Chiang Mai Med Bull 2005;44(4):137-145.

Original article

AN ANALYSIS OF NASAL RESPONSES AFTER HOUSE DUST MITES CHALLENGE IN PERENNIAL ALLERGIC RHINITIS

Sukit Roongapinun, M.D.,[1] Nutthiya Kraiwapan, M.D.,[1] Supranee Fooanant, M.D.[2]

[1]Department of Pharmacology, [2]Department of Otolaryngology, Faculty of Medicine Chiang Mai University

Abstract The nasal allergen challenge has been widely used in studying allergic rhinitis. A number of factors and limitations are involved, however, they are rarely reported in perennial allergic rhinitis patients. This report is a sub-analysis from our routine challenges of 44 patients with perennial allergic rhinitis, who are allergic to house dust mites-the most common allergen in Thailand. We described the subjective and objective (i.e. rhinomanometry) responses after house dust mite provocation and addressed the factors involved in nasal responses. The patients underwent a serial challenge with mixtures of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* by the disc method. The discs were placed bilaterally at 10-min intervals onto nasal mucosa. Just before the next provocation, the individual symptoms, total symptom score, and nasal airway resistance were assessed.

All symptoms, nasal airway resistance and nasal airflow were altered in a dose-dependent manner. The concentration that produced significant discrepancy from the baseline was 50 AU/mL for congestion and pruritus, and 100 AU/mL for rhinorrhea and sneezing. Clinical symptoms following the allergen challenge increased in accordance with wheal size to the antigens, *Dermatophagoides pteronyssinus* in particular (p=0.03) and disease severity (p=0.03). Increase in nasal airway resistance agreed with the congestion score (p=0.001), total nasal symptoms score (p=0.008), skin reactivity (p<0.001), and disease severity (p=0.02). In this study, the complete nasal obstruction led to 19 (7.4%) immeasurable resistance data in 11 patients (25.6%), especially, at 1,000 and 5,000 AU/mL. No serious adverse events were noticed.

Nasal allergen challenge is an effective approach to induce the symptoms and nasal airway resistance in perennial allergic rhinitis. The sneeze was unexpectedly less countable. Congestion and itching were the earliest symptoms found. Wheal size to antigens and disease severity are useful practically in predicting nasal responses. **Chiang Mai Med bull 2005;44(4):137-145.**

Keywords: nasal allergen challenge, nasal airway resistence, house dust mite, perennial allergic rhinitis

Nasal allergen challenge (NAC) essentially involves the diagnosis as well as the pathophysiologic and pharmacologic studies of allergic rhinitis. Unlike pollen challenge ground

Address requests for reprints: Sukit Roongapinun, M.D., Department of Pharmacology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. E-mail:sroongap@mail.med.cmu.ac.th

Received 5 December 2004, and in revised form 18 July 2005

work,[1,2] nasal responses after house dust mite challenge in perennial allergic rhinitis (PAR) have been rarely described. In fact, house dust mites cause the most common type of allergic rhinitis in Thailand. This analysis focused on, (a) the nasal reactions of forty-four house dust mite-sensitive rhinitics after serial house dust mite challenges, and (b) finding factors determining their nasal symptoms and nasal airway resistance. This study would ease the researchers into performing NAC more precisely and validly. The present report is a sub-analysis of our primary study, the allergen challenge for determining the cut-off level for positivity in perennial allergic rhinitis.[3]

Patients and methods

The protocol and consent form for the study were reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Chiang Mai University. Written informed consent was obtained from all subjects prior to enrollment. The study was carried out at the clinical pharmacology unit, where an emergency kit was always accessible.

The allergic rhinitis patients were included by meeting the following criteria: (1) age between 15-50 years, (2) diagnosis of perennial allergic rhinitis confirmed by history, physical examination and a positive skin test (mean wheal > 3 mm of negative control) to house dust mites (Der p, Der f),[4] and (3) no prior medication in a limited period of time before the study period (i.e. 1 week for a decongestant, 2 weeks for non-sedating antihistamine, and 4 weeks for topical or systemic steroid). The *exclusion criteria* were as follows: (1) history of severe asthmatic attack or anaphylaxis, and (2) relevant septal deviation, polyps, or sinusitis that remained active. Healthy controls were enrolled (n=28, 10 males, 18 females, 28.5±3.8 yrs, range 21-45 yrs). Symptom scores of pruritus, rhinorrhea, and obstruction were graded by patients as follows: 0= symptom not evident, 1= symptom present but not bothersome, 2= symptom bothersome but not intolerable, and 3= symptom persistent and intolerable.[5] Sneezing score was 0 for no sneeze, 1 for 1-5 sneezes, 2 for 6-10 sneezes, and 3 for 11 or more sneezes.[6] Total nasal symptom score (TNSS) was derived from the sum of all symptom scores. Grading of skin reactivity to the house dust mite was given as +1 for <3 mm, +2 for 3-5 mm, +3 for 5-7 mm, and +4 for >7 mm.[7]

Nasal allergen challenge

The patients underwent NAC by the disc method.[8] Briefly, the subjects was challenged with diluent (0.4% phenol in 0.9% normal saline solution) to prove the impurity of allergen solvents. In this study, the measurements at diluent challenge were regarded as a baseline of all parameters. A mixture of *D. pteronyssinus* and *D. farinae* (Therapeutic graded, Allertech, Thailand) was prepared in 50, 100, 500, 1,000, and 5,000 AU/mL, and 20 microliters were pipetted to two dry filter paper discs (punched out Whatman filter paper no.1, Whatman, England). The allergen discs were bilaterally placed over the inferior aspects of the inferior turbinates for 30 sec. The incremental doses of allergen were placed at 10-min intervals. The assessment of nasal symptom scores and total nasal airway resistance (NAR) was performed before the next challenge.

Active rhinomanometry

The nasal cavities were always inspected to confirm the absence of nasal secretions before measuring the NAR. The nasal airflow

and NAR were measured with computerized anterior rhinomanometry (Rhinomanometer, PC 200 ATMOS, Germany). Reading the NAR at 75 Pa of pressure gradient was based on a previous study in Thai.[9] The total NAR was derived from the following equation 1/ NAR_{total} = 1/NAR_{right} + 1/$NAR_{left.}$[10]

Statistical analysis

The Mann-Whitney test was used to analyze the symptom scores. Spearman's correlation study was employed to find the correlation among symptom scores, disease severity, and skin reactivity grading. The statistical software was MedCalc version 7.1 (MedCalc, Belgium). The statistical significance was defined for all tests at $p< 0.05$. All comparisons were based on two-sided tests.

Results

A total of 44 patients (17 males, 27 females, age 31.5+7.7 yrs, range 20-45 yrs) were enrolled into the primary study and analyzed for this report. One of 44 patients had immeasurable NAR from the first measurement, therefore, only 43 data were included in the NAR analysis. They all had persistent symptoms, and 25 of them (56.8%) had a moderate-to-severe degree of severity. Most patients had a wheal size grade of + 2 to Der p (61.3%) and Der f (70.4%). On arrival, the average total nasal airflow was 377.0+170.1 mL/sec and the total NAR, 0.25+0.15 Pa/mL/sec. The diluent did not affect the nasal responses determined by the unchanged TNSS and NAR before and after diluent challenge. Although, flow changes and itching score revealed significant changes.

The nasal symptoms generally responded well to the allergen challenge in a dose-dependent manner. The itching (p=0.007) and congestion (p=0.01) score rose significantly from the diluent baseline after 50 AU/mL of allergens, whereas the secretion (p=0.001) and sneezing score (p=0.05) rose significantly after 100 AU/mL. The individual scores, including itching, secretion, and congestion all mounted to a similar extent (Fig 1; p>0.05). However, the sneezing score increased to a lesser extent in relation to other symptoms (Fig 1; p<0.001 from 50 to 5,000 AU/mL).

The TNSS elevated significantly after 50 AU/mL (p=0.0004) compared to the healthy controls (Fig 2). The number of patients with TNSS > 5 was 11 (25%) at 1,000 AU/mL, and 37 (84.1%) at 5,000 AU/mL (Fig. 3). At the end of the challenge, 97% of patients complained of pruritus, 95.4% had rhinorrhea or obstruction, and 70.5% sneezed once or more. All sneezes occurred in the first 5 min after the allergen challenge.

The NAR was increased from 0.27±0.2 Pa/mL/sec after starting the diluent challenge to 1.70±2.3 Pa/mL/sec at the end of the challenge. NAR was clearly elevated with 1,000 and 5,000 AU/mL of allergens (Fig. 4, p=0.001 compared to controls). Nasal airflow was reduced in a stepladder pattern from 348.1±140.3 mL/sec to 221.5±152.2 mL/sec. According to the equation of resistance, the tranasal pressure was divided by flow.[11] Then, the NAR could not be obtained in this case. However, it should be realized that these cases were in fact markedly obstructive, since the severe blockage led to absence of flow. These sorts of immeasurable data (IM) were revealed in 19 of 258 total measurements (7.4%) from 11 of 43 patients (25.6%) at mostly 1,000 and 5,000 AU/mL (Fig 5). To the contrary, there were 5 patients (11.6%) at 1,000 AU/mL and 6 (13.9%) at 5,000 AU/mL who failed to illustrate an increase in NAR over the diluent baseline. Bilateral provocations led to an asym-

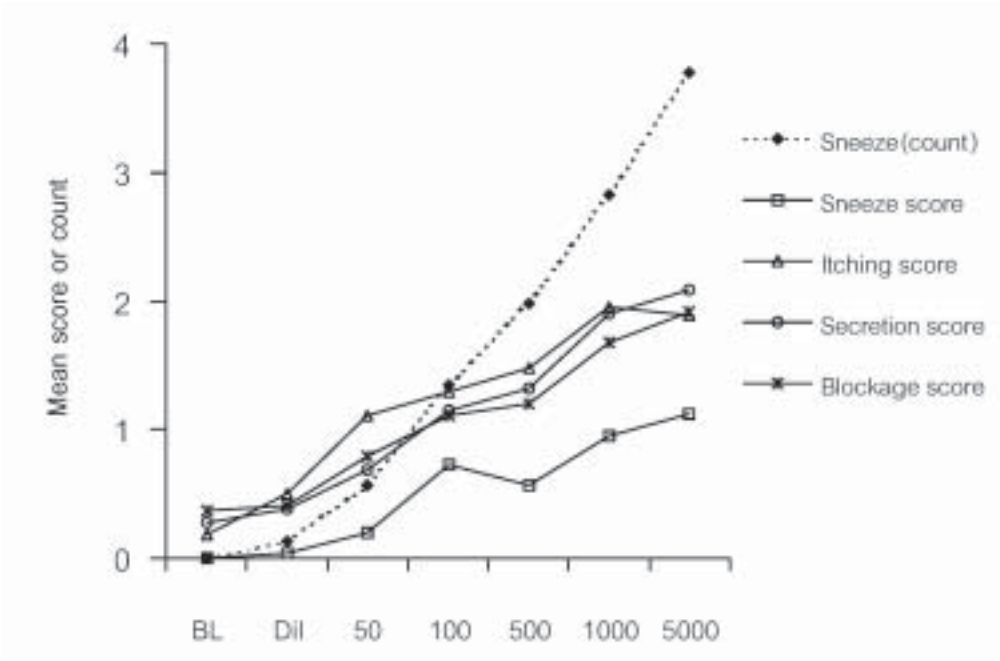

Figure 1. Individual symptom scores during allergen challenge. There is a statistical difference between sneeze score and other scores from an allergen concentration of 50 to 5,000 AU/mL (p<0.001).

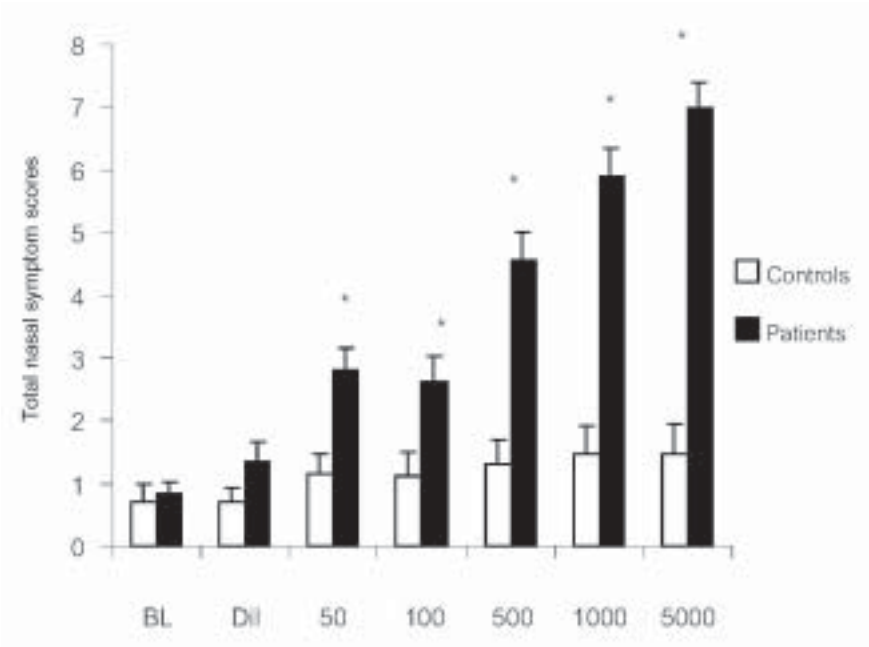

Figure 2. Total nasal symptom score (mean±SEM) of patients versus controls during challenge. *p<0.001 compared to controls.

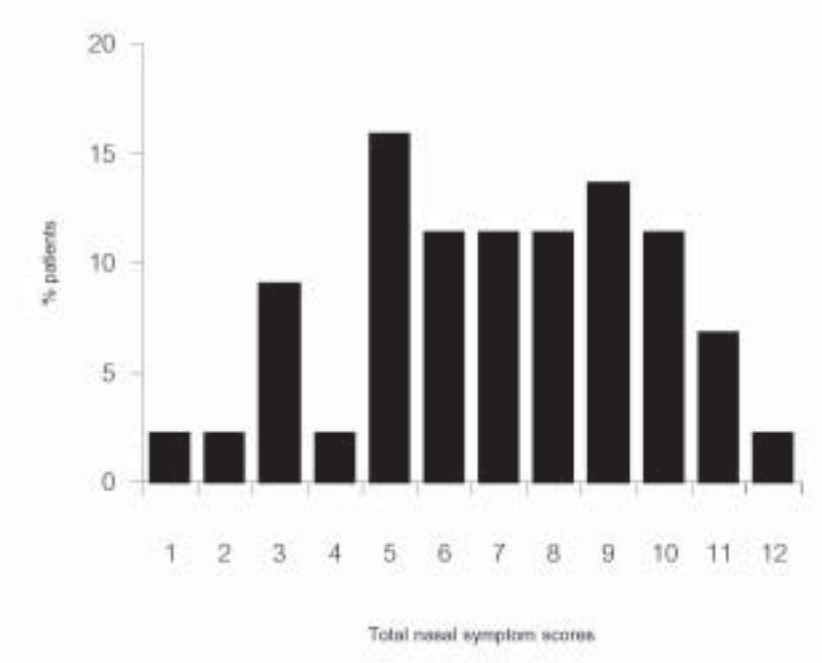

Figure 3. Total nasal symptom scores (percentage of patients) responding to an allergen concentration of 5,000 AU/mL.

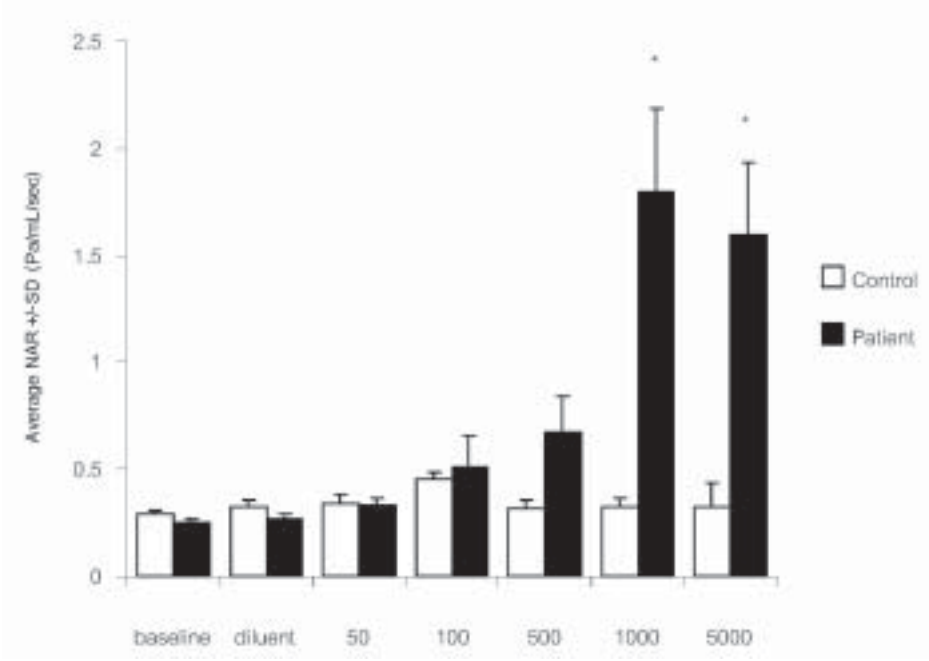

Figure 4. Average NAR+SD (Pa/mL/sec) following various allergen concentrations. * p=0.001 compared to the controls.

metrical rise in NAR (n=22, 51.1%). The rest were either bilaterally elevated (n=16, 37.2%) or bilaterally unresponsive (n=5, 11.6%).

Furthermore, it was found that the nasal

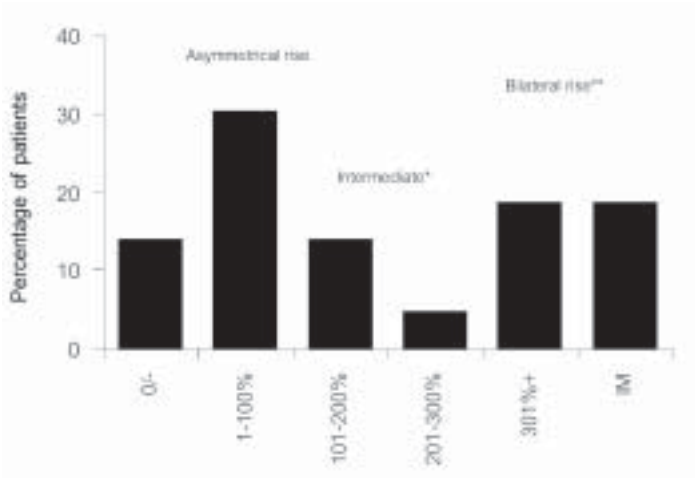

Figure 5 The percentage increase in NAR of patients with perennial allergic rhinitis (n=43) after serial nasal allergen challenges (see methods). IM denotes the immeasurable data (see text). The number of patients with bilateral responses from either intermediate or bilateral rise is superior to the asymmetrical rise (Fisher's Exact test, **p*=0.045 , ***p*=0.0002).

Table 1. Appraisal of skin reactivity grading and disease severity in relation to nasal responsiveness

Nasal responses	Parameters of interest	Evaluated correlation (Spearman's Rho, p-value)
Sneezing score	Der p size	Fair (r=0.353, *p*=0.03)
	Der f size	Poor
Itching score	Der p & Der f size	Poor
Secretion score	Der p & Der f size	Poor
Congestion score	Der p size	Fair (r=0.35, *p*=0.02)
	Der f size	Fair (r=0.33, *p*=0.03)
Total nasal symptom score	Der p size	Fair (r=0.461, *p* =0.03)
	Der f size	Poor
Total nasal symptom score	ARIA disease severity	Fair (r=0.326, *p*=0.03)
Nasal airway resistance	Der p size	Good (r=0.571, *p*=0.001)
	Der f size	Good (r=0.664, *p*=0.0003)
Nasal airway resistance	ARIA disease severity	Fair (r= 0.336, *p*=0.02)

responses increased in accordance with the wheal size to the antigen and disease severity (Table 1). The nasal symptom scores, which correlated with sex, age, body mass index, birth month, and nasal airflow on arrival were not noted. The increase in NAR also correlated with the congestion score (r=0.487, *p*=0.001) and TNSS at 1,000 AU/mL (r= 0.458, *p*= 0.008).

The most common adverse experiences from the test were a stinging sensation and odor disfavor from placing a 5,000 AU/mL disc into the nasal mucosa. No systemic reaction occurred during the test.

Discussion

The study of clinical responses following nasal allergen challenge is scarce in perennial allergic rhinitis (PAR), although many authors have reported biochemical or cytologic stud-

ies after house dust mite challenge. In general, NAC offered good responses in most patients (70-85%) by symptom score criteria of five or more. Concerning the rhinomanometry, most of the patients (86.1-88.4%) responded to either one of two doses in our challenges.

Most symptoms were negligible often 15 min of challenge, even though nasal congestion was confirmed by NAR and rhinorrhea persisted further (data not shown). A previous study confirmed an increase in NAR (for 10-30 min) and rhinorrhea (at 1 hr in 92% of cases).[1] Sneezing in this study was observed invariably in the first five minutes, as reported in another study.[1] Sneezing count was emphasized on because of its possible sign of allergen exposure and it might be an objective tool. Unfortunately, around 30% of cases in our study had never experienced a sneeze. We encountered a median of 1.5 sneezes (range 0-12) at 1,000 AU/mL, and 3 sneezes (range 0-12) at 5,000 AU/mL. A distinctively gradual increase in sneezing score was found (Fig. 1), therefore, we agreed with lower sneeze counts in the sneeze score as recommended in one guideline.[12]

Lebel et al.[2] reported that in pollen sensitive subjects rhinorrhea was present in 100% of positive challenges, with nasal obstruction in 97%, pruritus in 60% and sneezing (scoring >3 sneezes) in 50%. This PAR study found 97% pruritus, 95.4% rhinorrhea or obstruction, and 70% sneezing (presence of sneeze, once or more). Perhaps, a different weight regarding various symptoms in rhinitis questionnaires[13,14] is warranted.

The dose that produced a significant increase in itching and nasal congestion was lower than that for sneezing and rhinorrhea (50 vs 100 AU/mL). This might correspond with the observation that nasal blockage caused by chronic inflammation was more pronounced in PAR.[15,16]

It has been found that the wheal size to the allergen correlated with the nasal responses.[7,17] In addition to skin reactivity, we revealed that ARIA disease severity[18] modestly predicted the nasal responses. Thereby, it is advisable to implicate nasal responses to the nasal allergen challenge. Regarding skin-nasal interelationship, the mechanism likely results from the high IgE level found in these patients,[19] which can effectively accommodate the degranulation of mast cells located in both the skin and nasal mucosa. However, we and others[19] found that Der f is less valuable than Der p in terms of predicting nasal responses, and reflecting the different antigenicity of Der p and Der f.[20]

We showed that there was a correlation between increasing NAR and congestion score evaluation, indicating the effective subjective assessment in our model,[21] and the bimodal pattern of increase in NAR was noted (Fig 5). We hypothesized that patients possibly possess the disintegrative vascular capacitance in response to the allergen, and then we conducted the unilateral NAR analysis. After bilateral provocations, we found that the nasal resistance often increased in a unilateral fashion, as previously described.[22,23] As a result, the total NAR from certain patients was not increased greatly.

Conclusion

Nasal allergen challenge is an effective approach that produces nasal symptoms and a rise in NAR. Wheal size to antigens (Der p, in particular) and disease severity can partly determine nasal responsiveness. The sneeze seems less countable. Priming with persistent

allergens within the household may influence higher sensitivity of the nasal congestion in PAR patients. Rhinomanometry is a fairly good method for producing evidence of nasal obstruction after nasal provocation. Nevertheless, bilateral provocations mostly resulted in unilateral response. Generally, nasal allergen challenge is tolerable.

References

1. Wang D, Smitz J, Waterschoot S, Clement P. An approach to the understanding of the nasal early-phase reaction induced by nasal allergen challenge. Allergy 1997;52:162-7.
2. Lebel B, Bousquet J, Morel A, Chanal I, Godard P, Michel FB. Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grass-pollen grains. J Allergy Clin Immunol 1988;82:869-77.
3. Roongapinun S, Wajajamreon S, Fooanant S. Diagnostic Intervention by Allergen-induced Nasal Obstruction Simultaneously Evaluated by Anterior Rhinomanometry (DIAGNOSE-AR study). [Poster Presentation, World Allergy Organization Congress XVIII, 2003, Vancouver, Canada]
4. Duffy DL, Mitchell CA, Martin NG. Genetic and environmental risk factors for asthma: a cotwin-control study. Am J Respir Crit Care Med 1998; 157:840-5.
5. Dolovich J, Moote DW, Mazza JA, Clermont A, PetitClerc C, Danzig M. Efficacy of loratadine versus placebo in the prophylactic treatment of seasonal allergic rhinitis. Ann Allergy 1994;73:235-9.
6. Pipkorn U. Budesonide and nasal allergen challenge testing in man. Allergy 1982;37:129-34.
7. Kanthawatana S, Maturim W, Fooanan S, Trakultivakorn M. Skin prick reaction and nasal provocation response in diagnosis of nasal allergy to the house dust mite. Ann Allergy Asthma Immunol 1997;79:427-30.
8. Wagenmann M, Baroody FM, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. The effect of terfenadine on unilateral nasal challenge with allergen. J Allergy Clin Immunol 1994;93:594-605.
9. Bunnag C, Jareoncharsri P, Dachpunpour P, Vitavasiri A. Nasal airway resistance in asymptomatic Thai population. Siriraj Hosp Gaz 1995;47:721-5.
10. Gerth VW, Dieges PH. Comparison of nasal responsiveness to histamine, methacholine and phentolamine in allergic rhinitis patients and controls. Clin Allergy 1987;17:563-70.
11. Davis SS, Eccles R. Nasal congestion: mechanisms, measurement and medications. Core information for the clinician. Clin Otolaryngol Allied Sci 2004;29: 659-66.
12. Gosepath J, Amedee RG, Mann WJ. Nasal provocation testing as an international standard for evaluation of allergic and nonallergic rhinitis. Laryngoscope 2005;115:512-6.
13. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of allergic rhinitis symptoms in an adult Danish population. Allergy 1999;54:1194-8.
14. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995; 8:483-91.
15. Naclerio R, Solomon W. Rhinitis and inhalant allergens. JAMA 1997;278:1842-8.
16. Naclerio RM. Pathophysiology of perennial allergic rhinitis. Allergy 1997;52:7-13.
17. Klaewsongkram J, Ruxrungtham K, Wannakrairot P, Ruangvejvorachai P, Phanupak P. Eosinophil count in nasal mucosa is more suitable than the number of ICAM-1-positive nasal epithelial cells to evaluate the severity of house dust mite-sensitive allergic rhinitis: a clinical correlation study. Int Arch Allergy Immunol 2003;132:68-75.
18. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) in collaboration with the World Health Organization (WHO). J Allergy Clin Immunol 2001;108: S147-S336.
19. Dokic D, Jovanovic S, Berghaus A, Brunnee T. Diagnosis of nasal allergy to the house dust mite. Rhinology 1991;29:117-23.
20. Pernas M, Sanchez-Ramos I, Sanchez-Monge R, et al. Der p 1 and Der f 1, the highly related and major allergens from house dust mites, are differentially affected by a plant cystatin. Clin Exp Allergy 2000; 30:972-8.

21. Simola M, Malmberg H. Sensation of nasal airflow compared with nasal airway resistance in patients with rhinitis. Clin Otolaryngol Allied Sci 1997;22: 260-2.
22. Simola M, Malmberg H. Nasal histamine reactivity; relationships to skin-test responses, allergen provocation and symptom severity in patients with long- continuing allergic rhinitis. Acta Otolaryngol 2000;120:67-71.
23. Wang D, Clement P. Assessment of early- and late-phase nasal obstruction in atopic patients after nasal allergen challenge. Clin Otolaryngol 1995;20: 368-73.

การประเมินการตอบสนองของจมูกในผู้ป่วยภูมิแพ้จมูกอักเสบชนิดเป็นตลอดปีที่ได้รับการกระตุ้นโพรงจมูกด้วยไรฝุ่น

สุกิจ รุ่งอภินันท์, พ.บ.,[1] ณัฐิยา ไกรวพันธุ์, พ.บ.,[1] สุปราณี ฟูอนันต์, พ.บ.[2]

[1]ภาควิชาเภสัชศาสตร์, [2]ภาควิชาโสต ศอ นาสิกวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บทคัดย่อ การกระตุ้นโพรงจมูกด้วยสารก่อภูมิแพ้ถูกนำมาใช้อย่างแพร่หลายในการศึกษาโรคภูมิแพ้จมูกอักเสบ แต่มีรายงานในผู้ป่วยภูมิแพ้จมูกอักเสบชนิดเป็นตลอดปีไม่มากนัก รายงานฉบับนี้รายงานการตอบสนองของจมูกภายหลังการกระตุ้นโพรงจมูกด้วยไรฝุ่นในผู้ป่วยภูมิแพ้จมูกอักเสบชนิดเป็นตลอดปีจำนวน 44 ราย โดยประเมินอาการทางจมูกด้วยคะแนนตามความรุนแรง ร่วมกับการวัดการอุดตันของโพรงจมูกด้วยเครื่องไรโนมาโนเมททรี

ผลการศึกษา พบว่า ระดับความรุนแรงของอาการทางจมูก แรงต้านในโพรงจมูก และอัตราเร็วของอากาศที่ผ่านโพรงจมูก สัมพันธ์โดยตรงกับความเข้มข้นของไรฝุ่นที่ใช้กระตุ้น ความเข้มข้นที่ทำให้ผู้ป่วยมีอาการคัดและอาการคันจมูกมากขึ้นเมื่อเทียบกับก่อนได้รับการกระตุ้นด้วยไรฝุ่นคือ 50 เอนติเจนยูนิต ต่อ มล. และความเข้มข้นที่ทำให้มีน้ำมูกและอาการจามมากขึ้นคือ 100 เอนติเจนยูนิต ต่อ มล. ความรุนแรงของอาการที่เกิดขึ้นภายหลังการกระตุ้นโพรงจมูกด้วยไรฝุ่นสัมพันธ์กับขนาดของตุ่มนูนที่เกิดจากการทดสอบภูมิแพ้ทางผิวหนังด้วยไรฝุ่นและระดับความรุนแรงของโรคภูมิแพ้จมูกอักเสบของผู้ป่วย ผลไรโนมาโนเมททรีมีความสัมพันธ์กับคะแนนอาการคัดจมูก คะแนนรวมของอาการทางจมูกทั้งหมด การทดสอบทางผิวหนัง และระดับความรุนแรงของโรคภูมิแพ้ ในการศึกษานี้ไม่พบผลข้างเคียงที่รุนแรงจากการกระตุ้นโพรงจมูกด้วยไรฝุ่น

การกระตุ้นโพรงจมูกด้วยสารก่อภูมิแพ้เป็นวิธีที่มีประสิทธิภาพในการก่อให้เกิดอาการในโพรงจมูกของผู้ป่วยภูมิแพ้จมูกอักเสบชนิดเป็นตลอดปี ซึ่งภายหลังการกระตุ้นด้วยไรฝุ่น จะเกิดอาการคัดจมูกและอาการคันนำมาก่อน ส่วนอาการจามเกิดน้อยกว่าที่คาดไว้ ขนาดของตุ่มนูนที่เกิดจากการทดสอบผิวหนัง และระดับความรุนแรงของโรคของผู้ป่วยสามารถใช้ทำนายการตอบสนองของจมูกได้
เชียงใหม่เวชสาร 2548;44(4):137-145.

คำสำคัญ: การกระตุ้นโพรงจมูกด้วยสารก่อภูมิแพ้ ภูมิแพ้จมูกอักเสบชนิดเป็นตลอดปี แรงต้านในโพรงจมูก ไรฝุ่น