

ORIGINAL ARTICLE

Nasal treatment with a microemulsion reduces allergen challenge-induced symptoms and signs of allergic rhinitis

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Abstract

Conclusions. Intranasal microemulsion treatment can attenuate allergen challenge-induced nasal symptoms and plasma exudation in allergic rhinitis. We hypothesize that the mechanism of action involves modification of the allergen–mucosa interaction. The present observation suggests a novel principle for prevention in allergic rhinitis. **Objective.** To evaluate a specific microemulsion as a treatment for allergic rhinitis in an acute allergen challenge model. **Patients and methods.** Patients with allergic rhinitis were examined out of the pollen season. Treatment with a single dose of a specific microemulsion was given in a single-blind, placebo-controlled, and crossover design using a nasal pool device. Nasal allergen challenges were carried out and symptoms of allergic rhinitis were scored. Furthermore, nasal lavages were performed and levels of the plasma protein α_2 -macroglobulin were measured as an index of exudative inflammation. **Results.** The allergen challenges produced significant increases in nasal symptoms ($p=0.007$) and in nasal lavage fluid levels of α_2 -macroglobulin ($p=0.008$). The challenge-induced symptoms as well as the plasma exudation were attenuated by treatment with the microemulsion ($p=0.016$ and 0.012 , respectively, compared with placebo).

Keywords: Airway, inflammation, plasma exudation, rhinitis

Introduction

Allergic rhinitis is a condition possibly experienced by as many as 25% of the population in affluent countries [1]. There are established treatments for this disease including antihistamines, glucocorticosteroids, and specific immunotherapy [2], as well as more recently introduced therapies such as leukotriene antagonists [3] and specific anti-IgE [4]. Despite the fact that these treatments are all potent and useful, there is a need for novel ones. Specifically, there is a need for treatments that would add to the efficacy of the established regimens and would be associated with minimal side effects.

In preliminary experiments, we have observed that certain lipid-based compositions with microemulsion characteristics appear to reduce allergen challenge-induced effects in allergic rhinitis. In the present study, involving patients with allergic rhinitis examined out of the pollen season, we examined whether or not intranasal administration of a specific

microemulsion affects nasal allergen challenge-induced symptoms and plasma exudation. Plasma exudation is a key feature of inflammatory processes in allergic rhinitis it can be monitored by analysis of nasal lavage fluid levels of the plasma protein α_2 -macroglobulin [5].

Patients and methods

Study design (Figure 1)

A microemulsion was given intranasally to patients with allergic rhinitis in a single-blind, placebo-controlled, and crossover design. Thereafter, nasal challenge with pollen allergen was performed. Nasal symptoms were scored, nasal lavages carried out, and lavage fluid levels of α_2 -macroglobulin measured as an index of plasma exudation. The study was approved by the Ethics Committee at Lund University, Lund, Sweden, and informed consent was obtained.

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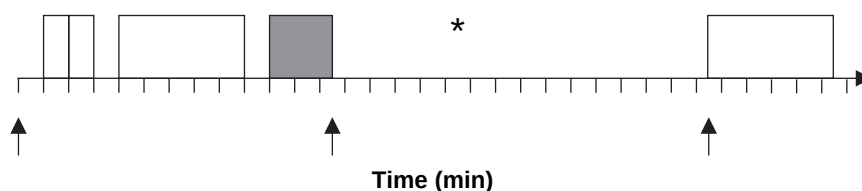


Figure 1. Scheme of the experimental procedures for each of the two treatment runs. Open symbols indicate nasal lavages with saline. Note that only the two 5 min lavages were collected for analysis. The filled symbol indicates the 2.5 min treatment with placebo/microemulsion. *The point in time when the allergen challenge took place. Arrows indicate time points for scoring of nasal symptoms.

Subjects

Nine patients were recruited to the study (one woman, nine men). The mean age was 25 years (range 22–28). The subjects had a history of seasonal allergic rhinitis. Skin prick tests were used to verify atopy (birch or grass pollen allergen) and to exclude perennial allergic conditions (house dust mites, molds, and cat/dog dander). History taking and physical examination were undertaken to exclude patients with respiratory tract infections, chronic nasal diseases, and structural nasal abnormalities. The patients had been without treatment for at least 2 months before the study.

Treatment

Nasal administrations of the microemulsion and placebo (isotonic saline) were carried out using a nasal pool device [6]. In the present study, 14 ml of each solution were used and the solutions were kept in the right-hand side of the nasal cavity for 2.5 min. The solution was then recovered back into the pool device. Two weeks elapsed between visit 1 and 2.

The lipid composition was a mixture of glycerol monooleate (34%, w/w), propylene glycol (23%), polyethylene glycol 400 (18%), sesame oil (11%), polysorbate 80 (4%), and isotonic saline (10%).

Allergen challenge

Nasal allergen challenges were carried out 5 min after the treatments. The patients received either birch or grass pollen allergen (ALK-Abello, Hørsholm, Denmark). The challenges were carried out using a spray device delivering 100 μ l per actuation. The allergen was delivered to the right-hand side of the nasal cavity as a single actuation in a dose of 3000 Standard Quantity Units (SQ-U).

Nasal symptom scores

Symptoms were scored three times per visit: at the start of the visit, immediately after the treatment, and 10 min after the allergen challenge. Sneezes were counted and transformed into a score: 0, 0 sneezes; 1, 1–4 sneezes; 2, 5–8 sneezes; and 3, >9

sneezes. Nasal secretion and blockage were scored: 0, no; 1, mild; 2, moderate; and 3, severe symptoms. As previously established [7,8], a total nasal symptom score (range 0–9) was calculated.

Nasal lavages and analysis

Nasal lavages with saline (9.0 g/l) were carried out on four occasions per visit using a nasal pool device [6], but only two of these lavages were collected. After the first recording of symptoms, but before administration of the lipid composition/placebo, two 1 min lavages were performed to remove solutes that might have accumulated on the mucosal surface for an unknown period of time (discarded). Thereafter, a 5 min baseline lavage was carried out, and this lavage was collected. Ten minutes after the allergen challenge, a second 5 min saline lavage was carried out and collected. The lavages were centrifuged (325 g, 4°C) and supernatants frozen (–20°C). α_2 -Macroglobulin was measured using a radioimmunoassay (detection level 7.8 ng/ml) [9]. The intra- and inter-assay coefficients of variation of this assay are between 3.8–6.0% and 3.1–7.2%, respectively.

Statistics

Differences in symptom scores and lavage fluid levels of α_2 -macroglobulin, respectively, between observations at placebo and active treatment were examined by the Wilcoxon signed rank test. Similarly, observations before and after treatment within each treatment were examined by this test. A power estimate for the effect of microemulsion treatment on nasal symptoms was calculated [10]. Data are presented as median values (inter-quartile ranges).

Results

Nasal administration of the microemulsion was not associated with any untoward symptoms as reflected by unaffected symptoms scores following its administration compared with observations following administration of placebo ($p=0.462$) (Table I).

The allergen challenges produced significant increases in nasal symptoms ($p=0.007$, compared

Table I. Nasal symptom scores at baseline, and following microemulsion treatment and allergen challenge, respectively.

Timing	Nasal symptom score (range 0–9)		
	Placebo	Microemulsion	<i>p</i> value
Baseline	1.0 (1.3)	1.0 (1.3)	0.706
Post treatment	1.0 (1.3)	1.0 (1.5)	0.462
Post allergen challenge	6.0 (1.5)	4.0 (2.3)	0.016

The symptom score was reduced following topical microemulsion treatment.

with pre-challenge). These challenge-induced symptoms were reduced by 33% by treatment with the present microemulsion ($p=0.016$, c.f. placebo) (Table I). Notably, part of this effect was through a significant reduction in nasal blockage ($p=0.026$, c.f. placebo). Focusing on total nasal symptoms, the power to detect a difference between placebo and the microemulsion was >90% at $p<0.05$.

The allergen challenges also produced significant increases in nasal lavage fluid levels of α_2 -macroglobulin ($p=0.008$, c.f. pre-challenge). This challenge-induced plasma exudation was reduced by 62% by treatment with the microemulsion ($p=0.012$, c.f. placebo) (Table II). Indeed, the allergen challenge failed to produce significant plasma exudation when the patients had received microemulsion ($p=0.093$, c.f. pre-challenge).

Discussion

In the present study, involving patients with seasonal allergic rhinitis, we have shown for the first time that intranasal administration of a specific microemulsion can attenuate allergen challenge-induced nasal symptoms and plasma exudation. Our observation suggests the possibility that topical treatment with microemulsions should be evaluated as a novel treatment for allergic rhinitis alone or in combination with topical drugs already in use for the treatment of this condition.

The present study was of a single-blind design since the texture of the lipid composition was noticeably different from that of saline. Nasal instillation of a large volume of the composition did not give rise to any rhinitis symptoms. The innocuous nature of the microemulsion was expected

since the constituents are widely used as pharmaceutical excipients and are known to feature a very low toxicity [11]. This nature of the composition indicates a possibility also of using it as a vehicle for various pharmaceuticals.

Nasal administration of the present lipid composition was shown to reduce allergen-induced nasal symptoms of allergic rhinitis. For comparison with established treatments, topical and oral antihistamines (given as single doses) would be expected to have similar effects in the present acute challenge model [9], whereas topical glucocorticosteroids (given as a single dose) may have no or only minor effects [12]. We regard the present level of efficacy as promising in terms of viewing microemulsions as potential treatments for allergic rhinitis. Further studies in additional disease models, as well as studies in association with natural allergen exposure, are warranted to evaluate this possibility. Also, explorations of other lipid compositions may be considered.

In the present study, a large volume of the lipid composition was temporarily administered to the nasal cavity using a nasal pool device. This mode of administration may be unlikely as a treatment option, but was chosen to test the feasibility of the present lipid composition as a topical treatment for allergic rhinitis. Further studies are warranted to elucidate whether or not other modes of administrations, including nasal sprays, nasal drops, etc., would be equally effective. Such studies may also focus on the duration of the effect of microemulsion treatment.

Exposure of the bronchial airways to lipids may produce lipid pneumonia. This condition is mostly associated with mineral oils [13], but has also been

Table II. Nasal lavage fluid levels of α_2 -macroglobulin at baseline and following microemulsion treatment/allergen challenge.

Timing	α_2 -Macroglobulin ($\mu\text{g/ml}$)		
	Placebo	Microemulsion	<i>p</i> value
Baseline	0.2 (0.2)	0.2 (0.3)	0.317
Post allergen challenge	1.3 (1.4)	0.5 (1.2)	0.012

Levels of α_2 -macroglobulin were reduced following topical microemulsion treatment, indicating an anti-plasma exudation effect.

reported in infants after nasal administration of large volumes of vegetable oils [14]. In the present study, no adverse symptoms suggestive of lipid pneumonia were reported following nasal administration of a large volume of microemulsion. The risk of lipid pneumonia should be considered if nasal microemulsion treatment is developed. However, the risk may arguably be low if a small volume is given (e.g. using a nasal spray device).

Extravasation, lamina propria distribution, and luminal entry of plasma are key features of airway inflammation and allergic rhinitis [5]. Accordingly, it has been demonstrated that acute allergen challenge produces plasma exudation [9]. In the present study, allergen challenge increased the nasal mucosal output of the plasma protein α_2 -macroglobulin, as expected. The present lipid composition exerted an anti-plasma exudation effect, indicating that the ability of allergen to produce exudative inflammation was significantly reduced by the treatment.

The present lipid composition is self-assembling and constitutes an isotropic fluid phase. It spreads spontaneously onto hydrophilic surfaces rather than forming droplets. Based on this characteristic, we hypothesize that isotropic fluid phase lipid compositions may interfere with allergen–chock organ interactions by coating the mucosal surface. The lipid compositions may also encapsulate particles such as hydrophilic pollen grains and reduce allergen release. We consider it likely that topical administration of isotropic fluid phase lipid compositions, by the above mechanisms, may also prevent other particular agents from insulting the nasal mucosa.

Wolters-Arts et al. [15] have previously shown the importance of triacylglycerides for pollen germination and pollen-tube formation. In addition, Bufer [16] has demonstrated that breakdown products of lipids may block release of allergens from pollens. Bufer [16] also suggested the usefulness of applying mineral oil to the nasal mucosa of patients with seasonal allergic rhinitis to reduce allergic symptoms, and that fatty acids may be helpful in the treatment of allergic rhinitis. However, no data have been provided to substantiate this suggestion and no reports of self-assembling lipid organizations such as microemulsions have been put forward.

In conclusion, intranasal microemulsions can attenuate allergen challenge-induced symptoms and plasma exudation in allergic rhinitis.

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