ORIGINAL ARTICLE

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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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 (Placebo 7.29, Active 6.07, p = 0.033) and specifically for running nose (Placebo 2.56, Active 2.03, 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 2.03, placebo 2.56, p = 0.017) and specifically for running nose (active 7.29, placebo 6.07, p = 0.033).

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 ($\leq$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.

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 $\pm$ 20% ($\pm$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 $\pm$ 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 $\pm$ 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 $\pm$ 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
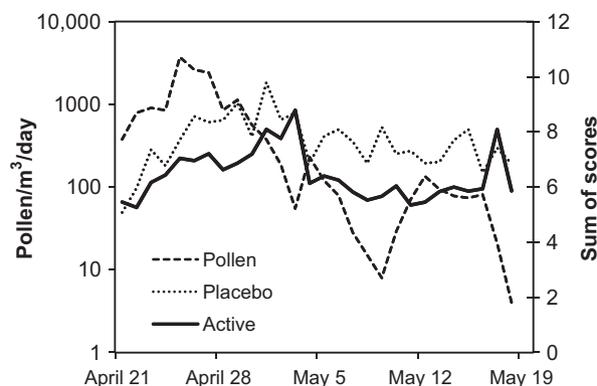
Table 1 Sum of symptoms scored retrospectively at night. Figures with significant reduction of scores are marked in bold.

Question	Treatment	n	Mean	p-value
(a) 2 days after pollen counts $\leq$ 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 Sum of nasal symptoms day by day in respective groups. Daily pollen concentrations in log scale.

(a) Birch *(Betula)* pollen
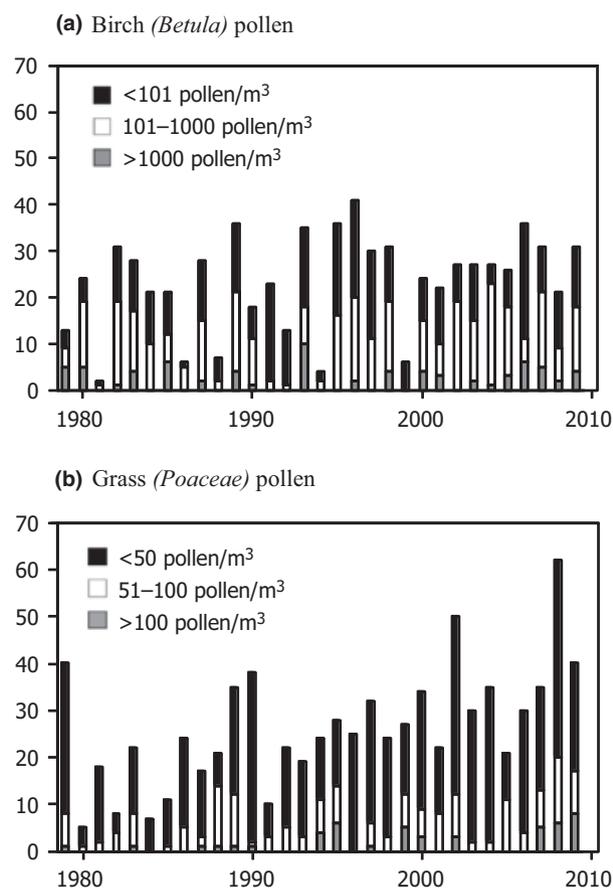

(b) Grass *(Poaceae)* pollen

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

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