

Short communication

Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA)

Background: We have aimed to determine the sensitivity and specificity of a simpler technique with less risk than oral provocation to diagnose aspirin-induced asthma (AIA).

Methods: We studied a group of 20 AIA patients compared to a control group with 40 aspirin-tolerant patients (confirmed by oral provocation test): 10 asthmatic patients and 30 healthy subjects. A nasal provocation test (NPT) with lysine acetylsalicylic acid (L-ASA) was carried out. Nasal and pulmonary functions were monitored with anterior active rhinomanometry (AAR) and spirometry. An L-ASA solution (900 mg/ml L-ASA, equivalent to 500 mg/ml acetylsalicylic acid) was diluted with saline solution. We administered four increasing doses: 5, 25, 50 and 100 mg/ml acetylsalicylic acid (ASA) with saline solution control. Nasal and pulmonary functions were monitored with rhinomanometry and spirometry. The patients were controlled for nasal inspiratory peak flow and expiratory peak flow.

Results: The results showed high sensitivity and specificity: 80% and 92.5%, respectively, with an 84.2% positive predictive value and an 89.2% negative predictive value. The patients had no bronchial or systemic symptoms, and no decreases over 20% were recorded in the FEV₁.

Conclusion: NPT has a high sensitivity and specificity in the diagnosis of AIA. An oral provocation should be performed to confirm the result whenever the clinical situation of the patient permits it.

**A. Alonso-Llamazares,
C. Martínez-Cócer,
J. Domínguez-Ortega,
T. Robledo-Echarren,
M. Cimarra-Alvarez,
M. Mesa del Castillo**

Allergy Department, Hospital Clínico San Carlos,
Madrid, Spain

Key words: aspirin-induced asthma; diagnosis; nasal provocation test.

Ana Alonso Llamazares
Allergy Department
Hospital Clínico San Carlos
C/Martin lagos s/n
28040 Madrid
Spain

Accepted for publication 2 January 2002

Studies to determine drug hypersensitivity are the third cause for consultation to the allergist after rhinitis and bronchial asthma (1) and nonsteroidal anti-inflammatory drugs (NSAIDs) are the second most frequent agent causing drug hypersensitivity in importance after antibiotics (1).

The prevalence of aspirin-induced asthma (AIA) or aspirin nonallergic hypersensitivity (2) is high in a certain population group, reaching figures of up to 30–40% in those asthmatic patients who have nasal polyps and chronic rhinosinusitis (3–7). Thus, it must be diagnosed early and correctly since its consumption, along with other drugs in the NSAIDs group, must be avoided (8–10).

It is difficult to verify AIA in our consultation because no *in vitro* test presently exists to diagnose this entity and oral provocation continues to be the reference test or “gold standard.” In spite of this, oral provocation cannot always be carried out (11, 12) due to its inherent risk. Bianco (13) was the first to introduce the inhaled provocation test with aspirin as a faster method with less risk than oral provocation. Based on the above, other

authors have attempted to find alternative methods, such as bronchial and nasal provocation (14–22), to oral provocation and to determine the sensitivity and specificity of these techniques which are easier to apply and have less risk.

Nasal obstruction is a subjective sensation, so it would be useful to have an objective technique that measures the airflow obstruction. The rhinomanometry measures nasal air resistance and allows us to measure variations occurring during nasal provocation (23). Anterior active rhinomanometry (AAR) has some advantages (23). It is easy and relatively quick, it can be used in children and its pressure and volume can be recorded. However, there are some disadvantages: there is a risk of deforming the ostium with the nose pieces (but not the face-mask); only one nostril can be monitored at a time; it cannot be used in the case of septal perforation; the instruments must be calibrated for each determination and can be problems with the face mask. We followed the recommendations of the Committee for the Standardization of Rhinomanometry (24).

The nasal provocation reproduces the symptoms in the

organ under controlled conditions, making it possible to determine the cause–effect relationship between the agent and the nasal response.

Material and methods

Patients

The test was performed in 60 subjects: 20 AIA patients (14 men and six women with 23–59 years old) and 40 aspirin-tolerant subjects, confirmed by oral provocation test with 1 g of aspirin: 10 with bronchial asthma (18–58 years old) and 30 healthy subjects (29–35 years old). Two of the 10 ASA tolerant asthmatics had been operated on for nasal polyps.

The group AIA patients were diagnosed by oral provocation with aspirin (13 patients), or by a clinical background of severe bronchospasm that had required admission to the intensive care unit for treatment (seven patients). Eight of these patients had been diagnosed with nasal polyps which had required surgery, some of them several times. Their baseline FEV₁ was between 47% and 94%.

The patients continued to receive asthma drug therapy with inhaled β -stimulants and inhaled corticosteroids; however, the nasal corticosteroids and antihistamines were discontinued 48 h prior to the nasal provocation and antileukotrienes 1 week before. None of the patients had received any systemic corticosteroids in the month prior to the provocation study or any other medication one week beforehand.

Exclusion criteria were the existence of rhinoconjunctival or bronchial symptoms at the time of the study, respiratory tract infection in the month prior to the test, baseline rhinomanometry not fulfilling the normality criteria (19, 20), unspecific nasal hyperresponsiveness (increase in NAR greater than 50% after saline instillation).

Signed informed consent was obtained from all of the patients in our department prior to the drug provocation.

Nasal challenge with lysine acetylsalicylic acid (L-ASA)

A nasal provocation test (NPT) with L-ASA was carried out and the nasal and pulmonary functions were monitored with AAR and spirometry. The rhinomanometer (Rhinospir 164, Subel SA, Barcelona, Spain) and the spirometer (Datospir 92, Subel SA, Barcelona, Spain) were calibrated on the day of the test.

NPT was performed on two consecutive days. On day one, after the 30 min adaptation period, a baseline nasal and pulmonary function with AAR and a spirometry test were performed. Except for the hours dedicated to sleep, the patients measured their nasal inspiratory peak flow and expiratory peak flow every 2 h until the NPT.

The NPT was performed on day two, performing a baseline rhinomanometry and spirometry after the patients remained at rest for 30 min. A 0.3-ml saline control solution was administered in both nostrils (by direct instillation with a micropipette) and nasal airway resistance (NAR) was measured after 10 min. An L-ASA solution (Inyesprin[®], Andr maco-Gr nenthal) containing 900 mg/ml of L-ASA, equivalent to 500 mg/ml of acetylsalicylic acid (ASA), was diluted with saline solution. Four concentrations, 5, 25, 50 and 100 mg/ml, of ASA were used in the test. If no significant increase was produced in the NAR after the instillation of the diluent control saline solution (increase in NAR greater than 50%) the test was performed. The first dose, 0.1 ml of the 5 mg/ml ASA solution, was applied in the nostril with less resistance (inferior turbinate). Rhinomanometry and spirometry were performed 10 and 20 min later, respectively. After this, if the response was negative, the next dilution (0.1 ml of the 25 mg/ml ASA solution) was administered in the same nostril, with rhinomanometry and spirometry control. If the response continued been negative, we administered the following doses (0.1 ml of the 50 and 100 mg/ml ASA solution) with a total ASA accumulated dose of 18 mg. After the last exposure, NAR and FEV₁ were monitored every 60 min if the response had been positive and only in the first 60 min if it

had been negative. The patient measured nasal inspiratory peak flow and expiratory peak flow every 2 h during the next 24 h except for the sleep period.

Positive criteria of *early reactions* were considered to exist when the symptoms appeared, the increase of NAR > 100% (150 Pa/cc/s); decrease of FEV₁ > 20% and *late reactions* were considered to exist when there was a variability of expiratory peak flow > 20% and decrease of nasal inspiratory peak flow > 50%.

A statistical analysis was performed, calculating the parameters that measure the internal validity of a test, that is, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results

Sixteen of 20 AIA patients (80%) had a positive response to the nasal challenge with L-ASA: five patients with a total ASA accumulated dose of 3 mg, one patient with 8 mg and the rest of 10 patients with 18 mg. In 14 of the 16, an increase greater than 100% was observed in the NAR; 10 had nasal symptoms of nasal congestion and rhinorrhea and 4 patients had a dual immediate and late response. None of them had bronchial or systemic symptoms and no decreases in FEV₁ greater than 20% were recorded, even in those patients whose FEV₁ < 70%, and no variability > 20% in expiratory peak flow were recorded.

The nasal provocation with L-ASA was negative in 27 of 30 aspirin-tolerant healthy subjects and in all aspirin-tolerant asthmatic patients (10 subjects; 92.5%). A positive response, all occurring in the early response period, was obtained in three patients whose NAR increased by more than 100%: one patient with 3 mg and two patients with 18 mg of ASA accumulated dose. None of them suffered nasal symptoms. After this, we performed an oral provocation to confirm the aspirin tolerance.

Statistical analysis: the sensitivity and specificity were 80% and 92.5%, respectively, with an 84.2% positive predictive value (PPV) and a 90.2% negative predictive value (NPV).

Discussion

Specific nasal provocation is a widely used method (25) in the study of patients with allergic rhinitis. Our method not only controls the symptoms but it can also objectively measure the response in the nasal function. The upper respiratory tract is an accessible organ that can be easily monitored. Furthermore, due to the histology similarity of the upper and the lower respiratory tracts, the response obtained after nasal provocation should be similar to that obtained after the bronchial one. In addition, when L-ASA is administered directly into an organ such as the nasal mucosa, where absorption is very poor, the risk of suffering a serious reaction is much less than with oral provocation (11, 12) and even than with bronchial provocation (13–17).

Bianco (13) was the first to introduce the inhaled

provocation test with aspirin as a faster method that had less risks than the oral test. Since then, other authors (14–17) have used the test with good results. Nasal provocation with aspirin has been used (18–22) in an attempt to find a faster and safer diagnostic method than oral provocation for the diagnosis of AIA. Pawlowicz (18) and Patriarca (19) were the first to objectively measure the effect of the nasal provocation test with aspirin on the lung and nasal function. Pawlowicz et al. (18) performed a nasal provocation test in seven patients who had been diagnosed with aspirin intolerance by means of bronchial provocation with L-ASA. In all seven patients, a decrease of at least 15% was observed in the FEV₁ after nasal provocation. The L-ASA dose they used in the nasal challenge was 36 mg, equivalent to 20 mg acetylsalicylic acid. The solution was administered by means of an atomizer of compressed air, which could make the solution reach the lower respiratory tract.

Patriarca (19) found low sensitivity (37.8%) in 45 patients, with high specificity (92.1%). This could be a consequence of the lower dose administered in the provocation. None of their patients showed a significant decrease in FEV₁. Later on, Wellbrock et al. (20) performed a nasal provocation in 153 patients, finding 67% and 84% sensitivity and specificity, respectively, and only two patients had bronchial symptoms.

The values found in the Milewski group (21), which included 41 patients, were very similar to ours, with 86.7% sensitivity and 95.7% specificity. In that study, the patients were administered a 16-mg only dose of acetylsalicylic acid, 8 mg in each nostril, by means of direct instillation. No patients had a significant decrease in the FEV₁. This technique was similar to that used by us, but with some differences. We administered four increasing doses of ASA in one nostril (the nostril with less nasal airway resistance). When we initially administered only one dose of 20 mg of ASA, the patients suffered from rhinorrhea and pruritus. For this reason we changed the method of the NPT, using increasing doses as it is used in the specific nasal provocation with allergens. When Casadevall (22) administered a dose of 25 mg of L-ASA in each nostril, he found 73% sensitivity and 94% specificity. This author used acoustic rhinometry to monitor the nasal function.

In agreement with other previously mentioned authors (18–22), our study shows that nasal provocation has a high sensitivity and specificity as a diagnostic test in asthmatic patients with AIA. In most of the patients, the

responses obtained were clearly observed when the nasal airway resistance was controlled, and they did not present nasal symptoms, so that the nasal function should be monitored objectively. In those cases in which the patients showed symptoms, these were limited to the upper respiratory tract, with no evidence of systemic and bronchial symptoms or significant decreases in the FEV₁ in asthmatic patients.

The control of the nasal inspiratory peak flow is also an objective measure of the late response which also presents great specificity (26–28). Late reactions have not been observed by other authors in the nasal or bronchial provocation test with ASA (14–22), although it has been described by Park (29). In our study, these responses have not been very frequent and, for this reason, nasal inspiratory peak flow and the expiratory peak flow would not need to be measured in all patients.

Therefore, we have demonstrated that the aspirin nasal provocation test is not only a rapid but also a safe test, even though some of the patients had a 47% baseline FEV₁. As long as they are in a stable condition, nasal provocation can be performed in asthmatic patients with deteriorated pulmonary function, when no oral or bronchial provocation can be carried out. Therefore, the pulmonary function is not a limitation of the aspirin nasal provocation test as occurs in the case of the oral or bronchial provocation.

It has been demonstrated that this technique has some limitations since it is difficult to interpret the response in those patients with an altered nasal function that may cause high nasal resistances, turbulent nasal flows or unspecific nasal hyperresponsiveness. Therefore, these patients should be excluded from the study.

As other authors have recommended (21, 22) the nasal provocation test could be the first choice test in the diagnosis of AIA. Since, as we have observed, a negative response does not exclude aspirin nonallergic hypersensitivity, an oral or bronchial provocation could be necessary to confirm the result whenever the clinical situation of the patient permits it (30).

In conclusion, aspirin nasal provocation is a fast and a safe diagnostic technique which has a high sensitivity and specificity for the diagnosis of aspirin-induced asthma. In addition to being a technique that is well tolerated by the patients, it is easy to monitor and can be done on an ambulatory basis. All in all, it can be considered an alternative in the diagnosis of aspirin intolerance with less risk than the oral or bronchial provocation.

References

1. ALERGOLÓGICA., Alergia a Medicamentos. Sociedad Española de Alergología e Inmunología Clínica y Alergia e Inmunología Abelló, SA, Madrid;1995:185–213.
2. JOHANSSON SGO, HOURIHANE JO'B, BOUSQUET J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
3. HEDMAN J, KAPRIO J, POUSSA T, NIEMINEN MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;**28**:717–722.

4. LARSEN K. The clinical relationship of nasal polyps to asthma. *Allergy Asthma Proc* 1996;**17**:243–249.
5. CASTILLO JA, PICADO C. Prevalence of aspirin intolerance in asthmatics treated in a hospital. *Respiration* 1986;**50**:153–157.
6. RACHELEFSKY GS, COULSON A, SIEGEL SC, STIEHM ER. Aspirin intolerance in chronic childhood asthma: detected by oral challenge. *Pediatrics* 1975;**56**:443–448.
7. SETTIPANE GA, CHAFEE FH, KLEIN DE. Aspirin intolerance. II. A prospective study in an atopic and normal population. *J Allergy Clin Immunol* 1974;**53**:200–204.
8. VANE JR. The mode of action of aspirin and similar compounds. *J Allergy Clin Immunol* 1976;**58**:691–712.
9. SZCZEKLIK A. Mechanism of aspirin-induced asthma. *Allergy* 1997;**52**:613–619.
10. SZCZEKLIK A, STEVENSON D. Aspirin-induced asthma: Advances in pathogenesis and management. *J Allergy Clin Immunol* 1999;**104**:5–13.
11. QUIRALTE J, BLANCO C, CASTILLO R, DELGADO J, CARRILLO T. Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenge in 98 patients. *Allergy* 1996;**98**:678–685.
12. QUIRALTE J, ENRÍQUEZ C, BLANCO GUERRA R, et al. Reacciones adversas a antiinflamatorios no esteroideos: manifestaciones clínicas durante la provocación controlada en 82 pacientes. *Rev Esp Alergol e Inmunol Clín*, 1995;**10**:263–271.
13. BIANCO S, ROBUSCHI M, PETRIGNI G. Aspirin sensitivity in asthmatics. *Br Med J* 1981;**282**:146.
14. FRAJ LÁZARO J. Provocaciones bronquiales con AAS-lisina. *Alergol e Inmunol Clín* 1999;**14**:29–34.
15. ROSADO A, VIVES R, CANTO G, BARBARROJA J, CUEVAS B, RODRIGUEZ J. Lysine acetyl-salicylate bronchial provocation test in diagnosis of respiratory reactions caused by NSAIDs. *J Allergy Clin Immunol* 1999;**103**:S200.
16. PHILLIPS GD, FOORD R, HOLGATE T. Inhaled lysine-aspirin as a broncho-provocation procedure in aspirin-sensitive asthma: Its repeatability, absence of a late-phase reaction and the role of histamine. *J Allergy Clin Immunol* 1989;**84**:232–241.
17. DAHLÉN B, ZETTERSTRÖM O. Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. *Eur Respir J* 1990;**3**:527–534.
18. PAWLOWICZ A, WILLIAMS WR, DAVIES BH. Inhalation and nasal challenge in the diagnosis of aspirin-induced asthma. *Allergy* 1991;**46**:405–409.
19. PATRIARCA G, NUCERA E, DIRIENZO V, SCHIARINO D, PELLEGRINO S, FAIS G. Nasal provocation test with lysine acetylsalicylate in aspirin-sensitive patients. *Ann Allergy*, July 1991;**67**:60–62.
20. WELLBROCK M, MERTENS J, CORNELLIUS M, BRASCH J. Intranasal provocation with lysine acetylsalicylic acid. *HNO* 1993;**41**:577–581.
21. MILEWSKI M, MASTALERZ L, NIZANKOWSKA E, SZCZEKLIK A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. *J Allergy Clin Immunol* 1998;**101**:581–586.
22. CASADEVALL J, VENTURA PJ, MULLOL J, PICADO C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerance asthma: evaluation of nasal response by acoustic rhinometry. *Thorax* 2000;**55**:921–924.
23. A OLIVÉ PÉREZ. Nasal provocation test (NPT) through previously active rhinomanometry: Physical and mathematical reasons. *Alergol Immunopathol* 1989;**17**:291–299.
24. CLEMENT PAR. Committee report on standardization of rhinomanometry. *Rhinology* 1984;**22**:151–155.
25. MELILLO G, BONINI S, COCCO G, et al. Standardisation of nasal provocation tests. *Allergy* 1997;**52**:26–33.
26. S. JIMENEZ-TIMÓN J, VIGARAY M, CIMARRA C. Martínez Cócera. Nasal challenge in patients allergic to *Alternaria*. *Allergy* 1997, 52, 37, 208–209.
27. HOLMSTROM M, SCADDING GK, LUND VJ, DARBY YC. Assessment of nasal obstruction. A comparison between rhinomanometry and nasal inspiratory peak flow. *Rhinology* 1990;**28**:191–196.
28. KRAYENBUHL MC, HUDSPITH BN, SCADDING GK, BROSTOFF J. Nasal response to allergen and hyper-osmolar challenge. *Clin Allergy* 1988;**18**:157–164.
29. PARK HS. Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients. *Clin Exp Allergy* 1995;**25**:38–40.
30. MELILLO G, BALZANO G, BIANCO S, et al. Oral and inhalation provocation tests for the diagnosis of aspirin-induced asthma. *Allergy* 2001;**56**:899–911.