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REVIEW

Methyl-cellulose powder for prevention and management of nasal symptoms

Todor A. Popov [a], Nils Åberg[b], Jean Emberlin[c], Peter Josling[d], Natalia I Ilyina[e], Nikolai P Nikitin[f] and Martin Church[g]

[a]Clinic of Allergy and Asthma, Medical University Sofia, Sofia, Bulgaria; [b]Department of Paediatrics, University of Gothenburg, Gothenburg, Sweden; [c]Allergy UK, Sidcup, UK; [d]Herbal Research Centre, Battle, UK; [e]State Science Centre, Russian Federal Medical Biological Agency, Moscow, Russia; [f]Clinical Accelerator, Douglas, UK; [g]Allergie-Centrum-Charité, Universitätsmedizin Berlin, Berlin, Germany

ABSTRACT

Introduction: HPMC-p, an inert micronized powder form of hydroxy-propyl-methyl-cellulose, when insufflated nasally, provides a natural barrier against pollen allergens and noxious agents. This overview assesses the efficacy and safety of this patented powder product and delivery system without an analogue among the cellulose derivatives.

Areas covered: Twenty-six studies with HPMC-p were critically appraised to obtain an updated characteristic of the product. Most studies assessed the efficacy of HPMC-p as a nasal barrier enforcing measure: one experimental setup evaluated its ability to prevent or delay the diffusion of allergen through it, two clinical studies used allergen provocation tests, and the remaining relied on clinical criteria in open real world or placebo controlled designs. Two studies checked if HPMC-p could enhance the efficacy of drugs applied nasally to treat local symptoms. The studies, using either nasal allergen challenge or natural exposure of patients to environmental allergen, support the hypothesis that HPMC-p possesses barrier enforcing properties. Also, acute and clinical experiments indicated that intra-nasal application of HPMC-p following local relief medications enhances their ability to suppress symptoms and reduces their long-term use.

Expert commentary: Nasal insufflation of HPMC-p provides a mucosal barrier, reducing the nasal symptoms and enhancing the effects of local relief medications.

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Methyl-cellulose; hydroxy-propyl -methyl-cellulose; micronized powder; allergic rhinitis; prevention; mucoadhesion; nasal drugs efficacy enhancement

1. Introduction

1.1. Allergic rhinitis and allergen avoidance

Allergic rhinitis (AR) is the most common chronic noncommunicable disease of the human population. While it may not be life threatening, it interferes with the daily routine and sleep. AR is also associated with the risk of asthma development or worsening [1]. Therefore, the goal of AR management is to prevent and relieve symptoms, targeting also the underlying local and systemic inflammation [2]. A key component of the strategy to keep the condition of the nose under control is allergen avoidance. However, instructing the patients to avoid allergens does not help much in the case of ubiquitous allergens. An alternative to confinement in a sealed allergen-free environment would be to cover the nasal mucosa with a protective layer of inert material. Such an approach is referred to as 'barrier-enforcing measures'[3].

The nose is the gatekeeper of the lungs: it is the first filter to remove some of the dust particles contained in the ambient air. Elegant studies have demonstrated that there are interreactions between upper and lower airways, meaning that any adverse changes in the nasal mucosa could reflect negatively on the structures inside the chest [4]. Generally, the nasal mucosa, which is the first line of resistance against airborne allergens and irritants, plays a leading role in the development of sensitization to allergens and inflammatory reactions. The local inflammation in the relatively small area of the nasal cavity may spill over to the paranasal sinuses, the lower airways and may affect the body as a whole. Keeping the nose free of inflammation is a prerequisite for a healthy lung and freedom from allergies [5].

The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative was started at the turn of the century with the publication of a detailed guideline on the diagnosis, classification, prevention, and treatment of rhinitis disorders and their link to asthma and other pathologies [6]. ARIA is constantly evolving, setting out a practical platform for AR management putting together in a structured way all the information which has emerged as a result of decades devoted research.

An important message stemming from ARIA states that all patients with AR should be instructed to try to avoid allergens. Precluding the contact between the nasal mucosa and the harmful agents in the ambient environment which attack it (allergens, irritants, indoor and outdoor pollutants, microorganisms) is the simplest and most natural approach to preventing nasal symptoms. This can be achieved by seclusion in places devoid of the offending agents, which is not feasible for people leading an active life. Alternatively, so-called 'barrier-enforcing' measures can be implemented, which directly protect the nasal mucosa and block the contact with potentially harmful substances such as allergens and particulate matter. In this context, barrier-enforcing measures may be viewed as a means to achieve allergen avoidance and all patients may be

CONTACT Todor A. Popov ted.popov@gmail.com Clinic of Allergt & Asthma, Alexander's University Hospital, 1, St. Georgi Sofiyski St. BG-1431, Sofia, Bulgaria.

recommended to use such an approach. Ideally, if implemented properly, this strategy could make the use of any other therapeutic action unnecessary. Attempts have been made to use different substances as barrier enhancers. These include white vaseline [7,8], pollen blocker cream [9], lipid-based ointment [10,11], microemulsion [12,13], liposomal formulation [14], seawater gel [15].

Many of the listed approaches had not been progressed to the stage of commercialization. For instance, a study using a product of the broad variety of cellulose derivatives formulated as topical liquid nasal spray has not proven efficacious in a nasal challenge test model [16].

In a real world, though, rhinitis symptoms tend to recur again and again, making it necessary to resort to therapeutic means to abate them and to suppress the underlying mucosal inflammation by means of appropriate drugs (many of them applied intranasally) in line with the ARIA guidelines. In a recent appraisal, some of the leading authors of ARIA have reviewed the newest therapeutic options for the treatment of AR and have listed cellulose-derived powders [17] among the emerging pharmaceutical and biological preparations. Among these, microcrystalline *Hydroxypropyl-methylcellulose* has been developed into a patented formula and patented delivery device and licensed in the management of AR.[1] It presents a smart treatment option which is now commercially available and is beneficial as both a barrier enforcing measure and as a vehicle to enhance the effect of nasally applied drugs in line with the ARIA recommendations for the management of AR (Figure 1).

1.2. Introduction to the compound

Hydroxypropyl-methylcellulose (HPMC) ethers belong to an extensive family of water soluble polymers that bind, retain water, thicken, form films, and lubricate when applied on skin or the mucosal surface [18]. A synonym for HPMC is *Hypromellose*.

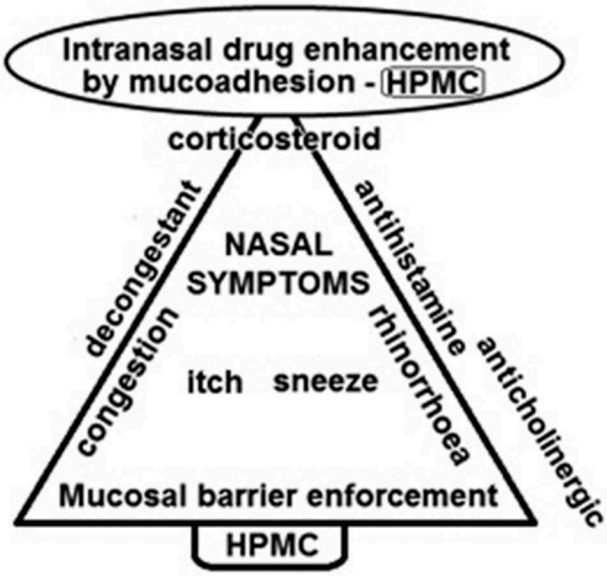

Figure 1. Diagnosis and management of AR (created using information from [2]).

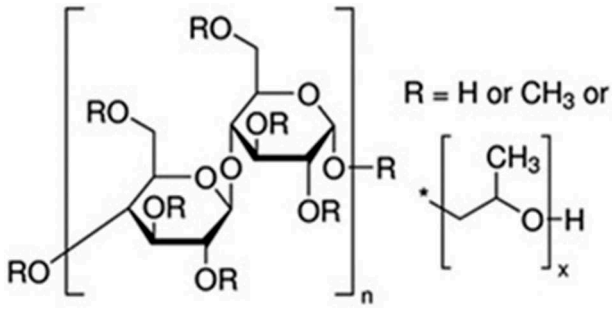

Figure 2. The basic structural element of the chain of the HPMC polymers.

These are semisynthetic, inert, viscoelastic polymers derived from cellulose, the most abundant polymer in nature, and have an exceedingly broad variety of applications. The core building block of HPMC is an anhydrous glucose ring to which hydroxypropyl and methyl residues are linked by ether bonds (Figure 2).

HPMC is white or pale white cellulose powder or particles. Many chemical types of cellulose, each available in different grades and physical forms are used as thickeners, binders, film formers, surfactants, lubricants, protective colloids, and emulsifiers. For the purpose of 'mucosal barrier' in the nose and 'enhancer of nasal drugs,' a specifically selected brand is applied by means of a patented delivery system in the form of microcrystalline powder [19]. Thus, HPMC-p is the only cellulose derivative marketed as a powder, whose efficacy, effectiveness, and safety are analyzed in this overview. It is licensed as a Class 1 Medical Device throughout the EU and most of the World apart from the USA where it is registered as a Class II Medical Device with the FDA.

1.3. Safety

Being a synthetic modification of the natural polymer, it has an excellent safety profile. It is approved by FDA as GRAS[2] and in the EU as both a direct and an indirect food additive. Based on the no-observed-adverse-effect level (NOAEL) of 5000 mg/kg body weight/day from a 90-day feeding study in rats, a tolerable intake for ingestion of HPMC by humans of 5 mg/kg body weight/day is posited and, as such, is more than 100-fold greater than the estimated current consumption of 0.047 mg/kg body weight/day [20].

2. Clinical studies

Historically, it was the mucosal barrier approach which was tested first clinically. The mere idea sparkled from an observation in the 1990s that despite working in rather dusty environment, the employees in a factory making cosmetic facemasks utilizing HPMC as an ingredient never sneezed; after 'sniffing' some of the powder, a person with flourishing symptoms of nasal allergy experienced dramatic relief. Subsequently, the substance was developed into a patented microcrystalline product with standardized characteristics and a specialized delivery device was created, which will be referred to as

HPMC-p further down this article. A review was published in 2007 summarizing the first trials that were done [21].

2.1. Evidence supporting the effect of HPMC-p as 'barrier-enforcing measure'

The first proof-of-concept study was performed in spring 2003 [22]. It was designed as an open-label trial to determine whether HPMC-p could prevent or reduce classic hay fever attacks from occurring among volunteers with a history of seasonal AR during the pollen season. The study was started ahead of the pollen season in the Midlands of the UK with the recruitment of 102 volunteers with a mean age of 44 years, of whom 36 were women. Volunteers filled in questionnaires with their reflective assessment of their seasonal symptoms and relieving medications in the previous year. Patients assessed their general well-being on a daily basis in diaries using a 5-point scoring system (1 = worst, 5 = best). Patients were allowed to take also oral antihistamines and ocular cromolyn solution as eye drops. The effect of treatment was also graded from 1 (not effective at all) to 5 (very effective) for drugs as for HPMC-p. The analysis took into consideration the daily pollen counts in the area and showed that the overall average 'well-being' score of subjects on HPMC-p alone was 3.85 (out of a maximum 5), which was interpreted as ability of the preparation to control hay fever quite 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 hay fever attacks throughout the study period and most graded HPMC-p as more effective and with fewer side effects than the pharmaceutical treatments with which they had experience.

This pilot study was followed by double-blind placebo-controlled randomized trials evaluating the ability of HPMC-p to suppress natural exacerbations in patients with seasonal AR during the pollen season.

Emberlin *et al*. conducted a double-blind, placebo-controlled study on 97 adult hay fever sufferers from the UK, over the grass pollen season of 2004 [23]. Participants were assigned randomly to two groups: on HPMC-p (n = 47, 19 males) and on placebo/powder lactose/(n = 50, 21 males). Subjects were matched by age and gender. 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 analyzed in relation to pollen counts. Significant differences were found in the amounts of rescue medication taken by the active and placebo groups: more people in the placebo group took rescue treatments than those in the active group ($p < 0.05$). No significant differences were found 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. The authors concluded that regular use of HPMC-p during the pollen season allowed reduction of the amount of rescue medication taken. In the placebo group, the amount of rescue medication taken 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.

Aberg *et al*. performed a double-blind, placebo-controlled study during the birch pollen season in Southwestern Sweden in 2009 [24]. They recruited 53 children and adolescents aged between 8 and 18 years with AR attributed to birch pollen. All children were on daily oral antihistamine. Reminders and reporting of symptom scores were made by Short message service (SMS) on mobile phones for reminders and recording symptom scores, which proved an excellent logistics tool. Daily pollen counts were analyzed as a covariate. There was a significant reduction in total symptom scores from the nose in the active group ($p = 0.033$) and specifically for symptom 'rhinorhoea' ($p = 0.017$). The best effect was seen after days with low or moderate pollen counts (<100/m^3). No clinically significant adverse effects were seen. The authors concluded that the product reduces symptoms of SAR in children and adolescents. The association of better results with lower pollen counts was interpreted to mean that the use of HPMC-p is optimal in mild-to-moderate disease.

Aberg *et al*. conducted another double-blind, placebo-controlled study in 107 adult patients (18–40 years of age) with AR due to grass pollen in a designated area of Ukraine in the spring of 2013 [25]. The study population involved 107 subjects (18–40 years of age): 54 subjects on HPMC-p and 53 subjects on placebo. Daily severity of nasal congestion, rhinorrhea, sneezing, lower airway, and ocular symptoms (ranked from 1 to 6) were reported as text messages every evening. SMS on mobile phones were used as reminders of treatment and reporting of symptom scores. They 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 the effect of treatment at follow-up visits (both $p < 0.001$) confirmed a high efficacy. The pollen concentrations during the study were in the lower range, which was assumed to have contributed to the pronounced efficacy, reemphasizing that HPMC-p is best suited in subjects with mild-to-moderate disease.

Subsequently, the results of the study in Ukraine were analyzed in more detail [26]:

- 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 intergroup 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 $p < 0.0001$);
- the number of subjects without other symptoms was about twice as high as in the placebo group over the entire period ($p < 0.0001$).

The authors concluded that HPMC-p provided extensive protection against all symptoms from both upper and lower airways in subjects with clinical allergy to grass pollens with a reduction of the severity of the symptoms and significant increase of the number of symptom-free subjects.

Other studies were designed to prove the 'barrier effect' of HPMC-p by means of *in vitro* diffusion technique and by *in vivo* allergen challenge.

A pivotal study from a theoretical point of view was performed by Diethart *et al*. [27]. It explored the hypothesis that the gel formed after moisture absorption in the nose acts as mechanical barrier that prevents allergen diffusion toward the nasal epithelium. The experimental setup was designed to measure *in vitro* the diffusion of *Dermatophagoides pteronyssinus* allergen 1 (Der p 1) through HPMC and agar gels after 15, 30, 60, 180, and 360 min, and assessing the allergen diffusion rates by ELISA. Agar blocks were used to simulate the nasal mucosa and control samples without the HPMC gel layer were used as comparators. The control samples with no applied HPMC gel barrier absorbed 72.2% of the Der p 1 solution after 15 min and 100% after 60 min. In comparison, the HPMC and agar gel layers both significantly delayed Der p 1 diffusion: after 15 min 0.76% had diffused through the HPMC gel layer compared to 28.1% which diffused through the agar layer; after 360 min, 14.1% of the baseline Der p 1 crossed the HPMC gel layer while 100% had diffused through the agar layer. The conclusion was that HPMC gel significantly reduces Der p 1 diffusion *in vitro* compared to no barrier and to an agar gel layer. This is likely to be due to the small mesh size of the polymer network of HPMC and has important practical implications.

Emberlin *et al*. performed a study aimed at investigating the efficacy of HPMC-p applied to the nose for the control of persistent AR in adults due to house dust mite allergy [28]. The study followed a double-blind, placebo-controlled cross-over design and was conducted on 15 adults with persistent rhinitis, diagnosed positive to Der p1 by skin prick tests. The placebo was lactose powder. Challenge was by measured dose of homogenized allergenic dust. The study took place in the spring of 2006 before the main pollen season. 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 as reported by the subjects (nasal blockage, itching of nose, throat, and eyes), peak nasal inspiratory flow (PNIF) and peak expiratory flow (PEF). The results showed significant differences for sneezing, itchy nose, runny nose, and ECPs in nasal secretions. Some results were also significantly different between the placebo and the active arms for PNIF and for PEF. There were no adverse reactions. Thus, HPMC-p was proven to have significant effects in reducing some symptoms of persistent perennial rhinitis due to house dust mite allergy.

Four studies on the efficacy and safety of HPMC-p as a barrier enforcement measure were carried out in Russia and published in the peer reviewed journal of the Russian Allergological Society. These are not found by the online search engines due to peculiarities of the Russian bibliographical system. As they encompass a good number of subjects, it is worth presenting them in table format (Table 1) [29–32].

Table 1. Russian studies.

Study	Design	Subjects	Variables	Results
Zacharzhevskaya [29] (2009)	Prospective, open label, 4-week study, 5 visits	Subjects with PAR, n = 48, 2–64 years, 25 adults and 23 children	SS: 0–3 (worst) HPMC tolerability score: 4 grades; QoL: 0–100 (worst); AE.	Significant reduction of SS for all symptoms at week 1; QoL impairment score reduced by half at end of study. AE: nasal crusts – 1 patient; burning in the nose – 3 patients; itching and sneezing – 1 patient.
Geppe [30] (2010)	Prospective, open label; 2 arms, 6-week study, 4 visits	Children with SAR, n = 50, 4–14 years, 30 on HPMC and 20 controls	SS: 0–4 (worst), reduction of other medication use.	Significant reduction of SS for all symptoms at week of children significantly improved by day 5; reduction rescue medication; AE: 8% of children – transient tinkling the nose; in 2 children sneezing → HPMC discontinuation
Angotoyeva [31] (2011)	Prospective, open label; 2 arms, 40-days study, 2 visits	Patients with SAR and PER (n = 30), healthy controls (n = 30); 15–70 years.	QoL; mucosal inflammation (nasal swabs), MCC, CBF, Overall assessment by patients.	Significant improvement of QoL; no effect on MCC and CBF; reduction of mucosal inflammation; 80% of patients assessed effect as 'very good,' 5% as 'excellent,' 15% as 'modest;' in 25% of patients – transient tinkling in the nose after application.
Penchenko [32] (2011)	Prospective open label, 4-week study, 5 visits	Patients with SAR, n = 30, 15–33 years: 20 on HPMC and 10 controls.	QoL: 1–7 worst; SS: 0–4 (worst).	Significant reduction of SS scores for nasal congestions and rhinorrhea in the HPMC group after week 1 and all symptoms after week 4 unlike the control patients; significant difference in QoL scores between patients on and without HPMC.

AE: adverse events; CBF: ciliary beat frequency; HPMC: hydroxyl-propyl-methyl cellulose; MCC: mucociliary clearance; QoL: quality of life; PAR: persistent allergic rhinitis; PER: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; SS: symptom scores.

Two review papers on the product characteristics and the related internationally published papers were also published in the journal of the Russian Allergological Society [33,34].

In an open-label observational trial, Minov et al. assessed the efficacy and safety of HPMC-p as add-on treatment in 74 subjects with mild seasonal AR [35]. Patients were given oral cetirizine with or without HPMC-p and followed up for 10 days. Scores on a five-point scale for the separate symptoms were documented on days 5 and 10 since initiation of treatment. The percentage of subjects on cetirizine + HPMC-p scoring 'major' or 'complete' relief was significantly higher than those on cetirizine alone. A low frequency of adverse effects was registered equally in both groups.

Recently, an original research paper was published in China [36]. It was an open-label study of 36 patients with seasonal AR randomized into 18 subjects on HPMC-p and 18 control subjects treated with physiological sea water. Subjective symptoms, disease-specific quality of life, nasal airway resistance, and the sense of smell were compared between the groups on day 14 and day 28 after initiation of treatment. The group on HPMC-p was superior to the control group in assessed outcomes ($p < 0.05$). No adverse events were recorded in either group. The authors inferred that HPMC-p possesses a clinical curative effect when used in the treatment of AR and does not cause adverse reactions.

2.2. Evidence for the HPMC-p 'enhancement of the effect of nasally applied drugs'

If HPMC-p is applied after a drug is instilled in the nose, the subsequent gel barrier would hold it in place and by prolonging its contact with the mucosa would enhance its therapeutic effect. Thus, not only can severe rhinitis sufferers use HPMC-p along with their regular nasal drug treatment, but they can derive extra benefit by combining different preparations and achieve maximal synergy between them after sealing the applied mix with a puff of the powder. As opposed to commercially available fixed-dose combinations, HPMC-p empowered combinations may have more than two components, which can be subsequently discontinued sequentially ensuring treatment flexibility and personalized approach.

The study to test this concept was a double-blind placebo-controlled study in 40 patients (mean age 35 years, 23 women) with perennial persistent AR [37]. They were randomized to receive 1 puff of oxymetazoline followed by 1 puff of either HPMC-p or placebo (lactose) daily for 7 days and then only oxymetazoline rescue medication for another week. PNIF was measured for 360 min following oxymetazoline and HPMC-p/placebo insufflation on days 1 and 8 and at single point on day 15. Symptoms assessments visual analog scales (VAS) and total nasal symptom scores. HPMC significantly enhanced oxymetazoline-increased PNIF at days 1 ($p = 0.042$) and 8 ($p = 0.006$). Baseline PNIF was greater in the HPMC-p 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-p group showed further amelioration at day 15. Rescue medication was smaller in the HPMC-p group between days 8 and 15. Interestingly, in these studies, the achieved symptom improvement continued for a week after discontinuation of HPMC-p, implying a possible 'healing' effect on its own. Thus, this study not only provides evidence to conclude that HPMC-p enhanced decongestion through mucoadhesion, but also that it may be augmenting the mucosal barrier in AR, which explains the carry-over efficacy of oxymetazoline for a week after the application of HPMC-p stopped.

The study to be carried out was designed to test whether the documented beneficial effect of HPMC-p translated into clinical benefits in a real life setting [38,39]. Thirty-six symptomatic seasonal AR patients (25 male, median age 31 years) were instructed to treat their symptoms locally with intra-nasal decongestant (xylometazoline) and/or antihistamine (azelastine) and/or corticosteroid (mometasone), or, if symptoms persevered, with oral bilastine or prednisone. Patients were randomized to 'seal' the effect of each local application with one puff of either HPMC-p or placebo (lactose). They completed diaries with symptom scores (0–3/worst/), and medications (1 score for any drug application). 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. The study reflected patient behavior in a 'real-life' setting. Patients started filling out diaries at the onset of the 2015 grass pollen season. They had the freedom of judgment to apply locally a decongestant (oxymetazoline) and/or H1-antihistamine (azelastine) and/or corticosteroid (mometasone) followed by HPMC or placebo (lactose), or to resort to oral rescue medication with H1-antihistamine (bilastine) or corticosteroid (prednisolone). They completed diaries with symptom scores (0–3, higher scores indicating worse symptoms), and medications (1 score for any drug application). At the end of the pollen season diaries were collected, the calendar period when all patients had put in entries was determined and scores were summed up separately for the nasal symptoms and for the medication that was used. The following information was extracted from the diaries: total nasal symptom scores (TNSS) comprising scores for congestion, rhinorrhea, nasal itching and sneezing; total medication scores (TMS), broken down also into local and systemic drugs; combined symptom and medication scores (CSMS) equal to the sum of TNSS and TMS. The primary end point, CSMS was significantly ($p = 0.03$) lower in the HPMC-p group, which was mostly at the expense of the reduced TMS, while the TNSS difference did not reach significance. The disparity in the reduction of TMS and TNSS when using HPMC indicates that in daily life people may rather prefer to cut down on their drugs after attaining partial relief than to continue with treatment so as to achieve maximal symptom control. Following treatment, PNIF increased in the HPMC-p arm by 60% vs. 31% in the placebo one. The before/end of season differences in PNIF and EBT favored the HPMC-p patients compared with the placebo users, $p = 0.01$ and $p = 0.007$, respectively. We inferred that HPMC augmented the local therapeutic response in the nose by suppressing the seasonal surge of airway inflammation followed by a subsequent relief of the nasal symptoms.

3. General conclusion

HPMC-p is a valuable adjunct to the treatment of nasal symptoms by protecting the mucosal barrier from airborne allergens and irritants and by enhancing the pharmacological effects of nasally applied drugs.

4. Expert commentary

An ARIA update from 2016 provides an in-depth analysis of the treatments available for subjects with AR [40]. It suggests a much more liberal platform for management of these patients, stating that the ultimate goal is acceptance on the part of those treated with subsequent improvement of their quality of life. It also recognizes the fact that in a real world most patients with mild disease would rather resort to self-treatment making use of the readily available over-the-counter (OTC) formulations. Many subjects would prefer to use natural products to keep their symptoms at an acceptable level. The explanation that HPMC-p sets up a mechanical barrier to the offending environmental hazards sounds logical and appealing. The clinical relevance of this approach has been demonstrated in all the clinical studies carried out so far, in which patients reduced the use of any other rescue pharmaceutical medications.

An issue worth revisiting is the very limited role attributed nowadays to decongestants in the management of AR. As early as the middle of the last century, the concept of 'rhinitis medicamentosa' was coined and subsequently the dogma that nasal decongestants should not be used for more than 5–10 consecutive days was established [41,42]. A recent critical review of the literature by a medical panel yielded discordant results, as some authors reported a harmful effect of nasal decongestants on the nasal mucosa, while others did not identify any significant changes [43]. The studies looking at the interaction between HPMC-p and nasally applied oxymetazoline uncovered an unexpected synergy when the decongestant is 'sealed in place' by the cellulose gel, which appears to enhance and prolong its action [37]. This effect carries over for at least one week after discontinuation of the oxymetazoline/HPMC-p treatment. It is worth exploring the nature of this relationship to investigate if it would allow the use of lower doses/concentrations of local decongestants, and if longer decongestant usage under the protection of HPMC-P may prevent damage to the nasal mucosa. The significance of such studies relates to the fact that in real-life settings many patients use freely accessible nasal decongestants anyway.

As for the moderate-to-severe cases of AR, the role of the consulting physicians emerges as a more important determinant of the treatments choices. The ARIA panelists focused on ranking several treatment options involving intranasal antihistamines, intranasal corticosteroids, oral antihistamines, and oral leukotriene receptor antagonists, alone or in double combinations, in subjects with seasonal and perennial AR [40]. The ensuing recommendations, however, were only conditional (no strong recommendation was formulated), with mostly very low and low certainty of evidence. This state of the art prompts the necessity of more research, which would not only bring in greater numbers of patients for future analyses, but would also identify new approaches optimizing the effectiveness of existing formulations. HPMC-p has the potential to augment and enhance the efficacy of nasally applied drugs and offers a unique opportunity to seal together combinations of two or more nasal preparations at the discretion of the treatment physician in line with the principles of personalized and precision medicine [44]. As these are not fixed combinations, a big advantage of one such strategy would be the flexibility to maneuver on a day-to-day basis depending on the severity and nature of the nasal symptoms.

5. Five-year view

It does not seem likely that new classes of accessible and affordable drugs will make their way into the treatment of AR in the five years to come. Under these circumstances and in view of the diversity of conditions and healthcare systems across the globe, the evolution of AR management would most likely be confined to fine tuning of the existing therapeutic means. A large variety of pharmaceutical formulations belonging to different therapeutic classes of drugs are licensed for AR management as OTC and prescription products [45]. Similarly to asthma treatment with fixed combinations of drugs applied by inhalation, a fixed combination of two pharmaceutical products, azelastine hydrochloride and fluticasone propionate, has been licensed for AR management [46–48]. Development along this fixed combination line involves substantial costs and does not allow flexible personalized treatment. We believe that an alternative approach to fixed-dose combinations in otorhinolaryngology could be achieved by sequential application of individual nasal formulations and keeping them in place by means of subsequent insufflation of HPMC-p.

The general trend for avoidance of pharmaceutical preparations would also impact the developments in the field. Even 'non-drowsy' antihistamines can have a 'hangover' effect and long-term use of steroids is abhorred by subjects with 'corticophobia.' Some sufferers will already be taking medication for other reasons and will not want to add on more systemic drugs. Pregnant or breast-feeding women and parents of school age children will conceivably want to abstain from oral drugs. Achieving symptom control in such individuals by natural products would be appealing.

Key issues

- HPMC-p is a cellulose derivative that has been formulated as a patented powder with a patented delivery system.
- HPMC-p provides unique benefits along two avenues:
  - mucosal barrier enforcing measures and prevention;
  - enhancement the effects of nasally applied drug treatment(s).
- HPMC-p on its own may provide relief of asthma symptoms in many patients.
- HPMC-p may possess a 'healing' on top of its 'avoidance' effect.
- HPMC-p has a very favourable safety profile.
- HPMC-p is particularly effective in mild to moderate disease.

- HPMC-p is not toxic and its dosage can be increased to match the allergen load.
- HPMC-p can be used to enhance the effect of nasally applied drugs.
- HPMC-p can combine under its seal different drugs ensuring synergic effects.
- HPMC-p allows personalized and flexible treatment through combining drugs.

Notes

1. Nasaleze®, Manufactured by Nasaleze Ltd. Douglas, Isle of Man, IM4 4QE, UK; www.nasaleze.com.
2. GRAS = Generally Recognized As Safe. sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act.

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