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Histamine threshold and nasal hyperreactivity in non specific allergic rhinopathy

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SUMMARY

The authors studied the histamine threshold (endpoint concentration for a 100% pressure gradient increase at a flow of 0.25 liter/second) in a group of 29 patients suffering from non specific allergic rhinopathy and a control group of 15 normal subjects. The result of the nasal challenge was measured with two different methods of rhinomanometry: the passive anterior rhinomanometry (P.A.R.) and the active anterior rhinomanometry (A.A.R.).

There existed a slightly significant difference ($P \leq 0.05$) in histamine threshold between the patient and the control group. The 21 in duplo performed histamine challenges showed the very good reproducebility of the method.

Finally, the A.A.R. method turned out to be slightly more sensitive than the P.A.R.-method.

Nasal hyperreactivity is a condition of some patients in which there exists an overreactivity of the nasal mucosa on non specific endogenous or exogenous stimuli. Normal subjects also react to these stimuli but not in such an excessive and prolonged way as hyperreactive patients do.

According to Melon (1964), McLean et al. (1979), Van Cauwenberge (1980), Broms et al. (1981), Andersen et al. (1982), Mygind and Lowenstein (1982), Cole (1982), Eccles (1982) these stimuli can be from endogenous (physical stress, mechanical irritation, endocrine stimulation or poor venous return) or exogenous (thermal, mechanical stimulation, humidity, or drug induced) origin.

This hyperreactive condition is often seen in patients with non specific allergic or non atopic rhinopathy. Other authors have named this condition non specific perennial rhinitis or vasomotor rhinitis (Hansel, 1953; Mygind, 1978; Huizing, 1979; Svensson, 1981). The symptoms of this condition are very similar to those of atopic rhinopathy and can be induced in normal as well as in patients by a nasal provocation test with histamine.

The purpose of this study was to find out if there exists a different histamine threshold (endpoint concentration) during nasal provocation in normal subjects and patients with non specific allergic rhinopathy. A second goal was to confirm the reproducebility of the nasal histamine challenge test. A third aim consisted in

comparing the value of the active and passive anterior rhinomanometry for measuring the result of the nasal challenge.

MATERIAL AND METHODS

A first group consisted of 29 patients with typical complaints of nasal obstruction accompanied by sneezing and eventually rhinorrhea. All these patients had negative allergen skin tests for grass, weed, trees, house dust, house dust mites, animals, molds and/or negative RAST score for the same allergens.

12 of these patients had only one nasal provocation test and 17 had two nasal provocation tests with an interval of at least 14 days. Therefore, 46 nasal provocations with histamine were carried out in this group of patients.

A second group consisted of 15 normal test subjects. In this control group, 11 test subjects had only one nasal provocation test and 4 had two nasal provocation tests. Therefore 19 nasal provocation tests were performed in the control group.

Before performing a nasal provocation test, the use of drugs, three days to the test, was ruled out. The nasal provocation test was carried out in the following way: the nasal patency was measured (initial value), then a control solution aerosol was applied to both nasal cavities for one minute with a Heyer nebulizer, then the nasal patency was measured immediately after the application and again after five minutes, then a histamine aerosol was applied in the same way for one minute and the same measurements were performed. Eight different concentrations of histamine were used i.e.: 0.25 mg/ml, 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 4 mg/ml,

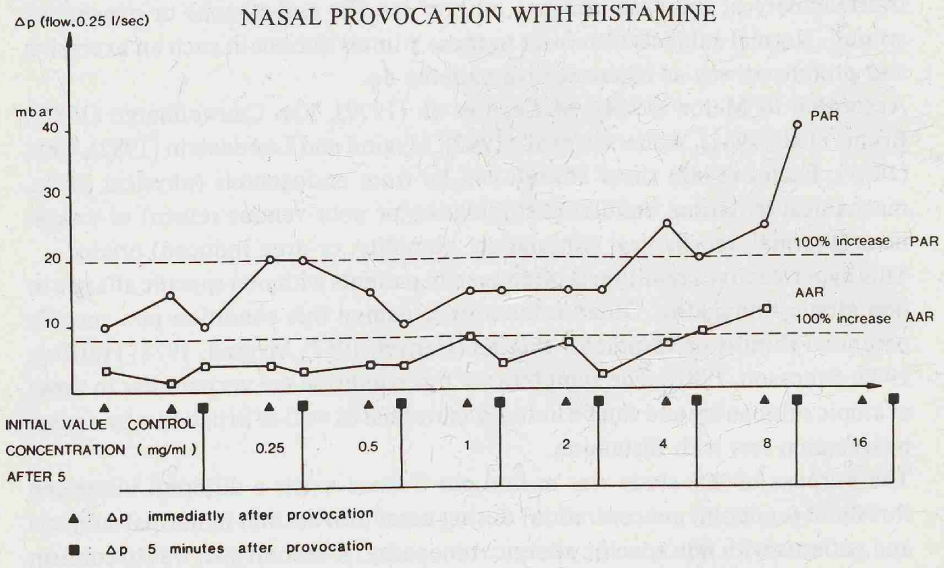

Fig. 1a. Both methods of rhinomanometry show a 100% increase at 4 mg/ml histamine.

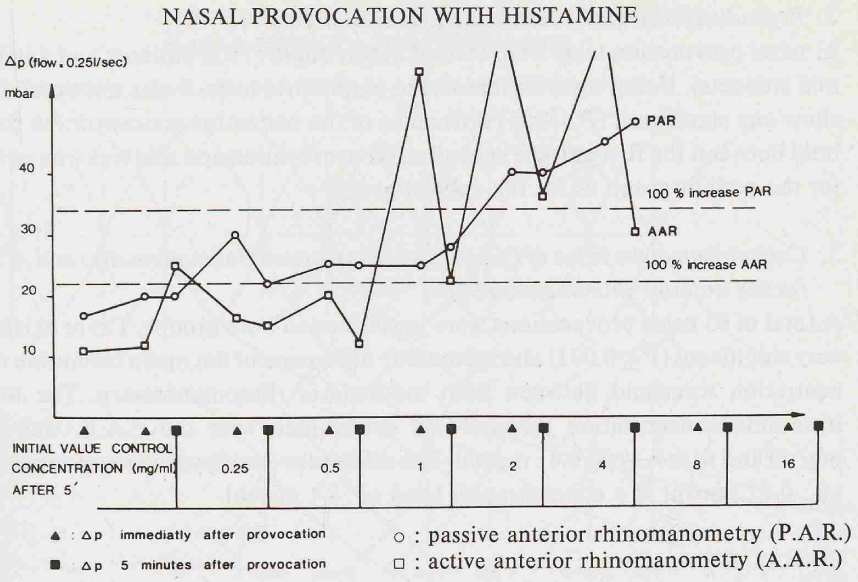

Fig. 1b. The A.A.R. shows at a 100% increase at 1 mg/ml and the P.A.R. at 2 mg/ml histamine.

8 mg/ml, 16 mg/ml, 32 mg/ml. The test was stopped when there occurred a decrease of the nasal patency untill twice the initial value (a 100% increase of the resistance) was obtained for at least five minutes. This endpoint concentration was noted as the histamine threshold. The pressure gradient at a flow of 0.25 liter per second (measure for the nasal resistance: Clement et al., 1978), was measured with the passive anterior rhinomanometer (P.A.R. rhinomanometer of the Heyer Company). For the active anterior rhinomanometer according to Bachman (A.A.R. rhinomanometer of the EVG Elektronic Vertriebs - GmbH, Ludwigshafen), the pressure gradient at a flow of 0.25 l/sec was measured in order to have comparable data with the P.A.R.

RESULTS

1. *Comparison of the mean histamine concentration threshold between patients with non specific allergic rhinopathy and a control group*

It appeared that there existed a slightly significant ($P \leq 0.05$) difference of histamine concentration threshold between both groups. The patient group had a mean histamine threshold of 3.22 mg/ml with P.A.R. and a 2.47 mg/ml threshold with the A.A.R. The mean histamine concentration threshold of the control group was 4.90 mg/ml with the P.A.R. and 3.23 mg/ml with the A.A.R.; these values are significantly higher than those for the patient group.

2. *Reproducebility of the histamine provocation test*
21 nasal provocation tests were carried out in duplo (17 in patients and 4 in normal subjects). Using three different non parametric tests, it was not possible to show any significant ($P > 0.05$) difference of the histamine concentration threshold between the first and the second nasal provocation and this was true as well for the patient group as for the control group.

3. *Comparison of the value of P.A.R. (passive anterior rhinomanometry) and A.A.R. (active anterior rhinomanometry)*
A total of 65 nasal provocations were performed in both groups. There existed a very significant ($P \leq 0.001$) and systematic difference of the mean histamine concentration threshold between both methods of rhinomanometry. The mean histamine concentration threshold as determined with the P.A.R. was 4.18 mg/ml and with A.A.R. 3.41 mg/ml. The difference itself however was very small i.e.: 0.77 mg/ml at a concentration level of ± 4 mg/ml.

CONCLUSION

From the results one can state that:

1. As a rule the chance of finding a histamine threshold lower than 4 mg/ml will be higher in patients with non specific allergic rhinopathy (vasomotor rhinitis) than in normal test subjects, although there exists a very important overlap.
2. The nasal provocation test, in the way it is carried out in this paper, gives a histamine threshold which is very reproduceble both in patients and in normal test subjects.
3. With the active anterior rhinomanometry (A.A.R.) one finds a mean histamine concentration threshold which is very significantly lower than with the passive anterior rhinomanometry (P.A.R.). The difference, however, is very small (less than one concentration step).

DISCUSSION

From the literature one knows that in the lower respiratory tract histamine elicits stronger responses in atopic patients than in normal test subjects (Curry, 1946; Tiffeneau, 1959; Voorhorst, 1962). In the upper respiratory tract, the results of histamine nasal challenge on patients with and without atopy are contradictory. Some authors (McLean et al., 1977; Cuercio et al., 1979; Svensson, 1981) reported equal nasal reactions on histamine challenge in normal and atopic subjects while others (Okuda, 1977; Okuda et al., 1982; Borum, 1979) on the contrary found differences in histamine sensitivity of both groups. Borum (1979) showed a more marked nasal response on histamine aerosol provocation in patients with perennial rhinitis (specific and non specific); this finding was confirmed in our

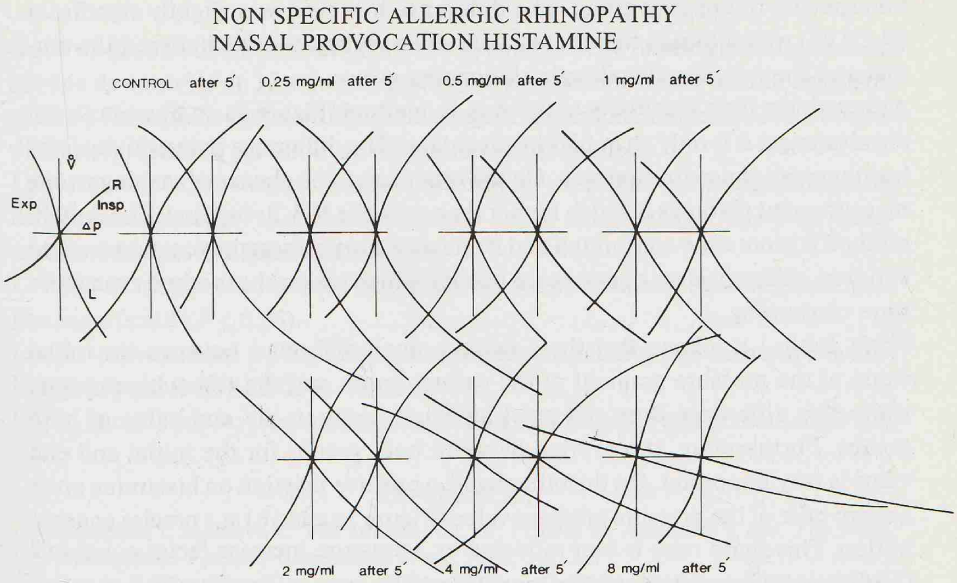

Fig. 2a. Histamine provocation becomes positive at 4 mg/ml (left nasal cavity).

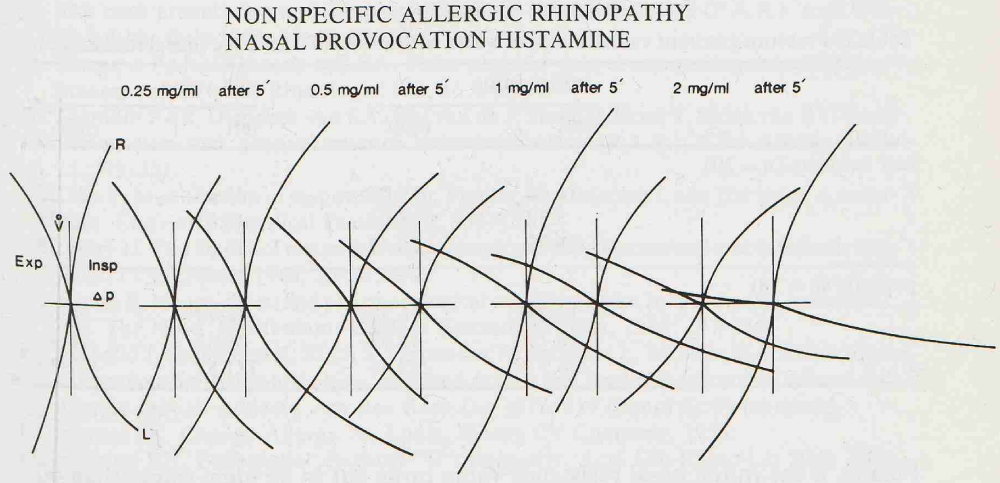

Fig. 2b. Histamine provocation becomes positive at 1 mg/ml (left nasal cavity).
- horizontal axis: pressure gradient
- vertical axis: flow
- right upper - left lower quadrant: right nasal cavity recording
- left upper - right lower quadrant: left nasal cavity recording

non specific rhinopathy group. The difference however, was slightly significant ($P \leq 0.05$) which means that there exists an important overlap between the normal and the non specific allergic rhinopathy group.

Although the high sensitivity of the A.A.R. method (Figure 2a en b) seems to be an advantage, it is only an apparent advantage. The difference in sensitivity is far less than one concentration step. On the other hand, the chance of making wrong measurement readings is much higher than with the P.A.R. method. The A.A.R. method is more time consuming and if one wants to perform provocation tests on children, different sizes of masks are needed which makes the method even more time consuming.

From Table 1 it follows that there exists a small difference between the initial value of the pressure gradient of the patient group and the test subject group, while this difference does not exist anymore between the end value of both groups. Furthermore, the overlap between both groups for the initial and end value is very important. On the other hand, a positive reaction on histamine gives a sharp raise of the pressure gradient value (Figure 1a and 1b) at a precise concentration. This sharp raise is best reflected by a pressure increase factor equal to 2 (a 100% increase of the initial value). This 100% increase is rather independent from the initial value because it is the concentration of the histamine at which this increase occurs that is important. This was already demonstrated by the authors in a previous study about nasal allergen challenge (Clement et al., 1981).

Table 1. Pressure gradient value in mm of water with a flow of 0.25 l/sec (nasal resistance).

	initial value		end value	
	left	right	left	right
test subjects (n = 20)				
$\bar{x}$	11.60	9.05	43.45	21.55
s	5.32	5.04	18.35	21.23
s^2	28.25	25.42	336.67	450.58
patients (n = 38)				
$\bar{x}$	13.05	16.58	38.79	28.63
s	15.71	15.92	26.67	20.91
s^2	246.97	253.44	711.52	437.32

Finally, if the initial nasal resistance value turns out to be high, (more than 40 mbar at an inspiratory flow of 0.25 l/sec), it becomes impossible to perform a nasal provocation test with the A.A.R. because in this situation a positive provocation will result in such an increase in nasal airway resistance, that the 0.25 l/sec flow cannot be reached anymore whatever the pressure gradient may be.

RÉSUMÉ

Dans un groupe de 29 patients avec une hyperréactivité nasale aspécifique et un groupe de contrôle de 15 sujets normaux, les auteurs ont étudié le seuil de provocation à l'histamine (concentration finale pour une augmentation de 100% du gradiant de pression à un débit de 0.25 litres par seconde).

Le résultat de la provocation nasale a été mesuré avec deux méthodes différentes de rhinomanométrie: la rhinomanométrie active antérieure (AAR) et la rhinomanométrie passive antérieure (PAR).

Le seuil à l'histamine entre les patients et les sujets normaux était différent mais peu significatif ($P \leq 0.05$).

Les 21 provocations à l'histamine, exécutées en double, ont démontré la très bonne réproductabilité de la méthode.

Enfin, la méthode AAR semblait être un peu plus sensible que la méthode PAR.

REFERENCES

1. Andersen I, Mølhave L. The ambiant air. In: Proctor D, Andersen I, eds. The Nose. Amsterdam: Elsevier Biomedical Press, 1982; 307-36.
2. Borum P. Reactivity of the nasal mucosa. In: Pepys J, Edwards AM, eds. The Mast Cell, Pitman Medical, 1979; 761-6.
3. Broms P, Malm L, Svensson G. Nasal airway resistance in perennial non allergic rhinitis. Rhinology 1981; 18:73-9.
4. Cauwenberge van P. Het neusslijmvlies in beeld. Laboratoria Substantia. Brussel, 1980; 1-41.
5. Clement PAR, Dishoeck van EA, Wal van de RJ, Stoop AP Hoeck GT, Strick van R. The nose provocation and the passive anterior rhinomanometry (P.A.R.). Acta Oto-Rhino-Lar Belg 1978; 32:56-63.
6. Clement PAR, Dishoeck van EA. Some physical data about passive anterior rhinomanometry (P.A.R.) Rhinology 1978; 16:149-64.
7. Clement PAR, Dishoeck van EA, Wal van de J, Stoop P, Hoek T, Strick van RV. Nasal provocation and passive anterior rhinomanometry (P.A.R.). Clin Allergy 1981; 11:293-301.
8. Cole P. Modification of inspired air. In: Proctor D, Andersen I, eds The Nose. Amsterdam: Elsevier Biomedical Press, 1982; 351-75.
9. Curry JJ. The action of histamine on the respiratory tract in normal and asthmatic subjects. J Clin Invest 1946; 25:785-91.
10. Eccles R. Neurological and pharmacological considerations. In: Proctor D, Andersen I, eds. The Nose. Amsterdam: Elsevier Biomedical Press, 1982; 191-214.
11. Guercio J, Saketkhoo K, Birch S, Fernandez R, Tachmes L, Sacknor MA. Effect of nasal provocation with histamine, ragweed pollen and ragweed aerosol in normal and allergic rhinitis subjects. Am Rev Resp Dis 1979; 119 (Suppl 4):69 (abstract).
12. Hansel FK. Clinical Allergy. St. Louis: Mosby CV Company, 1953.
13. Huizing EH. Differential diagnosis of rhinopathy. Acta Oto-Rhino-Lar Belg 1979; 33:556-60.
14. Luchtmeyer J. De atopische en aspecifieke rhinopathie. Drachten: meyerij "De witte raaf", 1981; 1-70.
15. McLean JA, Mathews KP, Solomon WR, Brayton PR, Ciarkowski AA. Effect of histamine and metacholine on nasal airway resistance in atopic and non atopic subjects. J Allergy Clin Immunol 1977; 59:165-70.

16. McLean JA, Mathews KP, Solomon WR, Brayton PR, Brayne NK. Effect of ammonia on nasal resistance in atopic and non atopic subjects. Ann Otol Rhinol Laryngol 1979; 88:228–33.
17. Melon J. Physiopathologie générale de la muqueuse nasale. Acta Oto-Rhino-Lar Belg 1964; 18:246–71.
18. Mygind N. Perennial rhinitis. Chapt 15. Blackwell Scientific Publications, 1978; 224–32.
19. Mygind N, Lowenstein H. Allergy and other environmental factors. In: Proctor D, Andersen I, eds. The Nose. Amsterdam: Elsevier Biomedical Press, 1982; 377–97.
20. Okuda M. Mechanisms in nasal allergy. Part I. ORL Dig 1977; 39:26–33.
21. Okuda M. Basic study of nasal provocation test. Archs Oto-Rhino-Lar 1977; 214:241–6.
22. Okuda M, Ohtsuka H, Watase T. The pathophysiology of the nasal histamine sensitivity in allergic rhinitis. Memorial lecture for receiving the Award of Merit of the Belgian-Dutch Symposia: Allergy in otorhinolaryngology. The Hague, May 28, 1982.
23. Svensson G. Treatment of allergic and vasomotor rhinitis. Thesis. Lund, 1981; 1–150.
24. Tiffeneau R. Hyperexcitabilité bronchomotrice de l'asthmatique sequelle des agressions bronchoconstructives allergiques. Acta Allerg 1959; 14:416.
25. Voorhorst R. Basic factors of allergy. Leiden: Stenfert Kroese, 1962.

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