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Evaluation of Threshold Criteria for the Nasal Histamine Challenge Test in Perennial Allergic Rhinitis

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SUMMARY **Nasal reactivity to histamine was determined in patients with perennial allergic rhinitis and in control subjects. A histamine titration method delivered by a metered dose pump was used. Stuffiness, itching, and the number of sneezes were recorded, nasal secretions measured, and nasal airway resistance was recorded by active anterior rhinomanometry. Increased nasal reactivity to histamine was observed among rhinitic patients and inversely correlated with the severity of nasal symptoms. A 3-fold increase of post-saline nasal airway resistance (NAR) best differentiated the nasal responses to histamine in rhinitic patients from those in control subjects. A histamine dose of ≤ 2.5 μg provoked a 3-fold increase in NAR, strongly suggesting moderate or severe symptomatic rhinitis in most cases. Nasal provocation techniques might be a useful tool for objectively assessing disease severity and response to treatment in perennial allergic rhinitis.**

Allergic rhinitis is one of the most common allergic diseases. Its assessment relies mainly on the subjective evaluation of nasal symptoms. However, measurements of changes in nasal patency following a challenge with histamine or an allergen provide useful objective information.[1-3] The nasal histamine challenge test can differentiate allergic rhinitis patients from controls,[3-7] but there is no consensus on a standardized method of nasal provocation. This study attempts to standardize the histamine nasal challenge test and to determine which method of assessing dose response curves best discriminates between controls and patients with perennial allergic rhinitis.

PATIENTS AND METHODS

Patients

Study subjects included both patients attending Maharaj Nakohn Chiang Mai Hospital Allergy Clinic as well as hospital staff and students. Individuals with respiratory tract infections during the preceding month and patients receiving immunotherapy were excluded. Study subjects were classified as having symptomatic perennial allergic rhinitis by skin prick tests and complaints of nasal stuffiness, sneezing and aqueous rhinorrhea, which occurred on at least 50% of the days in every month of the year. All classifications were performed by a single investigator (SK). Perennial rhinitis patients had positive skin prick reactivity to one or more common allergens including house dust, house dust mites (*Dermatophagoides farinae* and *D. pteronyssinus)*, and cockroach allergen extracts (Greer Laboratories, Inc., Lenoir, NC, USA). Histamine solution (1 mg/ml) was used as a positive control. None of the subjects had nasal polyposis or septal deformity. Medication was withheld 2 days prior to testing; topical corticoste-

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roids and long-acting antihistamines were withheld 4 weeks prior to testing. The study was approved by the Medical Ethics Committee of the Chiang Mai University, Faculty of Medicine and all subjects provided written informed consent.

Assessment of symptoms and signs

Subjects were questioned about nasal congestion, rhinorrhea, itching, and sneezing during the 2 previous weeks. Mucosal/turbinate swelling, secretions, and turbinate color were assessed by direct nasal inspection. Symptoms and signs were scored from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe); the maximum total score possible was 18. Baseline scores of ≤ 6 was considered mild, a score of 7-11 was moderate and ≥ 12 was severe.

Nasal histamine provocation test

Subjects waited 30 minutes before the test to allow nasal mucosa to become acclimatized. After rhinoscopy, a control solution of phosphate-buffered saline was sprayed into each nostril using a metered dose pump delivering exactly 100 µl of solution. Increasing doses of histamine hydrochloride (0.025, 0.25, 2.5, 25, 125, and 250 µg of histamine base per 100 µl) were then applied to both nostrils at 5 minute intervals. After each provocation, nasal secretions were collected on a paper handkerchief. Secretions were measured by weighing the handkerchiefs before and after collection; itching and stuffiness were scored, and sneezes were counted. Nasal airway resistance (NAR) was measured by active anterior rhinomanometry (Rhinomanometer PC200, ATMOS, Germany) three times in each nostril immediately before the next provocation. The median value of three consecutive measurements was the NAR. The more reactive side was considered.

Statistical Analysis

Nasal resistances were compared by analysis of variance and Student's *t* test. Baseline symptom and sign scores of rhinitic patients and control subjects were compared by the Mann-Whitney U-test. Results from the nasal provocative tests were log-transformed and compared among groups with parametric tests. Sensitivity, specificity, positive predictive value, and negative predictive value were assessed at arbitrary "cut off" points with standard 2 by 2 contingency tables in which "disease" and "non-disease" were tabulated against "positive" and "negative" tests.[8]

RESULTS

Evaluation of nasal provocation test response results are shown in Table 1. Eighty four subjects were enrolled, 40 of whom had perennial allergic rhinitis. Rhinitic patients had more nasal stuffiness , mucosal edema, and significant higher baseline NAR values (Table 2). Nasal reactivity to histamine was greater in the right nostril

Table 1. Evaluation of nasal provocation response.

Clinical findings				Rhinomanometry (l/sec-Pascal)	
Nose itching		***Sneezing***		**Fold difference from baseline values.**	
none	0 Point	none	0 P	≤ 1	0 P
mild	1 P	mild	1 P	> 1- 2	1 P
moderate	2 P	moderate	2 P	> 2- 3	2 P
severe	3 P	severe	3 P	> 3	3 P
Nasal stuffiness		***Hypersecretion***			
none	0 P	(fold increase in secretion wt. from baseline values).			
mild	1 P	≤ 1	0 P		
moderate	2 P	> 1- 3	1 P		
severe	3 P	> 3- 5	2 P		
		> 5-10	3 P		
		> 10	4 P		

in 64% of cases; was greater in the left nostril in 28% and was bilaterally equal in 8%. One mild rhinitis patient could not complete the provocation test because of excessive sneezing after 25 μg dose of histamine and data from this subject were not included in the analysis.

A 1 point increase in the itching score, a 5-fold increase in the weight of nasal secretions, a 3-fold increase in NAR, and a total symptom/sign score of 12 or more significantly discriminated rhinitic patients from control subjects (Table 3). There were significant increases in nasal reactivity to histamine in rhinitic patients compared to controls. Patients with severe nasal symptoms had higher nasal reactivity to histamine than did those with mild symptoms (Figure 1). Patients with rhinitis required almost twenty times less histamine to provoke a 3-fold increase in NAR than did control subjects (Table 3). Baseline difference in NAR did not affect results (data not shown). Most controls (37 of 44) required more than 10 μg to provoke a response; all but one subject responded to histamine doses > 2.5 μg. There were no significant differences in geometric mean end-point histamine doses between controls and patients with mild rhinitis; however, significant differences were detected between moderate and severe rhinitis. Most severe rhinitic patients (8/10) and half of the moderate group (9/18) responded to < 2.5 μg of histamine. Sensitivity, specificity and predictive values are shown in Table 4.

Table 2. Demographic data, baseline nasal stuffiness symptoms, mucosal edema and nasal airway resistance.

Characteristics	Controls (n = 44)	Rhinitis (n = 40)
Median age (yr)	22 (9-46) [a]	22 (9-38)
Sex (M/F)	23/31	22/18
Stuffiness score	0.5 (0.8)[b]	1.6 (1.0)*
Mucosal edema score	1.7 (0.8)	2.2 (0.7)*
Total NAR[c]	0.3 (0.1)	2.2 (5.3)*
(l/sec-Pascal)	(0.1-0.6)[a]	(0.1-17.5)

[a] range
[b] mean (SD)
[c] determined at 150 Pascal
* $p < 0.05$ compared to controls

DISCUSSION

The increased NAR demonstrated in our study is consistent with the findings of other inves-

Table 3. End-point histamine dose (μg) provoking nasal responses. Data represent geometric mean (range).

Nasal Responses	Controls (n = 44)	Rhinitis (n = 39)	p-value	Fold difference
Itching[a]	17.8 (0.3- >250)	4.8 (0.3-125)	0.01	3.7
Stuffiness[a]	4.3 (0.3-125)	2.8 (0.3-125)	0.62	1.5
Sneezing[b]	68.0 (2.5- >250)	26.3 (0.03- >250)	0.08	2.6
Secretion wt[c]	76.3 (0.3- >250)	39.3 (0.3- >250)	0.04	1.9
NAR[d]	56.7 (1.0- >250)	2.9 (0.03->250)	<0.0001	19.6
Total score[e]	97.7 (9.0- >250)	17.4 (0.1- >250)	<0.0001	5.6

[a] One point increase in symptom score.
[b] Presence of sneeze
[c] Five fold increase from baseline value.
[d] Three fold increase from baseline value.
[e] Total score of ≥ 12 points.

Table 4. Sensitivity, specificity and predictive values of the histamine nasal challenge test.

Threshold criteria	Cumulative end-point histamine dose (μg)			
	0.25	2.5	25	125
Nasal itching	0.2/0.9[a] (0.6/0.5)[b]	0.5/0.8 (0.7/0.6)	1.0/0.2 (0.5/0.9)	1.0/0.1 (0.5/1.0)
3-fold increase in NAR response	0.3/1.0 (1.0/0.6)	0.4/1.0 (0.9/0.7)	0.6/0.7 (0.6/0.7)	0.9/0.5 (0.6/0.8)
Total score ≥ 12 points	0.05/1.0 (1.0/0.6)	0.2/1.0 (1.0/0.6)	0.7/0.8 (0.8/0.7)	0.8/0.4 (0.6/0.7)

[a] Sensitivity/specificity
[b] Positive/ negative predictive values

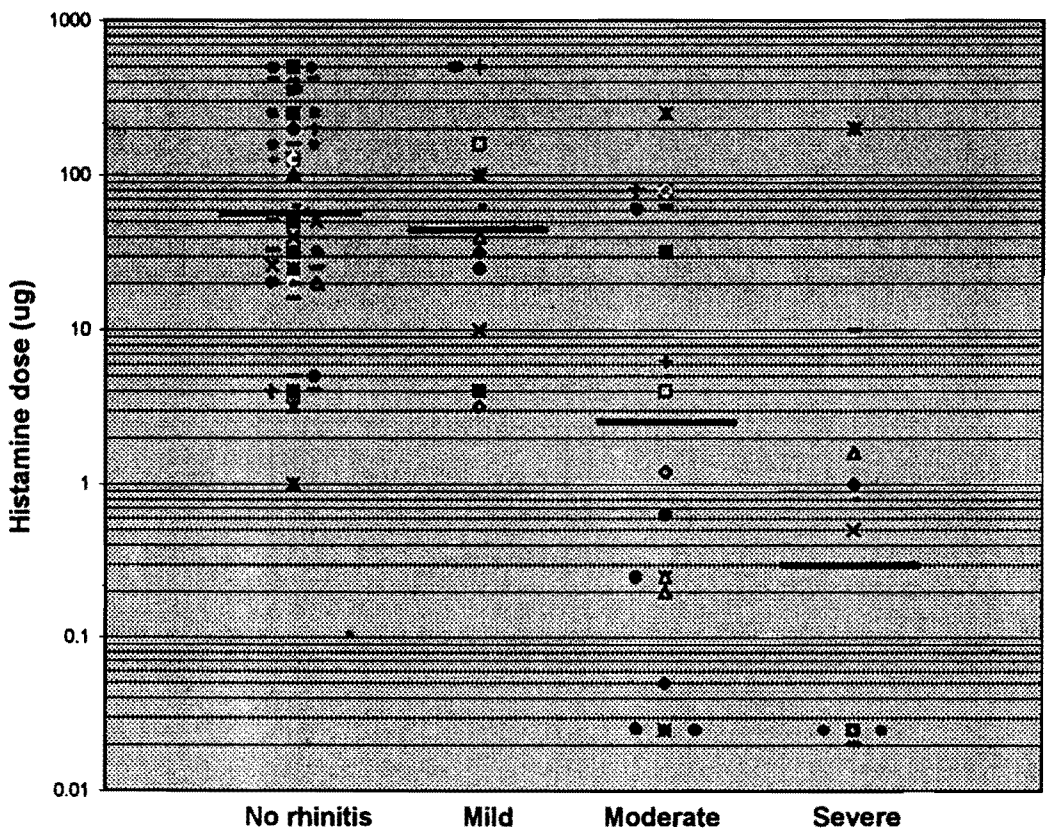

Fig. 1. End-point histamine dose provoking 3-fold increase in NAR response from baseline values in 44 control subjects and 39 patients with mild (n = 11), moderate (n = 18) and severe (n = 10) perennial allergic rhinitis. Solid lines represented the geometric mean.

tigators.[2-7] The routine use of rhinomanometry to the management of patients with allergic rhinitis is hampered by wide variability in the results of repetitive testing.[1] However, this method can give reproducible results when a change in NAR response is used as the endpoint.[7, 9] Neither sneezing nor nasal stuffiness differentiated rhinitis patients from controls in our investigation, in contrast to some published reports.[2-3] The best discriminator was a 3-fold increase in NAR compared to baseline value. NAR response could also separate mild rhinitic patients from those with moderate or severe symptoms. We found, as have others, that baseline difference in NAR did not affect outcome.[4, 9] Neither 1- nor 2-fold increases in NAR discriminated between the two groups (data not shown). Additional useful markers of disease were a 1-point increase in the itching score, a 5-fold increase in the weight of nasal secretions, and a total symptom/sign score of 12 points or more. Nasal symptom score criteria are particularly useful in individuals unable to perform NAR.

A 3-fold increase in NAR provoked by 2.5 μg histamine had specificity and high positive predictive value for diagnosing allergic rhinitis, but lacked sensitivity (Table 4). Raising the dose of histamine dose to 25 μg would increase sensitivity but decrease specificity and positive predictive value.

Allergen skin testing has been commonly used to diagnose allergic rhinitis because it is simple, rapid, cheap, sensitive and reproducible, However, a positive result only indicates an IgE response to a specific allergen. Histamine nasal provocation testing, however, offers an objective assessment of severity and nasal reactivity to non-specific stimuli. This technique could be of use in evaluating the response to different treatments for perennial rhinitis. We found that the nasal histamine provocation method was useful in assessing non-specific nasal reactivity and severity and that NAR was the most sensitive threshold criterion.

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