at the 1% level in differences in the distribution frequencies of Likert scores for any of the individual symptoms. However, some significant differences were found at the 5% level (Table 4). These differences were such that symptom scores were higher in the placebo group than in the active group.

No significant differences occurred between the total Likert symptom daily scores for the active and placebo groups (Figure 1 and Table 4), using a non parametric test of difference in central tendency.

The number of times that the inert cellulose powder was taken by the active group compared to the placebo group (Figure 2) was similar. On most days a few people in each of the groups forgot to take their powder, or did not take it for various other reasons such as having a cold.

Very few visits to GPs for allergy related symptoms were recorded for either group. No significant differences were detected in the number of people in each group reporting symptoms of colds or flu. No adverse reactions were reported by any of the participants in the study. Of the 19 people who did not complete the 4 weeks of trial, 4 said that they did not like the feel of powder in the nose, 1 went on holiday and 14 gave no reason for giving up.

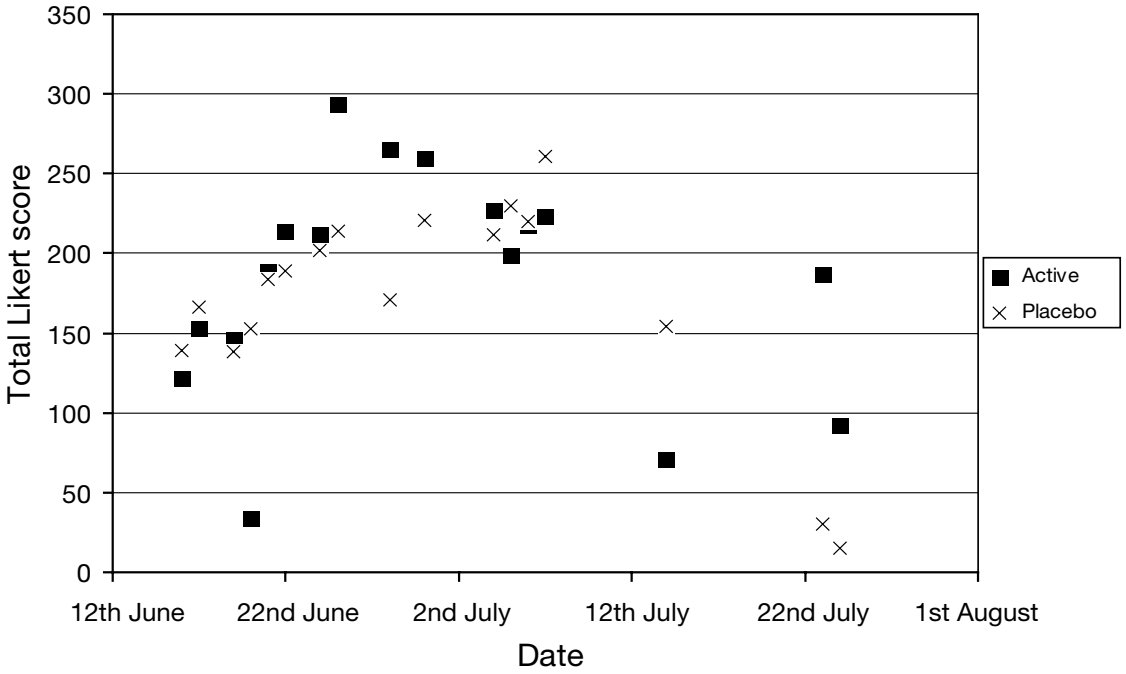

Figure 1. *Total Likert scores for active and placebo groups on days with very high, high or moderate pollen counts*

Table 4. *The differences in symptom scores between active and placebo groups over the study period*

	Chi^2 value	Significance	Degrees of freedom (n – 1), based on number of classes for frequency
Sneezing			
Moderate pollen count days	6.31	Not significant	4
Running nose			
Moderate pollen count days	10.05	Significant at 5%	5
High and very high pollen count days	8.04	Not significant	5
Blocked nose			
Moderate pollen count days	8.17	Not significant	5
High and very high pollen count days	12.16	Significant at 5%	5
Watering eyes			
Moderate pollen count days	5.78	Not significant	4
High and very high pollen count days	5.92	Not significant	5

Rescue medication

Significant differences were found in the overall amounts of rescue medication taken by the active and placebo groups (Figure 3 and Table 5). For simplicity, in Table 5, both the inert cellulose powder and the placebo are referred to as 'Nasal powder' as the subjects did not know what they were taking. Almost all of the treatments are 'once a day', the exceptions being some herbal remedies. The results are analysed on a daily basis so there is a measure of the amounts taken.

Considering individual types and combinations of remedies, the predominant pattern was such that more people in the placebo group took treatments than those in the active group. This was apparent for all the types and combinations with the exception of homeopathic remedies and a combination of nasal sprays and eye drops. Antihistamines were by far the most frequently used type of medication (Figure 3). In the active group, 29% of people took only antihistamines compared with 33% in the placebo group (Figure 4). There was no significant difference between these groups, but when

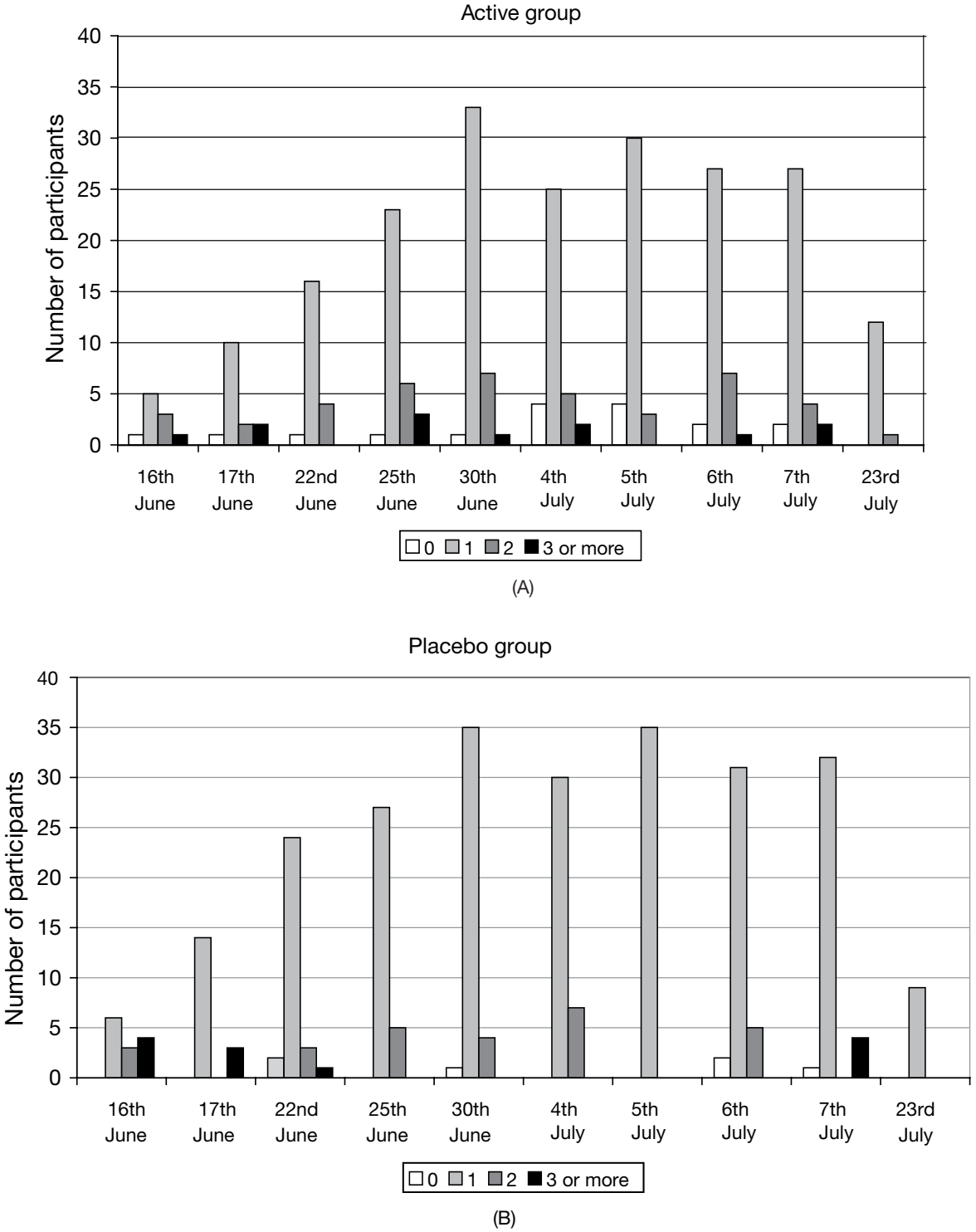

Figure 2. *The number of times each day the nasal powder was taken by (A) the active and (B) placebo groups on days with high or very high pollen counts*

overall use of antihistamines is considered (i.e. people using antihistamine whether or not it is in combination with other medication), the percentage in the active group was 34% compared with 48% in the placebo group (significantly different at $p < 0.05$). Taking into account all days with grass pollen counts at high or very high only, the figures are 34% for the active group and 45% for the placebo group (significantly different at $p < 0.05$). The Mann–Whitney U-tests are reinforced by results from correlation (d.f. = 15, Rho statistic =

Table 5. *Summary of statistical tests on medication taken by the active and placebo groups during the study period*

Overall medication taken	Chi ^{2} value significant at $p \leq 0.1$	Degrees of freedom ($n - 1$)
Very high, high and moderate pollen days	51.32	–
Very high and high pollen days	20.73	–

Mann–Whitney U-test results on medication categories	p values (< 0.05 = significant)	Degrees of freedom ($n - 1$)	Means		SD	
			A	P	A	P
High and very high pollen days, medication – nasal powder only	0.288	9	15.6	13.7	7.62	6.2
Combined pollen days, antihistamine (+ nasal powder)	0.000	16	8.23	31.4	3.9	12.1
High and very high pollen days, antihistamine (+ nasal powder)	0.048	9	9.4	33.2	4.17	12.32
Combined pollen days, nasal spray (+ nasal powder)	0.037	16	2.47	4.06	1.66	2.19
Very high and high pollen days, nasal spray (+ nasal powder)	0.179	9	3.2	4.5	1.33	2.17
Combined pollen days, eye drops (+ nasal powder)	0.103	16	1.8	2.76	1.07	1.6
Very high and high pollen days, eye drops (+ nasal powder)	0.050	9	2.1	3.1	0.88	1.85

Combined pollen days are those with very high, high or moderate grass pollen counts
A = active group
P = placebo group

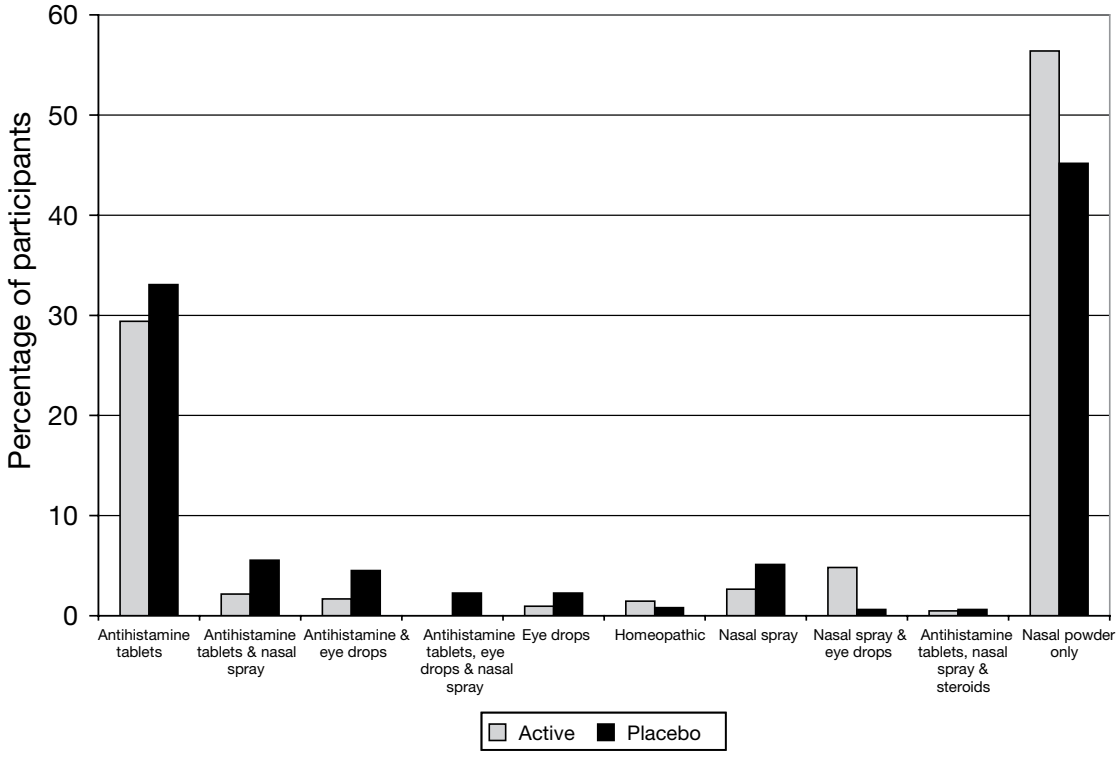

Figure 3. *Percentage of participants in the active and placebo groups taking different types of hay fever treatments over the study period*

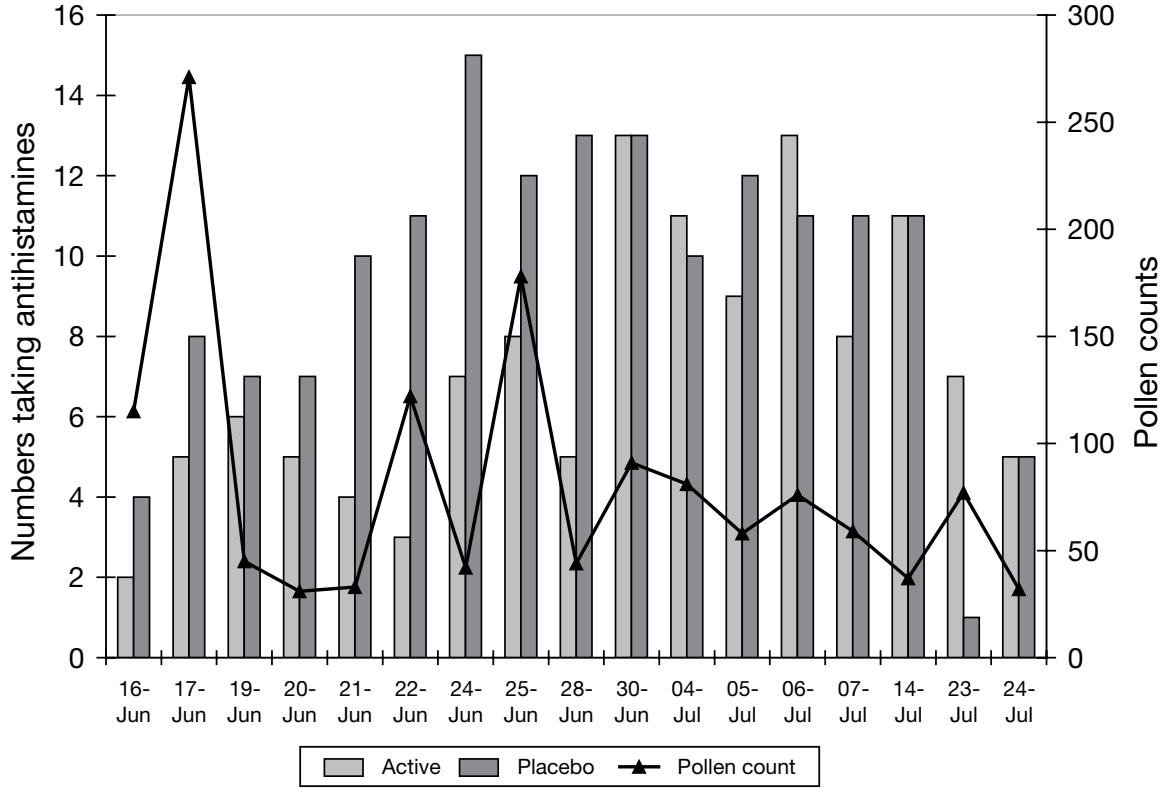

Figure 4. *Numbers of people taking antihistamines in the active and placebo groups on days with very high, high or moderate pollen counts over the study period*

1.91) which is not significant at 1% or 5% levels of probability. This indicated that there was no significant relationship between the data sets for the two groups and that they were different.

Nasal sprays were the second most frequent type of medication used. Taking all the days with grass pollen counts at moderate or above, 10% of the active group took nasal sprays compared to 14% of the placebo group (significantly different at $p < 0.05$). In the case of eye drops, there is no significant difference between the results for the two groups in the data for days combined but considering only high and very high grass pollen count days, 7.5% of subjects in the active group used eye drops compared to 11.3% in the placebo group (significantly different at $p < 0.05$).

The placebo group participants took a wider range of medication combinations than those in the active group. Very few subjects in either group took steroids or homeopathic remedies. Fifty-seven per cent of subjects in the active group took the inert cellulose powder only, with no rescue medication, on days with counts at moderate or over, compared with 44% in the placebo group (Figure 5).

Discussion

The main differences in the results between the two groups occurred in the amounts of rescue medication taken. This measure is widely used in research on allergy and related areas, for example by Rolinck-Werninghaus *et al.*[11], Miller *et al.*[12] and Roefaro and Daryanari[13]. The overall significant difference in the amounts of medication taken is reinforced by the results of tests on individual types. The significantly different results in the amounts of medication taken by the active and placebo groups show similarities across three types of hay fever medication i.e. antihistamines, nasal sprays and eye drops. This constancy of outcome helps to confirm the results. The only case in which more rescue medication was taken by the active group than the placebo group, was in the group taking nasal sprays and eye drops without antihistamines. This suggests that the inert cellulose powder may not have an effect on eye symptoms but the sample size is small and this aspect would have to be investigated further.

The results show that there are few significant differences in the symptom scores during the trial for the two groups in the cases of individual symptoms (sneezing, runny nose, blocked nose, watering eyes). The subjects did not all experience each of the symptoms that were monitored. They were also taking medication if they wanted to. Consequently, the total Likert scores are not high and this is not unexpected.

The amount of rescue medication taken by the placebo group was significantly more than that taken by the active group, both overall considering all types of medication and also in the individual cases of antihistamines, nasal sprays and eye drops. There were no significant differences in the demographic profiles of

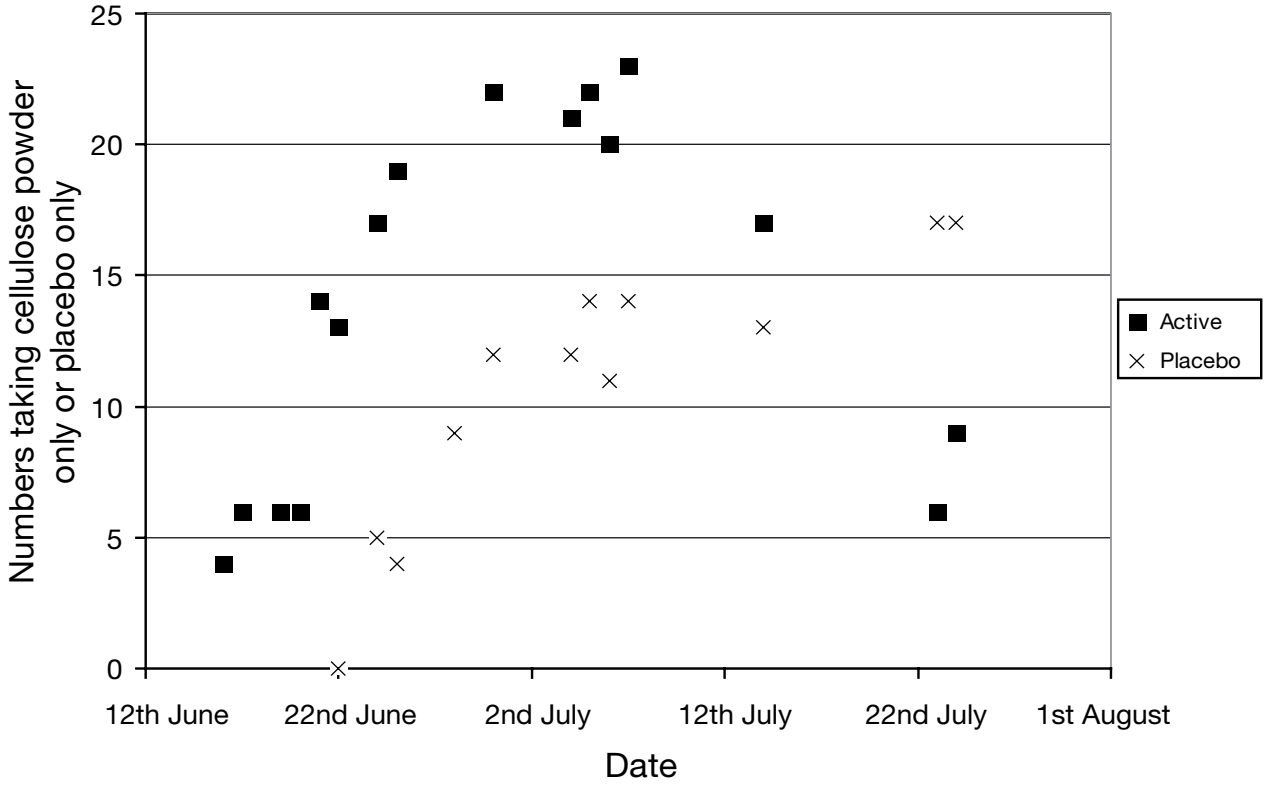

Figure 5. *Numbers of people taking cellulose powder only or placebo powder only on days with very high, high or moderate pollen counts over the study period*

the two sample groups or in the severity of their reported symptoms in previous grass pollen seasons. This indicates that the inert cellulose powder was operating to reduce the symptoms of hay fever in the active group.

The 2004 grass pollen season

The 2004 Worcester grass pollen season was less severe than average. The first 2 weeks of June followed a typical pattern of many days with high counts but after this, rainfall was above average (108% of long term norm). Despite the unusually low severity of the grass pollen season overall, there were sufficient moderate, high and very high days during the trial to provide an adequate sample (pollen count categories for grass are moderate 30–49 grains per cubic metre, 50–149 high, 150 or over very high). Due to the season being below average severity, the results were analysed for those days with moderate, high or very high grass pollen counts only. Once inflammation is established some symptoms can persist on days when pollen counts are lower. However, in this study use of medication is an outcome measure and this is more likely to be related to the days with pollen counts above the threshold. In a season which is markedly below average severity the inclusion of substantial periods with low pollen counts could distort the results.

Apart from grass pollen, the other main pollen types in the air during the trial were Nettle (*Urtica* spp.), with minor amounts of oil seed rape (*Brassica napus*) and weeds such as Plantain (*Plantago* spp.) and Mugwort (*Artemisia* spp.). The thresholds of response to these taxa are not well established due to lack of clinical evidence but the days when moderate, high or very high pollen counts occurred for these other types coincided with those for grass, due to the overriding influence of weather conditions on pollen release and dispersal.

Discussion of results

The data generated from this study were from self reporting by volunteers who had been admitted to the trial on the basis of a baseline questionnaire. These aspects could produce some bias and subjectivity in the data which needs to be considered. For example, in some of the participants the diagnosis of hay fever in the peak grass pollen season was based on their description of the symptoms and the timing of them. However, the application of the exclusion and inclusion criteria was designed to eliminate those with perennial rhinitis which could be caused by indoor allergens or by non-allergic rhinitis.

The scale of severity of symptoms is relative and may be applied differently by individuals. However, the use of Likert scores is a well established and accepted methodology and the relatively large sample size would reduce any bias. The results from the baseline questionnaire have shown no significant differences in the severity of the symptoms reported by the two groups at the start of the study.

In the trial itself it is possible that the use of the placebo powder could have caused some 'wash out effect'. If this was the case, then the outcome would be to decrease the differences between the results for the two groups, whereas certain significant differences have been detected.

Towards the end of the season there are 2 days (July 6th and July 23rd) on which more people in the active group took antihistamines than those in the placebo group (Figure 4). Similarly there are 2 days (July 23rd and 24th) when the total Likert scores for the active group are higher than those for the placebo group (Figure 1). These differences are not statistically significant due to the small sample sizes (2 days in each case). The subjects did not report irritation from the powder. It is possible that the active group took less anti-inflammatory medication earlier in the season and may have suffered more nasal infiltration by inflammatory cells which will take longer to settle down.

It is reasonable to suppose that the few significant differences in the symptom scores shown between the two groups in the data from the diary cards, reflect a real difference due to the action of the cellulose powder combined with the amounts of rescue medication taken. Exposure to a large amount of grass pollen on days with very high counts would present a severe challenge to hay fever sufferers and could result in all hay fever sufferers, who are allergic to grass pollen, having some symptoms despite taking treatments[14].

Although it is very likely that someone who had hay fever in June and July would be allergic to grass pollen, it is possible that they were allergic to other types such as weeds and summer flowering trees either in addition to grass or on their own. All types of pollen released in June and July tend to have high counts during the same sort of weather as grass pollen due to the influence of variables such as temperature, rainfall and wind. It is extremely unlikely that pollen counts for weeds and the few summer flowering trees would be low on days when the grass pollen count was moderate or high. This factor would tend to produce synchronisation of symptoms for hay fever sufferers at this time of year.

These results provide evidence that the inert cellulose powder reduces the need to take rescue medication for the symptoms of hay fever. Further research is needed to explore the effects of the cellulose powder in controlling symptoms of hay fever when the subject is not taking any medication and also to determine the degrees of protection conferred in different pollen concentrations (moderate through to very high). It would also be useful to run comparative studies between the cellulose powder and conventional medications. In addition, research is needed to investigate how the cellulose powder works because an understanding of the mechanisms is likely to help in the development of the product and in the extension of its applications.

Both of these aspects will be addressed by challenge tests planned to take place outside of the pollen season. Known amounts of grass pollen allergen will be introduced to the noses of subjects under controlled conditions when they are not taking medication for hay fever and the response will be monitored both for expression of symptoms and physiological reactions. The outcome of these experiments will help the design of further trials. In particular, it would be useful to determine whether the inert cellulose powder can be employed to reduce or even eliminate the use of steroids in pollen allergy, including some cases of asthma.

Although the mechanism of action is unknown, the fact that cellulose is an inert substance which develops a gel-like consistency on contact with moisture indicates that it is likely that the primary mechanism of action of the product is to produce a simple mechanical barrier to the allergenic component of the pollen grains preventing them from triggering an inflammatory response on the mucosal membrane. The benefit of this product is that it has the potential ability to reduce the need for the use of other medication such as decongestants and intranasal steroids which are known to have significant side effects. There is also an economic benefit as the over the counter cost of the cellulose powder works out at less than 50% of the daily cost of antihistamines. It is about the same cost as or slightly less than the daily dose for most nasal sprays.

Acknowledgements

Declaration of interest: The study was sponsored by Kisska International Ltd.

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Double blind, placebo controlled cross over trial of inert cellulose powder, by nasal provocation with grass pollen to assess efficacy of the product in controlling symptoms of hay fever.

Emberlin JC, and Lewis RA.

Poster presented: *EAACI* in Vienna, June 2006.

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Double blind placebo controlled cross over trial of inert cellulose powder, by nasal provocation with grass pollen to assess efficacy of the product in controlling symptoms of hay fever

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++Consultant in Respiratory & General Medicine, Worcestershire Royal Hospital, Charles Hastings Way, Worcester WR5 1DD UK

Introduction

Inert cellulose powder has been on sale in the UK as a remedy for hay fever since 1994. It is applied to the inside of the nose where it forms a gelatinous coating. The results of a double blind placebo controlled study which the authors conducted on 98 hay fever sufferers over the 2004 grass pollen season showed that the active product group used significantly less rescue medication than that using the placebo (Current Medical Research and Opinion 2006;22:2:275-285). The aim of this study was to explore the effects of the cellulose powder in controlling symptoms when subjects are not taking any medication.

Method

A double blind placebo controlled cross over trial was conducted on 11 adult hay fever sufferers (diagnosed to be allergic to grass pollen but not to tree pollen by SPT and who had symptoms in the previous two summers). The sample size was set by a power calculation. The trials were in the spring before the grass pollen season. The placebo was lactose powder. Exclusion criteria were applied e.g. those with perennial rhinitis or asthma. Ethical approval was given by the National system of research ethics committees. Powder (real or placebo, order randomised) was put into the nose, followed by grass pollen equivalent to 350 grains per cubic metre air. At baseline and at regular intervals after challenge, scores were taken for 6 symptom categories, nasal secretions were sampled for ECP, and measures were taken of nasal peak inspiratory and expiratory flow. All measurements were continued in the clinic for 4.5 hours, then symptom scores and basic lung function were repeated at 6.5 hours and at 24 hours after challenge.

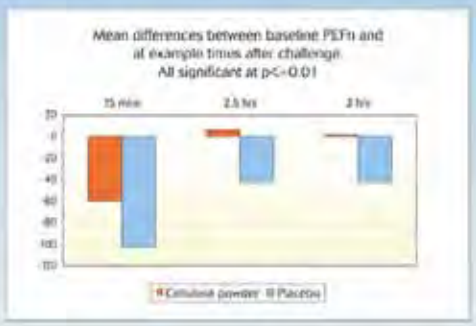
Results

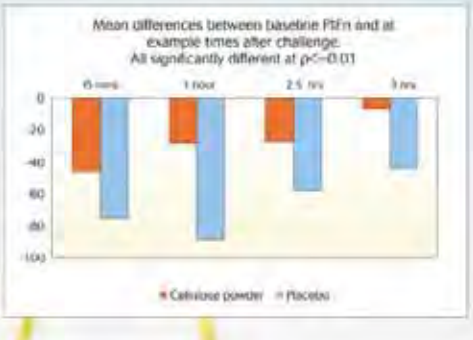
Significant differences ($p<=0.05$ and $p<=0.01$) occurred in the data at various times from challenge in peak nasal expiratory flow between placebo and active treatments, and also in nasal PIF, in sneezing and in itching eyes. The results for other lung function tests and symptoms were slightly under the level for significance. The results for the nasal secretions were significantly different at $p<=0.05$. No adverse reactions occurred.

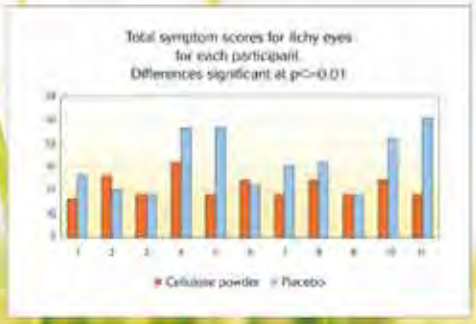
Conclusion

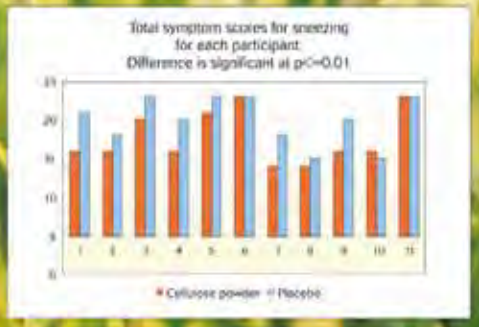
The results of the trial show that the inert cellulose powder can have significant effects in reducing symptoms of sneezing and itchy eyes due to grass pollen allergy. It can also have significant effects in reducing nasal inflammation, as measured as nasal PEF, PIF and as ECP in secretions. The results indicate that the use of inert cellulose powder can help to alleviate symptoms of hay fever.

Acknowledgement - This study was funded by Kisska International Ltd makers of Nasaleze









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A double blind, placebo controlled cross over trial of cellulose powder by nasal provocation with Der p1 and Der f1.

Emberlin JC, and Lewis RA.

Poster presented: *EAACI*, in Gothenburg, June 2007.

Published: *Current Medical Research and Opinion*. 2007; 23(10); p2423-2431.

ALLERGY Nasaleze®
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A double blind placebo controlled trial of cellulose powder as a remedy for persistent allergic rhinitis, by nasal provocation with Der p1 and Der f1

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Background

The study aimed to investigate the efficacy of inert cellulose powder applied to the nose for the control of persistent allergic rhinitis in adults due to house dust mite allergy. The powder has been registered as a medical device in the UK since 1994 and is on sale in many countries as a remedy for hay fever. Two previous trials by the authors have demonstrated the efficacy of the powder in the control of some symptoms of hay fever.

Method

A double blind placebo controlled cross over trial was conducted on 15 adult persistent rhinitis sufferers (male and female, diagnosed positive to Der p1 and/or Der f1 by SPT) and with symptoms over the previous two years, the placebo was lactose powder. Base line measurements were taken. Subjects were symptom free at the start of each trial. Challenge was a 0.01µg dose delivered to each nostril, of homogenised dust containing 5µg of Der p1 and 5 µg of Der f1 per g. The study took place in the spring before the main pollen seasons. The primary outcome measures were observed severity scores for symptoms (sneezing, nasal secretion and runny eyes) and amount of ECP in nasal secretions. The secondary outcome measures were symptom scores by subject report (nasal blockage, itching of nose, throat and eyes), nasal peak inspiratory and expiratory flow. Observations and measurements were taken 5 mins after challenge then at every 15 mins for the first hour, then at 30 min intervals until 4 hours, then at 6 hours and at 24 hours to observe any late phase reactions. The second trial for each subject was at least 7 days after the first visit. The order of treatments was randomised. Ethical approval was given by the NHS local ethics committee REC no 05/Q2801/104.

Fig 1 Total symptom scores for itchy nose from challenge to 4.5 hours later. Differences are significant at p=<0.05. Subject one had no symptoms.

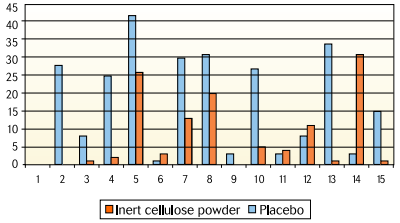
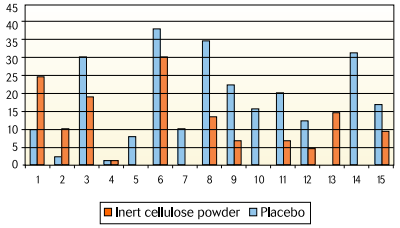


Fig 2 Total symptom scores for running nose from challenge to 4.5 hours later. Differences are significant at p=<0.05



Adult Dermatophagoides farinae taken from SEM at 3,500 times magnification. Actual size about 0.33mm long.

Adult male of Dermatophagoides pteronyssinus taken from 400 times magnification.

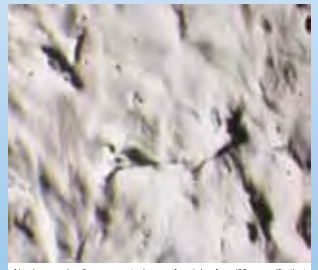
Results

The results show significant differences (p=<0.05) for sneezing, itchy nose, runny nose and ECPs in nasal secretions. The results were also significant at this level for peak nasal expiratory and inspiratory flow but there was considerable variation. The results for other symptoms were not significantly different between the cellulose powder and the placebo. There were no adverse reactions.

Conclusions

The inert cellulose powder can have significant effects in reducing some symptoms of persistent rhinitis due to house dust mite allergy.

Nasaleze powder dry (taken from 100 x magnification)



Nasaleze powder after exposure to damp surface (taken from 100 x magnification)

Fig 3 PIFn mean of differences from baseline from immediately after challenge to 4.5 hours later. Difference is significant at p=<0.05. Readings are in l/min.

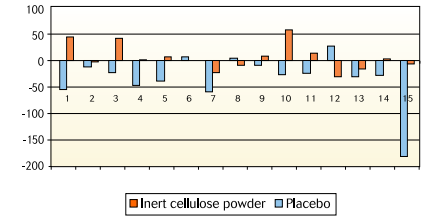
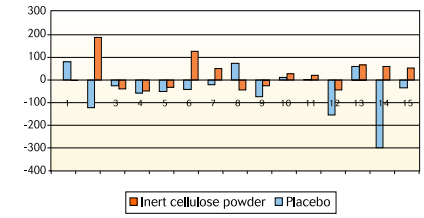


Fig 4. Mean PEFn readings for individuals as differences from baseline. Mean is for 7 readings taken from after challenge to 4.5 hours later. For participant one there was no difference from baseline to mean PEFn when using the cellulose powder. Readings are in l/min.



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ORIGINAL ARTICLE

A double blind, placebo-controlled cross over trial of cellulose powder by nasal provocation with Der p1 and Der f1

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Key words: **Cellulose – House dust mite – Provocation test – Rhinitis**

ABSTRACT

Objective: The purpose of this study was to assess whether inert cellulose powder would reduce the response to nasal challenge with house dust mite antigens. The study aimed to investigate the efficacy of inert cellulose powder applied to the nose for the control of persistent allergic rhinitis in adults due to house dust mite allergy. The powder has been registered as a medical device since 1994 and is available in many countries as a remedy for hay fever. Anecdotal evidence reported that it reduced symptoms of persistent rhinitis but no scientific evidence exists for this.

Research design and methods: A double blind, placebo-controlled cross over trial was conducted on 15 adult persistent rhinitis sufferers (diagnosed positive to Der p1 and/or Der f1 by SPT) and who had symptoms over the previous 2 years. The placebo was lactose powder. Challenge was by measured dose of homogenised allergenic dust. The study took place in the spring of 2006 before the main pollen seasons.

Main outcome measures: The primary outcome measures were observed severity scores for 3 symptom categories and the amount of ECP in nasal secretions. The secondary outcome measures were symptom scores by subject report (nasal blockage, itching of nose, throat and eyes), nasal peak inspiratory (PIFn) and expiratory flow (PEFn).

Results: The results show significant differences for sneezing, itchy nose, runny nose and ECPs in nasal secretions. Some results are also significantly different between placebo and active for PIFn and for PEFn (all at $p = 0.05$). There were no adverse reactions.

Conclusions: The inert cellulose powder can have significant effects in reducing some symptoms of persistent rhinitis due to house dust mite allergy.

Introduction

The trial reported in this paper aimed to investigate the efficacy of inert cellulose powder applied to the nose for the control of symptoms of persistent allergic rhinitis in adults due to house dust mite allergy. Allergic rhinitis is a heterogeneous disorder that has high prevalence but is often undiagnosed[1]. Symptoms include one or more of sneezing, itching, nasal congestion and rhinorrhoea and can have a notable impact on quality of life as

well as exerting a high economic cost. In a two step cross-sectional population based study in 6 European countries the prevalence of subjects with clinically confirmable allergic rhinitis ranged from 17% in Italy to 29% in Belgium with an overall value of 23%[2]. This large scale study confirmed that allergic rhinitis has a high prevalence in Western Europe and is frequently undiagnosed. In addition, within the population with allergic rhinitis, 29% had persistent rhinitis. Bauchau and Durham report that this group had more severe symptoms and a greater self awareness[3]. In the USA, allergic rhinitis affects approximately 20–40 million people[4] of whom 20% are intermittent, 40% persistent and 40% of cases are mixed[5].

Inert cellulose powder (Nasaleze*) has been registered with the Medicines and Healthcare Products Regulatory Agency (formerly Medical Devices Agency) since 1994 and is on sale in many countries, including the UK, as a remedy for hay fever. It is applied to the inside of the nose where it forms a gelatinous coating. It is thought that this layer prevents the allergens from reaching the mast cells in the nasal mucosa. Two previous trials have been conducted by the authors to investigate the efficacy of the powder in the control of hay fever[6,7].The results showed that the product reduces some symptoms. No adverse reactions were reported and the trials confirmed the powder as a low cost remedy with no known side effects.

Anecdotal evidence suggested that the powder also reduces symptoms of persistent rhinitis but scientific evidence was lacking. The principal objective of the current trial was to determine if the inert cellulose powder has a significant effect in the control of symptoms of persistent allergic rhinitis due to house dust mite allergy when no other medication was being taken.

Patients and methods

Basic study design

A double blind placebo controlled cross over trial with allergen provocation was conducted on 15 adult persistent rhinitis sufferers who had symptoms over the previous 2 years. The placebo was lactose powder. The study took place in the spring of 2006 before the main pollen seasons.

Ethical considerations

Ethical approval was given by NHS Hereford and Worcester local ethics committee REC number 05/Q2801/104. The study complies with the declaration of Helsinki.

Patients

Fifteen adult patients were recruited both male and female during the month before the trial. The sample size was set by a power calculation which indicated that the probability was 90% that the study would detect a treatment difference at a two sided 1.00% significance level if the true difference between the treatments is 1.609 units. This is based on the assumption that the within patient standard deviation of the response variable is 1.000.

Potential volunteers were sent a Baseline questionnaire 1–2 months before the trial which included questions on monthly occurrence and severity of symptoms, treatments used etc. People who seemed to be suitable were invited for a skin allergy test if they had not had one in the previous year. Selection was then based on the following. Inclusion criteria were subjects who have had a positive skin prick test for house dust mite allergen (Der p1 and/or Der f1) performed within the previous 12 months (wheal diameter at least 75% as large as histamine control), subjects who have had persistent rhinitis symptoms for a minimum of 2 years and were being treated by a doctor for this and who have no history of asthma. Principal exclusion criteria were people with asthma, upper respiratory viral infections, nasal deformities, pregnant women and people who have any other adverse medical conditions. Subjects must not have taken antihistamines in the preceding week or have used corticosteroids within the preceding 30 days.

Study design

Before the start of each trial the subjects were interviewed to explain the procedures in detail and to check for the presence of the symptoms that would be monitored, namely, sneezing, runny nose, itchy eyes, running eyes, itchy nose, itchy throat and itchy throat/palate. The symptoms were assessed by observation and by questionnaire which took approximately 30 min. If the subject had these symptoms that day they were excluded from the trial and another appointment was made. No medication was permitted to be taken by the subjects during the trial.

A pre wash (2.5 mL sterile saline) was given to each nostril and allowed to dry for 15 min. The saline wash was retained for analysis for ECPs (Eosinophil cationic proteins)[8]. Baseline PIFn (Nasal peak inspiratory flow) and PEFn (Nasal peak expiratory flow) were taken

* Nasalez is a registered trade mark of Nasaleze International Ltd

(best of three noted) using a computerised system (Vitalograph 2120 operated with the Vitalograph Spirotrac 4.20 software). Baseline symptom scores were also recorded.

Powder (real or placebo labelled as A or B, order randomised by blind draw) was put into each nostril as two applications per nostril from a plastic bottle with a patented valve applicator and was allowed to settle for 15 min. During the application the subjects were asked to breathe in but were told not to sniff. The powder was applied by a trained member of staff (either a nurse or a post doctorate researcher). The placebo was a lactose powder of similar particle size to the cellulose and in identical plastic bottles. New bottles were used for each application.

An allergen challenge was delivered to the nostrils by a Morrow Brown microspoon[9], equivalent to 5 µg of Der p1 and 5 µg Der f1 per g of inert carrier fine particle dust (particles 15–100 µm). The dust was prepared in house and the allergen content was checked by 3 separate repeats of ELISA for Der p1 and for Der f1 each with 5 replicates at 4 serial dilutions. The dose given was 0.01 µg of homogenised dust mix in each nostril.

At baseline and at regular intervals after challenge, scores were taken for sneezing, itchy eyes, running eyes, itchy nose, running nose, itchy throat and itchy throat/palate graded as symptoms 0 = absent, 1 = very mild, symptoms hardly noticeable, 2 = mild, symptoms noticeable intermittently but do not interfere with any normal daily activities, 3 = moderate, symptoms noticeable all the time but do not interfere with any normal daily activities, 4 = severe, symptoms interfere with normal activities some of the time, 5 = very severe, symptoms interfere with normal everyday activities constantly. They were taken 5 min after challenge, every 15 min for the first hour after challenge then at 30 min intervals until 4 h after challenge, then at 6 h and at 24 h to observe any late phase reactions.

Nasal secretions were sampled for ECPs and measures were taken of PIFn and PEFn at 5 min after challenge, 15 min later, then at 30 min intervals for a further 2 h , then again at 4 h. At 6 h and 24 h after challenge peak flow readings were taken.

Nasal secretions were taken by inserting pre-weighed Whatman number 1 filter strips (Whatman Ltd, England) into the nostrils (left and right separately) following the methodology described by Knowles *et al.*[10] which is acceptable to subjects and minimises stimulation that could lead to extra sneezing or secretions. The strips were stored in eppendorf tubes (pre-weighed), re-weighed then frozen until analysis. Any with blood stains were discarded. The nasal wash taken at baseline before the start of each session and the samples of nasal secretions taken through the trials were analysed for ECPs using the Pharmacia Unicap system by the Department of Immunology, Northern General Hospital, Sheffield.

The second visit for each subject for the trial with the alternative powder was at least 7 days after the first visit.

The primary outcome measures were observed severity scores for symptoms (sneezing, nasal secretion and runny eyes) and the amount of ECP present in nasal secretions. The secondary outcome measures were symptom scores by subject report (nasal blockage, itching of nose, itching of throat, itching of eyes), PIFn and PEFn.

The participants and researchers did not know the identity of the powders until after the analysis was completed.

Subjects

Seven female and eight male subjects were recruited ranging in age from 18 to 60 years (modal age range 38–47 years). All had consulted their doctors about 'year round' symptoms of rhinitis. The recruits were selected on the basis of replies to a baseline questionnaire, an interview covering the baseline questions and the results of a skin allergy test. The baseline questionnaire and interview included questions designed to investigate whether patients had symptoms due to their house dust mite allergy. For example, subjects were questioned with regards to the severity of their symptoms and when and where they experienced these symptoms. Only those patients who had a suitable symptom history were recruited. The possibility of sensitisation to other allergens which may have been present in the home during the time the trial was undertaken was not taken into account. Subjects were symptom free at the start of the trial.

Some differences in the severity of rhinitis symptoms experienced over the previous 2 years were noted in the recruitment questionnaire (Table 1) but all of the recruits had persistent symptoms of frequent sneezing and runny nose to some degree. All of the subjects were allergic to Der p1 and 10 were also allergic to Der f1. The differences in subject profile were considered in the interpretation of the results. For example, the results of the skin allergy tests and the range and severity of symptoms reported in the baseline questionnaire were considered.

Statistical analysis

In most cases nonparametric tests of significant difference (Mann–Whitney and Wilcoxon tests) were applied as these do not assume normality and can be used to test ordinal variables. Student *t*-tests were used where possible

Table 1. *Profile of the 15 participants*

(a) Age, gender and symptom severity reported on recruitment questionnaire for the 15 participants

Participant No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Gender M/F	F	M	F	F	M	M	M	M	F	F	F	F	M	M	M
Age range	38–47	58+	38–47	38–47	58+	28–37	58+	58+	38–47	58+	28–37	18–27	58+	48–57	38–47
Symptom scores as estimate for severity over the last 2 years; symptoms 0 = none,1 = slight, 2 = moderate, 3 = severe															
Sneezing	2	2	3	2	3	3	1	2	2	1	3	2	3	3	3
Itchy eyes	2	0	3	2	2	3	1	3	2	0	2	1	1	3	2
Running eyes	0	1	2	2	3	1	1	2	0	2	2	0	1	3	3
Running nose	2	2	2	2	3	2	2	2	1	2	3	1	3	3	3
Blocked nose	0	2	2	3	3	3	0	3	3	0	3	2	0	3	3
Headache/tiredness	0	1	2	2	2	3	0	3	2	2	1	1	1	2	3
Itchy throat/mouth	2	2	2	2	2	1	0	2	2	0	2	0	3	3	2
Total symptom score	8	10	16	15	18	16	5	17	12	7	16	7	12	20	19
Seasonality of symptoms over last 2 years															
	All year but less in winter	All year	All year	All year	All year	All year	All year	All year	All year	All year	All year	Any time of year but not constantly	All year	All year	All year

(b) Skin test results and medication used routinely for rhinitis

Participant No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Skin test result*															
Der f1 (mm)	No	No	4.0	4.0	No	No	4.0	7.0	6.0	No	5.5	6.5	6.0	5.0	3.5
Der p1 (mm)	6.0	4.0	5.0	5.0	3.5	5.5	5.0	6.0	5.0	5.5	5.5	6.5	4.0	7.5	5.6
Medication used for symptoms of rhinitis**															
	NS, A, S	P	A	NS	NS	N	N	N	ST	N	A	N	A	NS	NS, A

*Y = yes then diameter of wheal (all at least 75% diameter of histamine control)

No = negative test result

Medication used**: A = antihistamine tablets; NS = nasal spray; P = pseudoephedrine hydrochloride; S = steroids; ST = sudafed tablets; NS = not specified; N = none

in cases of interval scale data. The level of probability was set at 0.05 or higher for acceptance. In many cases the data sets were highly skewed so descriptive statistics such as standard deviation are not useful. However, these have been included for comparison in some cases.

Results

No adverse reactions occurred. All 15 participants completed both stages of the trial.

In the cases of several of the symptom categories the scores were low or zero for many of the subjects. This may have been because the patients did not have allergic sensitivity to house dust mite. The low scores or absence of some symptoms could have been due to the relatively low amount of the challenge given and to the subjects' tendency to get only certain types of symptoms rather than all of the ones being monitored.

Primary outcome measures

Symptom scores

In the results for symptoms of runny nose (Figure 1), the differences overall are significant at the $p \leq 0.05$ level. Means are 8.8 cellulose powder and 15 placebo with SD 8.4 and 11.5, respectively. The confidence intervals of the means are 4.0 and 6.1 at $p \leq 0.05$.

In the case of sneezing, the difference in symptom scores is significant at $p \leq 0.05$ (means were 3.5 cellulose powder and 9.5 placebo, SD 3.6 and 10.2, confidence interval of the mean 1.4 and 5.2, respectively at $p \leq 0.05$). However, 4 subjects did not have symptoms.

Six subjects did not have any symptoms of running eyes on either stage of the study. A further 5 had only very low scores and spasmodic symptoms. Of the other 4, three had zero scores with the cellulose powder but had total scores for the placebo of 17, 10 and 10, and one subject had a total score of 6 with the placebo against 1 with the cellulose powder.

Eosinophil cationic proteins

The results show a wide variance between ECP; however, there is a general trend towards the presence of larger amounts of ECP after the first 20 min following challenge (Table 2). In the samples taken 5 min after challenge (numbers 1–15), 7 of the participants had higher levels of ECP when the placebo was used than when the cellulose powder was used. This is compared with 3 subjects who had lower levels of ECP when on placebo than when on cellulose powder. The remaining 5 subjects had negligible differences. The same pattern is evident in the next set of readings, taken at 20 min after challenge. At 60 min after challenge, the level of ECP in some of the samples increased notably. Eight of the subjects had higher ECP levels with the placebo and in 5 cases, the differences were very large (over 100%). In 3 cases this difference occurred the opposite way round (results for cellulose powder were > 100% more than placebo). In the other four cases the results for the two wings were similar. Considering the magnitude of readings, for those at or over 2000 µg/L, 13 are with the placebo and 9 with the cellulose powder. For those at or over 4000 µg/L seven are with the placebo and 4 with the cellulose. For readings at or over 6000 µg/L four are with the placebo and only 1 is with the cellulose. The readings for the placebo are significantly different from those for the cellulose powder ($p \leq 0.5$), for the readings taken at 60 min and at 90 min after challenge.

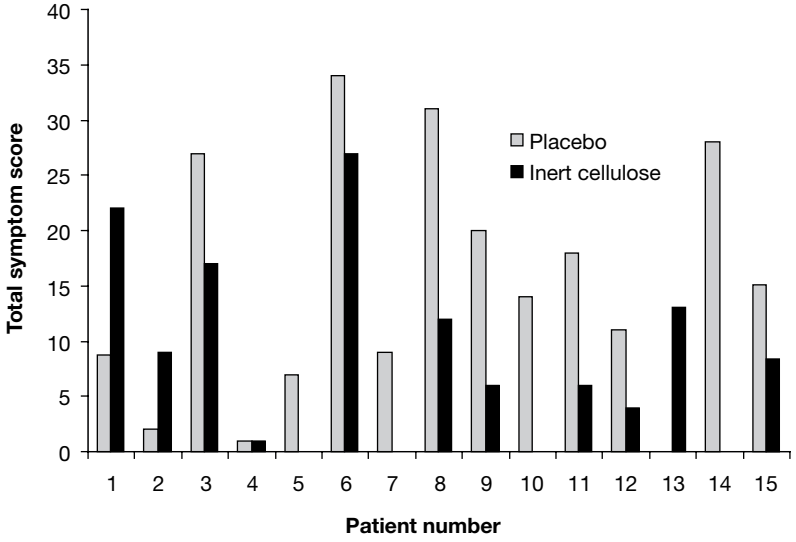

Figure 1. *Total symptom scores for running nose from challenge to 4.5 h later. Means are 15 for placebo, SD 11.5 and 8.8 for cellulose powder, SD 8.4. Differences are significant at* p ≤ *0.05. Vertical axis is total symptom score, horizontal axis is patient number*

Table 2. *ECP results per participant at 5 min, 20 min, 60 min and 90 min after challenge*

Time after challenge in min	5		20		60		90	
	C	P	C	P	C	P	C	P
Participant								
1	64	1174	250	240	250	940	2072	487
2	136	80	77	304	288	303	54	200
3	271	278	59	64	825	315	220	500
4	1020	546	943	1212	2033	2313	1232	2548
5	250	100	375	645	176	120	250	863
6	284	304	902	111	833	946	1024	131
7	120	1008	300	1100	158	3540	300	249
8	860	675	N	307	5025	441	4085	185
9	968	2678	392	2033	3038	1050	736	1125
10	381	450	580	429	461	255	317	1011
11	3906	436	549	215	3061	10857	422	4500
12	248	5882	1606	2562	1916	7317	832	804
13	1025	1503	1954	710	7500	331	731	15575
14	1130	786	429	354	2919	284	1000	895
15	1136	990	1622	6383	4110	952	1485	5000
Totals	11799	16891	10038*	16667	32592	29966	14760	34072

C: cellulose powder; P: placebo; N: no data; *One missing reading

ECP shown as µg/L. Differences are significant at $p \leq 0.05$ between placebo and cellulose treatments for the readings taken at 60 min and at 90 min after challenge

Secondary outcome measures

For symptoms of itchy nose (Figure 2) the difference in the results overall is significant at $p \leq 0.05$. Means are 17.2 with placebo and 7.8 with cellulose powder with SD 14.1 and 10.2, respectively. Confidence intervals of the means are 7.1 and 5.2 at $p \leq 0.05$. However, one subject had no symptoms and in 4 cases the total symptom scores were higher with the cellulose powder than with the placebo. In three of these cases the differences are not large but in one case there is a very marked difference.

For the other two symptom categories there are no significant results. For itchy mouth/palate, eight of the subjects had zero scores on both stages of the trial. For itchy throat, 5 subjects did not have any symptoms on either stage of the trial. The results for the other ten subjects are very similar for placebo and cellulose powder apart from one subject who had a total symptom score of 36 for the placebo and 24 for the cellulose powder.

Nasal flow readings

In the majority of cases mean PIFn readings were notably better compared to baseline, after challenge when the inert cellulose powder was used, compared to the results when the placebo was used (Figure 3). The mean difference is significant at $p \leq 0.05$. Means are –25 (placebo) and –3 (cellulose powder) with SD –7 and –29. The confidence intervals of the means are 50 and 14.7, respectively.

The mean peak PEFn results were significantly better ($p \leq 0.05$) after challenge when the inert cellulose powder was used compared with when the placebo was used (Figure 4). However, in three cases (numbered 1, 3 and 8 on the figure) the results were better with the placebo than with the inert cellulose powder. The means were –43 (placebo) and 22 (cellulose) with SD 96 and 95. The confidence intervals of the means were 48 and 47, respectively.

In several subjects there were marked differences with a clear pattern of decreased PEFn when using the placebo. These general patterns both for overall results and for individual subjects were apparent through the time course of the study.

Discussion

Although there was only a 1 week wash out period, no order effect was noted between wash out with active and placebo treatment. Also Baseline nasal resistance was noted to have returned to baseline after a minimum of a 1 week wash out period.

The results display considerable variance but this is not unexpected in trials such as this. A lot of factors may influence the outcomes, including thresholds of

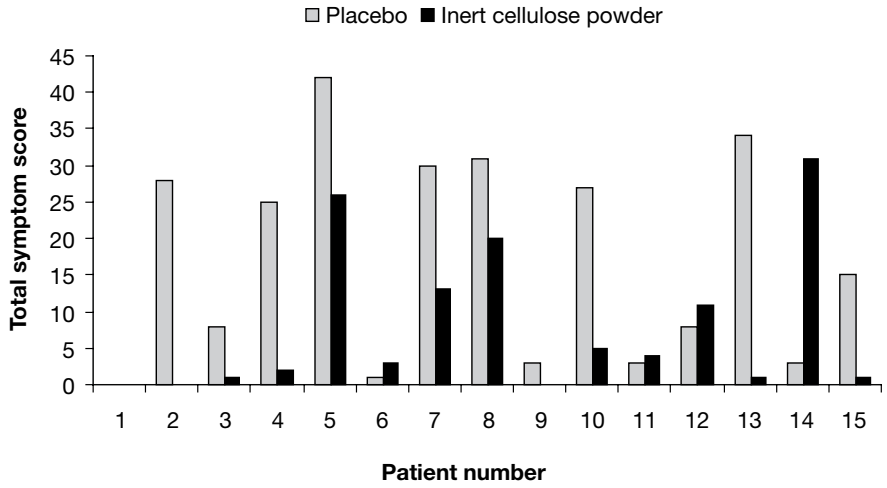

Figure 2. *Total symptom scores for itchy nose from challenge to 4.5 h later. Mean for placebo scores =17.2, SD 14.2, mean for cellulose powder scores is 7.8, SD 10.2. Differences are significant at* $p \leq 0.05$. *Subject one had no symptoms. Vertical axis is total symptom score, horizontal axis is patient number*

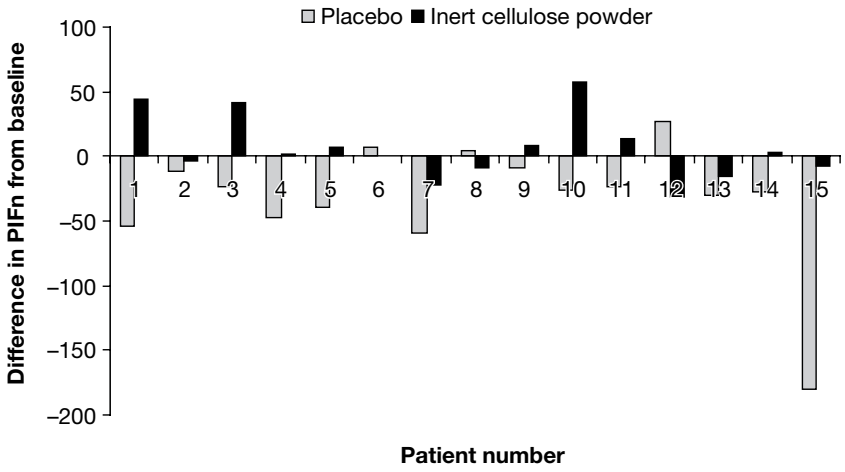

Figure 3. *PIFn mean of differences from baseline from immediately after challenge to 4.5 h later. Overall mean for placebo is –25, SD 47, overall mean for cellulose powder is –3, SD 25. Difference is significant at* $p \leq 0.05$. *Readings are in L/min. Vertical axis is difference in PIFn from baseline, horizontal axis is patient number*

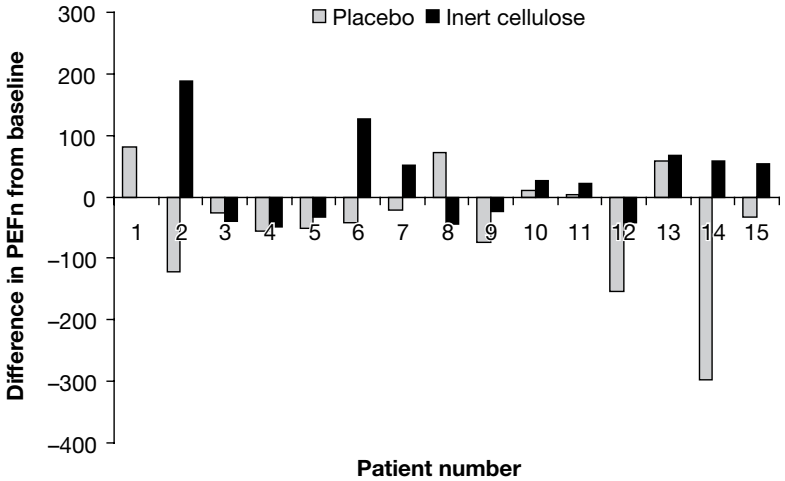

Figure 4. *Mean PEFn readings for individuals as differences from baseline. Mean is for 7 readings taken from after challenge to 4.5 h later. Overall mean for placebo is –43, SD 96. Overall mean for cellulose powder is 24, SD 69. For participant one there was no difference from baseline to mean PEFn when using the cellulose powder. Readings are in L/min. Vertical axis is difference in PEFn from baseline, horizontal axis is patient number*

sensitivity. Although all of the subjects had positive skin prick tests results to Der p1 and 10 were also positive to Der f1, the reaction to the challenge could differ notably. The challenge was set at a fairly low level even though the subjects had no history of asthma. Crude reference points for risk levels for asthma due to Der p1 and Der f1 exposure have been cited as for sensitisation > 2 µg/g dust, and for symptoms > 10 µg/g dust[11,12], but comparable figures for rhinitis are lacking. These thresholds would apply to a continuous exposure and little information is available to predict reactions when the allergen is applied in one dose. Previous studies have indicated that nasal provocation by house dust mite allergens may also provoke concomitant asthmatic symptoms during the late phase reaction[12]. This is not exclusive to people with a history of asthma and we wanted to minimise the risk of this complication in the study whilst having the possibility of invoking some symptoms of rhinitis.

Some previous research projects have used nasal spray with phosphate buffered saline (PBS) with concentrations of house dust mite allergen extracts[13]. This approach was not considered suitable for this trial as we were interested in achieving conditions which were as close as possible to those in real life. The challenge was, therefore, delivered as a homogenised and standardised dust rather than as a spray.

Currently the powder is supplied in plastic containers and is dispensed through a patented valve system by a squeezing action. The amount of powder delivered per puff is approximately the same but it may not be constant. This aspect was minimised by having a standard technique and only two people making the applications.

The challenge was given as one delivery of allergen to the nose. Other work has examined the effect of continuous allergen challenge on clinical symptoms and mediator release in dust mite allergic patients[14] over 8 h. In this double blind placebo controlled cross over study the whole sample population showed a rise of nasal and ocular symptoms which were perceptibly but not significantly attenuated by active drug treatment. ECPs exhibited a constant level over the whole provocation period.

The study was designed to detect both early and late phase reactions. Early phase response occurs within minutes of the allergen challenge and tends to produce sneezing, itching and clear rhinorrhoea. Late phase response occurs 4–8 h after allergen challenge and is characterised by congestion, fatigue, malaise, irritability and possibly neurocognitive deficits. However, in this study the development of late phase reactions was not evident, possibly due to the low level of the challenge.

Eosinophil cationic proteins in nasal fluid have been used frequently as a marker for local inflammation[15,16]. Previous research has established that this marker is an effective measure of degranulation and thus activation of the eosinophils[17]. In order to maintain the blind nature of the trial the collation and analysis of the results was done by different people from those who assisted with the challenge tests.

Conclusion

The results of the trial indicate that the inert cellulose powder can have significant effects in reducing some symptoms of rhinitis due to house dust mite allergy. The results show significant differences between the placebo and active treatments for sneezing, itchy nose and runny nose, and ECPs in nasal secretions. Also the results indicate that when the inert cellulose powder is used the mean peak nasal expiratory and inspiratory flows are higher than when the placebo is used.

Further research is in progress to determine the mode of action of the cellulose powder, particularly its capacity to act as a barrier to the passage of allergens.

Acknowledgement

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ALLERGY
Nasaleze
natural hayfever and allergy prevention

Nasaleze cellulose powder delays house dust mite allergen (Der p1) diffusion in vitro.

Diethart B, Emberlin JC, and Lewis RA.

Poster presented: *EAACI*, Barcelona in June 2008.

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ALLERGY Nasaleze®
natural hayfever and allergy prevention

Nasaleze cellulose powder delays house dust mite allergen (Der p1) diffusion in vitro

Bernadette Diethart is studying under the guidance of Professor Jean Emberlin of the National Pollen and Aerobiology Research Unit at Worcester University www.pollenuk.com

This study was recently poster presented at the XXVII Congress of the European Academy of Allergology and Clinical Immunology Barcelona, Spain 7–11 June 2008 (www.eaaci2008.com)

Background: An inert cellulose powder (Nasaleze®) has been used since 1994 in the alleviation of allergic rhinitis. The powder is applied to the nose where it absorbs water and forms a gel which is thought to act as a mechanical barrier against allergens. The purpose of the study was to investigate this theory about the mechanism of action of the gel in relation to house dust mite allergen (Der p1).

Methods: The amount of Der p1 which diffused through the cellulose gel and an agar gel, which was used as a reference, were measured by ELISA and compared to the baseline allergen content of the solution applied to the gels. The allergen portion that passed the gels was measured at 15, 30, 45, 60, 180 and 300 minutes after application of the standard allergen solution.

Results: The diffusion of Der p1 was delayed by both gel layers. The amount of allergen diffused through the agar gel was not significantly different from the baseline values. After 15 minutes of incubation 69% of the baseline allergen amount had diffused through the agar gel which did not give a significant difference in the one-way ANOVA ($p = 0.15$). The amount of allergen that passed the agar then steadily increased until it reached baseline level after 180 minutes. Diffusion of Der p1 through Nasaleze cellulose powder showed a significant reduction of diffused allergen in all tests ($p = 0.001$ to 0.008). After 15 minutes of diffusion only 1.9% of the baseline amount had diffused through the cellulose gel. After 300 minutes 44.8% of the baseline Der p1 crossed the cellulose gel while 100% had diffused through the agar layer.

Conclusion: Allergens are small, water-soluble molecules that are able to diffuse through gels. However, the mesh size of the polymer chains in the gel determines the size of the molecules that can pass through and the speed of their diffusion. The mesh size in the Nasaleze cellulose powder is smaller than in agar gel.

Nasaleze cellulose powder does delay the diffusion of Der p1 significantly but due to the small size of allergenic proteins it is not able to act as an impermeable barrier. Therefore regular re-application of the powder to the nostrils has to be suggested for optimum efficacy of the product in the prevention and alleviation of allergic rhinitis.

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Natural Science

Hydroxypropylmethylcellulose gel application delays Der p 1 diffusion in vitro

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ABSTRACT

Background: A special hydroxypropylmethylcellulose powder (Nasaleze®) has been used for the alleviation of nasal symptoms of allergic rhinitis since 1994. The efficacy of the product has been recently proven but the mechanism of action was still largely unknown. The aim of the study was to investigate the hypothesis that the gel formed after moisture absorption in the nose might act as mechanical barrier that prevents allergen diffusion towards the nasal epithelium. Methods: The diffusion of Der p 1 through HPMC and agar gels was measured in vitro after 15, 30, 60, 180 and 360 minutes using ELISA. Agar blocks were used to simulate the nasal mucosa. Control samples without gel layer were obtained. Results: The control samples with no applied gel barrier absorbed 72.2 % of the Der p 1 solution after 15 minutes and 100 % after 60 minutes. In comparison, the HPMC and agar gel layers both significantly delayed Der p 1 diffusion. After 15 minutes 0.76 % had diffused through the HPMC gel layer compared to 28.1 % which diffused through the agar layer. After 360 minutes, 14.1 % of the baseline Der p 1 crossed the HPMC gel layer while 100 % had diffused through the agar layer. Conclusions: HPMC gel significantly reduces Der p 1 diffusion in vitro compared to no barrier and an agar gel layer. This is likely to be due to the small mesh size of the polymer network of HPMC and could have important implications for a preventative treatment of allergic rhinitis.

Keywords: Allergic Rhinitis; Der p 1; Diffusion Barrier; Hydroxypropylmethylcellulose

1. INTRODUCTION

Allergic rhinitis (AR) is a global health problem which affects up to 25 % of the adult population in industrialised countries and more than 40 % of children [1,2]. The rising prevalence of allergic rhinitis imposes a huge burden on the economy due to costs of treatment and loss of work productivity. Recent estimates of annual costs range from $2 to 5 billion in the U.S. alone [3-5]. The pathology of AR is associated with a severe impairment of the quality of life for those who suffer from it [6,7]. A reduction of quality-of-life impairment can be achieved by appropriate treatment of allergic rhinitis [7,8]. Modern medications such as antihistamines or corticosteroids can do a lot to help to alleviate symptoms and restore a normal lifestyle but many of them have unwanted adverse effects or are limited in their application [1,3,4]. Many people distrust these conventional medicines and therefore prefer to use complementary and alternative treatments. However, the therapeutic efficacy of many of these treatments is not supported by evidence and they might not be devoid of side effects [3,9].

A recent approach is offered by the use of an inert hydroxypropylmethylcellulose (HPMC) powder (Nasaleze ®) for allergy prevention and alleviation in the nose. Although the product has been registered as a class 1 medical device with the MHRA since 1991 and is sold over the counter in more than 50 countries worldwide, little work has been done on the effect of the powder on nasal symptoms. However, the efficacy of HPMC in decreasing symptoms of allergic rhinitis caused by grass pollen and house dust mite allergens was recently proven [10-12]. The investigators observed an improvement of symptoms when using HPMC for treatment of SAR and PAR. Nasal peak inspiratory flow (PIF) and peak expiratory flow (PEF) increased compared to placebo and some symptoms of allergic rhinitis including sneezing, itching and runny nose were alleviated significantly. Also the need to use rescue medication was found to be reduced. Considerable variance was observed in the results and some participants did not show any improvement. This was partly attributed to the application device which is suspected not to deliver constant doses [12,13].

The HPMC powder is applied to the nose using a specially designed dry powder dispenser bottle and forms a gel on the nasal lining by absorbing moisture from the nasal mucosa. It was hypothesised that this gel might act as a mechanical barrier preventing allergens from entering the mucosa [11,12]. However, no investigations on the mechanism of action of HPMC as an allergy treatment have been published as yet leaving the question how an inert cellulose derivative can offer relief to individuals affected by allergic rhinitis unanswered. Similar HPMC powders which also form hydrogels upon contact with liquids are widely used in controlled drug release formulations where they restrict the release of drug molecules through the tablet by serving as a barrier to drug diffusion [14]. Also, high-viscosity HPMC gels have been shown to limit glucose and cholesterol absorption in the gastrointestinal tract by creating a mechanical barrier [15,16]. Thus, it is assumed that HPMC gel might impede the passage of allergens in a similar manner.

The aim of this study was to investigate the possibility that HPMC gel might constitute a mechanical barrier to house dust mite allergen in vitro in order to gain information about the mechanism of action of HPMC in the alleviation of symptoms of allergic rhinitis.

2. METHODS

2.1. Materials

Hydroxypropylmethylcellulose powder was supplied by Nasaleze Limited, IOM. Der p 1 solution (in house reference, 7.5 µg Der p 1 per millilitre) was provided by Alk-Abello, Madrid.

2.2. Sample Preparation

Preparation of the samples took place in a cleanroom to minimise contamination by dust or allergens. All equipment needed for preparation was washed in isopropyl alcohol (70 %) for sterilisation and dried before each use. Ten ml of agar (1.5 %, prepared with 0.9 % saline solution) were cast into a petri dish. After cooling, small rectangles of equal dimensions (1 x 1 cm) were cut from the agar and then transferred to cleaned slides. Two lines of warm and therefore liquid Vaseline were drawn with a brush from the two edges of one side of the agar block to the edges of the slides to avoid diffusion of allergens through the side of the block (**Figure 1**). The position of the agar was marked on the bottom of the slide and the agar block was covered by a cover slip that sealed the upper surface of the agar. Allergen solution could therefore diffuse into the agar through only one free edge (**Figure 1**).

To test the barrier function of HPMC, a thin layer of HPMC gel was applied covering the edge of the agar which was used for allergen application. For this, 50 mg of HPMC powder were mixed with 1 ml physiological saline solution (0.9 %) to form a 5 % gel. Immediately after the mixing of the gel, 0.2 ml was applied to the open edge of the agar block using a 1 ml sterile syringe. The initial thickness of the gel layer was measured at 3 standard points. After covering with a cover slip, 20 µl of the allergen solution were applied to the HPMC gel covering the one side of the agar blocks limited by the Vaseline lines.

The slides were incubated at 35°C and 90 % relative humidity to simulate nasal conditions for 15, 30, 60, 180 and 360 minutes. After incubation the thickness of the HPMC layer was again measured. The agar blocks were then carefully removed from the slides and transferred to labelled microtubes containing 0.5 ml PBS-T as elution medium. Samples were shaken on an Autovortex for 20 seconds followed by shaking overnight on a lab shaker. Samples were stored frozen at -20°C.

2.3. Reference and Control Samples

To investigate the difference of diffusion through HPMC and agar, control samples were produced with an additional agar layer of 1.5 mm (average thickness of the HPMC gel layer calculated from measurements of HPMC samples using a digital caliper) to replace the HPMC gel and treated in exactly the same way as the HPMC samples.

Additionally, control samples with no allergen addi-

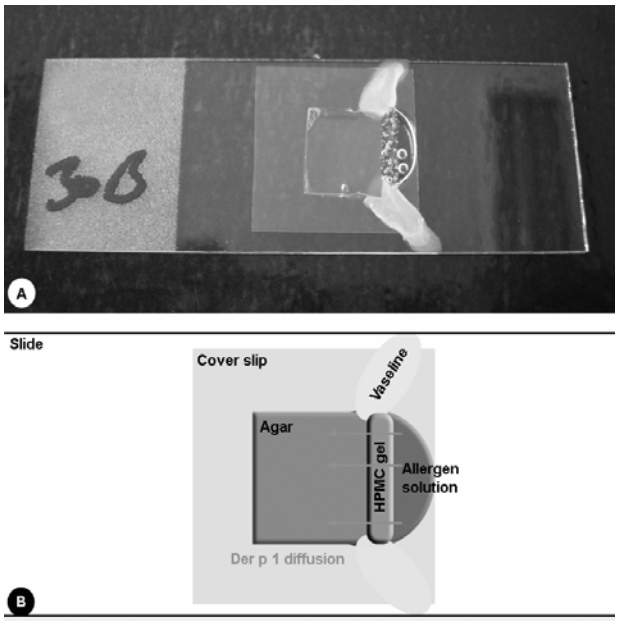

Figure 1. Photograph (A) and diagram (B) of experimental setup for sample preparation for ELISA measurements of Der p 1 diffusion through HPMC gel.

tion and no barrier addition, respectively were obtained.

Baseline measurements of the allergen amount in 20 µl of allergen solution were conducted by applying 20 µl of allergen solution directly to a microtube containing 0.5 ml of PBS-T. The microtubes were then treated in the same way as the microtubes containing the agar blocks.

2.4. ELISA Measurements

The monoclonal antibodies (mAbs) and Der p 1 allergen standards used in the assays were purchased from Indoor Biotechnologies, and the assays were performed according to the manufacturer's instructions.

2.5. Statistical Analysis

One-way ANOVA was applied for statistical analysis of the differences between Der p 1 diffusion in HPMC gel, agar gel and control samples, respectively. No serious violations of assumptions were observed. P values of 0.01 or less were considered to be statistically significant.

3. RESULTS

The mean baseline allergen content in 20 µl of the standard solution used was found to be 151.0 ng/ml (SD = 4.0 ng/ml). This is in good agreement with the calculated value of 150 ng/ml for the given dilution of a 7.5 µg/ml stock solution. All control samples with no allergen application were negative in the ELISA measurements.

The diffusion of Der p 1 molecules into the 1 x 1 cm agar blocks eluted for measurements was delayed with both gel barriers applied (**Table 1** and **Figure 2**). The amount of allergen diffused through 1.5 mm of 1.5 % agar gel was significantly different from the baseline values for the first 180 minutes ($p < 0.005$) but did not reach statistical significance after 360 minutes ($p = 0.628$). After 15 minutes of incubation, 28.1 % of the baseline allergen amount had diffused through the gel into the agar block (**Table 2**, $p < 0.0001$). The amount of allergen detected in the elutes of the agar blocks then steadily increased until it reached baseline level after 360 minutes of incubation (**Figure 2** and **Table 2**). The thickness of the agar layer applied as a barrier did not change during the measurement times from 15 to 360 minutes. In contrast, an initially 1.50 mm thick HPMC gel layer swelled to an average 3.34 mm in 360 minutes upon allergen solution application. Diffusion of Der p 1 molecules through 5 % HPMC gel showed a significant reduction of diffused allergen for all test times ($p < 0.001$). After 15 minutes 0.76 % of the baseline amount had diffused through the HPMC gel layer into the agar block compared to 28.1 % which diffused through the agar layer (**Table 2**). After 360 minutes, 14.1 % of the baseline Der p 1 crossed the HPMC gel layer while 100 % had diffused through the agar layer (**Table 2**). However, the HPMC data include several outliers and the standard deviation is high (**Table 1**). The mean coefficient of variation for all measurements for the HPMC gel was found to be 201.9 % which is very high compared to 37.8 % for agar.

Control samples with no barrier had absorbed 72.2 % of the baseline allergen content after 15 minutes and differences to baseline did not reach statistical significance after 60 minutes using a 99 % confidence interval ($p_{60min}=0.042$, $p_{360min}=0.990$).

4. DISCUSSION

Most of the commonly available treatments of allergic rhinitis affect the inflammatory processes (e.g. by abating mediator release or blocking receptors) initiated after

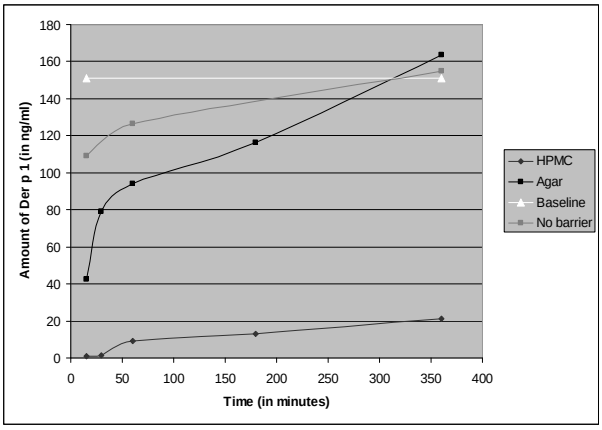

Figure 2. Amount of Der p 1 diffused through a 1.5 mm thick HPMC and agar gel layer, respectively compared to control (no barrier) and baseline allergen amount.

Table 1. Amount of Der p 1 diffused through a 1.5 mm thick HPMC and agar gel layer, respectively, amount of allergen absorbed without barrier (control) and baseline allergen amount in 20 µl of the applied solution.

	Amount of Der p 1 measured in samples (in ng/ml)				
Time (in min)	15	30	60	180	360
HPMC	1.15	1.57	8.98	13.17	21.34
Agar	42.46	78.98	93.92	116.46	163.59
No barrier	109.26	no value	126.62	no value	154.92
Baseline	151.04	151.04	151.04	151.04	151.04

Table 2. Fractions of allergen amount diffused through a 1.5 mm thick HPMC and agar gel layer, respectively and with no barrier compared to the baseline value of 151.04 ng/ml.

	Diffused fraction of Der p 1 (in % of baseline)				
Time (in min)	15	30	60	180	360
HPMC	0.76	1.04	5.94	8.72	14.13
Agar	28.11	52.29	62.18	77.11	108.31
No barrier	72.34	no value	83.83	no value	102.57
Baseline	100.00	100.00	100.00	100.00	100.00

allergen penetration into the mucosa and binding to IgE [1,17,18] and therefore represent symptomatic treatment. This means that inflammation and the associated damage of the mucosa are already established and the medication decreases signs of this inflammation while it is still on going. An ideal allergy treatment would inhibit the establishment of an allergic reaction altogether. Anti-IgE prevents binding of allergen to IgE antibodies and so inhibits a reaction while the allergens are already inside the epithelium [19]. HPMC might work at an earlier stage by preventing allergens from entering the mucosa in the first place by the generation of a mechanical gel barrier.

The present study aimed to investigate this possible barrier function of HPMC to allergens. The results obtained by ELISA-measurements show that HPMC significantly delays Der p 1 diffusion and that the amount of allergen diffused through the gel is even lower than indicated by preliminary tests [20]. This retardation might allow the mucosa to recover its physical integrity and the allergic reaction to decline. However, a complete barrier to Der p 1 diffusion could not be confirmed.

The retarded diffusion of solutes in hydrogels like HPMC gel or agar gel is well known and widely used for biotechnological separation methods such as electrophoresis or gel chromatography and in controlled release formulations [21,22]. The most comprehensible model developed to explain the diffusion delay of solutes in gels is the obstruction theory which assumes that the impenetrable polymer chains are obstacles that cause an increase in diffusional path length and additionally act as a sieve [21,24]. Therefore the mesh or pore size of the polymer network is a crucial parameter in the reduction of diffusion in hydrogels [25]. Hydrogels consist of high molecular weight molecules forming a threedimensional network which is dispersed in a continuous liquid medium [22,25]. Due to cross-links and entanglements of these molecules hydrogels can be described as a mesh with solvent filled spaces between the individual polymer chains which act as a filter for molecules larger than the spaces available [26,27]. Controlled release studies with FITC-dextran molecules of different molecular weights revealed that the critical molecular weight for diffusion in HPMC gels, which are characterised by a mesh size of 12 nm, lies between 65 and 66.5 kDa depending on the molecular weight of the polymer and the concentration of the gel [28]. Allergenic proteins usually have a molecular weight between 5 and 80 kDa [29,30]. This means that a great proportion of allergens theoretically are small enough to diffuse through the HPMC mesh spaces. Although Der p 1 (24 kDa) lies well below the mesh size of HPMC gels, a substantial delay in diffusion has been observed. Even though molecules larger than 65 kDa are stopped from diffusing through HPMC almost completely, all other smaller molecules will still be delayed by the longer diffusional path due to obstructions by the macromolecular chains and the slower water movement due to binding of water to the polymer. Furthermore, the mesh size and therefore the size of the spaces available for diffusion in weakly cross-linked homogenous gels is not stable but time-dependent and the size and location of the spaces change due to Brownian motion of the molecule chains [22,31].

In comparison to HPMC, the mesh size of a 1.5 % agar gel as used in this study has been observed to be between 70 and 800 nm [21,26]. Even the lowest of these values is almost six times larger than the mesh size of HPMC which explains the higher allergen diffusivity within agar gel.

The values obtained in the present study are valid for Der p 1 and allergens of the same or very similar molecular weight. It has been shown that the diffusion coefficient for globular proteins in agar decreases with increasing molecular weight and therefore radius of the proteins [21]. This leads to the assumption that allergens smaller than Der p 1 like Bet v 1 (17 kDa) or grass group 2/3 allergens (10-12 kDa) might be expected to diffuse faster whereas larger allergens like Amb a 1 (38-50 kDa) or Art v 1 (28-60 kDa) might exhibit slower diffusion velocities through the HPMC gel network.

The variability of the results of the measurements of Der p 1 diffusion through HPMC gel was high with a coefficient of variation (CV) of just over 200 %. In comparison, the CV of Der p 1 diffusion in agar gel was only about 37 %. For this reason the variation in the amount of allergen diffusing through the HPMC gel layer cannot solely be attributed to limitations in the methods that were applied. Similarly high variability of diffusion coefficients was obtained for mucus gels [32]. This was attributed to the heterogeneous nature of the

mucous gel producing uneven penetration profiles. Release from HPMC matrices for controlled drug release was found to be sensitive to alterations in the chemical composition and the polymer gel conformation and substantial batch-to-batch variations in release and swelling could be observed for a single type of HPMC [33,34]. The authors suspect that this might be due to aggregate formation in the gel causing transient cross-linking that could perturb diffusion in some places throughout the gel which cannot be predicted.

Due to its importance in controlled drug release, the effect of HPMC as a diffusion barrier for drugs has been studied extensively. However, no investigations of allergen diffusion in HPMC have been found in the accessible literature. It was confirmed in this study that HPMC gel delays Der p 1 diffusion in vitro. Other allergens need to be tested to extend the evidence for the efficacy of the product. Also many other factors will influence the efficiency of the product in vivo. For practicality reasons, the gel layer used in the experiments is thicker than the gel layer that can be expected to be established within the nasal cavity. Diffusion velocity is a crucial parameter needed to make assumption for in vivo conditions and should therefore be addressed in future research. A complete diffusion barrier is essential for the retardation of drug release [14] and similarly optimal coverage of the nasal mucosa is important since uncovered areas may allow free allergen entry and the provocation of an allergic response. Sub-optimum coverage is likely to reduce the efficiency of the product. The provision of a suitable powder delivery device therefore poses an important challenge for the maximisation of the efficacy of HPMC in the alleviation of allergic rhinitis.

In conclusion, a diffusion delay of Der p 1 in HPMC gel has been confirmed in vitro. This means that even though HPMC gel does not constitute an impermeable barrier to allergens, the significant delay of allergen entry into the mucosa could be beneficial to hay fever sufferers through the reduction of allergen exposure. This fairly novel way of treatment reduces the allergen load itself and not the symptoms caused after allergen entry into the mucosa. Thus, with the appropriate delivery device, HPMC could be a valuable, drug-free alternative for the treatment of allergic rhinitis. The efficacy of HPMC in hay fever treatment has been recently proven [10-12]. However, the research presented in this paper is the first to address the mechanism of action of HPMC in the alleviation of allergic rhinitis. This knowledge will allow improvements on the product to be made in order to increase its benefit to hay fever sufferers.

5. ACKNOWLEDGEMENTS

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A Review of the Efficacy and Safety of Nasaleze in the Prevention and Management of Allergic Rhinitis.

A meta-analysis paper by Professor Patrick JD Bouic, Division of Medical Microbiology, Department of Pathology, University of Stellenbosch, South Africa.

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ALLERGY Nasaleze®
natural hayfever and allergy prevention

A Review of the Efficacy and Safety of Nasaleze™ in the Prevention and Management of Allergic Rhinitis

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Abstract: Nasaleze™ is an inert cellulose powder which has been on sale in the UK since 1994 and is used as a remedy for hay fever. It is applied to the nasal passage where it forms a gelatinous coating, thereby trapping aero-allergens and preventing the initial allergic response. Some limited clinical studies have been conducted in predominantly adults but also in children: outcome measures included the reporting of symptoms by volunteers (sneezing, itching, blocked nose, etc) using questionnaires; prevention of symptoms when challenged to aerosolized allergens; concomitant use of rescue medication and the measurement of inspiratory air flow across the mucosa as well as the release of ECP in nasal washings. The product has been reported to be safe and well tolerated by all volunteers and warrant further investigation in larger studies.

INTRODUCTION

Seasonal and/or perennial allergic rhinitis is on the increase world wide, having increased two- or three fold over the last 15 years and current prevalence studies indicate that almost 15 million individuals are affected in the UK and 50-60 million people having been diagnosed in the USA alone [1]. It is often left undiagnosed due to the heterogeneity of the presenting symptoms, notably sneezing, itching, nasal congestion and very often, rhinorrhoea. Rhinitis is possibly one of the most debilitating conditions for sufferers due to the fact that the symptoms are often so severe that medications used during such crises are not fast-acting enough to provide relief and almost always induce side-effects which prevent the users from participating in normal day-to-day activities.

Nasaleze™, is an inert, micronized cellulose powder delivered in a patented delivery system. This proprietary grade powder is registered since 1994 and is currently on sale in many countries, including the UK. It is applied to the nasal mucosa where it forms a gelatinous coating, thereby preventing the airborne allergens from triggering the release of vasoactive substances from the mast cells lining the mucosa. It can therefore be considered not only as an effective measure to prevent the initial immunological reaction but also as a management strategy for reducing the symptoms of the allergic rhinitis once triggered.

This product has recently been commercialized in South Africa and is sold mostly through health store outlets or though some prescribing clinicians. It is relatively unknown although it has been available in the UK and some European countries. A mini-review of its properties and clinical benefits was therefore necessitated and this is presented herein: no other reviews of this product have been previously conducted.

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METHODS

A computerized literature search using the National Library of Medicine's Medline database and ScienceDirect journal access was conducted and any relevant articles referring to the product was extracted. Key words used for the search included: rhinitis & cellulose powder, Nasaleze, allergen challenge & powder, inert powder & rhinitis. This search yielded 5 published papers [2-6] and 4 poster presentations at congresses. They all referred to the work conducted using Nasaleze™, the product containing an inert cellulose powder. The congress poster presentations were often abstracts of the full articles and for this reason, they were excluded from this analysis: only the data of the published literature were extracted and is presented under the following categories:

a. Study designs and patient population studied

b. Study outcome measures, safety and product acceptability

c. Possibilities of product development

This review is no attempt to represent a meta-analysis of the published data since the literature is too limited and the study outcomes are too varied to conduct such an analysis.

RESULTS

A. Study Designs and Patient Populations Studied

Most of the published works deal with patients recruited by means of advertisements placed in national and local press media. The patients were required to complete pretrial questionnaires which pre-selected the patients based on predefined criteria for eligibility such as range of rhinitis symptoms, severity (requiring medication for management), time of the year when symptoms were at their worst, etc. The self-reporting questionnaire graded the patients on a point scale

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system (1 for severe uncontrolled symptoms to 5 for an indication of well-being, no symptoms): changes in any of the scores could be used to determine the eventual outcome of the interventional study.

In some studies, recruited patients participating in the study had recourse to rescue medication and this was recorded in daily journals since the use of concomitant medication was an indirect measurement of the efficacy of the Nasaleze™ product in the control of the patients' symptoms. In other studies, a new formulation (Nasaleze™ Travel) was compared to the routine preparation in the prevention of airborne infections which could have been acquired whilst traveling. Yet another study challenged volunteers to house-dust mite allergens and determined the efficacy of the Nasaleze™ product in preventing the allergic reaction. The studies are summarized hereunder in Table **1**.

All of the above studies made use of selected patient population either recruited *via* the general practitioners who referred their patients to the study sites or volunteers who responded to recruitment advertisements *via* the local press. The respondents were screened for participation in the studies and the criteria used included severity of symptoms based on allergy medication history, seasonality of symptoms (pollen counts also used to determine whether the symptoms corresponded to high allergenic challenge), accessibility for follow up, etc. In most studies, compliance was never compromised and fall out from the study was minimal since most volunteers benefited from the intervention. This in itself was an indication of the efficacy of the product in controlling the symptoms. The intervention periods were relatively short (4-8 weeks) and yet, efficacy outcomes were achieved and these were reported by the authors.

Although questionnaires were used to determine study outcomes (these could be considered as biased tools to measure efficacy), some studies made use of biomarkers which provided unbiased, quantitative laboratory data to corroborate the clinical outcome measures. These are reported in the following section.

B. Study Outcome Measures, Safety and Product Acceptability

The studies made use of questionnaires which was scored by the volunteers and these recorded their sense of wellbeing. Some limited laboratory biomarkers of successful intervention were also recorded in some studies. Furthermore, accessibility to rescue medication during some of the studies was considered as an unbiased measurement of the ability of the product being investigated to manage the symptoms of the patients. These results are summarized hereunder (Table **2**).

All of the studies clearly showed efficacy of the cellulose powder in reducing symptoms associated with either seasonal or chronic rhinitis without the need of the patient to make use of pharmaceutical drugs (although very few patients had such recourse). The most significant findings are that the product is well tolerated, safe and easy to apply. The independent measurements of efficacy included measurements of improved inspiration and expiration air flow implying that the use of the product lead to less inflammation and oedema at the mucosal surfaces. The use of the inert powder by children (and possibly pregnant women) is an added advantage: not many drugs can be used by these target populations without medical advice and warning.

The lack of significant difference in the symptoms scores between the placebo and active group in the study by Emberlin & Lewis [4] deserves some discussion: the authors reported that at the 1% significance level, no differences existed between the groups. However, at the 5% level, differences were reported by the volunteers for some symptoms such as "running nose" or "blocked nose" and this tended to correspond to days with lower pollen count days. However, these significant differences were lost when the total Likert score was compared between the groups.

C. Possibilities of Product Development

The study conducted using the cellulose powder as a carrier of bioactive molecules, in this case, an extract of garlic,

Table 1. Summary of Published Studies Making Use of Nasaleze™

Authors	Number of Patients Recruited	Patient Population	Type of Study	Duration of Study Period
Josling & Steadman (2003)	102 (66 females, 36 males).	Adults (mean age = 44 yrs): reporting seasonal rhinitis.	Open labeled: volunteers compared present product to previously used drugs.	6 weeks.
Aivazis W *et al.* (2005)	100 (47 girls, 53 boys).	Children (age range 1.5 – 18 years, mean age = 7.96 years).	Open labeled: measurement of mucocilliary clearance in allergic rhinitis pre- and post therapy with Nasaleze™	6 weeks.
Emberlin & Lewis (2006)	97 (57 females, 40 males).	Adults (mean age = not reported): hay fever sufferers.	Randomised, double blind, placebo-controlled. Patients recorded symptoms including Likert scores. Rescue medication permitted.	4 weeks.
Emberlin & Lewis (2007)	15 (7 females, 8 males).	Adults (modal age range 38-47 yrs): selected specifically for house dust mite allergy.	Double blind, cross over challenge study using Der p1 and Der f1 sensitivity.	1 month recruitment and 2 week actual study at clinic.
Hiltunen *et al.* (2007)	52 (gender distribution not stated)	Adults (mean ages not reported).	Randomised, double-blind study of Nasaleze™ vs Nasaleze™ Travel (with garlic extract) to determine prevention of airborne infections.	8 weeks.

Table 2. Outcomes, safety and Product Acceptability

Study	Significant Findings	Compliance and Safety	Conclusions Drawn by Authors
Josling & Steadman (2003):	77% of volunteers reported success (either good or excellent) by end of 6 weeks; average scores of 3.8 by men and 3.9 by women (5 indicating symptom free) were achieved: this was better when compared to pharmaceutical drugs used in the past; symptoms controlled within 0.1 – 3 hours after use.	No major problem: some volunteers reported some discomfort in throat due to powder. Only 8 patients required additional treatments.	Pilot study which clearly indicated that further investigations were warranted. Inert powder not medicated hence no side-effects with added advantage. Product well tolerated and provided fast relief.
Aivazis *et al.* (2005):	Only study conducted in children: statistically significant improvement in mucociliary clearance (39 mins. to 18.15 mins and this was directly related to improved peak nasal inspiratory flow rate (114.9 L/min to 144.4 L/min) implying less oedema and inflammation following use of product.	Excellent tolerance to product: no safety issues raised by volunteers.	The results imply the regeneration of ciliary epithelium. Product can be used by children.
Emberlin & Lewis (2006):	Blinded study in hay fever sufferers with significant differences in outcomes between groups: placebo used more rescue medication ($p < 0.05$) although Likert scores showed no differences.	No adverse effects reported during trial: both powders well tolerated. The placebo powder (lactose) may have provided some protection to the users.	The inert cellulose powder provides safe and effective protection thereby obviating the need for anti-histamine and other pharmaceutical drugs for the symptoms.
Emberlin & Lewis (2007)	Allergen challenge in house dust mite allergic individuals: significant decrease in biomarker ECP ($p < 0.05$) in nasal secretions as well as significant increase in measurements of nasal air flow ($p < 0.05$) when placebos compared to active. Cross over period of study proves efficacy of cellulose powder in preventing allergic reaction.	No adverse effects reported by any volunteer.	Nasaleze™ has ability to significantly reduce symptoms of persistent rhinitis due to house dust mite and possibly provides effective barrier to inhaled allergens.
Hiltunen *et al.* (2007):	Significantly less infections (all combined) reported by volunteers using powder enriched with garlic extract compared to users of powder alone ($p < 0.001$) and days affected by airborne pathogens also different between groups (less days reported ill, $p < 0.05$).	Volunteers continued with their daily travel plans and this study (albeit small) shows that garlic extract enriched cellulose powder provided effective barrier to airborne pathogens. No adverse effects reported by volunteers.	Cellulose powder can be used as effective carrier of bioactive molecules to prevent airborne pathogens during traveling.

presents exciting novel applications of the technology to address other important medical challenges. This trial showed that the active could be absorbed *via* a well vascularized mucosa and provide the efficacy sought (prevention of airborne infections). Numerous studies are currently searching for ways to deliver small amounts of antigenic peptides for immunization purposes since the immune cells of these surfaces are extremely powerful antigen presenting cells and are thus able to induce an immune response in the draining lymphoid organs. Also, the delivery of other natural molecules which have been described as effective anti-inflammatory compounds [7] for the management of chronic conditions affecting the mucosal surfaces is another area of research which warrants investigation by the manufacturers of the product.

CONCLUSIONS

The treatment of allergic rhinitis to date has relied heavily on drugs that act either as membrane stabilizers thereby preventing the degranulation of the immune cells lining the nasal mucosae and which contain vasoactive peptides (steroid based drugs) or on drugs that neutralize the release of histamines (generic anti-histamines). Most of these drugs are not without side effects: they cause drowsiness and cannot be used by pregnant women. The novel product Nasaleze™ represents a new management strategy in the control and management of allergic rhinitis: this inert cellulose powder is administered into the nasal passages and forms an impervious barrier to the aero-allergens to which the individual may be sensitized. It is a natural and safe product, does not contain any drugs and above-all, has shown itself to be effective under trial conditions (albeit small studies).

The powder was tested not only as a preventative approach to attacks of hay fever but also as a treatment to the symptoms of allergic reactions, it stops the sneezing within minutes (response within 0.3 hours) and allows the improvement of air flow into and out of the nasal passages, thereby implying that it decreases the degree of on-going inflammation and oedema which normally accompanies an allergic reaction. These findings were corroborated by the laboratory measurement of decreases in the nasal washings of released ECP (Eosinophilic Cationic Protein), a biomarker of cellular degranulation.

The use of the inert powder as a carrier medium for bioactive molecules such as garlic extract to prevent travel-associated infections showed interesting results: fewer infections were reported by the volunteers who applied this enriched powder during their travels locally and even internationally. The study however is not clearly defined due to the fact that some patients traveled internationally using air

travel while others may have been using local train travel. The study implies that other molecules could be tested using this safe carrier. Further studies using larger patient groups are certainly warranted and these should include other immune biomarkers of efficacy, such as IgE levels, specific IgE titers to offending allergens, etc.

DISCLOSURE

The author would hereby like to declare that he has no vested interest (financial or otherwise) in the product being reviewed in this article. The need for such a review was necessitated by the fact that the product was unknown at the time of its launch in South Africa.

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Efficacy and safety of medical device Nasaleze in prevention and treatment of persistent allergic rhinitis in adults and children.

Zakharzhevskaya TV, Sidorenko IV, Treskunov VK and Karaulov AV.

Poster Presented: Moscow XVI Congress for Man and Drugs in April, 2009.

ALLERGY Nasaleze®
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Efficacy and safety of medical device Nasaleze in prevention and treatment of persistent allergic rhinitis in adults and children

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This was presented at Moscow XVI Congress for Men and drug April 06-10, 2009.

Keywords: persistent allergic rhinitis, Nasaleze, ultra-disperse cellulose powder, clinical trial

Summary

This paper describes the findings of an open non-comparative clinical study of efficacy and safety of an ultra-disperse cellulose preparation in prevention and treatment of persistent allergic rhinitis (AR).

Introduction

Allergic rhinitis is a condition characterized by allergic inflammation, resulting from contact of allergens with nasal mucosa and associated with one or more of the following symptoms:

1. Nasal congestion
2. Nasal discharge
3. Sneezing
4. Nasal itching (1)

AR is one the most widespread allergic diseases. Not infrequently, it precedes other allergic disease, such as atopic dermatitis and bronchial asthma. Active manifestations of AR have a significant impact on the patient's quality of life, interfere with sleep and rest, and decrease capacity for work.

Methods of preventing and treating AR, which are currently available in an allergist's armamentarium, are not completely effective, are time-consuming, costly and associated with a number of side effects. The challenge of finding adequate means to prevent and treat AR is further aggravated in children and pregnant women, due to the lack of evidence confirming the safety of such medications in these categories of patients.

The usage of ultra-disperse cellulose may become a method of choice to prevent and treat AR.

After the registration and approval of micro-cellulose powder for medical application in Russian Federation, this open non-comparative study was conducted in 2009 to investigate the effectiveness and safety of medical device Nasaleze in prevention and treatment of allergic rhinitis.

Study design

Forty-eight patients with persistent allergic rhinitis were included into the study. The group consisted of 25 adults and 23 children of both genders, aged 2 to 62 years. The patients were examined weekly over the observation period of 4 weeks. Children were accompanied by their parents during their visits to the trial centre. At study enrollment, the patients were asked for their verbal and written informed consent, according to a form developed for this study in accordance with the Helsinki Declaration. One of the parents was requested to sign the consent form for an under-aged child.

In accordance with the study protocol, an individual record form was filled out for each patient and included passport data, initial case history and examination findings as well as the findings of follow up visits during the course of the study.

- The patients received one puff Nasaleze into each nostril 3 times a day over the course of 4 weeks. In case of insufficient effect they were allowed to use the preparation more frequently.
- The patients visited the investigator weekly, i.e. 4 times during the study period. The severity of AR symptoms and the tolerability of the product were assessed during each visit.
- The patients filled out a quality of life questionnaire and a visual analogue scale during initial and final visits.
- The effectiveness of treatment was assessed by investigator together with the patient (in case of children together with the parents) during the final visit.
- The patients were maintaining a diary with daily records of severity of AR symptoms, any side effects and need for other medications.

Subjects

Patients, who were enrolled into the study, came to the initial visits with a confirmed diagnosis of AR, supported by the findings of allergen tests and rhinoscopy.

Figure1. Characteristics of the study group.

Parameter	**Adults n=25**	**Children n=23**
Age	**18 to 62 years Mean - 40.2 years.**	**2 to 18 years Mean - 10.8 years**
Duration of AR	**13.8 years (2-40)**	**5.75 years (1-15)**
Bronchial asthma	**68%**	**24%**
Atopic dermatitis	**-**	**8%**
Pollenosis	**64%**	**79%**
Epidermal allergy	**82%**	**79%**
Nutritional allergy	**36%**	**33%**
Family history of allergy	**68%**	**92%**
Drug allergy	**23%**	**12%**

Figure 1 demonstrates that most of the subjects had several concomitant types of allergy. Household and epidermal types of sensibilization were most common. The presence of various allergy types was revealed by history taking and allergen tests. Concomitant bronchial asthma, nutritional or drug allergy was observed in many of the subjects. Nutritional and medicamentous types of sensibilization were commonly manifesting as nettle rash, and sometimes as asthmatic attacks. Most of the subjects had a family history of allergy. Therefore, AR was associated with other atopic conditions in most subjects of the study group. The sensibilization spectrum of the study group is presented in Figure 2.

Figure 2. Forms of sensibilization found in study subjects during allergen tests.

Types of allergens	**Adults (n=25), %**	**Children, (n=23), %**
Dermatophag. Pteron. *Dermatophag. Farine*	**100**	**100**
Pollen **Thereof:** **Trees** **Cereals** **Weeds**	**64** **79** **43** **21**	**79** **89** **74** **52**
Allergy to 2 or 3 types of pollen:	**57**	**68**
Epidermal allergy **Thereof:** **Cat** **Dog** **Horse** **Hamster**	**82** **94** **50** **11**	**79** **89** **79** **21** **5**
Allergy to 2 or more epidermal allergens:	**50**	**68**

With regard to the data in Figure 2, the following conclusions may be drawn. Firstly, all subjects enrolled in the study were sensitized to house dust mite allergens. Secondly, house dust mite allergy was frequently concomitant with epidermal and pollen allergies. The structure of sensibilization types was virtually similar in children and adults. A combination of household allergy with sensibilization to cat epidermis and tree pollen was very frequent in all age groups.

When interviewed, all patients participating in the study complained of the symptoms of actively manifesting AR of various severity grades: sneezing, nasal and nasopharyngeal itching, eyelid itching, nasal discharge, impaired nasal breathing. All symptoms were assessed for severity grading:

0. Absent (no symptoms)
1. Mild (symptoms do not influence the lifestyle)
2. Moderate (symptoms have a moderate impact on everyday lifestyle)
3. Severe (symptoms have a significant impact on the patient’s lifestyle and interfere with normal everyday activities).

Findings

Figures 3 and 4 demonstrate the improvement of AR symptoms in both adults and children in the course of regular administration of disperse cellulose powder.

Figure 3. Evolution of AR symptoms in the course of 4 week treatment with Nasaleze in adults.

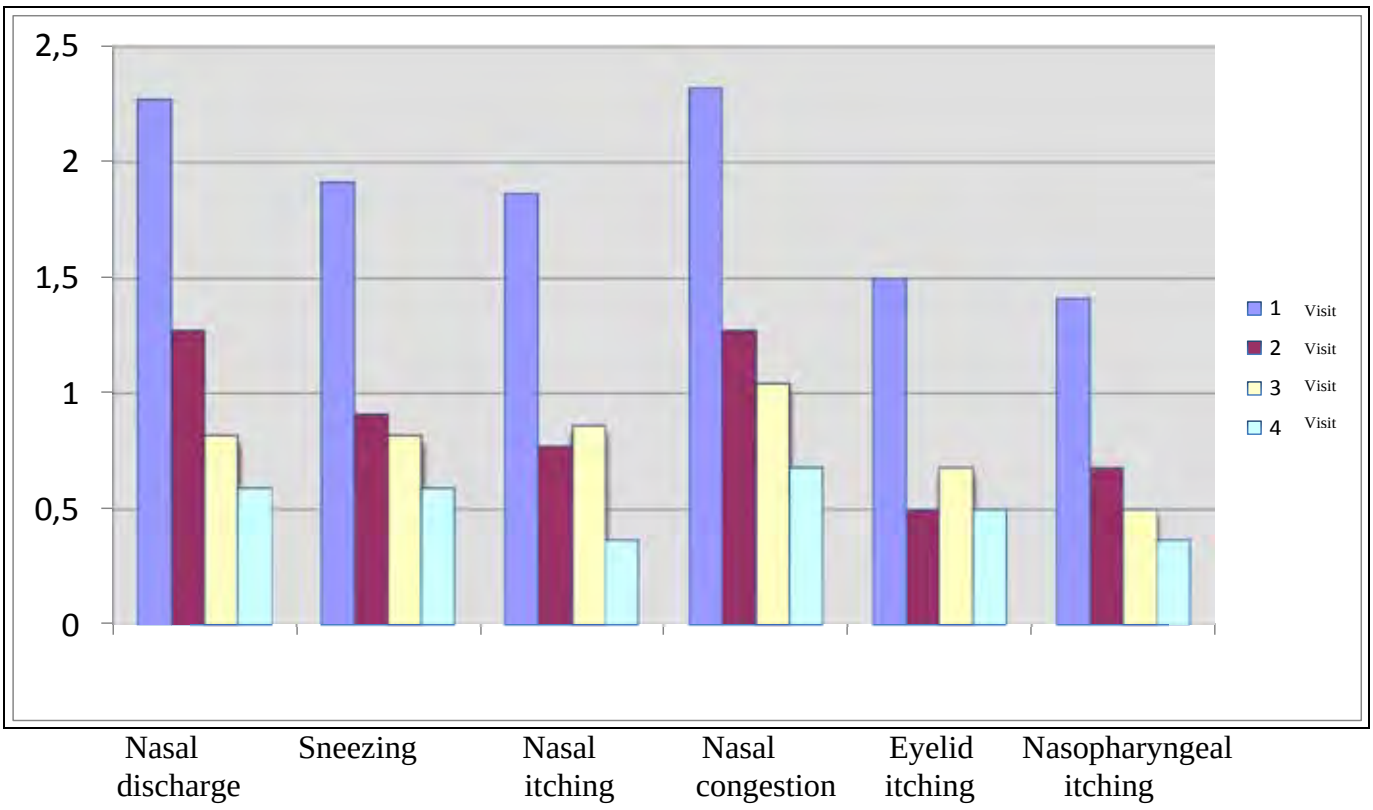
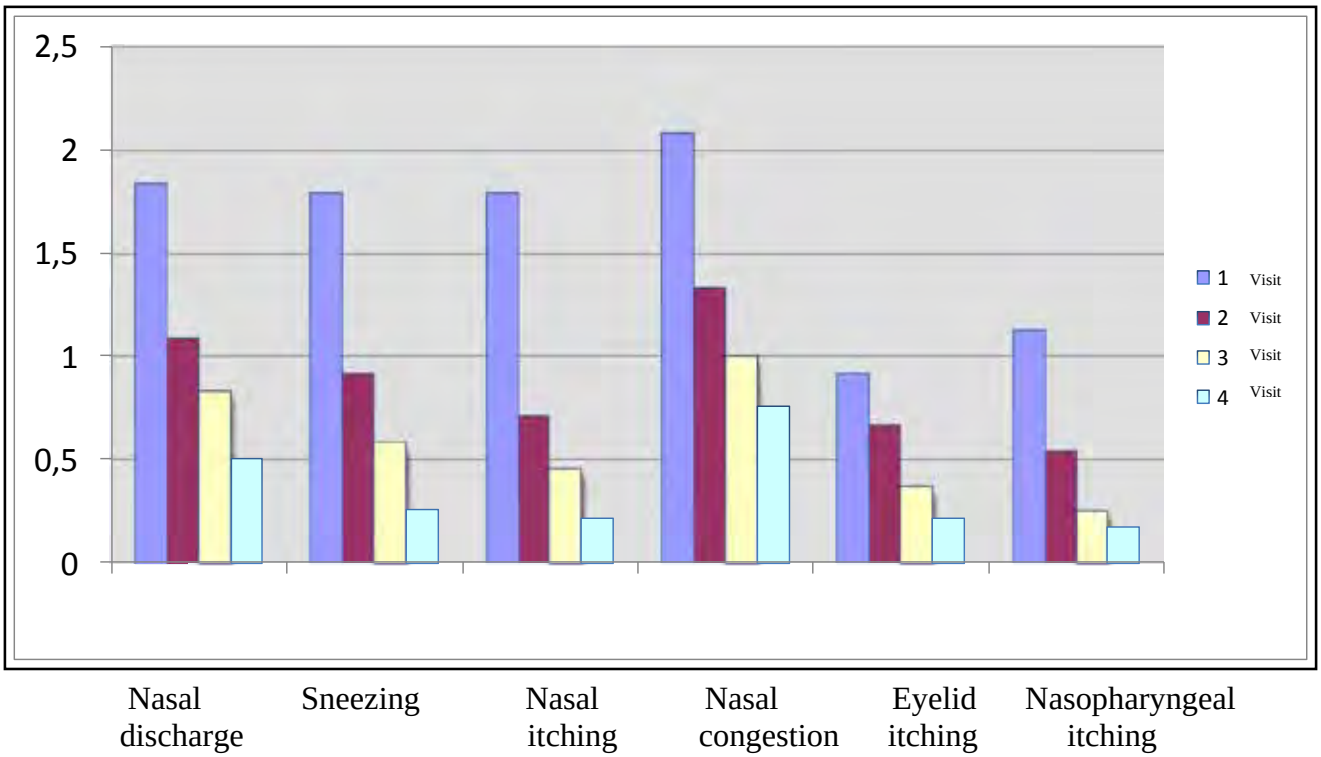


Figure 4. Evolution of AR symptoms in the course of 4 week treatment with Nasaleze in children.



Analysis of the data presented in Figures 3 and 4 demonstrates that the effects of micro-cellulose had an early onset. Improvement of all AR symptoms was observed already in the first week of therapy, and was especially significant by the end of the study period, both in children and in adults.

The following case record illustrates this trend: A 25-year old woman was diagnosed with perennial moderate allergic rhinitis 20 years ago. Allergy tests confirmed allergy to house dust mite and pollen of cereals and weeds. Family history includes allergic rhinitis in father and brother. Improvement of AR symptoms in the course of 4-week therapy with micro-cellulose powder is presented in Figure 5.

Figure 5. Effects of Nasaleze therapy on symptom scores in a 25-year-old patient.

	Nasal discharge	**Sneezing**	**Nasal itching**	**Nasal congestion**	**Ocular itching**	**Nasopharingeal Itching**
Initial symptoms	**3**	**2**	**2**	**2**	**1**	**0**
Study week 1	**2**	**1**	**1**	**1**	**0**	**0**
Study week 2	**1**	**1**	**2**	**1**	**0**	**0**
Study week 4	**1**	**0**	**0**	**1**	**0**	**0**
0. Absent (no symptoms) 1. Mild (symptoms do not influence the lifestyle) 2. Moderate (symptoms have a moderate impact on everyday lifestyle) 3. Severe (symptoms have a significant impact on the patient's lifestyle and interfere with normal everyday activities).						

Overall assessment of the outcomes of 4-week therapy with Nasaleze was conducted during the final visit. The investigator assessed the overall efficacy of cellulose micropowder together with the patient. The patients' judgement was based on their sensation of the symptoms, while the investigators analyzed the evolution of AR symptoms, visual scale scores, and the findings of the quality of life questionnaires. The results are summarized in Figure 6.

Figure 6. Assessment of the efficacy of Nasaleze.

Effectiveness	Adults (% of all adult subjects)	Children (% of all pediatric subjects)	Total (% of all subjects)
Very good	45	38	41
Good	50	62	57
Moderate	5	-	2
No effect	-	-	-

As it can be noted from the data in Figure 6, therapy with micro-cellulose powder was effective in varying degrees in all patients participating in the study. The majority of both adults and children (in the latter case the feedback was as a rule collected from the parents) assessed the efficacy of the product as good or very good.

Effectiveness of treatment is further confirmed by the improvement in quality of life of the patients treated with Nasaleze. The questionnaire, which was used to assess quality of life of AR patients before and after 4 weeks of treatment with cellulose powder is presented in Figure 7.

Figure 7. AR patient quality of life questionnaire.

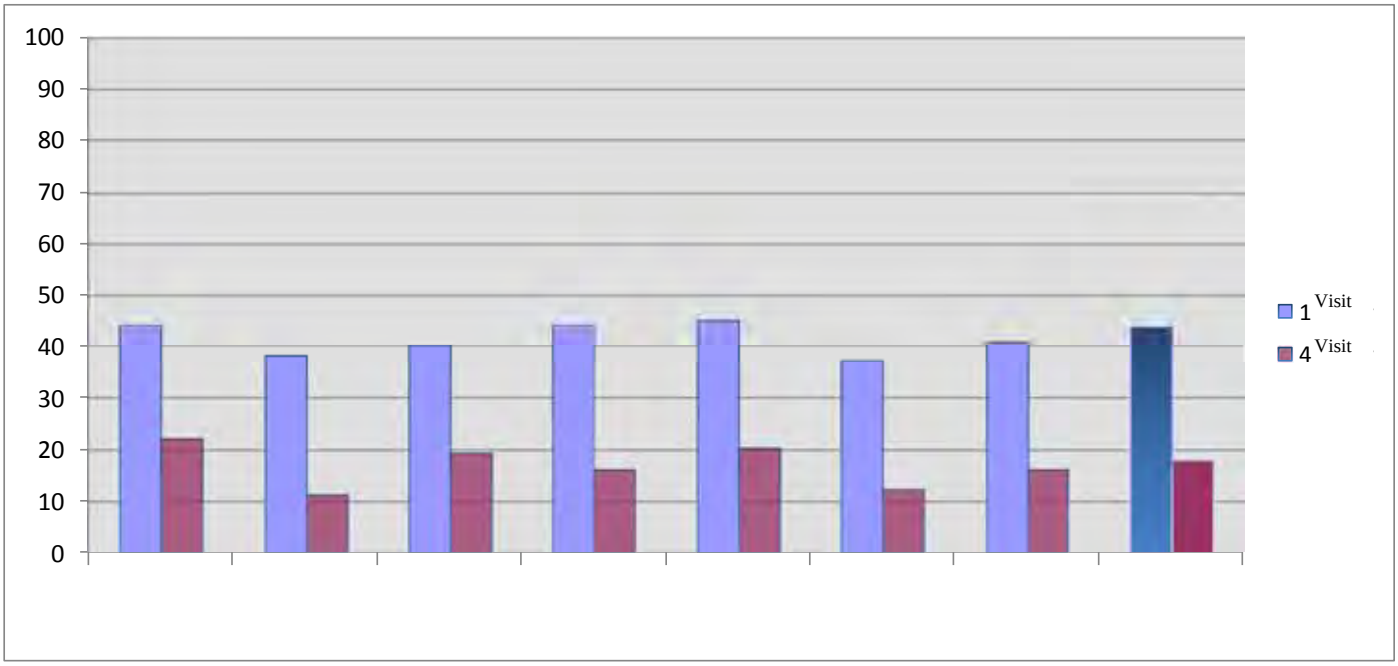
Types of activity	1.Usual activities at home and at work; 2. Communication; 3. Outdoor activities
Sleep	4. Difficult to fall asleep 5. Awaking during the night 6. Difficult to wake up
General symptoms	7. Fatigue 8. Thirst/dryness in the mouth 9. Decreased capacity for work 10. Sluggishness 11. Concentration problems 12. Headache 13. Depression
Practical problems	14. Must always carry tissues 15. Must rub nose and eyes 16. Must blow the nose all the time
Nasal symptoms	17. Nasal congestion 18. Nasal discharge 19. Sneezing 20. Postnasal drip
Ocular symptoms	21. Itching in the eyes 22. Epiphora 23. Pain 24. Swelling around the eyes
Emotional condition	25. Frustration, anger 26. Impatience, anxiety. 27. Irritation 28. Uneasiness.

Assessment scale:
0 – not disturbing
1 – almost undisturbing 3 – moderately disturbing 5 – very significantly disturbing
2 – slightly disturbing 4 – significantly disturbing 6 – extremely disturbing

The questionnaire covers various aspects of the patient's life, his/her physical an emotional condition and other factors, which may be negatively affected by AR.

The findings of the questionnaires are analyzed in Figure 8.

Figure 8. Assessment of quality of life by the patients before and after therapy with Nasaleze. (Scale of assessment: 100 % - Maximal impact of the disease on quality of life.)



Types of activity	Sleep	General symptoms	Practical problems	Nasal symptoms	Ocular	Emotional status	Overall score

It can be observed from the data in Figure 8, that quality of life of AR patients improved more than twofold in the course of treatment with micro-cellulose powder.

Both patients and investigators assessed the tolerability of Nasaleze. This assessment is summarized in Figure 9.

Figure 9. Tolerability of Nasaleze

Tolerability	Adults (% of total adult subjects)	Children (% of total pediatric subjects)
Very good	95	87
Good	5	9
Moderate	-	4
Poor	-	-
Description of unwanted effects	• Formation of crusts in the nose during 4 first days of therapy – 2 patients; • Burning in the nose – 1 patient	• Burning in the nose – 1 patient • Itching in the nose, sneezing for 1 hour after administration – 1 patient

As a rule, both children and adults reported good or very good tolerability of micro-cellulose powder. Occasional unwanted effects included: formation of crusts in the nose, burning in the nose, sneezing. These symptoms occurred in isolated cases and did not lead to discontinuation of therapy.

Conclusions

1. Nasaleze reduces the severity of AR symptoms already in the first week of treatment.
2. Nasaleze therapy is associated with a more than twofold improvement in the quality of life of AR patients.
3. Therefore, Nasaleze is an effective and safe method of prevention and treatment of allergic rhinitis both in adults and children.
4. Micro-cellulose powder is capable of creating a natural safe barrier protecting the airways from contact with allergens and oxidating pollutants.

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A nasally applied cellulose powder in seasonal allergic rhinitis (SAR) in children and adolescents; reduction of symptoms and relation to pollen load.

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ORIGINAL ARTICLE UPPER AIRWAYS AND SPECIFIC IMMUNOTHERAPY

A nasally applied cellulose powder in seasonal allergic rhinitis (SAR) in children and adolescents; reduction of symptoms and relation to pollen load

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Åberg N, Dahl Å, Benson M. A nasally applied cellulose powder in seasonal allergic rhinitis (SAR) in children and adolescents; reduction of symptoms and relation to pollen load. *Pediatr Allergy Immunol* 2011; **22**: 594–599.

Keywords:
allergic rhinitis; clinical trial; barrier protection; children; adolescents; pollen concentration

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Abstract

Background: A nasally applied cellulose powder is increasingly used in many countries as a remedy for allergic rhinitis. The absence of side effects makes the treatment particularly attractive in children. The efficacy in pollen allergic children, however, is not studied, nor is the relation to various pollen exposures.

Methods: During the birch pollen season in 2009, a double blind, placebo-controlled study was conducted in 53 subjects, aged 8–18 yr, with allergic rhinitis attributed to birch pollen. All children were on daily oral antihistamine. Reminders and reporting of symptom scores were made by SMS on mobile phones. Pollen was collected in a volumetric trap from which figures of pollen concentrations from 1979 to 2009 were available.

Results: There was a significant reduction in total symptom scores from the nose (active 7.29, placebo 6.07, $p = 0.033$) and specifically for running nose (active 2.03, placebo 2.56, $p = 0.017$). All symptoms from the nose, eyes and lower airways were lower in the active group but reached significance only as earlier. The best effect was seen after days with low or moderate pollen counts ($\leq 100/m^3$), the predominating pollen load over 31 yr in the area. No clinically significant adverse effects were seen.

Conclusions: The product reduces symptoms of SAR in children and adolescents. Original data on pollen concentrations over 31 yr are presented with levels mainly in the low range favouring the observed efficacy profile. SMS communication on mobile phone for reminders and recording symptom scores was an excellent logistics tool.

Allergic rhinitis appears to have increased in Sweden as well as in most affluent societies over the twentieth century [1, 2]. During childhood and adolescence, the prevalence of allergic rhinitis increases with age [3]. In school children, allergy to pollen is a predominant cause [4]. Apart from notable economic costs, many school children experience an adverse impact on their educational career [5]. A range of remedies and treatments are available on prescription and over the counter (OTC). Some of these may have adverse effects, and the relief is very often insufficient. Nasal steroid sprays are considered most efficacious but many sufferers are reluctant to take them because of 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 likely to be a reaction with moisture on the mucous membrane. A protective barrier on the nasal mucosa may prevent contact between inhaled allergen and mucosal cells. One placebo-controlled clinical trial in adults with grass pollen allergy showed a reduced need of rescue medication but no significant symptom relief [6]. The inert substance has been virtually free from adverse effects, making it a particularly attractive treatment option for children. Still, no controlled clinical studies in children have been performed. Our aim was to assess the efficacy in a common clinical setting along with an oral antihistamine. In Sweden, birch pollen allergy is the most common cause of seasonal allergic rhinitis (SAR). Furthermore, the birch pollen occurs during a school term and yearly examinations with high risks of interference between symptoms of SAR and school results [5]. Therefore, we found it particularly important to study the efficacy in birch pollen-induced SAR in children.

The studied product has been generally held to be most efficacious in slight and moderately severe allergic disease. This context also includes the load of pollen exposure. Therefore, the approach to pollen exposure was not only a daily monitoring during the study period; by a presentation of available data on local pollen occurrence over 31 yr, we infer our findings in a wider perspective.

Methods

Research design

Patients 8–18 yr old were recruited by newspaper advertising during February–April 2009. They all had a history of typical symptoms of SAR during springtime. They should not have used nasal steroids. At an appointment, the history was scrutinized and an assessment of the severity excluded a current need for nasal steroids. They were tested with a finger prick blood sample for ImmunoCap Rapid (Phadia). ImmunoCap Rapid is an *in vitro* system with immediate results for the most common respiratory allergies with a high accuracy regarding both sensitivity and specificity [7, 8]. Fifty-two children tested positive for birch pollen allergy. One child tested negative in the blood sample but with a strongly positive history and a positive skin prick test for birch pollen allergy during the same month the child was also included in the study. The patients were randomly assigned to active or placebo treatment three times daily from an identical container. The nasal powders were supplied in patent approved plastic containers, which deliver the powder from a nozzle when squeezed. The exact amount delivered is not standardized, and the variations of patterns of deposition in the nose are 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. The containers were labelled with serial numbers. The randomisation codes for active and placebo products were not revealed until the reported scores had been locked in a clean file at the end of the study. After the study was completed, all participants were informed whether they had taken the active or placebo products.

All children were given one orally soluble desloratadine tablet in a dose appropriate for age once daily during the treatment period. Each child was supplied with a mobile phone for instructions, reminders and reporting of symptoms, all by SMS. The medication and reporting lasted for 4 wk following the first increase in local birch pollen counts.

Three times a day, the patients were reminded by SMS to take their treatment including the nasal puffs and were asked to confirm the intake by a response SMS. At the evening reminder, 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 1–6. The figure *1* corresponded to *1* '*no trouble at all*', *2* '*little trouble*', *3* '*moderate trouble*', 4 '*rather much trouble*', *5* '*much trouble*' and *6* '*very much trouble*', *respectively*. From the nose, scoring of sneezing, running nose and blocked nose was reported. For the eyes and lower airways, respectively, only a concluding figure was used. Otherwise, the SMS procedure was assumed to be too complicated and time consuming for the children.

For pollen monitoring, a Burkard 7-day volumetric spore trap situated close to the study centre, at the roof top of the Central Clinic at Östra sjukhuset, at the eastern border of Gothenburg (57°72′N, 12°05′E) was used. The trap has been on the same location since 1979. The counts are representative for a wide area with a radius of ca. 50 km from the trap, encompassing the residence of all subjects in the study.

In the presentation of the pollen load in the study area, we have chosen the Threshold 30 method to identify the main pollen period [9] whereby the start and end of the pollen season are defined as the first and last days when the pollen count is greater than or equal to 30 grains/m^3. This method excludes the long tails of lower values at the start and the end of the season, which are likely to have less clinical significance. In addition, the first date must fall into a period when the pollen type in question was registered during ten consecutive days, to exclude isolated episodes of long distance transport.

Two threshold values that denote the likely severity of symptoms were used. Thus, the term 'high levels' describes a situation when pollen levels are within the range 101–1000 birch pollen/m^3 and 51–100 grass pollen/m^3 [10, 11], whereas 'very high levels' denotes birch pollen counts >1000 pollen/air and grass pollen counts >100 pollen/m^3, respectively. The thresholds for high levels represent the levels when most or all patients studied react with symptoms. The study by Davies & Smith [11], concerning grass pollen, was undertaken in Britain, and these levels may vary geographically. However, the corresponding data from South Scandinavia were not available.

Statistical methods

For each question, the mean score was calculated for the whole 28 days period for every child. Mean values for the sum of all scores as well as the sum of the nasal scores were also calculated. The two treatment groups were then compared using t tests. All results were based on intention to treat analyses. p values below 5% were considered significant. Days with a pollen count above and below 100/m^3 and day, respectively, were separated and analysed in the same way as the whole period. The study was approved by the ethics committee at the Sahlgren's Academy of the University of Gothenburg.

Results

An excellent compliance was obtained. Only 6% of all possible SMS-replies were missing, including one boy who withdrew because of throat irritation. One girl used nasal steroid as rescue medication for one day. Both belonged to the placebo group and are included in the intention to treat analyses. There were 25 children in the active and 28 in the placebo group. The gender distribution was 3/2 in favour of boys in both groups. The mean age was 11 in both groups. No clinically significant adverse effects were reported. A total

of eight children evenly distributed between the groups experienced some irritation in nose or throat following treatment.

Over the entire 4 wk, there was a general tendency to a reduction of all symptoms from nose, eyes and lower airways in the active group. The mean scoring for nose and eyes ranged between 2 ('little trouble') and 3 ('moderate trouble'). There was a significant reduction in total symptom scores from the nose (active 7.29, placebo 6.07, p = 0.033) and specifically for running nose (active 2.03, placebo 2.56, p = 0.017).

In Table 1, the efficacy is further elaborated and shows a general trend to an increased difference in mean scores between the groups with low and moderate pollen counts (≤100 pollen/m^3/day) as compared with when the pollen counts are high. During a situation with low or moderate pollen counts, there is a significant reduction not only in total nasal symptoms and running nose, but also in sneezing severity.

Pollen concentrations

The birch pollen season 2009 was intense but not a record high. The pollen index, i.e. the annual pollen sum, in Gothenburg 2009 was 152% of the mean of the period 1979-2009. The local birch flowering started 1 wk before the study beginning on April 21 with a maximum of 3700 pollen/m^3/day on April 25.

Table 1 Sum of symptoms scored retrospectively at night. Figures with significant reduction of scores are marked in bold.

Question	Treatment	n	Mean	p-value
(a) 2 days after pollen counts ≤ 100/m^3				
Sneezing	Placebo	27	**2.19**	**0.023**
	Active	25	**1.65**	
Running nose	Placebo	27	**2.35**	**0.019**
	Active	25	**1.79**	
Blocked nose	Placebo	27	2.21	0.23
	Active	25	1.88	
Eye symptoms	Placebo	27	1.79	0.84
	Active	25	1.75	
Lower airways	Placebo	27	1.59	0.51
	Active	25	1.45	
Sum of all symptoms	Placebo	27	10.14	0.081
	Active	25	8.50	
Sum of nasal symptoms	Placebo	27	**6.75**	**0.025**
	Active	25	**5.32**	
(b) 2 days after pollen counts > 100/m^3				
Sneezing	Placebo	28	2.39	0.15
	Active	25	2.08	
Running nose	Placebo	28	**2.67**	**0.038**
	Active	25	**2.19**	
Blocked nose	Placebo	28	2.56	0.29
	Active	25	2.27	
Eye symptoms	Placebo	28	2.50	0.52
	Active	25	2.33	
Lower airways	Placebo	28	1.63	0.54
	Active	25	1.50	
Sum of all symptoms	Placebo	28	11.75	0.15
	Active	25	10.37	
Sum of nasal symptoms	Placebo	28	7.62	0.074
	Active	25	6.54	

Figure 1 illustrates further the relation between symptom scores and pollen counts. Visually, there was a lag of 2 days between changes in pollen counts and subsequent symptoms. After the beginning of treatment, the symptoms intensified slower in the active group than in the group treated with placebo, and maximum of the score, which was lower in the former group, was reached about 2 days later. The decline of the pollen counts after the peak of pollen release was accelerated by rain during 1 wk beginning on May 3. In this case, the rain was associated with a more pronounced decline in the symptom scores of the active group than in the placebo group.

Figure 2 describes the pollen background in terms of a 31-yr survey of the pollen counts in the area. There were large variations in both the duration of pollen periods and the partition of days with low and moderate counts. For birch pollen (Fig. 2a), the percentage of days with low and moderate levels varied between 100% and 15%, mean 48 ± 20% (±SD = standard variation). If the pollen season instead is defined as the period when fresh birch pollen (locally produced or long-distance transported) is registered in a regular manner, i.e. from March 1 to June 30, the percentage of days with low or moderate levels varied between 73% and 100%, mean 90 ± 6%.

When the main grass pollen season is defined according to the Threshold 30 method (Fig. 2b), the total percentage of days with pollen levels with low and moderate levels varied between 100% and 33, mean 74 ± 17%. The period when grass pollen is registered more or less daily lasts from April 20 until September. We chose September 7 as an end date for calculations. The total percentage of days with low and moderate levels during this longer period varied between 88% and 100%, mean 95 ± 4%.

Discussion

Since 1994, this British remedy for hay fever has been on sale as a medical device, and it has been increasingly used in

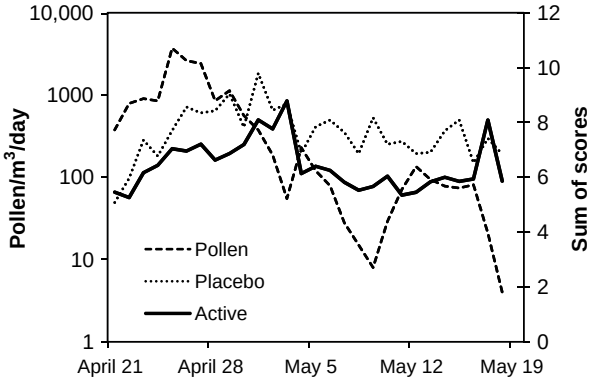

Figure 1 Sum of nasal symptoms day by day in respective groups. Daily pollen concentrations in log scale.

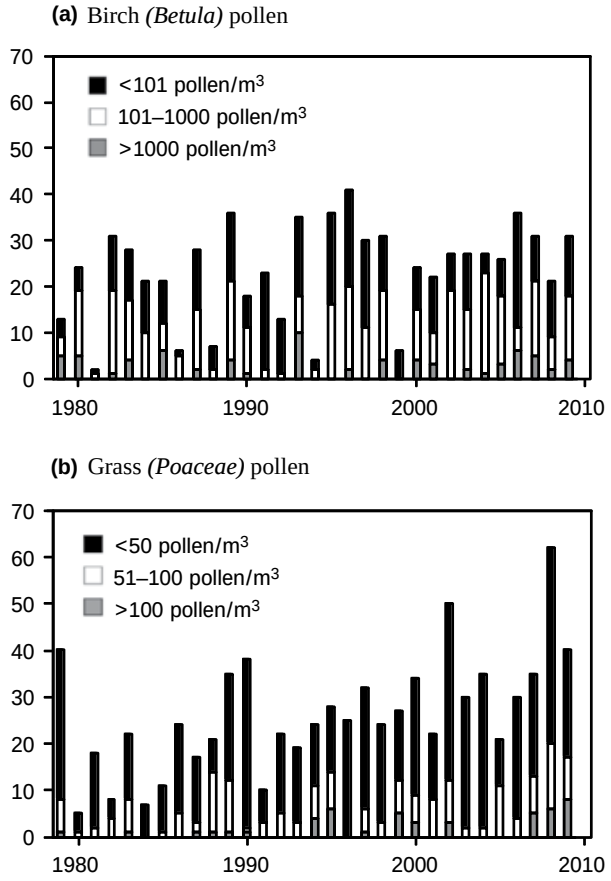

Figure 2 The number of days with different birch and grass pollen concentration levels in Gothenburg, Sweden during the years 1979-2009 and during the main pollen seasons, defined according to the Threshold30 method [9]. (a) Concentrations of birch pollen during the period March 1st–June 30th. (b). Concentrations of grass pollen during the period April 21st and September 7th.

many parts of the world. The inert cellulose powder has in various previous studies, mainly in adults, been free from clinically significant adverse effects [6, 12, 13]. The safety aspect of the product makes it particularly attractive for the treatment of children. This is the first placebo-controlled study in children in a clinical setting. It is also the first placebo-controlled study of the product proving a reduction in symptoms of SAR. In adults with grass pollen rhinitis, there was a reduction in rescue medication but no decrease in symptom scores [6]. We wanted to avoid that variable use of other treatments would confound the efficacy of the trial product. Therefore, we chose a fixed oral antihistamine dose throughout the study period, which is a common clinical context.

The inclusion of previously not published original data on the partitioning of days during the main pollen period into low, moderate, high and very high levels over the period 1979-2009 made it possible to assess our observed relation between pollen exposure and clinical symptoms in a wider perspective.

Another original feature with the study was the use of SMS on mobile phones for reminders and reporting of symptom scores. There are clear benefits of e-diaries as compared with paper records in terms of compliance and data safety [14]. The use of mobile phone logistics is a further development of the methodology that probably explains the unusually high compliance in this age group. The logistics also allow a continuous supervision of the study progress on an individual level. Some concern from the study staff regarding the SMS skill of the children (asking for SMS interest in the advertisement) was rudely mocked by the children at the first appointment.

Population

The main weakness of the study is the relatively small number of patients. Consequently, most of the general reduction in all symptoms did not reach statistical significance. The study population was quite homogenous with a laboratory confirmed allergy to birch pollen and a narrow range of severity; a history of asthmatic or other perennial symptoms was not allowed at inclusion, nor was a previous use or assessed need of nasal steroids. This background ought to minimize the risk of significant baseline group differences.

Dosage

We appraised a fixed dosage of three times daily to be both convenient and necessary to maintain controlled circumstances in our trial design as well as to reach a statistically significant reduction of symptoms. Still, it may not have been an optimal setting to prove the real efficacy of the product, particularly during a period of high pollen counts. It should be noted that most of birch pollen season in Sweden may be considered intense, as compared with grass pollen exposure, (Fig. 2). In clinical praxis, the dosage is usually 2–3 times daily basally during pollen season but with a possibility to increase the doses as needed to control symptoms. The inert nature of the product imposes no more than a practical upper limit of the dosage. The concurrent fixed antihistamine dosage may have hampered the breakthrough of pollen peak symptoms, but may also have constricted the range of scoring available for reduction after lower pollen counts. Given the aim of extensive symptom relief, our impression still is that the antihistamine treatment alone left a substantial need for further aid.

The optimal frequency of puffing the powder into the nostrils to obtain a 24-h protection of mucous membranes remains unknown and, as discussed earlier, may vary with the amount of allergen exposure. The ordinary clearance time of the nasal mucosa of < 30 min is prolonged for cellulose products, a fact that may be used for certain treatment purposes [15]. Another gel formulation from seawater was efficacious against allergic rhinitis in a four times daily regimen in a recent study [16]. The higher efficacy in the lower pollen range may indicate that a three times daily dose may be sufficient as a basic clinical regimen which might need to be adjusted according to the intensity of symptoms.

Efficacy

The profile of the effects with the predominating and statistically significant reduction of nasal symptoms is suggestive of a real biological effect. A less pronounced relief of ocular and bronchial symptoms may be secondary to the nasal effects in line with the concept of 'united airways' [17]. The number of patients, however, did not allow for statistical significance of the reduction of non-nasal symptoms.

The magnitude of reduction of nasal symptoms in the trial of about 20% was less than might have been expected from the clinical experience of the authors. Still, it corresponded to the cautious power calculations preceding the clinical part of the study and is not an uncommon mean effect in clinical trials, particularly in a probing phase. Given the background discussed earlier, the average symptom scores in the treatment group can be assumed to result from quite a wide scope of effects from very good to complete absence of effects.

The assumed mode of action of the cellulose powder is to form a gelatinous barrier preventing contact between pollen and the mucous membrane. It may be a matter of course that intense exposure may result in breakthrough of sneezing and running nose with blowing out of the powder/gel and a subsequent local absence of powder and effect. Such a sequence may be part of a dose–response relationship between the frequency of doses and efficacy. In the previous grass pollen study on the product [14], the dose was mainly once daily and this low dose may explain to the shortage of symptom reduction.

Nasal steroid sprays are recommended as the first choice in the international (ARIA) guidelines [18]. The guidelines do not discuss non-pharmacological products, probably because of the scarcity of studies of acceptable scientific quality in this context. In Sweden, however, the new intranasal corticosteroids with the profile of high efficacy and low bioavailability are not accessible OTC. Moreover, many parents still prefer to try non-pharmacological products for their children by other reasons.

Pollen exposure

The choice of birch pollen rhinitis in the study was firstly that it is the most common cause of SAR in Swedish children [4]. Secondly, for children with multiple pollen allergies, birch pollen symptoms usually are the first of the total season. In severe birch pollen allergy, patients often have a crossreaction to hazel and alder earlier in the spring. Already at recruitment, however, we excluded children with perennial allergic symptoms or seasonal symptoms in the months preceding birch flowering. We believe that absence of all symptoms previously in the same year may have contributed to a narrow range of severity. Most children in Sweden with grass pollen allergy also have a birch pollen allergy [4], and the baseline condition in a study of grass pollen allergy would have been more heterogeneous.

There was a general pattern with a variation of symptoms proportionally to a log scale of pollen concentrations with a lag of about 2 days. Lower pollen concentration caused milder symptoms as well as an amelioration of the protective effect of the cellulose powder. This is coherent with the discussion about sufficient dosage above and likewise the generally held opinion that the cellulose powder primarily protects against slight and moderate symptoms.

A pollen load of 100 birch pollen/m^3/day, the upper limit for moderate levels, appears to constitute a threshold with relevance for the efficacy of the product.

In fact, low or moderate levels, when the product thus appears to subdue symptoms, predominate during the birch pollen season, as illustrated by the retrospective statistics from 31 yr (Fig. 2a). Although these levels differ between grass and birch pollen [10, 11], the method also appears to be applicable to birch pollen. In practice, the method cuts off the long tails with very low pollen amounts and irregular pollen occurrence at the beginning and the end of the season.

The predominance of low or moderate values is still more pronounced with respect to grass pollen than birch pollen (Fig. 2b). Therefore, it is quite possible that the product in the given dosage should be even more efficacious in grass pollinosis, a more common condition in a global perspective.

Conclusions

We demonstrated that an inert cellulose powder (Nasaleze®) causes a significant alleviation of nasal symptoms in SAR in children. The best efficacy was seen after a low–moderate birch pollen load, a concentration representing major parts of the Swedish pollen season. The product could be effectively combined with oral antihistamine, the most common treatment of SAR [6].

Acknowledgments

Kisska International Ltd and Green Medicine AB sponsored the study in terms of supplying test products, support of the logistics including mobile phones and funding for the nursing staff. We are grateful to the registered nurses Kerstin Sandstedt and Mainor Åmark for skill patient contact and testing and to the senior lecturer Lars Wahlgren, University of Lund, for statistical analyses. We want to thank Dr. S.O. Strandhede, former leader of the Pollen Laboratory at the University of Gothenburg, and all pollen analysts throughout the years.

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Intranasal Inert Cellulose Powder in Prevention and Management of Seasonal Allergic Rhinitis (SAR) in children.

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Intranasal Inert Cellulose Powder in Prevention and Management of Seasonal Allergic Rhinitis in Children.

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Purpose:

To study the efficacy and safety of the intranasal inert cellulose powder (Nasaleze®) in the UK, Nasaval®) in Russia) to prevent seasonal exacerbation of allergic rhinitis (AR) in children. The Study was throughout 6 weeks between April and June 2009.

Materials and Methods:

Open randomized study in order to evaluate the efficacy and safety of the intranasal inert cellulose powder to prevent exacerbation of seasonal allergic rhinitis (AR) in children. Depending on the treatment all children were divided into the following groups: in Group 1 (Main Group), the inert cellulose powder in a special device was administrated to 30 children twice a day; in Group 2, 30 children received Montelukast 5 mg a day; in Group 3, 20 children received Sodium Cromoglicate 2 doses of 50 mg x 2 times a day; in Group 4, 30 children received Budesonide 50 mg 3-4 times a day. AR symptoms were assessed in the case monitoring timetable for the patients per visit. (Table 1.) Comparative description of the surveyed patients are in Table 2.

Table 1.

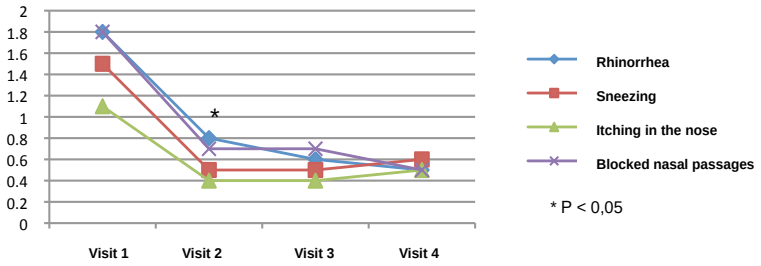
Study	Visit 1	Visit 2	Visit 3	Visit 4
Informed consent	X			
Questionnaire	X			
Collection of medical records	X			
Patient examination	X	X	X	X
Criteria for inclusion and exclusion	X			
Number Randomization	X			
Inert Cellulose Powder Issue	X			
Symptoms of seasonal allergic rhinitis (on a point scale: 0 - no symptoms, 1 - low level of intensity, 2 - moderate level of intensity, 3 - severe)	X	X	X	X
Treatment adjustment		X	X	X
Assessment of adverse events		X	X	X
General doctor and patient assessment		X	X	X

Table 2.

	Inert Cellulose Powder (N=30)	Montelukast (N=30)	Sodium cromoglicate (N=20)	Budesonide (N=30)
The average age of the patients (years)	8,3	8,9	7,9	8,5
Minimum age of the patients (years)	4,0	6,0	2 ,0	6,0
Average duration of the illness (years)	3,1	4	3,5	3,8
Sensitization to pollen allergens	50%	52%	49%	56%
Mild AR	22 (73,3%)	20 66,7%)	15 (75,5%)	20 (66,7%)
Moderate and severe AR	8 (26,6%)	10 (33,3%)	5 (25%)	10 (33,3%)
AR and BA	5 (16,7%)	8 (26,7%)	4 (20%)	9 (30%)
Allergic conjunctivitis	50%	53%	48%	57%
Family history of allergic illnesses	20 (66,7%)	22 (73,3%)	15 (75,5%)	20 (66,7%)

Results:

Dynamics of the symptoms of allergic rhinitis in scores within 6 weeks in Group 1 (the Inert Cellulose Powder).

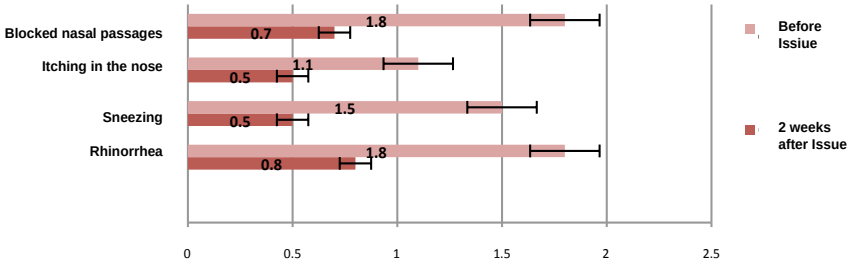


* P < 0,05

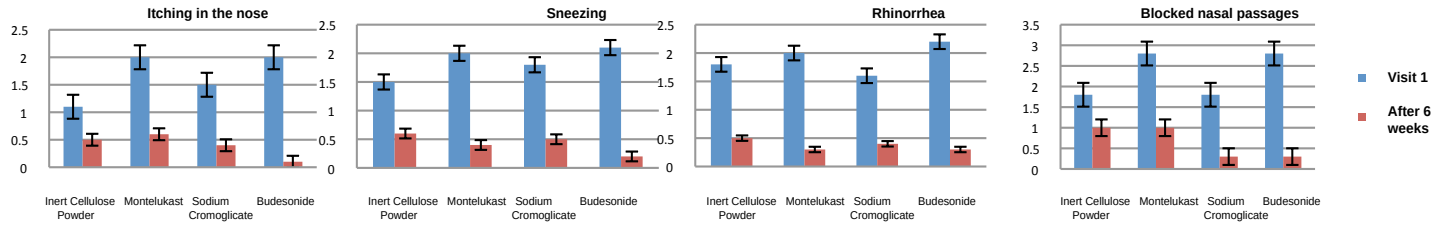
- The majority of patients (73%) noticed a distinct improvement in their condition by the fifth day.
- During the next 2 weeks, 12 children's (40%) symptoms disappeared completely.

Evaluating the efficacy of the Inert Cellulose Powder in children with AR during the first two weeks (p<0,05)

- Definite decrease of all SAR symptoms more than twice.
- 75% of patients before the prescription regularly received decongestants. During the Study 26,9% of patients occasionally received decongestants.



Efficacy of the Inert Cellulose Powder in children with seasonal symptoms AR within 6 weeks compared with other variants of treatment.



In the Main Group (Group 1) 9 children (34,6%) were receiving antihistamines occasionally, 7 children (26,9%) - decongestants, 3 children (10%) – nasal topical steroids. Comparing showed a significant improvement in symptoms of AR in all groups.

Side effects: 2 children (6,7%) in the Group 1 had increased sneezing, followed by removal of the drug. In the Budesonide group, two children was a slight nasal bleeding and burning of the nasal mucosa (6,7%).

Conclusion: The Inert Cellulose Powder reduces symptoms of AR, as well as other medicines. The children who received the Inert Cellulose Powder during pollen season, decreased frequency of use of antihistamines, decongestants and topical steroids. Preventative application of the Inert Cellulose Powder before contact with known allergens (pets, pollen allergens, house dust, etc.) reduces the symptoms of allergy. Using of the Inert Cellulose Powder for prevention of seasonal allergic rhinitis was proved. The Inert Cellulose Powder has minimal side effects and can be used in children from an early age.

New developments in the prevention and treatment of seasonal allergic rhinitis in children.

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Summary

An open-label, comparative, randomised study of the effectiveness and safety of using microdispersed cellulose powder (Nasaleze) to treat allergic rhinitis in children over a period of 6 weeks from April to June 2009 was carried out.

50 children aged between 4 and 14 with diagnosed seasonal allergic rhinitis (SAR) were observed. 30 children were given microdispersed cellulose powder. 20 children were put into a comparison group (control group) and received symptomatic treatment. The objective and subjective symptoms of SAR were assessed prior to treatment and at 2, 4 and 6 weeks after first using the product.

A positive result was observed in 26 patients (86.4%) from the first few days of using microdispersed cellulose powder. The product was not effective in 2 children (6.6%) with moderate to severe SAR and these children were also treated with nasal corticosteroids. 2 children (6.6%) experienced increased sneezing and their treatment with the product was stopped.

Children who received Nasaleze during the pollen season reduced the frequency of their intake of antihistamines, decongestants and topical steroids.

Introduction:

Allergic rhinitis is an illness which affects the mucous membrane of the nasal cavity and which then leads to allergic inflammation, with a high rate of occurrence in children. Allergic rhinitis often combines with bronchial asthma and can be the first sign of the development of an allergic process in the respiratory tracts. The development of allergic rhinitis, as a rule, combines with paranasal sinus involvement and is characterised by stuffiness of the nose, profuse mucous secretions and itching. A rhinoscopy can determine pronounced oedema of the mucous membrane, which can continue even after taking vasoconstrictive products, as well as a white or greyish tinge to the mucous [1]. A late diagnosis of allergic rhinitis and the delayed prescription of adequate and targeted treatment may lead to serious ENT complications.

Depending on the progress and deterioration of allergic rhinitis, children may experience intermittent (seasonal) and persistent (perennial) allergic rhinitis.

Seasonal allergic rhinitis in children is most often caused by the effect of pollen from trees, grasses and weeds as well as mould fungi on the child's body. The particular features of seasonal rhinitis include the frequency with which the illness intensifies. Allergic illnesses which develop in connection with sensitisation to plant pollen are called pollinosis (from the English word pollen).

An important link in the pathogenesis of pollinosis is genetically-determined increased IgE synthesis, including specific and anti-pollen IgE. The illnesses are most frequent during the season when the most widespread plants in the area are in flower.

Allergic rhinitis can be seen in the first year of a child's life, but is more frequent after 1-2 years as a result of the repeated influence of the allergens. The appearance of pollinosis is normally diagnosed in children over 3. The illness rate is higher during school age. The illness is often diagnosed late, with the clinical symptoms being regarded as signs of ARVI, infectious rhinitis, antritis or conjunctivitis.

The clinical symptoms of the illness recur year on year at the same time of year. There are *immediate symptoms* of rhinitis (itchiness, sneezing, rinorrhea and oedema of the mucous membrane), which are seen straight after contact with the allergen, and *symptoms of chronic rhinitis* (constant oedema, reduced sense of smell, and nasal hyperreactivity), which are caused by the development of chronic inflammation.

The main forms of pollinosis are *rhinitis, sinusitis, conjunctivitis and bronchial asthma.* This latter type often only develops in children after a few seasons of intensifying rhinoconjunctivitis.

Treatment of allergic rhinitis is complex and the first step is eliminating contact with the allergens. During the pollen season, in order to eliminate contact with the allergens, it is recommended that windows and doors be kept closed, an internal air conditioning system used, and time spent outdoors limited. It is often impossible to implement many of these measures with children.

Medicinal treatment has gradually increased as the severity of AR itself has increased: antihistamines - H1 HISTAMINE receptor blockers (claritin, aerius, telfast, kestin) some of which may be used in the form of a nasal spray (allergodil); mast cell stabilisers (kromoglin nasal spray, nasal inhaled corticosteroids (nasonex, flixonase, tafen). Highly effective allergen-specific immune therapy.

Since 2002 many countries have been using inert cellulose that creates a natural barrier in the nasal cavity. This protects the respiratory tracts against allergens entering the mucous membrane of the nose and the further penetration of the allergen with it then turning into an allergic reaction, in particular, allergic rhinitis [1-7].

Nasaleze is a microdispersed cellulose powder in a spray dispenser which protects the mucous membrane of the nose against pollutants and air allergens: plant pollen, everyday allergens, epidermal animal and bird allergens, and other microparticles which enter the nasal cavity when breathing in [2].

Prof. Richard Lewis at the Worcestershire Royal Hospital in Great Britain believes that the vast majority of microdispersed cellulose particles are too big to enter the human respiratory system when inhaled through the nose. When the microcellulose particles come into contact with any moist surface, including the mucous membrane of the nasal cavity, they absorb water and turn into a gel. The gel is removed through normal mucociliary clearance, which cleans away the normal secretions of the respiratory system.

The action mechanism is caused by the fact that the cellulose consists of long polymer chains which attach to intramolecular links. By including hydrophilic groups, it gradually swells and becomes easily soluble by the polymer in water.

The product is issued in the form of a dry spray in a special 500 mg bottle that dispenses the exact dose. It can be used as often as necessary. Recommended dose: one spray in each nostril 3-4 times a day (every 5-6 hours). It is recommended that Nasaleze be re-sprayed every time the nose is blown in order to restore the protective layer. Any nasal products used in the treatment of SAR should be used 10-15 minutes before the use of Nasaleze spray. The use of Nasaleze is also recommended before coming into contact with an allergen.

Previous research has shown a high level of effectiveness of microdispersed cellulose powder in the prevention and treatment of SAR.

Research into the drug in 102 patients with SAR [3] showed that Nasaleze was effective in 77% of patients (the average effectiveness rating on a 5-point scale was 3.8, where 5 represents no symptoms and full control). The symptoms were alleviated 0.1 – 3 hours after first using the product. Most patients rated Nasaleze spray as an effective treatment and prevention method for SAR. When using the product, patients noticed fewer side effects when compared with many other pharmaceutical products [3].

A double-blind, placebo-controlled study into the use of inert cellulose powder in adult patients for the alleviation of the symptoms of SAR was carried out in Great Britain. 97 adult patients with pollinosis took part in the study during the active pollen season [5]. The results show that when using inert cellulose powder, the need to use medicinal products to treat SAR is reduced.

The Aivazis V study [6] found that there was a significant decrease in the mucociliary clearance time when using Nasaleze spray in children with SAR, which may be connected with the regeneration and normalisation of the ciliated epithelia. Mucociliary clearance of the mucous membrane is the first line of defence of the nasal ciliated epithelium against inhalable particles such as allergens, pollutants and viruses. Cellulose strengthens the mucous membrane of the nose, which allows for the filtration of allergens and the inhalation of fresh air only into the lungs.

Volunteers took part in research into the symptoms of SAR, PEFn and PIFn respiratory functions and ECPs (eosonophil cationic proteins) after the provocation of a measured dose of grass pollen that was introduced into the nose via a micro-spoon [7].

The symptoms were analysed before the provocation and 24 hours afterwards. The microdispersed cellulose drug prevented the development of the symptoms of SAR (rhinitis, itching in the nose), and improved the PIFn, PEFn and ECP indexes when compared with the placebo group.

In Russia microdispersed cellulose was registered and given a marketing authorisation in 2009. The authors (T.V. Zakharzhevskaya, I.V. Sidorenko, V.K. Treskunov and A.V. Karaulov) carried out an open-label non-comparative study to assess the effectiveness and safety of Nasaleze spray in the prevention and treatment of allergic rhinitis. 48 patients took part in the study (25 adults and 23 children aged between 2 and 62) with persistent AR. The patients were observed for a period of 4 weeks [4]. It was found that Nasaleze reduces the intensity of the symptoms of allergic rhinitis during the first week of use and improves the quality of life of patients with allergic rhinitis when used more than twice.

We carried out an open-label, comparative, randomised study of the effectiveness and safety of using microdispersed cellulose powder (Nasaleze) in the preventative treatment of seasonal allergic rhinitis in children over a period of 6 weeks from April to June 2009.

50 children aged between 4 and 14 with diagnosed seasonal allergic rhinitis (SAR) were observed. 30 children were given microdispersed cellulose powder. 20 children were put into the comparison group and received symptomatic treatment. The objective and subjective symptoms of SAR were assessed prior to treatment and at 2, 4 and 6 weeks after first using the product. Nasaleze was used in accordance with the dosage recommendations: one spray into each nostril 3-4 times a day (every 5-6 hours). The patients were advised to re-spray Nasaleze every time they blew their nose or when likely to come into contact with an allergen, in order to restore the protective layer.

All of the patients taking part in the study were diagnosed with SAR. During the observation period, both groups were allowed to use concomitant antihistamines and GKS nasal sprays 15-20 minutes before using the microdispersed cellulose powder.

The objective and subjective symptoms of SAR were assessed prior to treatment and at 2, 4 and 6 weeks from first using Nasaleze. The results were recorded in the "Patient observation diary".

The average age of the patients in groups 1 and 2 was 8.3±3.2 and 8.7±3.7 respectively. The average duration of the illness was 3.1±0.87 and 2.8±1.0 years. Both groups showed a similar sensitisation to allergens: sensitisation to pollen allergens alone covered 50% of the children, for 38.4% of the children the symptoms of allergic rhinitis developed not only from plant pollen but from other allergens such as household dust and pet allergens.

Children with mild SAR accounted for 73.3% of the first group and 78% of the second group, while children with moderate to severe symptoms accounted for 20% of the first group and 22% of the second group.

Five children in the main group (16.7%) and four children (20%) in the control group suffered from bronchial asthma as well as seasonal allergic rhinitis.

20 children (76%) in the main group and 10 children (50%) in the control group had a significant family history of allergic illnesses, including seasonal allergic rhinitis.

None of the patients had received treatment for SAR prior to the start of the observation period.

The patients visited the doctor 4 times every 2 weeks (Table 1).

Table 1 Case monitoring timetable for the patients per visit.

Study	Visit 1	Visit 2	Visit 3	Visit 4
Informed consent	X			
Questionnaire	X			
Collection of medical records	X			
Patient examination	X	X	X	X
Symptoms of seasonal allergic rhinitis (on a point scale: 0 - no symptoms, 1 - low level of intensity, 2 - moderate level of intensity, 3 - severe)	X	X	X	X
Treatment adjustment		X	X	X
Assessment of adverse events		X	X	X
General doctor and patient assessment		X	X	X

Results of the study and discussion:

2 weeks after first taking microdispersed cellulose powder (Nasaleze), the main group noticed a definite drop in all SAR symptoms: rinorrhea decreased from 1.8±0.4 to 0.8±0.6 points; sneezing – from 1.5±0.6 to 0.5±0.6; itching in the nose from 1.2±0.5 to 0.4±0.5; blocked nasal passages from 1.8±0.5 to 0.7±0.6 ($p<0.001$) (Fig. 1.2). The majority of patients (73%) noticed a distinct improvement in their condition by the fifth day of using Nasaleze. Fig. 1-4.

During the next 2 weeks, 12 children's (40%) symptoms disappeared completely.

The remaining children noticed a decrease in their SAR symptoms: rinorrhea - to 0.6±0.6 points; blocked nasal passages - to 0.5±0.6; sneezing and itching in the nose remained unchanged ($p>0.5$)

6 weeks after first using Nasaleze spray the SAR indicators remained at their previous level.

Fig. 1 The course of SAR symptoms (rinorrhea, sneezing).

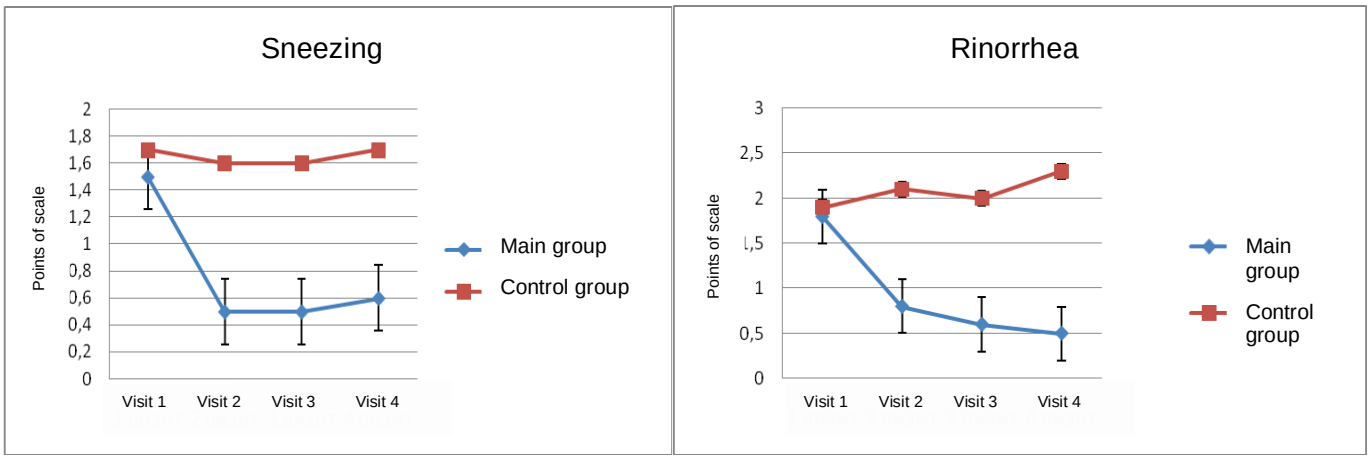
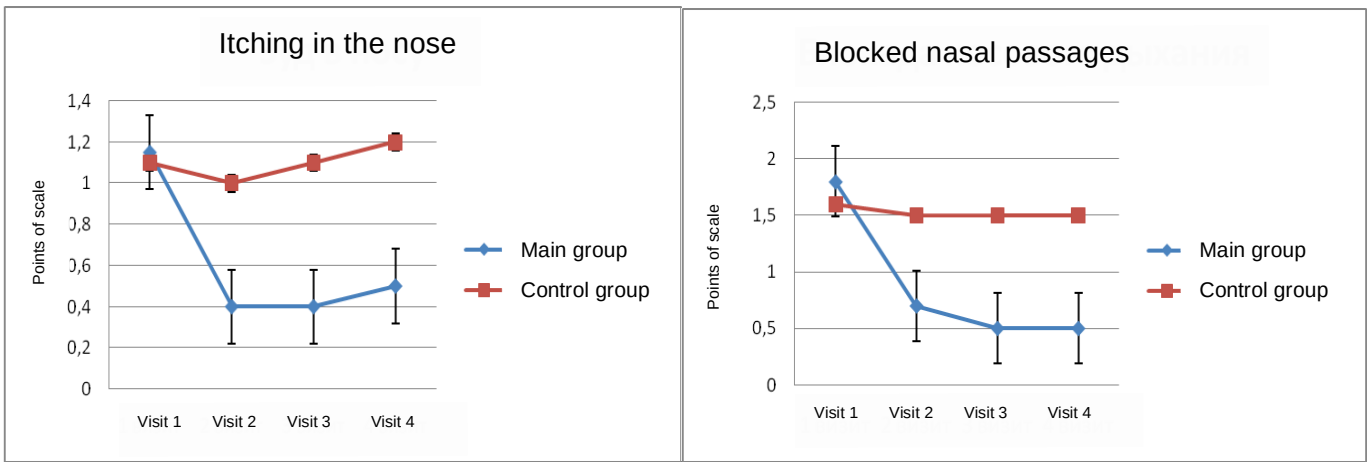
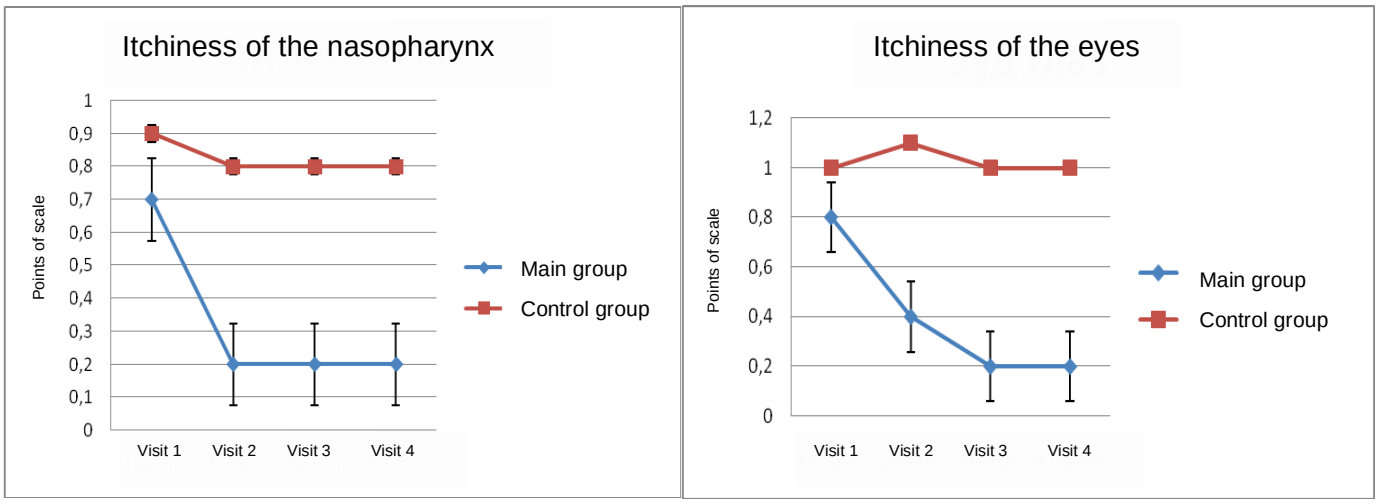


Fig. 2 The course of SAR symptoms (itching in the nose, blocked nasal passages).



They also noticed a decrease in other allergic manifestations. Two weeks after the start of the study, itchiness of the eyes decreased from 0.8±0.7 to 0.4±0.5 points; itchiness of the nasopharynx decreased from 0.8±0.8 to 0.2±0.4 points ($p<0.001$). After 4 weeks it had decreased to 0.2±0.3 points (Fig. 3).

Fig. 3 The course of SAR symptoms (itchiness of the eyes, itchiness of the nasopharynx).



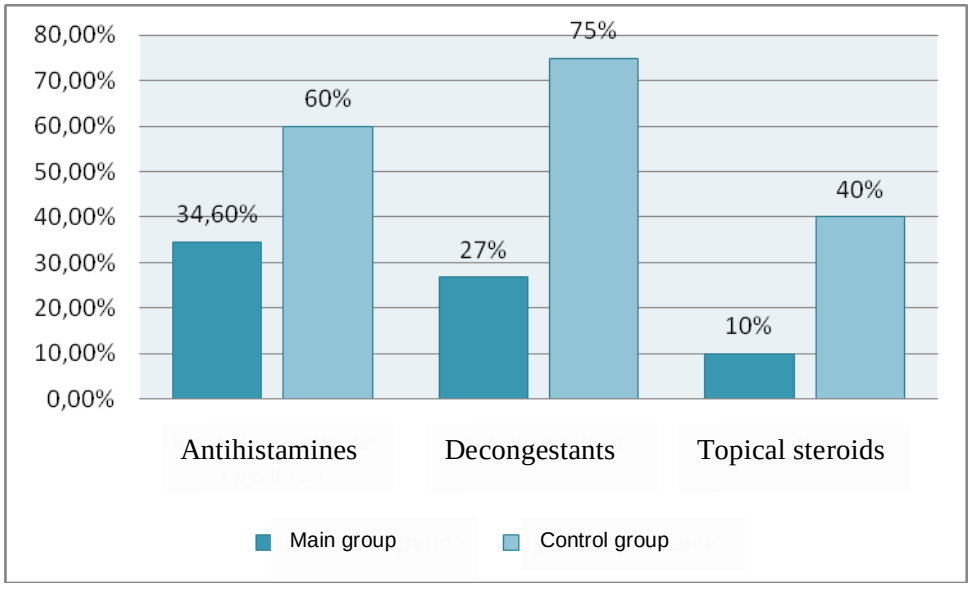
When using Nasaleze spray, 9 children (34.6%) occasionally took antihistamines, 7 children (26.9%) took decongestants and 3 children (10%) took topical glucocorticosteroids.

The product was not effective for 2 children (6.6%) with moderate to severe SAR and these children were also treated with nasal corticosteroids. 2 children (6.6%) experienced increased sneezing and their treatment with the product was stopped.

On the whole, the majority of parents and doctors (86.4%) assessed the microdispersed cellulose powder as highly effective for the preventative treatment of seasonal allergic rhinitis.

In the comparison group the symptoms remained constant for the entire observation period, which required the frequent administration of antihistamines for 8 children (60%), decongestants for 15 children (75%), and 8 patients (40%) sometimes used topical steroids (Fig. 4).

Fig. 4 Frequency of use of medical products to treat SAR.



Microdispersed cellulose powder thus had a noticeable effect on the symptoms of allergic rhinitis (rinorrhea, sneezing, itchy nose, blocked nasal passages, itchy eyes, itchy nasopharynx).

Conclusion:

It has thus been proven that microdispersed cellulose powder has a positive effect on the preventative treatment of SAR in children.

The marked effect of microdispersed cellulose on SAR symptoms definitely decreased but to a lesser extent for symptoms such as itchy eyes and nasopharynx.

It was proven that children who received Nasaleze during the pollen season had their intake of antihistamines, decongestants and topical steroids reduced.

The preventative use of Nasaleze spray when coming in contact with a known allergen (cat, dog and other animals) significantly decreased the development of allergic reactions.

It has been proven that it is advisable to use Nasaleze spray for the preventative treatment of seasonal allergic rhinitis.

Discussion:

The treatment of allergic rhinitis up to now has been based on the use of products which act either as membrane stabilisers, which prevent the degranulation of immune cells, or as histamine receptor blockers. The use of most of these drugs is restricted by age and length of treatment. The new product, Nasaleze, is a modern way of controlling the symptoms of and treating allergic rhinitis. This inert cellulose powder, when administered in the nostrils, forms a gel-like substance which is similar to the normal mucous membrane in the nose which, when it comes into contact with a moist surface (always present in the nasal cavity), prevents the release by airborne allergens of vasoactive substances from mast cells. This can be seen not only as an effective measure to prevent the initial immunological reaction, but as a chance to reduce the symptoms of allergic rhinitis which have already been observed.

Nasaleze is a natural and safe product which does not contain any chemical substances and which has proven effective in previous studies. [1-7].

It is important that the microdispersed cellulose powder is well-tolerated, safe and easy to use, and may be used in children of any age, starting from the very young.

In this study, Nasaleze facilitated the classification of SAR symptoms during the first few days after the start of inhalation. The children's medical records contained a lot of SAR symptoms over a long period which required the use of different pharmacological products with a certain range of side effects. 86.4% of the children experienced a definite reduction in the symptoms of SAR and the frequency of use of additional treatment methods decreased. The product was not effective in 2 patients with moderate to severe SAR. 2 patients stopped participating in the study on account of increased sneezing which could be classed both as in intensification in SAR symptoms and as a side effect of the product. This study showed that inert cellulose powder administered to the nasal cavity prevents the development of an allergic reaction to plant pollen and other irritants in children. Treatment using cellulose powder should be started as early as possible and continued throughout the entire season when there is increased pollen in the air; the number of applications per day may be increased as necessary. Children noticed a positive blocking effect of Nasaleze spray when coming into contact with pets, allowing them to minimise their allergic reaction.

Regular use of inert cellulose powder in the nostrils may effectively prevent and alleviate the symptoms of SAR.

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Open non-comparative study to evaluate the effectiveness of Nasaleze preparation for patients with allergic rhinitis.

Ilina N.

Published: *Russian allergy Journal*. 2011.

ALLERGY Nasaleze®
natural hayfever and allergy prevention

REPORT ON AN OPEN NON-COMPARATIVE STUDY TO EVALUATE THE EFFECTIVENESS OF NASALEZE PREPARATION FOR PATIENTS WITH ALLERGIC RHINITIS

Investigated preparation: Nasaleze (vegetable cellulose in a spray dispenser).
Manufacturer of the preparation: Nasaleze Ltd, Great Britain
Location where the study was conducted: Federal State Budget Establishment Immunology Institute State Science Centre, Russian Federal Medical Biological Agency, building 24, Kashirskiy Highway, Moscow.
Study director: Chief clinical physician, professor, doctor of medical sciences. N.I. Ilina

Introduction. Basis of the study.

Nasaleze, a micro-dispersed cellulose powder in a spray dispenser, is designed to protect the nasal mucous membrane from contact with pollutants and aeroallergens, as well as other micro-particles, which enter the nasal cavity during breathing. Nasaleze is used to prevent the development of the symptoms of allergic rhinitis (AR): nasal pruritis, swelling of nasal mucus and disruption of nasal breathing, prolific clear liquid discharges from the nose, sneezing attacks, etc. When the cellulose powder from the spray dispenser contacts the nasal mucus, it binds with the mucus of the nasal cavity lining and forms a strong gel-like film that covers the nasal cavity and serves as a natural barrier against aeroallergens.

Nasaleze is made up exclusively of natural components. It is an inert, natural, finely dispersed cellulose powder. It does not contain any systemic or locally active substances. Therefore, it is suitable for children and pregnant women.

Previous studies to evaluate the effectiveness of Nasaleze were based on the patient's subjective evaluation of the severity of AR symptoms under conditions of natural exposure to significantly causative aeroallergens. A study involving nasal provocation tests with measured doses of significantly causative aeroallergens on a backdrop of using the Nasaleze preparation with an evaluation of the changes in nasal obstruction and inspiratory nasal resistance will enable an objective evaluation of the effectiveness of the preparation for AR patients as a means of elimination therapy.

The goal of the study is to evaluate the effectiveness of Nasaleze preparation (vegetable cellulose) for patients with allergic rhinitis (AR).

Materials and methods.

Study Design. Prospective open non-comparative study.

The study included 30 patients, of both sexes (12 men (40%) and 18 women (60%)), suffering from allergic rhinitis and meeting the criteria for inclusion/exclusion. The mean age of the patients was 28.5 ± 2.9 years. The mean duration of illness was 10.7 ± 2.5 years (from 3 to 24 years).

The duration of the study was 3 months (selection of patients) and 7 days for testing and active observation.

Criteria for including patients in the study:

- the existence of the patient's informed consent to participate in the study;
- aged between 18 and 65 years;
- patients with a history of allergic rhinitis for no less than 2 years
- positive skin tests for dust and household or epidermal allergens
- absence of clinical symptoms of allergic rhinitis at the time of the study
- ability to adequately participate in the study process

***Criteria for excluding patients from the study*:**

- pregnancy, lactation
- presence of infections in air paths or nasal sinus cavities
- presence of anatomical anomalies of the nose (polyposis of the nose and paranasal sinuses, hypertrophy of nasal mucus, structural changes of the nasal cavity) that could significantly disrupt nasal breathing
- hypersensitivity to any of the components of the investigated preparation
- lesions of the mucous lining of the nose
- recent surgical interventions in the nasal cavity
- recent injuries to the nose
- smoking less than 4 hours before the testing
- clinical symptoms of rhinal conjunctivitis or bronchial asthma at the time of the study
- indicators of pulmonary function: FVC, FEV_1, PEF<85% of normal values, FVC/ FEV_1 <70% of normal values
- dermatological diseases in the developed stage (psoriasis, atopic dermatitis, contact dermatitis)
- occurrence of acute respiratory disease less than 2 weeks before or at the time of the study
- occurrence of decompensated diseases or acute conditions that could significantly affect the results of the study
- alcoholism, drug addiction, mental unbalance
- probable inability to meet the demands of the clinical study
- participation in any other clinical testing during the last 28 days
- simultaneous use of preparations that could influence the dynamics of the indicators used to evaluate the effectiveness of the therapy (**Table 1**)

Table 1. List of preparations prohibited during the study

Patients were not allowed to participate in the study if they had taken any of the preparations listed below during the period preceding the start of the study or during the study.
Ketotifen (72 hours)
Systemic decongestants (48 hours)
Nasal decongestants (48 hours)
Systemic and/or nasal glucocorticoids (2 weeks)
Antihistamine preparations (14 days)
Antileukotriene preparations (14 days)
Cromoglycates (14 days)
Adrenaline (24 hours)
Non-steroid anti-inflammatory medications (7 days)
Tricyclic psychotropic preparations (21 days)

Brief description of the programme.

During the introductory period, the patients were evaluated according to the criteria for inclusion/exclusion. During visit 1 (after the patient was accepted onto the study) the initial condition of the patient was determined and the peak nasal inspiratory flow (PNIF) was measured. Then a series of nasal provocation tests were conducted: first with a test reference liquid and, in the case of a negative reaction, with measured doses of significantly causative aeroallergens (without the use of Nasaleze), beginning with a minimum dilution of 1/512 with a gradual increase in the allergen dose (in the case of a negative result). The PNIF was measured after the application of each allergen dose. In the case of a positive result, the test was ended and the dilution of allergen at which a reaction was observed was noted. During visit 2 (3±1 days after the first visit) the patient's initial condition was evaluated and the PNIF was measured. Then the research physician sprayed a single dose of Nasaleze into each nasal passage of each patient. After 20 minutes following the application of Nasaleze, a series of nasal provocation tests were conducted with the specific allergen, until a positive result was obtained (using the method described above), after which the PNIF was measured.

The effectiveness of the preparation was evaluated based on a comparison of the nasal provocation test results obtained before and after the use of Nasaleze.

Results of the study.

Description of the group of patients in the study*.*

30 patients, of both sexes (12 men (40%) and 18 women (60%)), suffering from allergic rhinitis and meeting the criteria for inclusion/exclusion took part in the study. The mean age of the patients was 28.5 ± 2.9 years. The mean duration of illness was 10.7 ± 2.5 years (from 3 to 24 years).

The distribution of patients by severity of illness is shown in **Table 2**.

Table 2. Distribution of patients by severity of allergic rhinitis.

Total, n (%)	slight, n (%)	moderate, n (%)	severe, n (%)
30 (100%)	20 (66.7%)	10 (33.3%)	0 (0%)

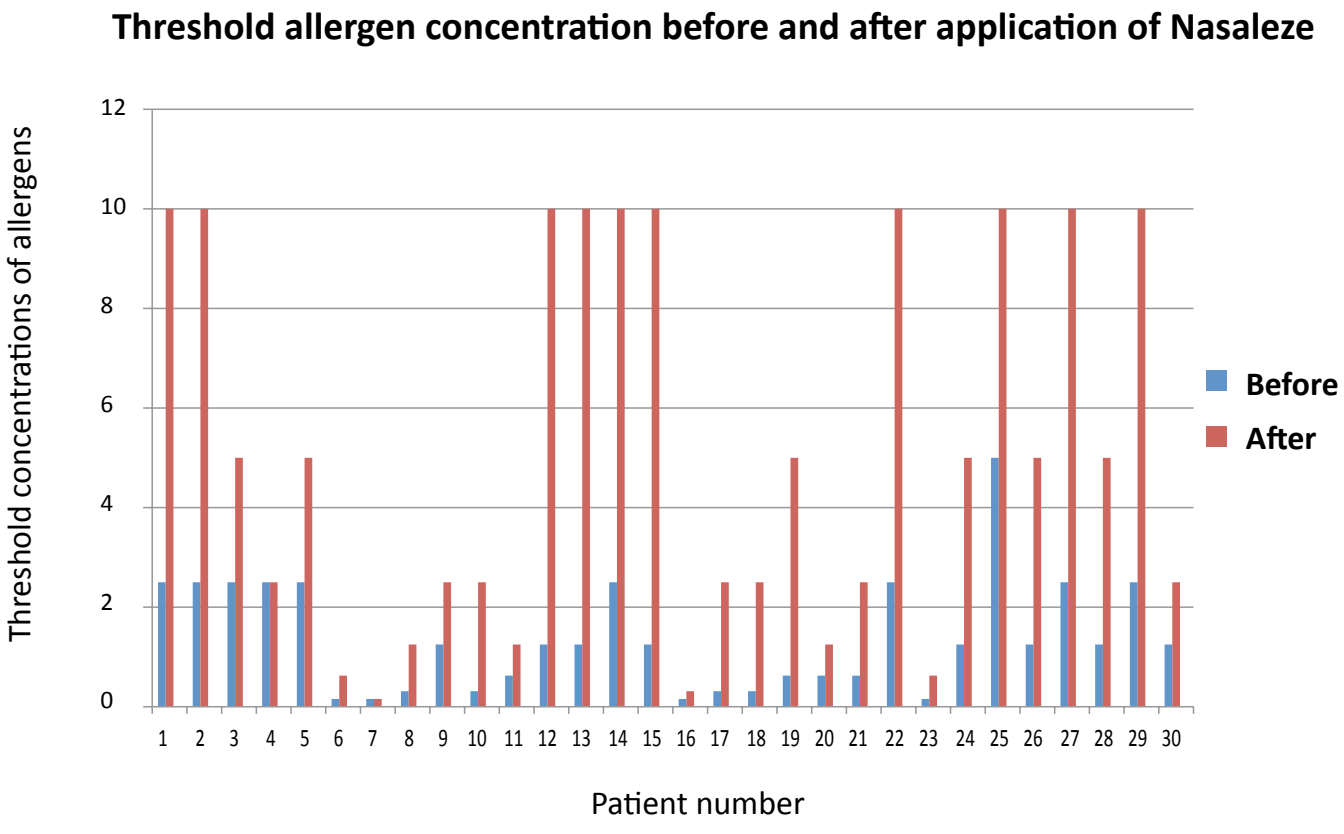
The allergic nature of the illness was confirmed in all the patients. All patients had a sensitivity to dust, 10 patients (33.3%) were also sensitive to household and/or epidermal allergens.

A total of 30 patients (100%) completed the study in accordance with the protocol.

Evaluation of the effectiveness of the therapy.

Of the 30 patients who completed the study, the therapy using Nasaleze was found to be effective in 28 (99.6%) of the patients, which showed a statistically valid decrease in nasal reactivity to a significantly causative allergen. Thus, the mean threshold concentration of allergen during the nasal provocation tests was initially 1250 PNU/ml, and after the application of Nasaleze, 5000 PNU/ml (Wilcoxon criterion $z=4.694$, $p<0,001$). However, in 4 patients, no development of symptoms was recorded, even with provocation by an allergen at the maximum concentration of 10,000 PNU/ml (**Table 3**). The best results were obtained in patients with isolated dust sensitivity and a mild period of rhinitis.

Table 3 .Dynamics of threshold concentrations of allergens before and after the application of Nasaleze.



Two patients for whom the preparation was not found to be effective had a combination of dust and household sensitivity. It is likely that the household sensitivity causes a persistent allergic inflammation of the nasal mucus and increased nasal hyper-reactivity, even though clinical manifestations of rhinitis are absent. Because Nasaleze does not have any anti-inflammatory or anti-allergic action, it is not be expected that the preparation could affect the course of an allergic reaction that is already developed, but as part of a complex AR therapy, the preparation could stop the further uptake of allergen with inhaled air.

Assessment of adverse reactions.

During the entire period of observation, none of the patients taking part in the study showed any adverse reactions.

Conclusion. Thus the study shows that:

1) Under conditions of allergen provocation, Nasaleze has a prophylactic action and prevents the development of an allergic reaction

2) The preparation is less effective in patients who have year-round allergic rhinitis

3) the use of Nasaleze will be effective if it is started before the beginning of contact and continues during the period of contact with a significantly causative allergen

4) it must be considered that after clearing the nose each time, the preparation must be applied again to renew the formation of the protective film

5) the advantage of Nasaleze is the high degree of safety, because it contains an inert, natural, finely dispersed cellulose powder and has no systemic action In connection with the above, Nasaleze can be used by children and by pregnant or breast-feeding women.

Nasal mucociliary clearance and mucoadhesion of hydroxypropylmethylcellulose of powder used for alleviation of allergic rhinitis.

Diethart B, Emberlin JC, and Lewis RA.

Poster presented: *EAACI*, in London 2010.

Nasal mucociliary clearance and mucoadhesion of hydroxypropylmethylcellulose powder used for alleviation of allergic rhinitis

Bernadette Diethart[1], Jean Emberlin[2], Richard Lewis[3]

Background:

An inert hydroxypropylmethylcellulose powder (Nasaleze®) has been used since 1994 in the alleviation of allergic rhinitis (AR). The powder is applied to the inside of the nose where the particles adhere to the nasal mucosa, absorb moisture and swell to form a gel. Its efficacy in reducing hay fever symptoms and its barrier function against Der p 1 allergen have been recently proven. Mucoadhesion and clearance of the gel influence the duration the barrier is efficient.

Methods:

For the investigation of the effect of HPMC application on mucociliary clearance a modified Andersen saccharine test was applied. Twelve healthy volunteers were tested after the end of the grass pollen season 2008. In order to test the baseline mucociliary clearance time (MCT) of each participant, saccharine solution (3 %) was applied to the anterior tip of the inferior turbinate in one nostril of the subjects by means of rayon tip swabs. The subjects were instructed not to sniff or sneeze and to report a sweet taste as soon as it was noted and time was measured from the moment of solution application. After baseline measurements, 10 mg and 20 mg of HPMC was sniffed into the same nostril. After 5 minutes to allow gel formation the Andersen test procedure was repeated.

Results:

The mean mucociliary clearance time at baseline was 11.14 minutes. This baseline MCT significantly increased to 35.45 minutes when 10 mg of HPMC were applied to the nostril prior to the test ($p < 0.0005$). Application of 20 mg resulted in a mean MCT of 50.37 minutes and thus a further increase >120 % (>420 % longer MCT compared to baseline). This elongation of MCT was statistically significant when compared to baseline and 10 mg HPMC ($p < 0.0005$).

Conclusion:

Mucus maintains a hydrated layer over the epithelium which serves as a protective barrier against pathogens and noxious substances. However, the mesh spacing of mucus is too large to constitute a diffusion barrier to most allergens. HMPC gel applied to the nose has been proven to be a barrier to allergen entry. The attachment of HPMC to nasal mucus (mucoadhesion) slows down nasal clearance which enables longer residence time of HPMC in the nose and thus increases the time HPMC can be effective as a barrier before it is cleared. Also, dehydration of mucus while the HPMC gel forms increases mucus viscosity, which might decrease the diffusion coefficient through the mucus resulting in lower allergen diffusion.

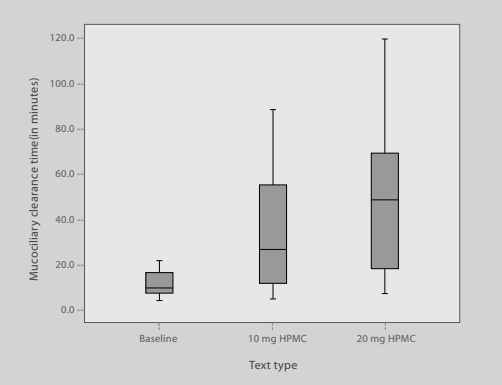


Figure 1: Boxplot of baseline MCT and MCT after nasal application of 10 mg and 20 mg of HPMC.

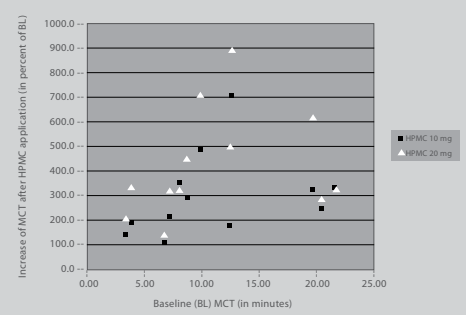


Figure 2: Relationship between initial MCT at baseline and degree of subsequent MCT increase after HPMC application.

	Women	Men
Number of participants	9	3
Mean age (in yrs)	32.8	37.0
Age range (in yrs)	25-40	25-60
Allergic rhinitis during last two yrs	3 (33.3 %)	1 (33.3 %)
Smoker	1	1

Table 1: Demographics of participants recruited for Andersen saccharine testing.

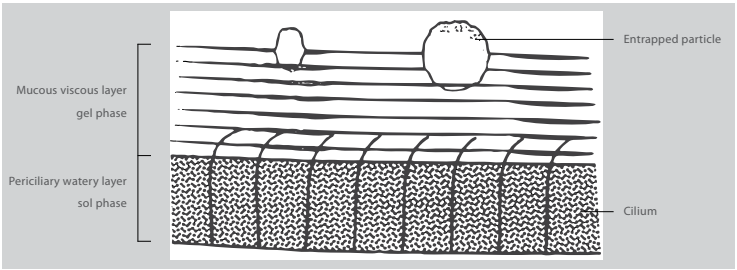


Figure 3: Viscous gel phase and periciliary fluid forming the mucus double layer (modified according to Quraishi et al. 1998).

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This study was sponsored by Kisska International Ltd. and the University of Worcester.

The Efficiency of Cellulose Powder extract in complex therapy of patients with intermittent allergic rhinitis.

Penechko EM, and Sizyakina LP.

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The efficiency of cellulose powder extract in complex therapy of patients with intermittent allergic rhinitis.

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The dynamics of allergic and immunologic indices of patients with intermittent allergic rhinitis at the relapse stage have been analysed. The advisability to prescribe cellulose powder extract in complex therapy of patients with intermittent allergic rhinitis is substantiated.

Key words: intermittent allergic rhinitis, cellulose powder extract.

Allergic rhinitis is related to a number of widespread diseases that affect between 10 and 20% of the population in various countries all over the world (1,3). This disease significantly impairs the quality of life of its sufferers, aggravates the course of bronchial asthma and promotes the development of other pathologies of the otorhinolaryngeal organs (sinusitis, otitis media and others) (2,4).

Modern approaches to treating allergic rhinitis include using elimination therapy, specific immunotherapy, pharmacotherapy and observing patients at an asthma school. In the case of both perennial (year-round) allergic rhinitis and seasonal rhinitis, it is not always possible to limit contact with allergens. For this reason, allergologists have always been interested by the idea of creating a barrier that can prevent allergens from acting on the nasopharyngeal mucous membrane. Topical medications play a significant role among the medicines used for this purpose (N.I. Ilyina, I.V. Sidorenko, 2003)

The purpose of this study was to evaluate the efficiency of a microdispersed cellulose powder in complex therapy of patients suffering from intermittent allergic rhinitis.

Materials and methods.

The study included 30 subjects aged between 18 and 33 who were suffering from moderate intermittent allergic rhinitis in the relapse stage. According to the results of the skin test, all subjects had a sensitivity to weeds. In 95% of cases, the allergens mainly responsible were pollen, ragweed, sunflower and Cyclachaena. The patients were divided into 2 groups: Group I (10 people) received standard therapy, including: second generation antihistamine medications from the cetirizine group, sorbents, topical glucocorticosteroids, and Group II (20 people) received the microdispersed cellulose powder (Nasaleze) in one spray into each nasal passage three times a day in addition to the basic therapy.

Observation period — 4 weeks. The patients visited the clinic once a week. At both the beginning and the end of the study, each patient filled out a questionnaire regarding the quality of life of someone suffering from allergic rhinitis, which they assessed according to a seven-point scale:

0 - No adverse effects,

1 - Almost no adverse effects,

2 - Mild adverse effects,

3 - Moderate adverse effects,

4 - Strong adverse effects,

5 - Very strong adverse effects,

6 - Severe adverse effects, both before and after treatment.

In order to carry out the set tasks, a battery of clinical, immunological and statistical methods was used.

The general clinical study methods included: recording the patient's medical history with regard to allergies; evaluating the severity of the symptoms with a number of points (runny nose, sneezing, itchy nose, nasal congestion, conjunctivitis, tickle in throat) according to the severity:

0 - Absent (no symptoms),

1 - Mild (symptoms are present, but do not affect normal life),

2 - Moderate (symptom causes discomfort but does not interfere with normal daily activity or sleep),

3 - Medium severity (symptom causes significant discomfort, interferes with normal daily activity or sleep),

4 - Severe (symptom occurs so strongly that it is necessary to change the course of treatment and use stronger medications).

The dynamics of the symptoms were evaluated before the start of the treatment and also on the 7th, 14th and 21st days after treatment began.

The immunological examination of patients was carried out during visits to the clinic and one month following the end of the treatment. A blood specimen for analysis was collected from the cubital vein in the morning on an empty stomach.

The various types of immunocompetent cells were identified by the indirect immunofluorescence method using a range of monoclonal antibodies (JSC "Sorbent LTD", Russia): CD3, CD4, CD8, CD20, CD16, CD25, CD95 and HLA-DR. The results were analysed with a 'Cytomics FC 500' **laser flow cytometry system** (Becman Coulter, USA**).**

The content of immunoglobulin classes IgA, IgM and IgG in the blood serum was analysed using the radial immunodiffusion method developed by G. Manchini et al. (1965), with monospecific serum manufactured by "ImBio" (Russia).

The quantity of circulating immune complexes (CIC) in the blood serum was analysed by precipitation with polyethylene glycol, following the method by V.Yu. Klimov (1986).

The intensity of the neutrofils' oxygen-dependent metabolism was evaluated in a spontaneous and stimulated nitroblue tetrazolium (NBT) restoration test according to the methodology suggested by V.V. Menshikov et al. (1987). The NBT test stimulation coefficient was calculated with the aid of the following formula:

$$\text{Coeff. stim.} = \text{NBT stim.}/\text{NBT spont.}$$

The statistical processing of the data was carried out using the software programs “Microsoft Excel” and “Statistica 8.0”. The non-parametric significance criteria (Mann-Whitney-Wilcoxon criterion) were evaluated.

Results and discussion.

During the first appointment, it was found that both groups of patients had clear symptoms of allergic rhinitis (Table 1). The clinical observation of the sufferers showed that among the group of patients receiving the standard treatment, a positive dynamic was observed in the course of the allergic rhinitis but, at the end of the study period, truly significant changes were only observed in symptoms such as runny nose (before 3.1±0.3 points, after 1.7±0.5 points) and stuffy nose (before 3.5±0.8 points, after 1.5±0.3 points).

An improvement in the condition of the second group was observed as early as the end of the first week following the first administration of the microdispersed cellulose powder (Fig. 1). Towards the end of the fourth week after the start of the study, the group of patients who had received the microdispersed cellulose powder were experiencing a statistically significant (for $p<0.05$) reduction in such symptoms as runny nose, from 3.2±0.7 points to 0.7±0.1 points, sneezing, from 2.8±0.5 points to 0.7±0.3 points, itchy nose, from 1.9±0.2 points to 0.4±0.1 points and stuffy nose, from 3.3±0.5 points to 0.6±0.3 points (Table 1).

In a comparison of the two study groups over the four weeks of observation, a real reduction in the severity of allergic rhinitis symptoms such as runny nose, sneezing, itchy nose and nasal congestion was observed in the second group of patients (Table 1).

The improvement in the quality of life of the patients serves as evidence of the effectiveness of the treatment. Thus, in the fourth week of the study, an analysis of the questionnaire results from the group who had received the microdispersed cellulose powder revealed a significant improvement in such subjective indices as: types of activity from 5.5±0.3 conventional units to 1.5±0.2 conventional units, sleep from 4.6±0,3 conventional units to 1.1±0.1 conventional units, general symptoms from 3.5±0.4 conventional units to 1.1±0.1 conventional units, practical problems from 1.5±0.2 conventional units to 0.9±0.05 conventional units, nasal symptoms from 4.7±0.2 conventional units to 0.5±0.05 conventional units, emotional state from 5.8±0.2 conventional units to 0.8±0.07 conventional units. ($p<0.05$ compared with original indices).

In contrast, in the group of patients who had received the standard therapy there were no diagnostically significant changes.

When the two study groups were compared after four weeks of observation, a real reduction was found in the severity of such subjective indices as: types of activity, sleep, general symptoms, practical problems, nasal symptoms, emotional state, in the group of patients who had received the microdispersed cellulose powder (Fig. 2).

All patients who took part in the study underwent a preliminary examination of their immune status before the start of the treatment. During this examination, elevated levels of secretory IgA and CICs were observed in both groups (Table 2). After completion of the treatment, the group of patients who had received the standard treatment did not show any essentially significant differences in the indices of their immune status, but in the group that received the microdispersed cellulose powder a marked reduction in CICs and normalisation of the secretory IgA content was observed (Table 2).

A comparative analysis of the effectiveness of including the microdispersed cellulose powder in the complex treatment of intermittent allergic rhinitis has shown that it leads to a faster alleviation of the symptoms of allergic rhinitis and improves the quality of life of patients.

Accordingly, the information presented in this study allows the conclusion to be drawn that including the microdispersed cellulose powder as part of the complex treatment for intermittent allergic rhinitis is beneficial.

Table 1

Dynamics of severity of allergic rhinitis symptoms

Symptom (points)	Standard therapy before treatment	Standard therapy after treatment	Standard therapy + Nasaleze before treatment	Standard therapy + Nasaleze after treatment
Runny nose	3.1±0.3	1.7±0.5*	3.2±0.7	***0.7±0.1**
Sneezing	2.7±0.9	1.7±0.6	2.8±0.5	***0.7±0.3**
Itchy nose	1.5±0.1	0.8±0.1	1.9±0.2	***0.4±0.1**
Stuffy nose	3.5±0.8	1.5±0.3*	3.3±0.5	***0.6±0.3**
Itchy eyes	1.7±0.5	1.5±0.4	1.5±0.2	1.4±0.1
Tickle in throat	1.4±0.2	0.9±0.3	1.4±0.1	0.9±0.3

Notes:

* - Statistically significant differences were noted in the patients who received the standard therapy compared with the results before the treatment ($p<0.05$)

** - Statistically significant differences were noted in the patients who received the standard therapy + Nasaleze compared with the results before the treatment ($p<0.05$)

*** - Statistically significant differences were noted in the patients who received the standard therapy + Nasaleze compared with the results of the standard therapy ($p<0.05$)

Table 2

Dynamics of immune system indices among sufferers of intermittent allergic rhinitis

	Standard therapy before treatment	Standard therapy after treatment	Standard therapy + Nasaleze before treatment	Standard therapy + Nasaleze after treatment
CD3 %	57.6±8.2	59.4±6.5	68±9.3	69±8.0
CD4 %	33.2±6.2	35.2±6.9	40±4.9	41.3±6.9
CD8 %	16.4±5.1	17.7±5.5	26.9±6.8	27.2±5.4
CD16 %	9.5±6.1	10.1±5.1	16.4±7.6	14.7±6.7
CD19 %	9.8±3.7	9.7±2.6	13.3±3.7	13.2±3.7
HLADR %	10.7±3.5	10.2±2.7	19.5±3.2	16±6.7
CD95 %	2.8±1.2	2.9±1.7	3.7±1.7	3.5±1.8
CD25 %	1.7±1.3	2.1±1.6	4.3±1.1	4.6±1.0
Ig A g/l	3.3±0.3	2.7±0.2	3.9±0.9	**1.9±0.5*
Ig M g/l	1.2±0.3	1.1±0.2	1.2±0.5	1.1±0.3
IgG g/l	11.8±1.1	10.8±1.1	12.4±2.1	12.2±1.5
CIC conventional units	81.3±18.2	77.3±11.2	103.3±34.9	54.8±16.9*
NBTspon.	103.8±21.4	106.7±17.4	123±21.7	134.5±22.9
NBTstim.	167.7±23.7	174.7±22.2	188.5±24.7	199.1±35.1
Coeff.stim.	1.5±0.1	1.4±0.1	1.6±0.2	1.5±0.1

Notes:

* - Statistically significant differences were noted in the patients who received the standard therapy + Nasaleze compared with the results before the treatment ($p<0.05$)

** - Statistically significant differences were noted in the patients who received the standard therapy + Nasaleze compared with the results of the standard therapy ($p<0.05$)

Figure 1. Dynamics of allergic rhinitis symptoms among patients who received Nasaleze

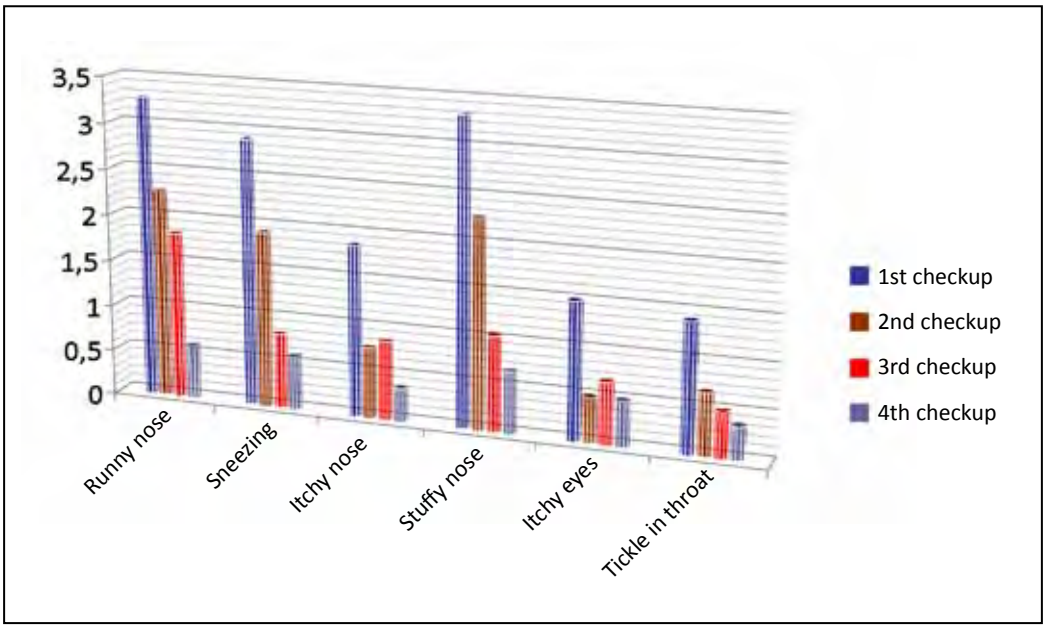
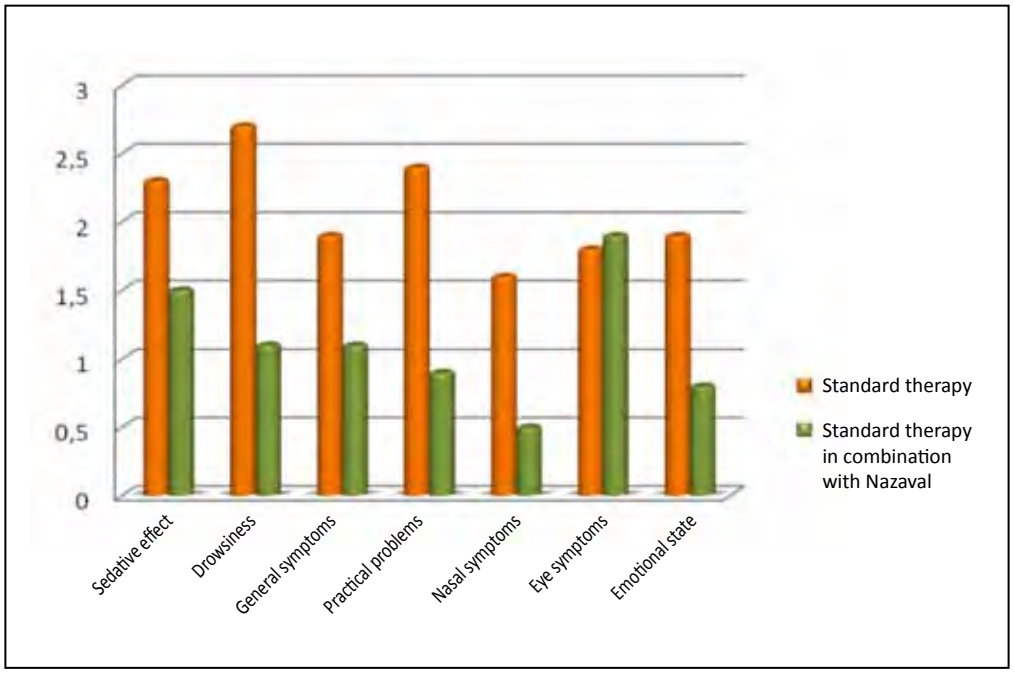


Figure 2. Evaluation of quality of life of a patient suffering from allergic rhinitis



Notes: Statistically significant differences were noted in the allergic rhinitis sufferers who received the standard therapy in combination with Nasaleze compared with the standard therapy group ($p<0.05$)

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Study of the effects of inert cellulose powder on the nasal mucosa.

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Study of the Effects of Inert Cellulose Powder on Nasal Mucosa

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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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Recommended for publication by Luss L.V.

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

Åberg N, Ospanova S, Nikitin N, Emberlin J, and Dahl A.

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1395

A nasally applied cellulose powder for seasonal allergic rhinitis (SAR) in adults with grass pollen allergy. Supplementary analyses of reduction of severity and duration of symptoms.

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Introduction

A nasally applied cellulose powder forms a gel layer which acts as a protective barrier on the nasal mucosa. The product is used increasingly in many countries as a remedy for allergic rhinitis. From this study in grass pollen allergic adults a significant efficacy on all airway symptoms has been reported previously. The present findings are based on further analyses regarding the relative reduction of severity and duration of symptoms

Study population and Methods

In May 2013, in two cities in the eastern part of Ukraine, a double blind, placebo controlled randomised parallel group study was conducted over a 4 week period in the grass pollen season in 108 grass pollen allergic subjects, 18-40 years of age.

Results

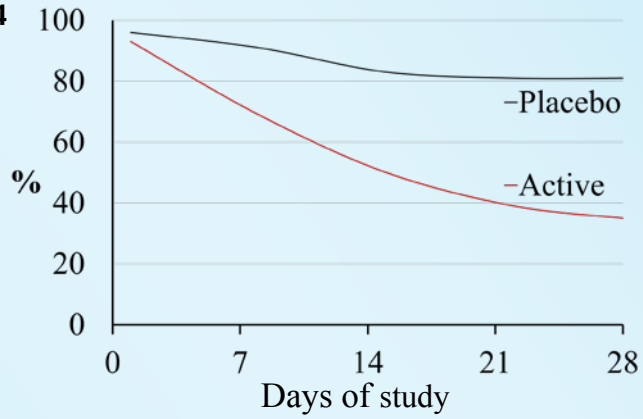
Table. All means of reported severity scores from upper and lower airways were approximately 50% lower in the actively treated group (each separately and altogether $p<0.001$).
No significant side effects were noted.

Mean of symptom scores during 4 weeks. Percent of potential maximum severity

Symptoms	Placebo n=53	Active n=54
Sneezing	36.3	13.0
Running nose	27.4	15.1
Blocked nose	26.5	15.1
Eye symptoms	23.5	11.7
Lower airways	18.4	8.9
Sum of nasal symptoms	26.7	12.4
Sum of all symptoms	23.9	10.5

Figure. Large group differences in freedom from symptoms developed during the treatment period. The rate of disappearance of nasal symptoms in the active group was more than double that in the placebo group. This difference was clinically and statistically significant (Kaplan-Meier log rank $p<0.001$),

Probability of nasal symptoms persisting



Conclusions

- ✓**Nasal application of an inert cellulose powder, in adults with grass pollen SAR, reduced the severity of all symptoms, also from the eyes and lower airways, with 50%.**
- ✓**An increasing effect with duration of treatment made more than half of the active group to became free from all nasal symptoms before the end of the study.**
- ✓**The eminent profile of safety and efficacy makes the product well suited as**
  - ➢**an early choice in treatment of SAR *in general***
    and in SAR in children, pregnant and breast feeding women, those operating machinery and the elderly *in particular*.
  - ➢**OTC-handling and self care.**

In relation to this presentation, I, the presenting author, declare the following, real or perceived conflicts of interest: I have received honoraria in relation to performance and reporting of the study.

Original Paper

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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.

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

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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

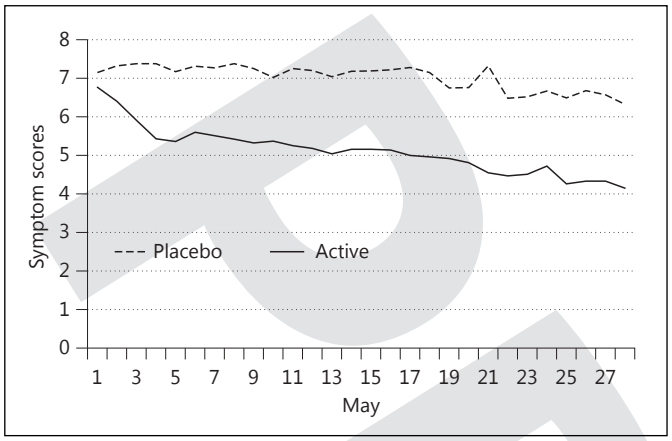

Fig. 1. Sum of nasal symptoms day by day in the respective groups (full analysis set, n = 107). Significance of daily group differences: May 1, nonsignificant, May 2, $p < 0.05$, May 3–28, $p < 0.001$.

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/m^3. 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 experimental 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/m^3. 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

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Effect of micronized cellulose powder on the efficacy of topical oxymetazoline in allergic rhinitis.

Valerieva A, Popov T, Staevska M, Kralimarkova T, Petkova E, Valerieva E, Mustakov T, Lazarova T, Dimitrov V, and Church MK.

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Micronized cellulose powder enhances and augments the effect of locally applied decongestant in patients with allergic rhinitis

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Background:

Prolonging the contact time of locally applied drugs with the nasal mucosa would improve their efficacy. One way is to develop dosage forms containing mucoadhesive polymers like methylcellulose.

An alternative would be to "seal" the applied nasal drug with adhesive powder so that the formation of a gel layer could delay its clearance. The aim of our study was to document the feasibility of this approach with objective measures.

Methods:

This double blind placebo controlled study was conducted in 40 subjects (mean age 35 years, 23 women) with persistent allergic rhinitis with prominent congestion. We randomized them to 1 puff oxymetazoline followed by either 1 puff of commercially available micronized cellulose powder (test treatment, TT) or lactose powder used as sham (reference treatment, RT). After the first application on Day (D) 1, peak inspiratory nasal flow (PNIF, L/min) was measured at minutes 0, 1, 2, 5, 15, 30, 60, 120 180, 240, 300 & 360, areas under the curve (AUC) were analyzed. After one week of regular b.i.d. treatment, the procedure was repeated on D8. Patients were followed up without regular treatment and baseline PNIF was measured on D15. We also evaluated the speed of the mucocilliary clearance by means of liquid saccharine tests. VAS & Patient diaries were used to estimate subjective symptoms.

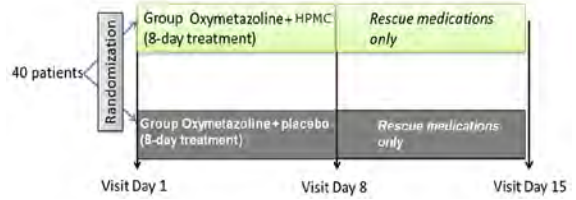
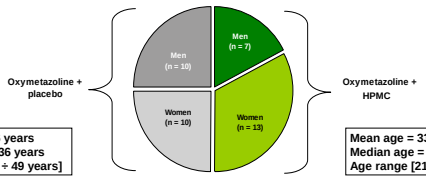


Figure 1. Study Design

Figure 2. Demographics



Results:

18 patients from each arm completed all 3 visits. AUCs at D1 showed superiority of TT, 56366.3 (mean) ± 3514.4 (s.e.m.), over RT, 46818.5±2847.3, P=0.042. On D8 this difference was further enhanced: 60855.7±3227.1 vs. 49411.1±2395.1, P=0.009. Baseline PNIF rose for both treatments from D1 to D8, but further increased in TT on D15 reaching statistical significance: TT vs RT: 93,1±5.4 vs 100.0±7.3, P=0.354 (D1); 135,6±10.0 vs 124,2±8.1, P=0.383 (D8); 158,1±10.9 vs 125,0±6.6, P=0.013 (D15). There was a clear trend demonstrating the slowing down of the nasal mucocilliary clearance for Visit 2 (P=0.07). Visual analogue scale measurements registered significant difference in congestion (D15-D1), P=0.03. Subjective symptoms showed wide variability across different patients; a trend was observed for itching and sneezing scores (D8-D1), P=0.06 and P=0.08, respectively.

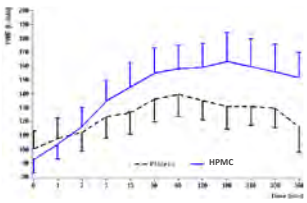
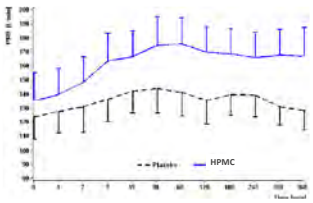


Figure3. PNIF at Visit 1

Figure 4. PNIF at Visit 2



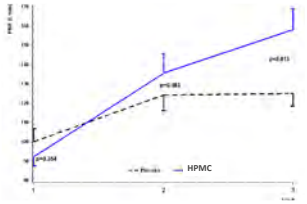
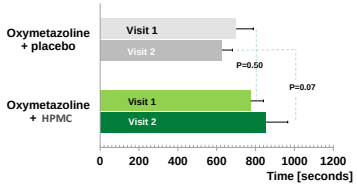


Figure 5. Baseline PNIF at D 1, 8, 15

Figure 6. Saccharine Clearance Test



Conclusions:

1. **Micronized methylcellulose powder enhances the decongestant effect of nasal oxymetazoline in patients with allergic rhinitis.**
2. **One week of such regular treatment augments the nasal patency and this effect carries over for another week after its discontinuation.**

References: 1. Tzachev CT et al. Br J Clin Pharmac 2002; 53 (1): 107-9.

Conflict of interests: There are no conflicts of interest in relation to the study.

Effect of micronized cellulose powder on the efficacy of topical oxymetazoline in allergic rhinitis

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ABSTRACT

Background: *Defective nasal barrier function is implicated in allergic rhinitis, which results in persistent inflammation and clinical symptoms, among which congestion plays a prominent role. In searching ways to improve the efficacy of nasally applied drugs in this condition, we tested the hypothesis that hydroxypropylmethylcellulose (HPMC), known as a mucoprotective agent, could enhance the efficacy of a decongestant (oxymetazoline nasal spray, 0.05%) by "sealing" it to the mucosa.*

Methods: *This double-blind placebo-controlled study was conducted with 40 patients (mean age, 35 years; 23 women) with persistent allergic rhinitis. The patients were randomized to receive 1 puff of oxymetazoline, followed by 1 puff of either HPMC or lactose powder (placebo) twice a day for 7 days and then only oxymetazoline rescue medication for another week. Peak inspiratory nasal flow (PNIF) was measured for 360 minutes after oxymetazoline and HPMC or placebo insufflation on days 1 and 8, and at a single point on day 15. Symptoms assessments involve visual analog scales and total nasal symptom scores.*

Results: *HPMC significantly enhanced oxymetazoline-increased PNIF at days 1 ($p = 0.042$) and 8 ($p = 0.006$). Baseline PNIF was greater in the HPMC group at day 15 ($p = 0.014$), indicative of further reduced nasal congestion. All nasal symptoms improved in both groups at day 8, but only the HPMC group showed further amelioration at day 15. Rescue medication was smaller in the HPMC group between days 8 and 15.*

Conclusion: *HPMC enhances decongestion through mucoadhesion but may also be augmenting the mucosal barrier in allergic rhinitis, which explains the carryover efficacy of oxymetazoline for a week after its discontinuation.*

Clinical Trial Registration: clinicaltrials.gov identifier: NCT01986582.

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To express symptoms of allergy, an individual must have both an atopic disposition and defective barrier function. The recognition of the importance of barrier function is relatively recent, derived from studies of atopic dermatitis in which abnormalities in the epidermal epithelium allow enhanced allergen penetration to induce immunoglobulin E sensitization and subsequent symptoms.[1–3] These observations stimulated the development of topical emollients as safe and inexpensive therapies.[4,5] Defective barrier function has also been implicated in the bronchi in asthma,[6] in the eye in allergic conjunctivitis,[7] and in the nose in allergic rhinitis.[8–16] The nasal epithelium is a highly regulated and impermeable barrier sealed by tight junctions.[9] Dysregulation of the tight junctions would allow increased allergen penetration to cause acute and chronic symptoms of allergic rhinitis.

The Allergic Rhinitis and its Impact on Asthma guidelines[17] recommend primarily pharmacologic therapies, *viz*. H_1 antihistamines and intranasal corticosteroids and decongestants for the treatment of allergic rhinitis. Whereas, procedures aimed at increasing barrier function provide a potential alternative safe therapy, research into these is in its infancy. The agent under investigation in this article is an inert dry hydroxypropyl-methylcellulose (HPMC) powder (NoAl; Nasaleze, Isle of Man, U.K.). Methylcellulose derivatives possess different ratios of hydroxypropyl to methoxyl substitution that determine their properties, such as viscosity, hydrophilicity, and gelling behavior when dissolved in water. The characteristics of the particular HPMC product here have been specifically tailored for intranasal delivery for the treatment of allergic rhinitis. Initial clinical trials have shown HPMC to be effective in both seasonal[18–20] and perennial[21] allergic rhinitis. Studies have concluded that it is safe and well tolerated,[22,23] and a review has been dedicated to the topic.[24]

Another effect of HPMC may also be considered. A reduction in rhinorrhea will slow down the clearance from the nose of locally applied drugs, thus prolonging

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their contact time and, theoretically, improving their efficacy. This possibility has been tested previously when administering intranasal xylometazoline with a different mucoadhesive agent in patients with perennial allergic rhinitis.[25] The results showed that the decongestant-mucoprotective agent combination had a greater and longer-lasting effect on nasal congestion and caused fewer adverse effects than decongestant alone. We attributed these effects at the time to the ability of HPMC to act as a mucoadhesive agent.

This article describes an initial double-blind study to substantiate the hypothesis that a combination of a mucoprotective agent with pharmacologic therapy will enhance the effectiveness of the latter. The pharmacologic agent that was chosen was oxymetazoline nasal spray, a potent agonist of α_1-and α_2-adrenergic receptors with an almost instantaneous onset of action and proven benefits in the management of nasal congestion.[26,27]

METHODS

This was a double-blind, randomized, parallel group, one-center study of patients with moderately severe–to–severe persistent allergic rhinitis by comparing treatment with nasal decongestant (oxymetazoline) immediately followed by nasally applied HPMC or placebo. The study was performed out of the pollen season, between November 2013 and January 2014. The study's objectives and protocols were approved by the local investigational review board (University Hospital "Alexandrovska," Medical University Sofia, Sofia, Bulgaria; reference 344/09/10/2013). All participants gave signed informed consent, and the study was conducted in accordance with the current standards for good clinical practice.

Forty patients with a confirmed clinical history of persistent moderate-to-severe allergic rhinitis (17 men and 23 women; age 35 years [18÷49 years], mean [range]) were enrolled in the study. The sample size of 20 patients per group was calculated based on the 20% effect size, with a power of 80% and a level of significance of 0.05 (2-tailed) by using as proxy our previous work,[26] in which we measured nasal resistance for our sample size calculation. To be included in the trial, patients needed to have active moderately severe–to–severe persistent symptoms of allergic rhinitis with prominent congestion. Inclusion criteria also were a positive skin-prick test (wheal >3 mm diameter) to at least one of a panel of perennial allergens, including *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* feathers mixture, cockroach, cat, dog, *Cladosporium, Penicillium, Aspergillus, Alternaria* (Stallergenes, SA, Antony, France). Exclusion criteria encompassed individuals with seasonal allergic rhinitis or nasal polyposis, patients with serious chronic comorbidities, with flu-like symptoms during the past 30 days, pregnant or lactating women, and individuals unable to give informed consent were excluded.

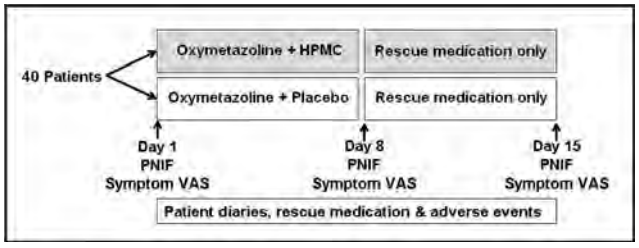

Figure 1. *Study protocol.*

The duration of the study for each individual was 15 days (Fig. 1). At enrollment, the patients were randomized at a 1:1 ratio by following a computer-generated sequence to be treated twice daily for 7 days with either 1 puff of oxymetazoline 0.05% nasal spray (Afrin, Schering Plough, Saint Clair, France), followed by either 1 puff of HPMC powder (NoAl, Nasaleze International Ltd., Douglas, Isle of Man, United Kingdom) (test treatment) or lactose powder from identically looking plastic bottles used as placebo (placebo treatment). During the following week, no regular treatment was given, and only puffs of oxymetazoline were allowed as rescue medication. The patients kept daily diaries of symptoms and rescue medication, and formal clinical assessments were made on days 1, 8, and 15. Peak nasal inspiratory flow (PNIF) was the objective assessment of the study. PNIF was measured by using a PNIF meter (In-Check Nasal; Clement Clarke International Ltd., Harlow, Essex, U.K.) on day 1 immediately before drug administration and at 1, 2, 5, 15, 30, 60, 120 180, 240, 300, and 360 minutes afterward. Similar measurements of PNIF were made on day 8, and a single measurement was taken on day 15.

A subjective assessment by patients of their symptoms was documented at their regular visits and daily in their diaries. During visits, overall discomfort due to allergic rhinitis symptoms was recorded on a 10-cm visual analog scale (VAS), which ranged from "no nasal symptoms" at 0 cm to "worst nasal symptoms ever" at 10 cm. The patients also rated, in their diaries, their stuffiness, rhinorrhea, itching, and sneezing by a symptom score between 0 (none) and 3 (worst). From this, the total nasal symptom score was calculated. The use of rescue medication and adverse events between days 8 and 15 were extracted from the patients' diaries.

Statistical Analyses

PNIF values were normally distributed, and differences within groups were analyzed by using Student's *t*-test for paired data and between groups by using the Student's *t*-test for unpaired data. Because the number of times that the patients resorted to rescue medication was not normally distributed, these results are given as median (25–75 percentiles), and group differences were assessed by using the Mann-Whitney *U* test. All tests

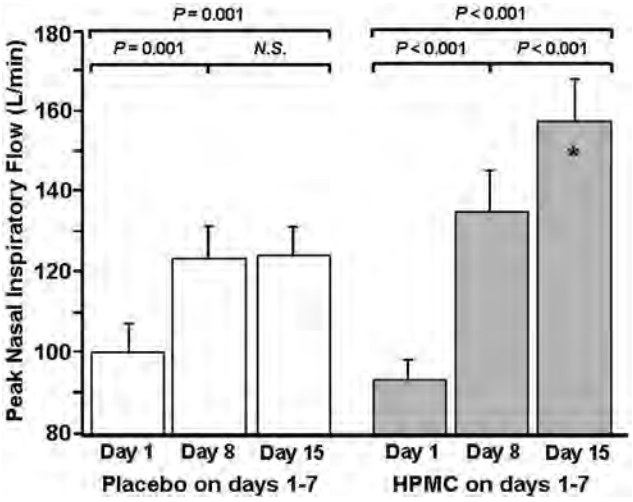

Figure 2. *Baseline PNIF values at days 1, 8, and 15. Each group contains results from 18 individuals. Significance values were calculated by using the Student's t-test for paired data. *The baseline PNIF of the patients treated with HPMC at 15 days was significantly ($p = 0.014$) higher than that of patients treated with placebo. This value was calculated by using the Student's t-test for unpaired data.*

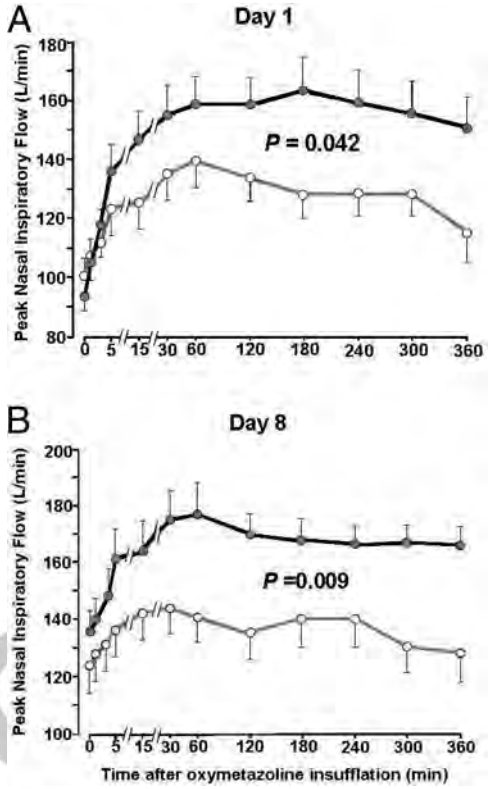

Figure 3. *PNIF values after insufflation of oxymetazoline on (A) day 1 and (B) day 8. The solid dots are the patients treated with HPMC and the open dots are those treated with placebo. Each group contains results from 18 individuals. Significance values were calculated by using the Student's t-test for unpaired data.*

were 2-tailed, and the threshold for statistical significance was set to $p < 0.05$.

RESULTS

Of the 40 patients recruited into the study, two dropped out from the test-treatment group, one for noncompliance and the other for headache; and two dropped out from the placebo group, one for concomitant disease and the other for a severe reaction to a cat. The remaining 36 patients completed all three visits and were included in the final analysis. Shown in Fig. 2, are the baseline PNIF values before oxymetazoline insufflation at the start of the study (day 1), after 7 days of treatment with HPMC or placebo (day 8), and after a further 7 days of only rescue medication (day 15). The results in the HPMC group showed a 26% increase ($p < 0.001$) in PNIF at day 8 and a further 21% increase ($p < 0.001$) at day 15. The total increase in PNIF between days 1 and 15 was 53% ($p < 0.001$). In the placebo group, there was a 24% in PNIF ($p < 0.001$) at day 8 but no further increase at day 15. There was no significant difference between groups on days 1 and 8, but the PNIF of the HPMC group was 26% greater ($p = 0.014$) than that of the placebo group on day 15.

The changes in PNIF after insufflation of oxymetazoline on days 1 and 8 are shown in Fig. 3. On both days, the effects of oxymetazoline were greater in patients also inhaling HPMC compared with placebo. On day 1, the area under the curve for the 360 minutes of observations for oxymetazoline was 20% greater in patients who received HPMC compared with those who received placebo (56,366 ± 14,910 sq. units versus 46,818 ± 12,080 sq. units; $p = .042$). On day 8, the area under the curve for oxymetazoline was 23% greater in the HPMC group than in the placebo group (60,855 ± 13,691 sq. units versus 49,350 ± 11,211 sq. units; $p = 0.009$).

The VAS assessments by patients on days 1, 8, and 15 of nasal congestion, rhinorrhea, itching/sneezing, and total nasal symptoms are shown in Table 1. In the placebo group, there were significant improvements in nasal congestion, rhinorrhea, and total nasal symptoms at day 8 but little or no further improvement thereafter. In the HPMC-treated group, there were similar improvements in these parameters at day 8. However, in this group, these improvements appeared to continue up to day 15. With total nasal symptoms, the improvement between days 8 and 15 was statistically significant ($p = 0.006$). There were no statistically significant differences between the groups. A similar pattern of results was obtained from analysis of the patients' diaries on days 1, 8, and 15 of the study. Of special mention is nasal itching/sneezing. With this symptom, there was no significant improvement in the placebo group. However, in the HPMC-treated group, there were significant improvements, of 56% ($p = 0.012$) and

Table 1 **The VAS assessments by patients on days 1, 8, and 15 of nasal congestion, rhinorrhea, itching/sneezing, and total nasal symptoms**

Symptom	Baseline VAS, (mean ± SE)	VAS (mean ± SE); % Reduction at 8 days	VAS (mean ± SE); % Reduction at 15 days
Congestion			
Placebo	56.6 ± 4.9	43.6 ± 5.7; 23 $p = 0.04$	47.2 ± 5.8; 17 N.S.
HPMC	65.0 ± 4.1	42.6 ± 6.4; 35 $p = 0.004$	36.2 ± 6.7; 44 $p < 0.001$
Significance of difference between groups		N.S.	N.S.
Rhinorrhea			
Placebo	51.9 ± 7.7	43.6 ± 5.7; 39 $p = 0.003$	47.7 ± 5.8; 23 $p = 0.04$
HPMC	59.7 ± 6.2	37.9 ± 6.9; 36 $p = 0.012$	32.5 ± 7.3; 46 $p = 0.013$
Significance of difference between groups		N.S.	N.S.
Itch/sneezing			
Placebo	27.7 ± 7.1	24.3 ± 5.9; 12 N.S.	21.2 ± 5.6; 23 N.S.
HPMC	32.8 ± 7.0	14.3 ± 4.5; 56 $p = 0.012$	8.5 ± 3.0; 74 $p = 0.013$
Significance of difference between groups		N.S.	N.S.
Total symptoms			
Placebo	68.4 ± 5.1	39.6 ± 5.8; 42 $p < 0.001$	41.7 ± 5.7; 39 $p < 0.001$
HPMC	70.2 ± 5.2	43.7 ± 6.0; 38 $p = 0.002$	34.2 ± 6.5 51% ($p < 0.001$)
Significance of difference between groups		N.S.	N.S.

SE = standard error; N.S. = not significant.
Significance values within groups were calculated by using the Student's t-test for paired data and between groups by using the Student's t-test for unpaired data.

74% ($p = 0.013$) at days 8 and 15, respectively. Also, the improvement between days 8 and 15 was statistically significant ($p = 0.02$). However, the differences between the treatment groups failed to reach statistical significance, mainly because of the number of patients who gave low itch/sneezing scores at all times (Fig. 4).

The median (25–75 percentiles) numbers of times the patients resorted to escape medication, puffs of oxymetazoline, during days 8–15 of the study were 8.5 (1–15.5) for the HPMC group and 16 (11.5–16) for the placebo group. There was a wide variability between the patients, which precluded the difference between groups being statistically significant ($p = 0.076$). However, 13 of the 18 patients who received placebo on days 1–7 took more than 2 puffs of oxymetazoline per day compared with only five patients treated with HPMC ($p = 0.04$, Fisher exact test). Adverse events were mild and infrequent. In the HPMC group, two patients had headache, two had intermittent coughing, one had common cold symptoms, and one had dysmenorrhea. In the placebo group, three patients had headache and one had flu-like symptoms. None of the events were persistent or considered to be drug related.

DISCUSSION

The primary objective of this study was to substantiate the hypothesis that a combination of a mucoprotective and mucoadhesive agent with pharmacologic therapy will enhance the effectiveness of the latter. This objective was achieved with the finding that an area under the curve for 6 hours of observations after oxymetazoline insufflation was significantly greater on the first and eighth days of HPMC therapy compared with placebo. In addition, there was a trend for continual improvement of rhinitis symptoms in the week after HPMC treatment but not in those who received placebo.

There are two possible mechanisms by which HPMC may act to enhance the effects of oxymetazoline therapy. The first is a purely physical one. Because HPMC

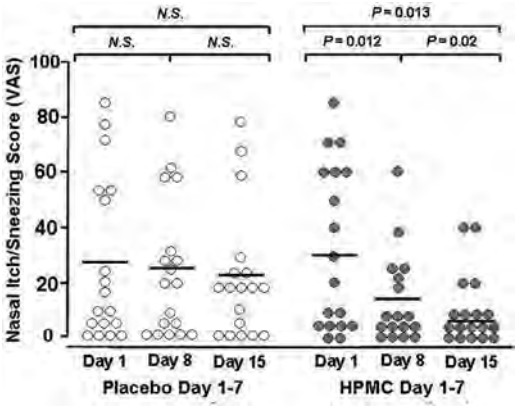

Figure 4. *Nasal itch/sneezing VAS scores on days 1, 8, and 15 of the study. The solid dots are the patients treated with HPMC, and the open dots are those treated with placebo. Each group contains results from 18 individuals. Significance values were calculated by using the Student's t-test for paired data. There were no statistically significant differences between the groups.*

was insufflated immediately after oxymetazoline, the formation of a gel layer above the decongestant would be likely to reduce its clearance from the nasal mucosa and thereby increase its effectiveness. Such effect would occur even with the first dose, as was seen on day 1 of the study. This was actually the starting point of our reasoning when planning the study. The second mechanism would be for HPMC to create an improved barrier to allergen penetration into the nasal mucosa. In the longer term, it would reduce the inflammatory events of the mucosal barrier thereby reducing nasal reactivity.[28–30] This activity is evidenced particularly by the increased baseline PNIF, an index of nasal congestion,[31] up to 15 days in the HPMC-treated group.

Nasal congestion is recognized to be the most important symptom in terms of impact on quality of life.[32,33] We have identified it as the prominent symptom that motivates patients to seek medical advice.[34] We also were aware that, in real life, people are driven by the discomfort due to a "stuffy nose" to buy over-the-counter decongestants to alleviate their discomfort oblivious of any consequences.[35–37] We reasoned that choosing the "decongestant" design to improve the benefits HPMC uses as a mucoadhesive agent, we could achieve longer intervals between the oxymetazoline applications.

In designing this study, we were cognizant of the Allergic Rhinitis and its Impact on Asthma guidelines recommendation[17] that nasal decongestants should be given only in short courses because, when used for more than 10 days, these lead to rebound congestion and rhinitis medicamentosa[38,39] However, doubt has been cast on the validity of this recommendation because neither the cumulative dose of nasal decongestants nor time period needed to initiate rhinitis medicamentosa has been conclusively determined.[40] Furthermore, the 2010 revision of the Allergic Rhinitis and its Impact on Asthma guidelines[17] grades the evidence related to the application of decongestants in allergic rhinitis as weak and lists this issue as unmet need for future research. In our study, we could find no evidence of rebound congestion or rhinitis medicamentosa after usage of oxymetazoline for 7 days and even 15 days if rescue usage is taken into consideration.

The primary subjective assessments of rhinitis symptoms were made by using VAS. Extensively investigated and validated in allergic rhinitis, VAS has been shown to correlate significantly with disease severity and quality of life.[41] In addition, it has been proven useful in the assessment of the effect of pharmacotherapies on symptoms.[42] Nasal congestion, rhinorrhea, and total nasal symptoms all improved in both groups at 8 days but continued to improve only in the HPMC group thereafter. Further evidence that individuals in the HPMC group felt better in the 8–15 day period was their smaller usage of rescue medication compared with the placebo group. Particular mention should be made of itching/sneezing, which was greatly improved by HPMC but not by oxymetazoline alone. Unfortunately, the study was powered for identifying statistical differences between the objective measurements of PNIF rather than the more variable subjective VAS assessments. Consequently, although there were definite trends for patients having less-severe symptoms when taking HPMC, differences between the groups failed to reach statistical significance.

As one might expect of a proof-of-concept study, our work has limitations related to the small sample size and the short duration of the observation. Furthermore, one might question the lack of a study arm with HPMC alone: initially we focused on the potential of HPMC as a mucoadhesive agent and did not anticipate the longer-lasting benefits, which we registered in the week after the discontinuation of treatment. Consequently, our work raised questions, which now need to be addressed by further research:

- Is the synergy offered by HPMC also valid for the other nasal symptoms? The answer to this question requires different study designs.
- Is the synergy offered by HPMC also valid for the other nasally applied drugs? This is a tantalizing possibility because it opens the door for increased effectiveness of drugs for local treatment, such as antihistamines, nasal corticosteroids, antimuscarinic agents, and combining these under the gelatinous HPMC mucosal cover.

In conclusion, our proof-of-concept study demonstrated that micronized HPMC powder enhances the decongestant effect of nasal oxymetazoline in patients with allergic rhinitis. It also showed that 1 week of such regular combined treatment reduced nasal con-

gestion in these patients, and this effect carries over for another week after its discontinuation. Thus, HPMC appears to be a safe and inexpensive adjunct to the therapy of allergic rhinitis.

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Real-Life Study on the Effect of Micronized Cellulose Powder as Add-On to Intranasal As-Needed Treatment of Subjects with Pollen Allergic Rhinitis

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Real-Life Study on the Effect of Micronized Cellulose Powder as Add-On to Intranasal As-Needed Treatment of Subjects with Pollen Allergic Rhinitis

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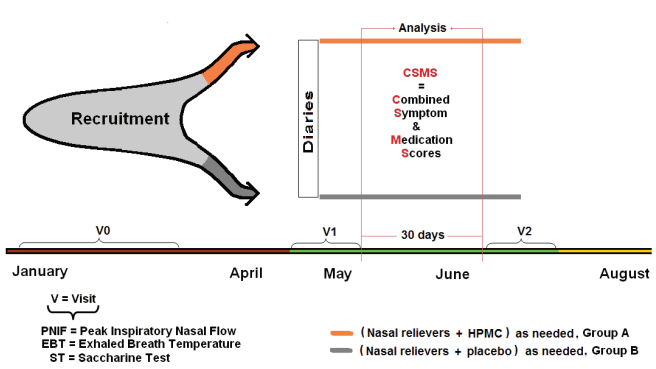
P: L41

BACKGROUND

The use of symptom relievers on demand is the most common approach in real life for treating exacerbations of allergic rhinitis. We have demonstrated previously that commercially available micronized *hydroxyl-propyl-methyl-cellulose powder (**HPMC**)* applied after local decongestant significantly enhances its action in subjects with persistent allergic rhinitis. This study investigated whether this beneficial effect of HPMC translates into clinical benefits in a real life setting.

METHODS



METHODS

Thirty-six symptomatic seasonal allergic rhinitis patients (25 male, median age 31 years) were instructed to treat their bothersome symptoms locally with intra-nasal:

- ***xylometazoline*** and/or

- ***azelastine*** and/or

- ***mometasone***

- or, if symptoms persevered, with oral ***bilastine*** or ***prednisolone***.

Patients were randomized to "seal" the effect of each local application with one puff of either HPMC or placebo (lactose powder). They completed diaries with symptom scores (0-3), and medications (1 score for any drug application); combined symptom and medication scores (**CSMS**) were calculated and used as primary outcome for the analysis. A sequence of 26 days with entries from all 36 patients at the peak of the pollen season was picked to reduce variability.

Objective measurements of Peak Nasal Inspiratory Flow (**PNIF**), measure of the level of nasal congestion, and Exhaled Breath Temperature (**EBT**), surrogate marker of airway inflammation, were made before and after treatment.

RESULTS

Fig. 1. CSMS before/after treatment (differeces)

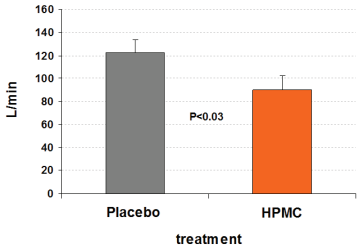
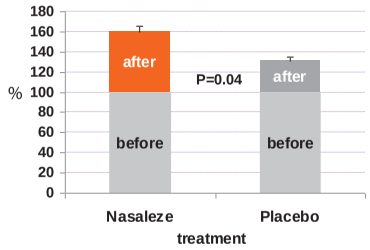


Fig. 2. PNIF before and after treatment



1. CSMS were significantly (P=0.03) lower in the HPMC group, 90±9 vs. 122±12, (mean ± SEM) (Fig. 1).
2. Following treatment PNIF increased in the HPMC arm by 60% vs. 31% in the placebo one (Fig. 2). The before vs. after treatment differences were in favor of the HPMC for both PNIF (P=0.01) and EBT (P=0.007).

CONCLUSIONS

In real life micronized cellulose (HPMC) applied following rescue local medications decreases symptoms and overall medication use and reduces nasal congestion/inflammation of subjects with pollen allergic rhinitis.

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Clinical efficacy of nasal cellulose powder for the treatment of allergic rhinitis

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Clinical efficacy of nasal cellulose powder for the treatment of allergic rhinitis

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Abstract Objective: To investigate the clinical efficacy of nasal cellulose powder for the treatment of allergic rhinitis. **Method:** Thirty-six cases of patients with allergic rhinitis were randomly divided into control group and experimental group, 18cases in each group. The control group was treated with physiological sea water and the experimental group with nasal fibrous powder. In 14, 28 days after drug evaluation in patients objective and subjective symptoms and signs improved nasal function (nasal airway resistance, the sense of smell) was compared. **Result:** The experimental group and the control group of subjective symptoms and objective nasal function were improved, but the experimental group was significantly higher than that of control group, the difference was statistically significant ($P<0.05$); Two groups of patients had no adverse reaction occurred. **Conclusion:** The clinical curative effect of Nasal cellulose powder used in the treatment of allergic rhinitis is distinct, without adverse reactions, and is conducive to improving patient stuffy nose, nasal itching, sneezing and other symptoms and improve the patients quality of life, is worth clinical use.

Key words rhinitis, allergic; nasal cellulose powder; nasal airway resistant; VAS scores; olfaction

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After the body contact allergens, the nasal mucosa non infectious inflammatory diseases, mainly caused by IgE. The main symptoms are nasal congestion, nasal itching, sneezing and a large number of water samples, and some patients were with asthma, allergic conjunctivitis, etc. In this study, 36 patients with AR were randomly divided into 2 groups. Physiological sea water and nasal cellulose powder were used for treatment, the results were reported as follows.

1 Data and methods

1.1 clinical data

According to the AR guidelines for diagnosis and treatment classification criteria of otolaryngology head and neck surgery rhinology group of Chinese Medicinal Association (2009,Wuyishan), and ARIA classification and grading criteria, selected 36 patients with allergic rhinitis, who were treated in our outpatient clinic from February to September, 2014. The patients were divided into control group and experimental group randomly, 18 cases in each group. There were 8 male cases and 10 female cases which the ages were from 19 to 40, the average age was (32.5 ± 4.1) in the control group, and the course of disease was 3 to 8 years; while there were 5 male cases and 13 female cases which the ages were from 18 to 49, the average age was (34.5 ± 4.4) in the experimental group, and the course of dis-

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ease was 2 to 10 years. Inclusion criteria: nasal symptoms (stuffy nose, nasal itching, sneezing, watery nasal discharge) was more than or equal to 2, skin prick test for clear allergic original pollen (+ +) or more. Exclude pregnancy, lactation women, non AR patients (not detectable allergen), serious deviation of nasal septum, nasal polyps, sinusitis, chronic hypertrophic rhinitis who were in the period of onset of asthma, severe organic heart disease, hypertension, stop nasal inhalation and oral antihistamines, corticosteroids and the patients who were anti leukotriene drugs for more than 3 weeks. This study had been approved by the medical ethics committee of our hospital, and all the patients signed the informed consent.

1.2 Methods

Control group: the patients with nasal were treated with physiological sea water partly, 3 times for each side of the nasal spray, 3 times a day. Experimental group: the patients were treated with fibrous powder partly, 3 times for each side of the nasal spray, 3 times a day[1].

1.3 Evaluation method of curative effect

1.3.1 VAS score After the division, basic information was collected in a unified way, nasal symptoms (including nasal congestion, nasal itching, sneezing, runny nose) and visual analogue scale (visual analogue scale, VAS) score [2], to take the average score of 4 items. To make the VAS to be a 10cm-long caliper, which was labeled 0 to 10 from left to right, respectively. 0 pointed for asymptomatic, 10 pointed for symptoms of extremely serious. Intermediate figures showed different levels, and evaluated the severity of patients and the corresponding numerical record, before the treatment and after 14, 28d's evaluation, respectively.

1.3.2 Nasal resistance measurement The German production ATMOS300 rhinomanometry instrument was taken, according to the Clement (1984) description of anterior rhinomanometry, to make the seat, quiet breathing, and the examination room temperature was controlled at 18-22 degree centigrade, while the humidity was controlled in 50%-70%. After the examination environment adapting for 30 min, the initial detection of subjects was taken. The average value of each position determination of 3 measurements were taken before the treatment and 14 and 28 days after treatment. [3-4]

1.3.3 Olfactory function determination Take the T&T Standard olfactory detection. The sniffing dilution factor was a quantitative analysis basis, selected 5 kinds of bromine, and each has 8 concentrations. Each stage was 5, 4, 3, 2, 1, 0, -1, -2, and 0 was the normal olfactory threshold concentration, the highest concentration was 5, while the lowest was 2. During the examination, the filter paper with the width of 0.7cm, the length of 15 cm was taken, dip the snuff reagent. Let the subjects sniff, a filter paper strip was for each bromine, each dip was 1cm. 5 kinds of bromine olfactory threshold average value was made for the bromine olfactory threshold. The results were recorded in the name of a bromine as the abscissa, and the concentration of bromine was as the ordinate on the olfactory sheet, the curve was used to reflect olfactory threshold level.

1.4 statistical treatment

Using SPSS 19.0 software for statistical analysis, the obtained number was taken by X square test and t test, $P < 0.0\ 5$ for the difference was statistically significant.

2 Results

Comparison of VAS scores between 2 groups of AR patients before and after treatment (Table 1).

Table 1 Comparison of VAS scores between 2 groups of AR patients before and after treatment

Group	Before treatment	After treatment for 14 days	After treatment for 28 days
Control	6.8 ± 1.20	6.2 ± 0.80	5.9 ± 0.15
Experimental	7.0 ± 0.90	4.3 ± 1.12[1)]	2.8 ± 0.75[1)]

Compared with pre-treatment, [1)] P<0.05.

Nasal resistance measurement results in 2 groups of patients before and after treatment in table 2.

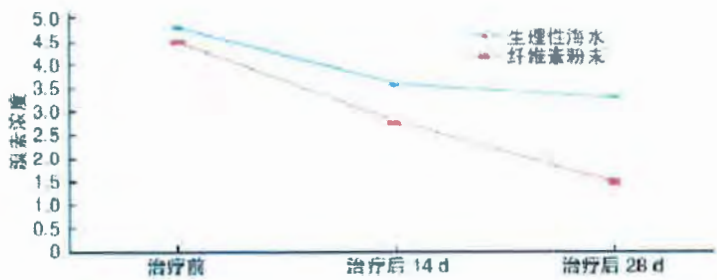
Olfactory function determination results in 2 groups of patients before and after treatment in picture 1.

Table 2 Nasal resistance measurement results in 2 groups of patients before and after treatment

kPa·s/L

Group	Before treatment	After treatment for 14 days	After treatment for 28 days
Control	0.67 ± 0.06	0.57 ± 0.04	0.52 ± 0.03
Experimental	0.65 ± 0.90	0.48 ± 0.08[1)]	0.30 ± 0.05[1)]

Compared with pre-treatment, [1)] P<0.05.



溴素浓度--the concentration of bromine
治疗前--Before treatment
治疗后 14d--After treatment for 14 days
治疗后 28d--After treatment for 28 days
生理性海水--physiological sea water
纤维素粉末--fibrous powder

Pic 1 Olfactory function determination results in 2 groups of patients before and after treatment

3 Discussion

The World Allergy Organization (WAO) survey indicated that 2.5 billion people were suffered from allergic diseases annually[5] and the patients were increasing year by year, wherein AR was very common allergic disease in clinic, which may be caused by air pollution, increasing SO_2 concentration, diet structure changes factors, and it seriously affected the patient's quality of life. For example, it could

affect sleep, leading to decline in work efficiency and learning memory [6]. It could be complicated with allergic inflammation, allergic sinusitis, nasal polyps, secretory otitis media, or cause allergic asthma, which was one of the important risk factors.

At present, the treatment principle of AR is to try to avoid contact with allergens, the correct use of anti-histamine drugs and glucocorticoids, if conditions were feasible, specific immunotherapy could take. The clinical commonly used treatments were corticosteroids and oral antihistamines for nasal cavity, which could improve the nasal symptoms of AR patients, but there is a certain degree of side effects. In this study, the control group used physiological sea water, could be directly cleaned the nasal cavity, to a certain extent, reduced the respiratory tract inflammation, and improved blood vessel leakage, mucosal edema[7], after treatment, the seasonal AR patients with nasal itching, nasal congestion and other symptoms had a certain improvement, but before and after treatment, the VAS score, nasal resistance and olfactory function were not significantly improved, the difference was not statistically significant. However, it has been reported that the usage of physiological sea water (75ml / AR) nasal irrigation could effectively improve the symptoms of the patients, improve the quality of life of patients. In the experimental group, the nasal cavity was inhaled with fibrous powder, and the powder was injected into the nasal cavity with a simple injection device. Its mechanism of action is the contact of fibrous powder and nasal mucosa of water vapor, then a gel layer is formed, and nasal mucosa on the protective barrier could stop the contact of inhalation allergen and mucosal. The gel layer and normal mucous similar, can help maintain clean air to the lungs in the conveying [8-10]. In the treatment after 1 ~ 2 weeks which reduced the severity of symptoms in allergic rhinitis, VAS score decreased significantly, nasal resistance, olfactory function were improved significantly, effectively alleviated the symptoms of sneezing, nasal itching, large amounts of water like tears, and almost no adverse reaction. In summary, fibrous powder into the nasal cavity to prevent allergic reactions to pollen and other irritants, AR treatment is safe and effective, which is a pharmaceutical preparation of safe, natural alternatives and it could also be used as prevention and treatment for children and pregnant AR women as the recommended activities. But larger samples and longer studies are needed to be confirmed.

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A Double Blind Placebo Controlled Study Documenting the effect of Nasally Applied Cellulose-Derived Powder in Subject Sensitized to Grass Pollen

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ABSTRACT

BACKGROUND: Nasally applied hydroxy-propyl-methyl cellulose (HPMC) powder, acting as a mucosal barrier against particulate matter, has been used increasingly since 1994. Clinical and experimental evidence has accumulated about its effectiveness in preventing symptoms in allergic rhinitis sufferers. The aim of our study was to further explore the efficacy of HPMC in reducing the severity of different symptoms in subjects sensitized to grass allergens during the pollen season and its ability to render them symptom-free.

METHODS: In a double blind placebo controlled study, 107 subjects (18- 40 years of age) sensitized to grass pollen were randomized to apply nasally HPMC powder (n554) or placebo (n553) 3 times daily for 4 weeks. Daily severity of nasal congestion, rhinorrhea, sneezing, lower airway and ocular symptoms (ranked from 1 to 6) were reported as text messages every evening.

RESULTS: The mean of severity scores were roughly halved in the active group for both nasal (p<0.0001), ocular (p<0.0001) and bronchial symptoms (p=0.0015); the inter-group differences increased during the study period for nasal and bronchial symptoms (both p<0.0001). The number of subjects without nasal symptoms increased in the course of time (group difference p<0.0001) and the number of subjects without other symptoms was about twice as high as in the placebo group over the entire period (p<0.0001).

CONCLUSIONS: HPMC powder provided extensive protection against all symptoms from both upper and lower airways in subjects with clinical allergy to grass pollen. It reduced the severity of symptoms and significantly increased the number of symptom-free subjects.

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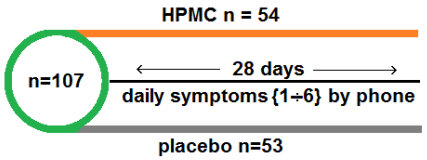

Fig. 1. Study design

RESULTS

The number of subjects without nasal symptoms increased in the course of time (group difference p<0.0001) (Figure 2) and the number of subjects without other symptoms was about twice as high as in the placebo group over the entire period (p<0.0001).

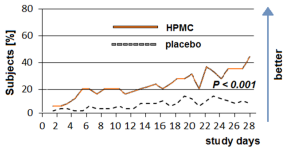

Fig. 2 Subjects without nasal symptoms over time

RESULTS

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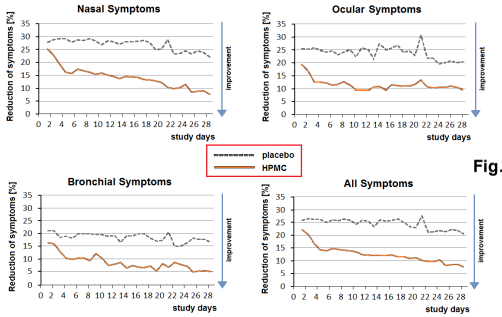

Fig. 3 Reduction of symptoms over time (in % of potential maximum score)

CONCLUSIONS

HPMC powder provided extensive protection against all symptoms from both upper and lower airways in subjects with clinical allergy to grass pollen. It reduced the severity of symptoms and significantly increased the number of symptom-free subjects.

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