

Nasal Provocation Tests in the Diagnosis of Urticaria Induced by Acetylsalicylic Acid

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ABSTRACT

Nasal provocation tests with lysine acetylsalicylic acid (ASA) have been used in the diagnosis of ASA-induced asthma and rhinitis. To establish its possible role in identifying aspirin sensitivity manifested by urticaria or angioedema, 18 patients suffering from chronic or acute recurring urticaria/angioedema (10 ASA-sensitive and 8 ASA-nonsensitive) were submitted to nasal provocation tests with freshly prepared solutions of lysine ASA. Clinical response and variation of nasal expiratory peak-flow were evaluated, classified according to previously defined scores, and compared. The results showed a significant difference between ASA-sensitive and ASA-nonsensitive patients, suggesting that this test can be an important diagnostic tool for ASA-induced urticaria/angioedema. (Allergy and Asthma Proc 18:319–322, 1997)

Acetylsalicylic acid (ASA) hypersensitivity is a common problem affecting 0.3% of normal subjects, 1.4% of patients with allergic rhinitis, 8–20% of patients with bronchial asthma, 14–23% of patients with nasosinus polypsis, and 23–28% of patients with chronic urticaria¹. Accurate diagnosis lies in challenge tests, but the traditional use of oral route may cause potentially dangerous generalized reactions,² and alternative routes have been tried in the last few years. Recently the nasal mucosa has been proposed by

several groups as an in vivo model to investigate the mechanisms involved in allergic and nonallergic reactions^{3,4,5}; nasal challenge tests using a solution of lysine-aspirin have been used to diagnose aspirin sensitivity manifested by bronchial symptoms.⁶ It proved safer when compared to other provocation tests, the responses being generally milder and easier to control.^{6,7} Nasal challenge is also less time-consuming and is, therefore, more suitable for routine use.⁶ In the present study the use of nasal challenge is extended to patients whose ASA-sensitivity is manifested by urticaria/angioedema, and its diagnostic efficiency in this situation is evaluated.

MATERIALS AND METHODS

Two groups of patients were studied:

- Group 1: 10 patients, 3 men and 7 women, aged 17 to 68 years (mean 42.1 ± 16.8), with ASA-sensitivity manifested by urticaria/angioedema (confirmed by oral ASA challenge test).
- Group 2: (control) 8 ASA-nonsensitive patients, 5 men and 3 women, aged 23 to 70 years (mean 44.6 ± 18.4), with chronic or acute recurring urticaria/angioedema.

Drug therapy with antihistamines and corticosteroids was stopped at least 5 days before challenge. All patients were asymptomatic at the time of the testing.

Nasal challenge was carried out starting with nasal instillation of a control saline solution (0.9% NaCl), followed by nasal instillation of freshly prepared lysine-ASA solutions containing 6 and 12 mg of ASA at 1-hour intervals. To achieve it, two solutions were prepared diluting Lisaspin (Euro-Labor S.A., Alfragide, Portugal) with normal saline to obtain concentrations of 90 and 180 mg/ml, equivalent to

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50 and 180 mg/ml of ASA. A dark-glass bottle with a nebulizer nasal applicator device was calibrated by weight (medium volume spray 0.12 ml) and used to instill one spray into the nose. Depending on the solution used, the spray was carrying 6 or 12 mg of ASA. Nasal decongestant was not used.

Nasal expiratory peak flow (NEPF) was evaluated before, and 15 and 60 minutes after each nasal instillation, using a Wright's peak flow meter (Healthscan Inc. U.S., USA), adapted to a mask. For each determination of NEPF the highest value of three trials was considered.

Scores were established as follows:

Clinical evaluation

- 0 = No symptoms or signs
- 1 = Symptoms without signs
- 2 = Symptoms and local signs
- 3 = Generalized reactions

Nasal expiratory peak flow (NEPF)

- 0 = No difference from baseline value
- 1 = Decrease by <20% from baseline value
- 2 = Decrease by 20%–30% from baseline value
- 3 = Decrease by >30% from baseline value

Statistical analysis was performed on a Macintosh computer with Exstatix software. Results are presented as mean $\pm$ SEM. Significance within groups was calculated by a Wilcoxon signed-rank test for matched pairs (2-tailed *p* values are reported), whereas significance between groups was calculated by a Mann-Whitney *U* test. A *p* value of 0.05 was considered significant.

Lung function tests (spirometry) were performed 20 and 60 minutes after each nasal instillation.

RESULTS

Group 1

No patient exhibited any symptom or sign after control solution instillation. Local signs were observed in three patients: Patient 1, sneezing 5 minutes after 6 mg ASA instillation; Patient 5, rhinorrhea 60 minutes after 12 mg instillation; and Patient 6, uvula edema 20 minutes after 12 mg instillation. Patient 10 had a mild urticarial rash 60 minutes after the second ASA instillation (12 mg), that subsided within 30 minutes.

Maximal changes in NEPF values are shown on Fig. 1. Basal value and value after control solution are similar in every case; mean basal value was 125.5 L/min $\pm$ 26.2, whereas the mean of minimal values obtained during the test was 84.0 L/min $\pm$ 20.2 ($z = -2.8$, $p = 0.005$). The decrease was less than 20% from baseline value in two cases, 22% in one, and greater than 30% in 7 cases.

NEPF values obtained by patients during the whole procedure and maximal negative variations are shown in Table I. Patients 3, 4, and 6 experienced a decrease in forced expiratory volume in 1 second (FEV1) of between 10% and 13% during the test, without clinical bronchial obstruction.

Group 2

No symptoms or signs were observed after control solution, nor were changes in NEPF. Two patients complained of itching nose after ASA instillation. No clinical signs were observed. Four patients had a maximal fall in NEPF of less than 20% from the basal value, and 2 other, between 20 and 30% (Fig. 2). Mean basal value was 112.5

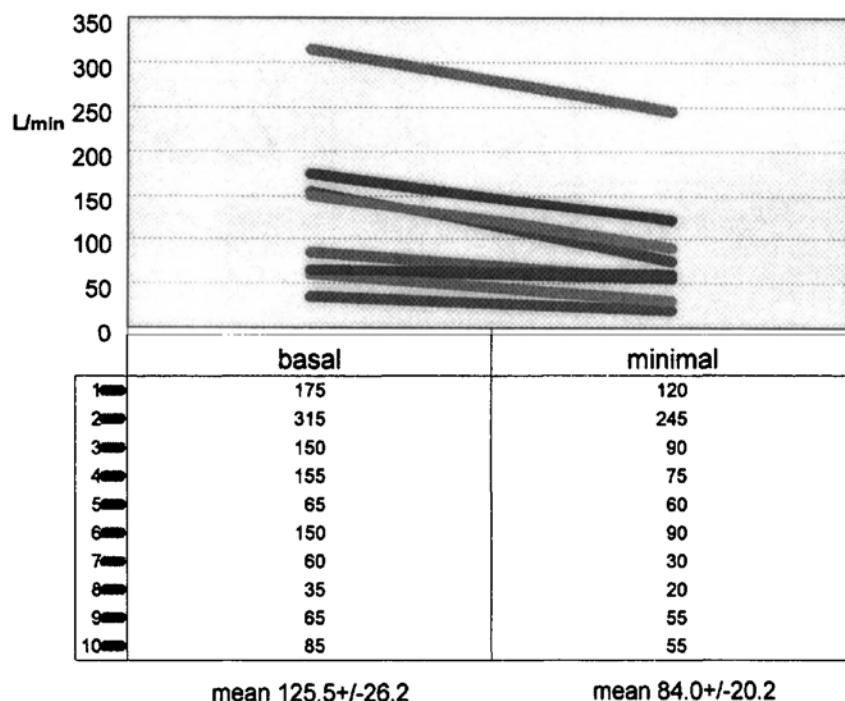


Figure 1. Group 1, Maximal patients NEPF variation.

TABLE I

NEPF Values Obtained during the Whole Procedure and Maximal Negative Variations—Group 1

Patients	Basal	6 mg- 15 mn	6 mg- 60 mn	12 mg- 15 mn	12 mg- 60 mn	NEPF var. (%)
1	175	120	170	160	165	-31.4
2	315	245	260	265	275	-22.2
3	150	155	160	100	90	-40.6
4	155	75	80	140	150	-51.6
5	65	70	80	75	60	-7.7
6	150	125	125	170	90	-40.0
7	60	50	50	50	30	-50.0
8	35	45	45	20	30	-43.0
9	65	55	55	70	75	-15.4
10	85	75	75	55	70	-35.3

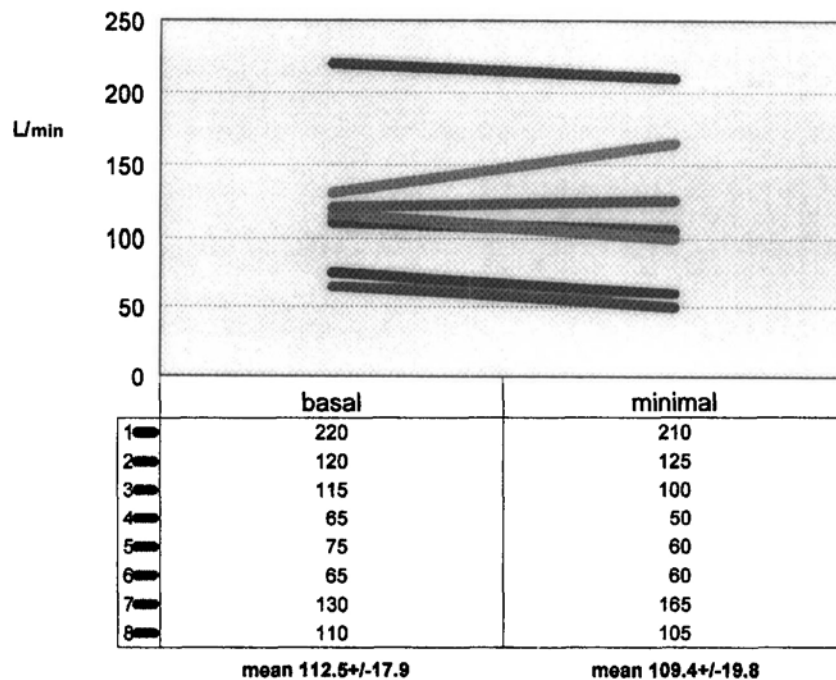


Figure 2. Group 2, Maximal patients NEPF variation.

L/min $\pm$ 17.9, with no significant difference from mean of minimal values during the challenge test (109.4 L/min $\pm$ 19.8). No changes in FEV1 were observed.

NEPF values obtained during the whole procedure and maximal negative variations are shown in Table II.

Comparison between groups

There was no significant difference between mean basal NEPF values. Partial and final scores for each patient are shown in Table III. Group 1 final mean score is 3.4 ± 0.48 , significantly higher than that of group 2, which is 1.2 ± 0.25 ($U = 6.5$; $p = 0.02$). If a final score value of 3 is considered the cut-off for positivity, the nasal aspirin

challenge test reaches 80% sensitivity and 100% specificity in the present study.

DISCUSSION AND CONCLUSION

In contrast to bronchial inhalation challenge, Pawlowicz and coworkers⁶ showed that aspirin nasal challenge is able to produce adverse nasal responses in asthmatic aspirin-sensitive subjects. Using the nasal test, they obtained a bronchial response in every patient who had responded to inhaled ASA, 10 and 20 mg being the doses that induced these responses. One of their patients developed urticaria during the nasal challenge. These facts led them to raise the hypothesis that nasal challenge might be used to

TABLE II

NEPF Values Obtained during the Whole Procedure and Maximal Negative Variations—Group 2

Patients	Basal	6 mg- 15 mn	6 mg- 60 mn	12 mg- 15 mn	12 mg- 60 mn	NEPF var. (%)
1	220	250	260	210	270	-4.5
2	120	150	125	135	130	—
3	115	100	100	145	150	-13.0
4	65	55	55	55	50	-23.1
5	75	60	65	90	80	-20.0
6	65	65	65	60	60	-7.7
7	130	170	175	180	165	—
8	110	110	105	120	130	-4.5

investigate aspirin sensitivity expressed in other organs.⁶ The present work tries to explore it further.

The ASA doses of 6 and 12 mg were chosen to perform the nasal challenges based on a study published by Picado et al.,⁵ in which 12 mg was the dose selected. With higher doses they observed an elevated frequency of intense irritative effects, which could be misleading and particularly dangerous to patients at risk to develop angioedema. In the same study, minor irritative symptoms in healthy subjects were registered with doses as low as 4 mg, and this type of reaction could explain the NEPF decrease of 23% and 20% in patients 4 and 5 of our control group. Alternatively, this decrease can be due to some lack of accuracy of NEPF and/or to the low basal NEPF value presented by these subjects, which implies that small absolute variations have a high relative value. This fact suggests that individuals with a low basal NEPF would be better excluded from this kind of test.

The three patients of group 1 who responded to 6 mg of ASA did so within the first 15 minutes, and two of them maintained a decreased NEPF 1 hour after the challenge. None of the three responded to 12 mg ASA; this could reflect a mucosal refractory period. A decrease in NEPF as a response to 12 mg ASA was observed within 15 minutes in three patients (only one maintained it until 60 minutes),

and 45 minutes later in the other two. These variable patterns of response, as well as symptoms other than nasal congestion that some patients experienced, are perhaps related to the fact that nasal responses have a wide variation among individuals. The way used to evaluate the responses in the present work takes this variability into consideration.

Although the present study has included a not very large number of patients, our results strongly suggest that nasal mucosa response to local instilled ASA can separate, with relatively high accuracy, ASA-sensitive from ASA-nonsensitive patients whose sensitivity is manifested by urticaria/angioedema. Local signs as well as a decrease in NEPF greater than 30% only occurred in ASA-sensitive patients, making possible to establish criteria for positivity in the absence of the usual patient cutaneous reaction. On the other hand, the procedure is short time-consuming, and has elicited no life-threatening reactions, corroborating previous reports.^{6,7} Wellbrock et al.⁷ described it as a safe test lasting a total of 100 minutes. These facts support that nasal ASA challenge deserves further investigation to establish its role in the diagnosis of aspirin-induced urticaria/angioedema.

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TABLE III

Partial and Final Scores for Each Patient

Group 1 scores				Group 2 scores			
Patient	Clinical	NEPF	Final	Patient	Clinical	NEPF	Final
1	2	3	5	1	0	1	1
2	0	2	2	2	1	0	1
3	0	3	3	3	0	1	1
4	0	3	3	4	0	2	2
5	2	1	3	5	0	2	2
6	2	3	5	6	1	1	2
7	0	3	3	7	0	0	0
8	0	3	3	8	0	1	1
9	0	1	1				
10	3	3	6				

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