Article ID: WMC00993

Efficacy Of Three Thixotropic Nasal Spray Preparations On Seasonal Allergic Rhinitis Assessed By Allergen Challenge In An Environmental Exposure Unit

Author(s):Ms. I. Luond-Valeskeviciute, Dr. Benedikt Haenggi, Dr. Joerg Gruenwald

Corresponding Author:
Dr. Joerg Gruenwald,
CEO, analyze & realize ag - Germany

Submitting Author:
Dr. Joerg Gruenwald,
CEO, analyze & realize ag - Germany

Article ID: WMC00993

Article Type: Original Articles

Submitted on:26-Oct-2010, 02:10:43 PM GMT **Published on:** 26-Oct-2010, 02:16:00 PM GMT

Article URL: http://www.webmedcentral.com//article_view/993

Subject Categories:ALLERGY

Keywords:seasonal allergic rhinitis; SAR; hay fever, pollen, nasal spray, thixotropy, thixotropic, allergen challenge, environmental exposure unit

How to cite the article: Luond-Valeskeviciute I, Haenggi B, Gruenwald J. Efficacy Of Three Thixotropic Nasal Spray Preparations On Seasonal Allergic Rhinitis Assessed By Allergen Challenge In An Environmental Exposure Unit . WebmedCentral ALLERGY 2010;1(10):WMC00993

Efficacy Of Three Thixotropic Nasal Spray Preparations On Seasonal Allergic Rhinitis Assessed By Allergen Challenge In An Environmental Exposure Unit

Abstract

Two studies were undertaken to assess the efficacy and safety of three thixotropic nasal sprays (IQM11, IQM12, IQM13) on seasonal allergic rhinitis (SAR). The three nasal sprays differ only with respect to the emulsifying agent used in the formulation. In the prospective, randomized, cross-over pilot study, 16 patients with a history of SAR received 2 x 0.14 ml IQM11 per nostril or no treatment and were exposed to grass pollen twice for 4 hours in an environmental exposure unit. The SAR symptoms rhinorrhea, nasal congestion, nasal pruritus, sneezing, eye itching, and eye tearing were rated every 15 min. The randomized, semi-blind, comparative cross-over clinical trial followed the same study design: 18 patients with a history of SAR received the same amount of nasal spray (IQM12, IQM13) or no treatment and experienced the allergen challenge three times for 3 hours each. The main nasal SAR symptoms as well as the Total Nasal Symptom Score (TNSS) were recorded every 15 min. The pilot study showed that the total scores of main nasal symptoms rhinorrhea and nasal congestion were significantly lower in the treatment group compared to the control group ($P < .05$). Sneezing improved highly significantly under therapy with the nasal spray ($P < .001$). In the comparative study, all symptoms showed statistically significant improvement ($P < .05$) with both nasal sprays with the exception of nasal congestion under therapy with IQM12. In conclusion, these two allergen challenge studies demonstrated that thixotropic nasal sprays are effective in reducing the main nasal symptoms in SAR patients.

Introduction

Allergic rhinitis is an IgE-mediated hypersensitivity reaction. It is characterized by rhinorrhea, nasal pruritus (i.e. nasal itching), nasal congestion and sneezing. Important non-nasal symptoms commonly associated with allergic rhinitis include itching eye, tearing eye, itching ears and/or palate, and eye redness. The occurrence of these symptoms is temporally connected to the exposure to allergens. The symptoms are seasonally provoked by pollen (seasonal allergic rhinitis, SAR, hay fever) or throughout the year, due to chronic exposure to dust mites, mold allergens or animal dandruff (perennial allergic rhinitis, PAR). According to the WHO, allergic rhinitis is a global health problem. It effects at least 10 – 25% of the world population, with increasing prevalence. Although allergic rhinitis cannot generally be considered a severe disease, it changes the social life and general wellbeing of the persons concerned and interferes with school performance as well as job productivity [1]. Allergic rhinitis considerably increases health care costs. Direct, indirect and intangible costs of allergic rhinitis were approximately €240 million in Germany in 2000 [2]. In 1990, the estimated health care costs for the U.S.A. for SAR alone were US $1.8 billion [3]. Allergen abstention seems to be the only causal therapy for allergic rhinitis. As an alternative to life in pollen-free areas (such as high mountains, deserts, etc.) recent research focuses on allergen abstention by way of local intervention: the application of a physical barrier on the nasal mucosa could inhibit or at least minimize its contact to air-borne allergens. First trials in the 1990's yielded a pollen protection cream (SIMAROline®). It contains purified white Vaseline and received marketing authorization as a medical device in 2000. The efficacy and safety of this product were thoroughly discussed; a clinical study could not support the claimed effects [4]. However, the research group "Immunology" at the Charité Hospital in Berlin confirmed clinical efficacy based on several case reports [5]. The German Society for Allergology and Clinical Immunology, on the other hand, does not agree with the proposed mechanism of action. It states that the cream could not reach the nasal mucosa and would remain in the nasal atrium [6]. The problem of the cream not reaching its destination is a valid

objection. However, using a gel with thixotropic properties can counteract this problem. Thixotropy means the mechanically induced liquefaction of a gel. The material changes from a solid into a liquid state by means of shaking. This is based on the fact, that the dispersal phase, when standing, acquires a certain scaffold structure, because of the forces of attraction between the particles. This structure is very labile and is at least in part be destroyed by mechanical impact. During the resting phase, the scaffold structures are restored and the viscosity rises again. The nasal sprays are supposed to be gels in their passive state; after shaking, they become liquid and can be applied to the nasal cavities with a pump. The spray finely disperses into the nasal caverns and sinuses. After reaching the mucosa, the preparation returns to its passive, gel like, almost solid state and acts as a protective coating, thereby minimizing the possibility of contact between pollen and mucosa. A prospective, randomized, cross-over clinical pilot study was conducted to establish whether the establishment of a physical barrier with lipophilic character shows a detectable and clinically relevant protection of the nasal mucosa against allergens. A further randomized, semi-blind, comparative cross-over clinical trial was carried out in order to optimize the formulation. Whereas the nasal spray utilized in the pilot study (IQM11) contained Glucate SS and Glucamate SSE-20 as emulsifiers, the two nasal sprays investigated in the comparative trial (IQM12 and IQM13) contained Xyliance and Tegin, respectively. All three nasal sprays are non-invasive and have no pharmacologically effective ingredients.

Subjects and methods

Patients

A total number of 16 patients were included in the pilot study. They had to fulfill the following criteria: age between 18 and 65, history of SAR due to grass pollen for ≥ 2 years, positive skin prick test to *Dactylis glomerata* within 24 months of enrollment (positive when hive ≥ 3 mm larger than negative control). Exclusion criteria were asthma bronchiale, with the exception of mild intermittent asthma (normal lung function, FEV ≥ 80% of individual normal value, symptoms during the day ≤ 2x weekly, symptoms during the night ≤ 2x monthly), concomitant therapy with a- and b-receptor blockers and antidepressants, glaucoma, cataract, ocular herpes simplex, clinically relevant deviation of laboratory parameters, rhinitis of different origin, chronic sinusitis, progressive systemic diseases, hypersensitivity to any of the constituents, previous organ transplantations, pregnancy and breastfeeding, drug abuse, or the use of any medication that could affect the outcome of the study. For corticosteroids, antihistamines, and antiphlogistics the washout periods were 2 months, 6 weeks, and 2 weeks, respectively.

A total of 18 patients were included in the clinical study, comparing the two nasal spray preparations IQM12 and IQM13. The study design corresponded to that of the pilot study. Here as well, main inclusion criteria were age between 18 and 65, a history of SAR and a positive skin prick test. Main exclusion criteria were asthma bronchiale (except mild intermittent asthma: normal lung function, FEV ≥ 80% of individual normal value, symptoms during the day ≤ 2x weekly, symptoms during the night ≤ 2x monthly), concurrent antiallergic therapy, concurrent severe diseases, pregnancy and lactation. Written consent to participate in the studies was given by each subject according to § 40 AMG (German Medical Law). Both studies were conducted at the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM), Hanover, Germany.

Sample size calculation

For the pilot-study, data from validation of the study centers showed that after 4 hours exposure to 4000 grass pollen/m3 without therapy, an average total score of 5.86 was achieved with a standard deviation of 1.62. The primary objective criteria postulated a statistical significant reduction of these total scores. The paired comparison of 16 data sets, using a standard deviation of 2.0, allows proof of a difference of 2.64 with a p-value of 0.05 and a power of 95%.

For the second study, it was tested to see if the intended sample size for an analysis of a simple crossover study could be reduced. This could be verified. The two-sided test for variations was performed on an α-level of 2.5%. The sample size calculation was performed using the SAS program Geesize version 3.1 from Rochon and Damen. Calculation of the sample size was therefore based on reanalysis of the previous simple crossover study.

Study protocol

The pilot study was performed as a prospective, randomized, cross-over trial, in which 16 patients with a history of SAR received a thixotropic nasal spray suspension (IQM11) and no treatment, respectively. The preparation contained liquid paraffin (40 %), glycerol, emulsifier (Glucate SS and Glucamate SSE-20), and water (55%). The patients were randomly assigned to two groups on the first day of

treatment. Randomization was carried out externally via a validated computer program. All patients were exposed to grass pollen twice for 4 hours in an environmental exposure unit. During the study, temperature (mean ± SD; 21 ± 2°C), relative humidity (40 ± 5%) and pollen count (approx. 4000 grains/m^3) were kept constant. One pollen exposure occurred after treatment with the nasal spray, the other was conducted without therapy. The first exposure was followed by the second after a 7-day wash-out phase. Group A started without treatment and received the nasal spray treatment at the second exposure, group B received the test preparation at the first exposure and no treatment at the second. A study nurse administered the nasal spray (2 x 0.14 ml per nostril) to each nostril 5 minutes before the allergen challenge. In order to exclude inhalation, the first spray was directed towards the nasal septum, the second towards the inside of the outer nose wall. As the control group received no treatment during the pollen exposition, a rescue medication (Sultanol® N spray) was provided. The study was not blinded because the no-treatment phase was obvious to both patients and staff. For practical reasons, the study had no placebo control, as there is no conceivable placebo for a physical barrier.

The comparative study was performed as a prospective, randomized, semi-blind cross-over trial following the same design as the pilot study with few exceptions. 18 patients were included and received the nasal sprays IQM12 and IQM13 and no treatment. IQM12 and IQM13 contained the emulsifiers Xyliance and Tegin, respectively. Xyliance (cetearyl wheat straw glycosides and cetearyl alcohol) is a PEG-free, biodegradable self-emulsifier. Tegin (glyceryl oleate) is also a PEG-free, based on plant raw materials and non-ionisable. Both substances are often used for oil in water emulsions in the cosmetic and pharmaceutical sector.

The random allocation sequences were generated without stratification. All patients were exposed to grass pollen three times for 3 hours each in an environmental exposure unit (constant environmental conditions, see above). The nasal spray was applied 5 minutes before exposure (2 x 0.14 ml per nostril as explained above). One pollen exposure was conducted after treatment with IQM12, one after treatment of IQM13 and one without therapy. Each exposure was followed by a one-week wash-out phase. Patients were randomly distributed into 6 groups with 3 patients each, following a double cross-over scheme:

A) IQM12, IQM13, no treatment

B) IQM13, no treatment, IQM12

C) no treatment, IQM12, IQM13

D) IQM12, no treatment, IQM13

E) no treatment, IQM13, IQM12

F) IQM13, IQM12, no treatment

The study was semi-blind, allocation to the nasal spray groups was double-blinded and the no-treatment phase was not. Again, the study had no placebo control for practical reasons. The study was conducted in September and October 2004 in order to avoid external pollen exposure.

Assessment

The 4-step rating scale as proposed by the FDA (Guidance for Industry. Allergic Rhinitis: Clinical Development Programs for Drug Products, US Department of Health and Human Services. Food and Drug Administration, April 2000) served as the efficiency parameter in both studies. In the pilot study, the main objective was the significant reduction of the total score of the SAR nasal symptoms rhinorrhea, nasal congestion, nasal pruritus, sneezing, as well as the non-nasal symptoms itching and tearing eyes, according to the rating scale in comparison to untreated controls. The participants documented the severity of the SAR symptoms before the beginning of the exposure and then every 15 minutes. The symptoms are rated on a 0 – 3 scale of severity:

0 = absent symptoms (no sign/symptom evident)

1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)

2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)

3 = severe symptoms (sign/symptom that is difficult to tolerate; causes interference with activities of daily living and/or sleeping)

Physical and nasal examinations, as well as laboratory tests, were conducted at the screening visit and at the final visit. Forced expiratory volume (FEV_1, Jaeger Masterscope® Systems) was measured before and every 60 minutes during allergen challenge as well as 60 minutes after exposure. A decrease of FEV_1 of more than 15% during pollen exposure was considered an adverse event. A decrease by 40% of the expected standard value caused immediate termination of the exposure and a rescue medication (Sultanol® N spray) was applied. The participants measured their peak expiratory flow rate (PEF) using a Mini-Wright peak flow meter before exposure, 1 hour after exposure, and then every 2 hours until bedtime. A decrease of more than 20 % was considered an adverse event and the patients had to inhale the

rescue medication. Values were recorded on diary sheets, which were handed in on the following day, along with documentation of any adverse events.

The primary objective in the comparative study was the evaluation of the Total Nasal Symptom Score (TNSS) of the FDA rating system. The patients were instructed to record the SAR nasal symptoms rhinorrhea, nasal congestion, nasal pruritus, and sneezing according to the rating scale at the beginning of the allergen challenge and then every 15 minutes for three hours. The symptoms were rated as stated above. Again, a decrease of FEV1 by 40% and of PEF by 20% meant termination of exposure and the patients had to inhale the rescue medication.

Secondary objectives were the time to individual maximal TNSS and the cumulative demand for rescue medication. For the assessment of safety, evaluation of tolerance by the patients, physical examinations, vital signs, laboratory parameters, and incidence of (severe) adverse events were analyzed.

Statistical analysis

The primary predefined efficacy endpoint of the pilot study was the average SAR symptom score during the 4 hours of allergen challenge. No secondary efficacy endpoints were phrased. Paired-treatment mean comparisons were performed using two-sided tests. Values of $P < .05$ were considered to be significant.

The primary efficacy assessment of the comparative study was targeted to evaluate whether at least one of the two test preparations demonstrated an effect on the course of the TNSS during the 3 hours of pollen exposure, differing from the control. The secondary efficacy assessment compared time to the maximum individual TNSS and the cumulative need for rescue medication. A suitable covariance structure allowed for intra-individual and temporal dependencies (Dunnett procedure).

Results

The treatment and the control groups of the pilot study and those of the comparative study were comparable with regard to sex, age, body weight and duration of SAR.

Table 1 shows the average symptom score during the 4 hours of pollen exposure for the treatment and the control group. With the exception of nasal pruritus, the total scores for the main nasal symptoms of allergic rhinitis were significantly lower in the treatment group compared to the control group. Sneezing even improved highly significantly ($P < .001$) under therapy with the nasal spray (see Figure 1). The score for nasal pruritus fell marginally short of significance at the 0.5 level. There were no significant differences in the non-nasal symptoms itching and watering eyes, in participants treated with the nasal spray. No adverse events were reported.

Table 2 shows the mean TNSS, as well as the average symptom scores for the main nasal symptoms of SAR during the 3 hours of allergen challenge, under therapy with IQM12 and IQM13. Compared to the control, all symptoms showed statistically significant improvement ($P < .05$) with the exception of nasal congestion under therapy with IQM12 (see Figure 2). Both IQM12 and IQM13 were most effective in lowering the nasal pruritus score (see Figure 3). Overall, IQM13 scored better than IQM12 (significance not tested). Concerning the time to reach the maximum TNSS, there were no differences between the groups: The two treatment groups as well as the control group reached maximum scores approx. 75 min after the onset of the allergen challenge. The symptoms remained at that level for the rest of the pollen provocation. Although the test medications did not delay the onset of symptoms, the positive effect of the treatment was stable throughout the 3 hours of the exposure. An intervention with rescue medication was necessary once during each of the three treatment periods; this low number of events does not allow for a detailed analysis. The majority of patients rated safety as good or very good. No physical discomfort was observed. No severe adverse events were reported. However, a noticeable accumulation of adverse events occurred in the IQM12 group when compared with the control group. As the total number was low, this accumulation cannot be statistically substantiated. A detailed comparison cleared these minor adverse events from a likely connection to the treatment. Laboratory parameters were collected only twice (at screening and at the end of the study) and therefore cannot refer directly to the treatment groups. In four patients, changes were observed which cannot be connected to a certain treatment or the sequence of the three treatment phases and which seem very likely to be connected to external causes.

Discussion

In the prospective, randomized, cross-over pilot study and the prospective, randomized, semi-blind cross-over comparative study, the efficacy and safety of three thixotropic nasal sprays (IQM11, IQM12 and

IQM13) were assessed in patients with a history of SAR. The three formulations differ with respect to the emulsifier. The assessment was done by repeated allergen provocation in an environmental exposure unit, which is a specially designed challenge room that ensures a highly controlled and standardized exposure of aeroallergens.

A significant treatment effect regarding the nasal symptoms of SAR, rhinorrhea, nasal congestion, nasal pruritus, and sneezing, was detectable in both the pilot as well as the comparative study after 4 and 3 hours of pollen exposure, respectively. The only exception occurred under treatment with IQM12 with regard to nasal congestion. Furthermore, the comparative study demonstrated a significant reduction in the TNSS. Slight differences in the efficacy of the three nasal sprays were detected: IQM13, containing Tegin as the emulsifier, was most successful in reducing the nasal SAR symptoms. However, with all three preparations the thixotropic approach was successful. In comparison to conventional treatment, the thixotropic nasal sprays are as effective as the topical corticoid loteprenol [7]. The three formulations did not cause noticeable drug-related adverse events or any serious adverse events. The safety and tolerability was good.

In conclusion, these two allergen challenge studies in subjects with SAR demonstrated that thixotropic nasal sprays are effective in reducing the main nasal SAR symptoms rhinorrhea, nasal congestion, nasal pruritus, and sneezing. They are as effective as intranasal glucocorticosteroids but do not achieve their intended action through pharmacological, immunological or metabolic means. As it is not supposed to interact with the human body, the thixotropic approach can be regarded as safer than any conventional method of treating SAR symptoms via a nasal spray.

Reference(s)

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108(5 Suppl): 147-334.
2. Werfel T, Kapp A. Kongressbericht: Zunehmende Prävalenz von Allergien. Deutsches Ärzteblatt 2004; 101: 1435-1437.
3. McMenamin P. Costs of hay fever in the United States in 1990. Ann Allergy 1994; 73(1): 35-39.
4. Klimek L, Gene-Schneider S, Mösges R, Hörmann K. Die Pollenschutzcreme SIMAROline ist wirkungslos bei saisonaler allergischer Rhinitis. Allergologie 2000; 23: 455-460.
5. Bublak R. Neue Nasencreme sorgt für Pollenkarenz. Ärztliche Praxis 2000; 22: 11.
6. Riechelmann H. Die Crème des Findigen – SIMAROline® Pollenblocker. Stellungnahme im Auftrag der Deutschen Gesellschaft für Allergologie und Klinische Immunologie. Allergo J 2000; 9: 200-201.
7. Krug N, Hohlfeld JM, Geldmacher H, et al. Effect of loteprenol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. Allergy 2005; 60: 354-359.

Tables

Table 1: Average symptom score during the 4 h of allergen challenge assessed by patients using IQM11 (mean ± SD)

Symptom	Control	IQM11
Rhinorrhoea	25.5 ± 6.0	21.3 ± 7.9*
Nasal congestion	24.2 ± 9.8	19.8 ± 9.2*
Nasal pruritus	17.5 ± 7.3	13.7 ± 7.7
Sneezing	15.0 ± 7.5	7.6 ± 4.8**
Eye itching	8.9 ± 9.8	5.4 ± 5.6
Eye tearing	3.4 ± 5.5	2.8 ± 4.6

* $P < .05$

** $P < .001$

Table 2: Average symptom score during the 3 h of allergen challenge assessed by patients using IQM12 and IQM13 (mean ± S.E. after Dunnett adjustment)

Symptom	Control	IQM12	IQM13
TNSS	5.29 ± 0.33	4.40 ± 0.34*	3.69 ± 0.29*
Rhinorrhoea	1.61 ± 0.10	1.32 ± 0.09*	1.18 ± 0.10*
Nasal congestion	1.37 ± 0.60	1.25 ± 0.10 (n.s.)	1.06 ± 0.10*
Nasal pruritus	1.33 ± 0.12	0.99 ± 0.14*	0.77 ± 0.13*
Sneezing	1.03 ± 0.11	0.78 ± 0.11*	0.70 ± 0.10*

* $P < .05$

Illustrations

Illustration 1

Figure 1: Sneezing - average symptom score during 4 h of allergen challenge using IQM11

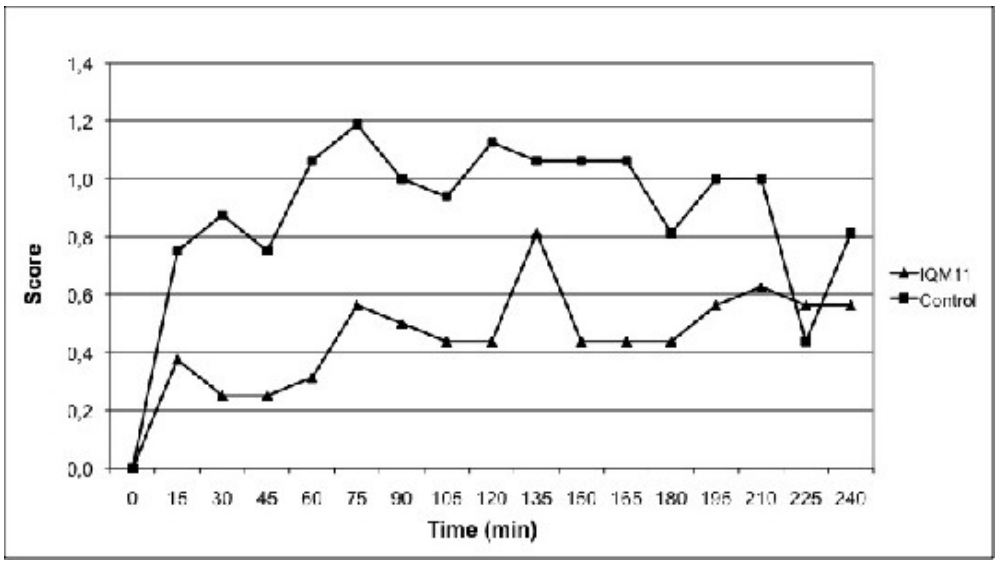


Illustration 2

Figure 2: Efficacy of IQM12 and IQM13 after 3 h of allergen challenge (control = 100%)

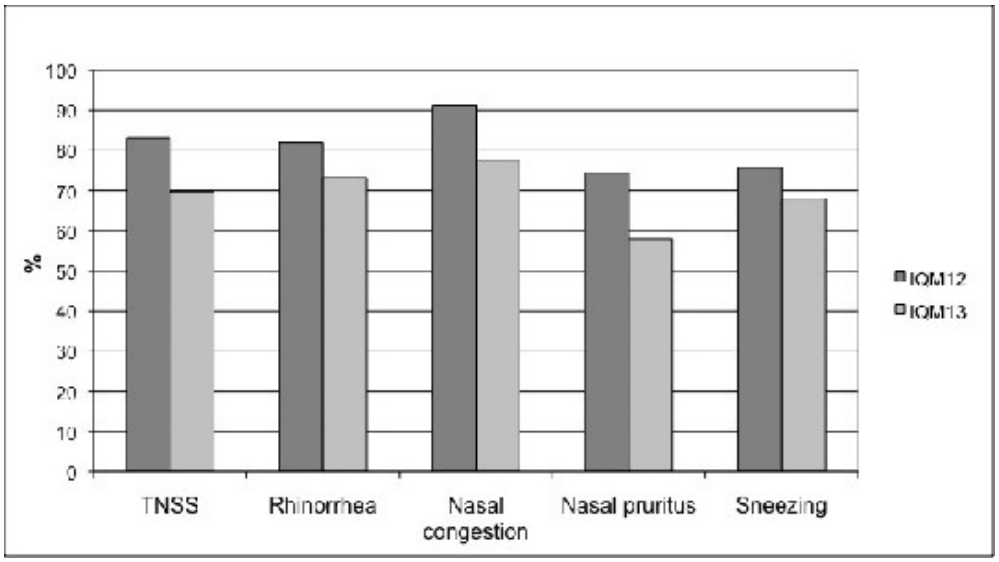
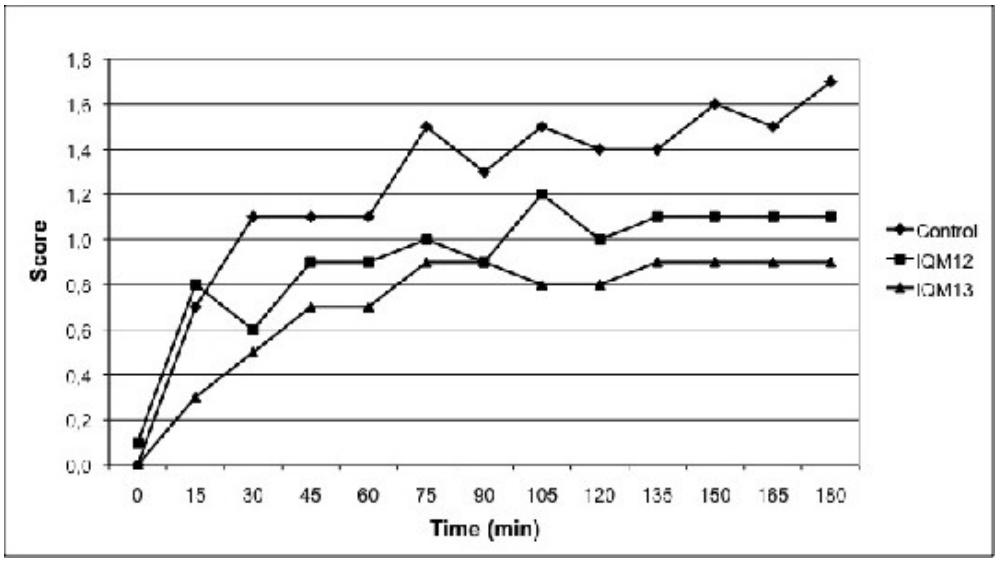


Illustration 3

Figure 3: Nasal pruritus - average symptom score during 3 h of allergen challenge using IQM12 and IQM13



Disclaimer