

The nose as a target organ in the diagnosis of severe aspirin-exacerbated respiratory disease

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ABSTRACT

Background: The nasal provocation test (NPT) with lysine aspirin is a useful tool in the diagnosis of aspirin-exacerbated respiratory disease (AERD), previously referred to as Samter's disease. The aim of the present study focuses on methodological interventions to show the usefulness of the NPT with lysine aspirin in differentiating AERD patients from aspirin-tolerant asthma (ATA) patients to improve the diagnostic efficacy and minimize the risk for adverse reactions compared with the gold standard.

Methods: Thirty AERD patients comprised the active study group while the control group consisted of 25 ATA patients. A combination of objective nasal aerodynamic response (i.e., nasal inspiratory flow and nasal inspiratory resistance) was evaluated by active anterior rhinomanometry and the subjective clinical nasal and extranasal symptoms (including forced expiratory volume) were monitored throughout the challenge.

Results: Fifty-five NPTs were successfully completed: sensitivity, 87%; specificity, 100%; positive predictive value, 100%; negative predictive value, 86%; global efficacy, 92.72%. No severe adverse reactions were recorded.

Conclusion: The present NPT with lysine aspirin proved to be a safe, efficient, and a timesaving method in the diagnosis of patients with AERD, even in those with severe rhinitis–rhinosinusitis and/or recurrent nasal polyposis.

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After β -lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common causes of adverse drug reactions¹ worldwide and count as the second cause of adverse reactions.² Aspirin intolerance is a clinical syndrome usually associated with severe and chronic inflammation in both upper and lower airways resulting in chronic rhinitis, sinusitis, recurrent polyposis, and asthma.³ The overproduction of cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄), which are potent proinflammatory mediators and bronchoconstrictors, is typical for the pathophysiology of aspirin-intolerant asthma.⁴ The prevalence of aspirin-induced asthma (AIA) in an adult population of asthmatic patients was reported to be as high as 21% when provocation tests were used for diagnosis.^{5–7}

It is essential to establish a diagnosis of aspirin-exacerbated respiratory disease (AERD). It is then possible to provide the patient with a long list of common drugs that must be avoided because of the high risk of a life-threatening reaction, indicating which NSAIDs can be taken safely.⁸ The diagnosis of AERD is often a difficult task in daily practice mainly because the clinical history is not always definitive and “*in vitro*”^{9,10} and skin tests are rarely useful.¹¹ Because the oral, single-blind, placebo-controlled challenge with aspirin is considered the “gold standard” but is not always feasible because of severe adverse reactions, alternative diagnostic methods have been developed.^{12–14} Although specific nasal,^{15–18} bronchial,^{19–22} and standardized guidelines⁸ have been released to diagnose aspirin hypersensitivity, a significant number of patients still need a single-blind, placebo-controlled challenge to confirm the diagnosis in daily practice. The aim of the present study is to optimize methodological aspects of the nasal provocation test (NPT) with lysine aspirin to improve the diagnostic efficacy and minimize the risk of adverse reactions in a selective group of patients with confirmed AERD.

MATERIALS AND METHODS

Patients

The patients were divided into two groups (Table 1), 30 subjects with AIA (7 men/23 women; 41.63 ± 14.94 years old) and 25 patients with aspirin-tolerant asthma (ATA; 5 men/20 women, 43.68 ± 11.64 years old). In the AIA group all patients presented respiratory symptoms (asthma and/or rhinitis) confirmed by a previous positive oral provocation test (OPT) with aspirin, in which 80% suffered simultaneously from asthma and rhinitis (Fig. 1). Nineteen patients (63.3%) had nasal polyposis (CT confirmed) and 33.3% of them had in the past needed at least one surgical polypectomy. Atopy was present in 13 patients (43%) shown by the positive skin-prick test and/or serum IgE of >0.35 kU/L to any of the most frequent aeroallergens (pollen, dust mites, molds, and animal dander).

The control group consisted of 25 ATA subjects who had previously shown a negative OPT up to 1 g of aspirin. All of them had asthma (100%), 84% had chronic rhinoconjunctivitis, and 7 subjects (28%) had nasal polyposis (Table 1). Atopy was present in only four subjects (16%). Those patients with severe nasal polyposis were excluded from the study if the minimum required nasal flows were not reached. The exclusion criteria were unstable basal respiratory disease (asthma and/or rhinitis), basal forced expiratory volume in 1 second (FEV₁) of $<70\%$, nasal surgery 3 months before the challenge, septal perforation, and/or respiratory infection 1 month before the challenge. Medication was stopped before the provocation test according to previously published schedules.⁸ The doses of topical (bronchial and nasal) steroids were minimized and not changed for 2 weeks before the provocation. This study was approved by the Ethics Committee of our hospital and all patients gave their signed informed consent.

NPT with Lysine Aspirin

A solution of lysine aspirin or lysine acetylsalicylate (L-ASA) was prepared for each patient on the same day the provocation test was performed. A crystalline L-ASA (Inyesprin; Andrómaco, Madrid, Spain) was provided in vials with 0.9 g, equivalent to 0.5 g of aspirin. Each solution was prepared with 1.8 g of L-ASA diluted to saline 0.9% to obtain a solution of 180 mg/mL (equivalent to 100 mg/mL of aspirin). The NPT began every morning (8:30 A.M.) to avoid any possible nasal cycle influence. After a resting period of at least 30 minutes, both active anterior rhinomanometry and

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Approved by the Ethics Committee of our institutions and informed consent was signed by all patients

The authors have no conflicts to declare pertaining to this article

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Table 1. Clinical features of patients included in the current study

	Case (n = 30)	Control (n = 25)
Atopy (past medical records)	13 (43.3%)	4 (16.0%)
Nonallergic rhinitis	19 (63.3%)	17 (68.0)
Allergic rhinitis	9 (30.0%)	5 (20.0%)
Nonallergic asthma	17 (56.3%)	20 (80.0%)
Allergic asthma	10 (33.3%)	2 (20.0%)
Nasal polyps	19 (63.3%)	7 (28.0%)
Previous surgery for nasal polyps	10 (52.63%)	6 (85.71)
Positive SBPCC (ASA 1 g)	30 (100.0%)	0 (0.0%)

SBPCC = single-blind placebo-controlled challenge; ASA = acetylsalicylic acid.

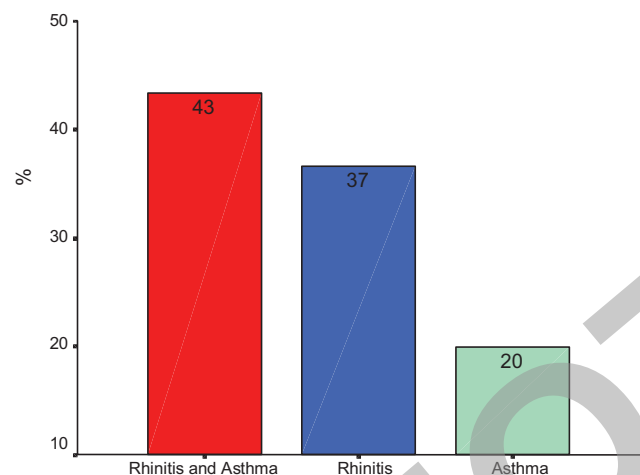


Figure 1. Respiratory symptoms confirmed by Oral Provocation Test (single-blind placebo-controlled challenge).

forced spirometry (Masterlab; Jaeger, Würzburg, Germany) were conducted to determine the basal nasal flow and FEV₁. Basal nasal inspiratory flow had to be at least 200 mm/s in one nostril. This being assured, 70 μ L of control solution (saline 0.9%) were sprayed into the best nostril during apnea (on completed inspiration). A significant decrease ($\geq 20\%$) in the nasal inspiratory flow 10 minutes after saline application was considered to show nasal hyper-responsiveness (NHR) and the nasal test could not be performed.

Only if NHR was excluded was a solution dose (70 μ L) containing 7 mg of aspirin sprayed into the same nostril and rhinomanometry was then performed every 10 minutes for the next 30 minutes. A second and final dose of 7 mg of aspirin (total cumulative dose, 14 mg) was only administered if no significant changes in the nasal/bronchial function were detected (see later in text). Rhinomanometry was performed every 10 minutes and spirometry was performed every 30 minutes for the next 3 hours.

The NPT was considered positive if one/both criteria were met:

1. Rhinomanometric criteria. A decrease of $\geq 40\%$ in the postsaline nasal inspiratory flow (NIF) (sustained for at least 10 minutes) and/or an increase of $\geq 60\%$ in the postsaline nasal inspiratory resistance (NIR) (sustained for at least 10 minutes).
2. Clinical criteria. A symptomatic score in excess of 3 points.

Local (nasal, conjunctival, and skin symptoms) or bronchial symptoms were recorded to assess the expected correlation between rhinomanometric and spirometric changes and clinical manifestations. The clinical score of symptoms ranged from 0 (absence) to 3 points (severe symptoms). Following the International Committee on Stan-

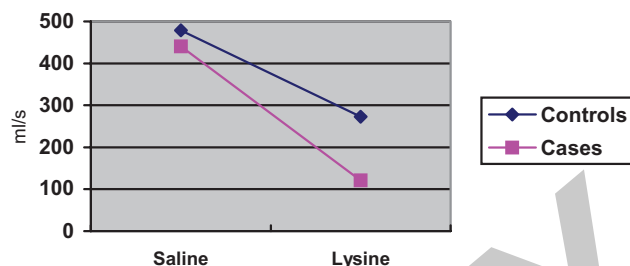


Figure 2. Rhinomanometry: Changes in nasal inspiratory flow after local lysine-aspirin.

dardization of Rhinomanometry recommendations,²³ nasal inspiratory flow and resistance were studied bilaterally in all patients. FEV₁ was recorded to evaluate eventual bronchial implication, and a decrease of $\geq 20\%$ of the basal value was considered to be a positive bronchial response.

Analysis of Data

All data were fully recorded in a computerized database and statistically analyzed using SPSS processor (Microsoft Corp., Redmond, WA). To validate this method, statistical parameters, such as sensitivity, specificity, predictive values, and efficacy were assessed.

RESULTS

Nasal Provocation Test

A total of 55 NPTs were successfully completed. Twenty-six of 30 AIA patients showed a positive test, and in the ATA group all 25 subjects had a negative NPT. Most of the nasal responses were ipsilateral (13/26) or bilateral (12/26), and 1 patient only showed a contralateral response. Twenty-two of the 26 AIA patients were administered a maximum cumulative dose of 14 mg of acetylsalicylic acid (ASA), but 4 of 26 subjects tested NPT⁺ with only 7 mg. Nineteen of the 26 positive NPTs (73%) were diagnosed within 50 minutes (48.07 ± 27.71 minutes) after the L-ASA application, and 7 of 26 showed a positive response within 2 hours. Basal NIF and NIR were significantly higher ($p < 0.05$) in the ATA group (451.16 ± 125.29 mL/s; 0.37 ± 0.12 Pa/cm³ per second) when compared with the AIA patients (384.66 ± 117.67 mL/s; 0.31 ± 0.11 Pa/cm³ per second). Basal NHR was excluded in both groups, and no differences ($p > 0.05$) were found in their postsaline NIF and NIR.

Post-L-ASA values were statistically different in each group. NIF decreased almost threefold (Fig. 2) in the AIA patients (64.83%) when compared with the ATA group (22.88%), and NIR increased fourfold (Fig. 3) in the AIA (156.57%) when compared with the ATA group (33.48%), showing a statistical difference ($p < 0.05$) for both aerodynamic parameters. No differences ($p > 0.05$) were found in basal FEV₁ in the two groups (100.48% in ATA group; 98.07% in AIA group) and no significant changes ($p > 0.05$) were found in either group at any time of the NPT. Only AIA patients showed a positive clinical score (in excess of 3 points) with exclusively nasal symptoms (rhinorrhea, congestion, sneezing, and pruritus). There were statistical differences in the final clinical score of the two groups with 7.6 ± 3.39 points in the AIA patients when compared with 0.92 ± 0.86 points in the ATA subjects.

Only 9 of the 26 positive NPT patients required medical treatment, and oral antihistamines were the most frequent medication (9/10) followed by topical steroids (only in 1/10 case). No inhaled β -agonist, systemic steroids, or adrenaline were needed at any time and no hospital admissions were required.

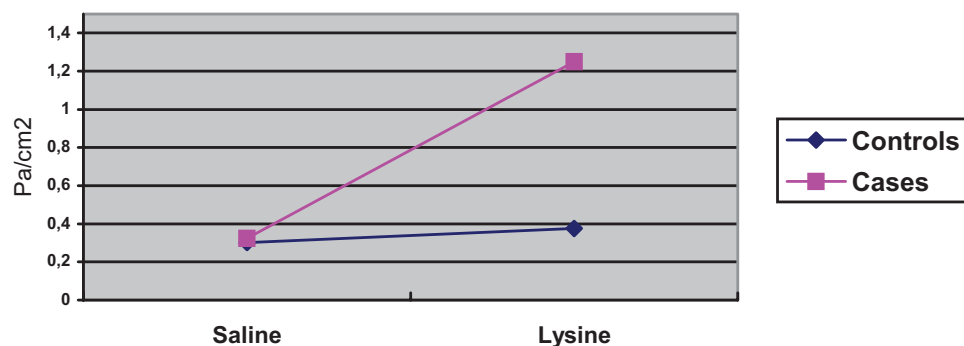


Figure 3. Rhinomanometry: Changes in nasal inspiratory resistance after local lysine-aspirin.

Table 2. Statistical values of different nasal provocation tests with lysine-aspirin

Case/Control	Patriarca <i>et al.</i> 45/38	Milewski <i>et al.</i> 41/23	Alonso <i>et al.</i> 20/40	González Pérez <i>et al.</i> 30/25
Sensitivity	37.8	86.5	80	87.0
Specificity	92.1	95.7	92.5	100.0
PPV	85.0	96.9	84.2	100.0
NPV	55.6	71.0	89.2	86.0
Efficacy	—	84.4		92.72

NPV = negative predictive value; PPV = positive predictive value.

Statistical Analysis

Overall sensitivity and specificity were 87 and 100%, respectively, and the positive predictive value was 100% with a negative predictive value of 86% and an overall efficacy of 92.72% (Table 2). The AIA group patients showed a significantly ($p < 0.05$) higher clinical score (7.6 ± 3.39 points) compared with the ATA group (0.92 ± 0.86). Five AIA patients presented mild bronchial symptoms (cough, with no significant changes in ventilatory data) related to the NPT and another five also showed a mild conjunctival response. No ATA patients from the control group presented extranasal symptoms.

DISCUSSION

The nose as a target organ in the diagnosis of AERD was first used by Pawłowicz²⁴ in 1990, while active anterior rhinomanometry was previously applied in different study protocols^{23,25,26} and rhinometry has also proved to be a promising technique as described by Casadevall *et al.*²⁷ To establish the usefulness of rhinomanometry in the most severely afflicted patients, consideration was given to some methodological interventions with a view to optimizing the current diagnostic method.

To reduce local L-ASA exposure and adverse reactions and to study different patterns of nasal response, a unilateral (single nostril) nasal challenge was performed. Most of the nasal positive aerodynamic responses were ipsilateral (13/26) or bilateral (12/26), and only one patient showed contralateral changes, indicating a possible involvement of neural mechanisms in airway responsiveness to a lysine aspirin stimulus.²⁸ With regard to the safety of the challenge, Makowska *et al.*²⁹ showed that even a specific bronchial challenge with aspirin may induce systemic symptoms and a bone marrow activation of leukocyte and eosinophil progenitor cells. Aspirin dosage seems to play a key role because those patients affected with a "most severe" degree of AERD who had tested positive bronchial challenge with a median of 6.8 mg of aspirin showed no extrapulmonary symptoms, whereas "less sensitive" individuals who had received a 10-fold

aspirin cumulative dose showed both bronchial and systemic responses.³⁰

Several delivery methods have been proposed to perform the nasal challenges.^{15,24} In the present study, the direct spray of L-ASA into the nostril was effective in reaching the nasal mucosa to elicit local symptoms with a low referred rate (7%) of postnasal drip. Because extranasal (and sometimes severe) symptoms have been previously described using different techniques^{24,25} a careful look into this methodological issue might well improve the final outcome of the nasal challenge.

As previously published, a final cumulative dose of 14 mg of aspirin was reached in this protocol,^{31,32} still far from those 30 mg and higher considered to be irritant to the nasal mucosa²⁷ and was, therefore, unable to validate the test. With respect to the positive criteria, a combination of both objective (rhinomanometric) and subjective (clinical score) was needed.

Interestingly, only 1 subject of the 26 who fulfilled positive rhinomanometric criteria did not reach a positive clinical score in excess of 5 points. In this particular case, clinical symptoms were finally elicited by an extra aspirin dose of 7 mg (final cumulative dose, 21 mg). A positive correlation between clinical (subjective) and rhinomanometric (objective) was achieved in 25 of 26 (96.15%) patients with a positive NPT. The parallel study of two main nasal aerodynamic parameters (inspiratory flow and resistance) made it possible to compare results throughout the course of the challenge. In the present study, NIR showed a fourfold greater accuracy than NIF in the objective measurement of nasal patency after local exposure to lysine aspirin.

Today, it is crucial to time medical procedures and according to recent guidelines⁸ at least 2 days are needed to arrive at a diagnosis (double-blind, placebo-controlled challenge) of aspirin intolerance. All of the nasal aspirin challenges performed in the current study were scheduled and completed in outpatient base facilities during a single morning (ranging from 2 hours up to a maximum period of 4 hours and 30 minutes) and may, therefore, be considered as a time-saving clinical process.

Because AERD is a dose-dependent condition, the diagnostic doses are closely related to the severity of adverse reactions and the safety of the procedure. The selected doses of aspirin (14 mg), along with the local reactions recorded, and the requirements of treatment make this NPT protocol a far safer method for this selected population compared with the OPT. On the grounds of the described late-phase respiratory reactions²² after NSAIDs challenges, a telephone survey was conducted on the following day to rule out late symptoms after each NPT has been completed. Although 33% of the patients with a positive NPT required treatment, no late reactions were recorded, *i.e.*, 66% of the patients with a positive NPT did not need to be treated during any period of the challenge, and no hospital admissions were required at any time during or after the nasal provocation.

In conclusion, as previously published, the NPT is a valid, efficient, and safe method to diagnose patients with AERD, especially those

presenting a nasal response to NSAIDs. The present nasal challenge with lysine aspirin shows equivalent results with a very low rate of adverse reactions in patients presenting severe AERD and it is a suitable timesaving procedure for daily practice.

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