

Acoustic Rhinometry and Aspirin Nasal Challenge in the Diagnosis of Aspirin-Intolerant Asthma: Clinical Finding and Safety Aspects

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Key Words

Aspirin-intolerant asthma • Acoustic rhinometry • Nasal challenge

Abstract

Background: The safety and utility of nasal provocation tests with lysine-aspirin (L-ASA) in the diagnosis of aspirin-intolerant asthma (AIA) have previously been described in a short series of patients. **Objectives:** To describe the clinical features and safety of an L-ASA challenge test in patients with AIA. **Methods:** We evaluated 72 patients (79% women), with a mean $\pm$ SD age of 47.9 ± 14.5 years. All patients were submitted to an L-ASA nasal provocation test (29 mg in each nostril) under acoustic rhinometry (AcR) control. Symptom score (0–3), visual analogical scale and nitric oxide determinations were performed at baseline and at 15, 30, 60 and 90 min. A decrease in nasal volume of at least 25% was considered a positive test. Nasal nitric oxide (nNO) and forced expiratory volume in 1 s were measured. **Results:** Nasal congestion and rhinorrhea represented 51 and 32%, respectively, of total symptoms. According to AcR data, the L-ASA challenge test was positive in 20% of patients at 15 min, an additional 36% were positive at 30 min, 18% at 60 min, and the remaining 26% at 90 min. nNO nasal values decreased but did not reach statistical significance. No pulmonary or systemic re-

actions were observed. **Conclusions:** Symptoms of nasal congestion associated with the reduction in nasal volume measured by AcR are the most useful parameters for establishing the diagnosis of AIA using the L-ASA nasal challenge. The method is very well tolerated and can be safely used even in patients with severe asthma.

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Introduction

Aspirin [acetylsalicylic acid (ASA)]-induced asthma (AIA) is a syndrome characterized by the combination of asthma, chronic rhinosinusitis with nasal polyposis, and intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs). In these patients, episodes of bronchospasm and nasal obstruction are precipitated by the ingestion of NSAIDs [1]. The prevalence of ASA intolerance varies from 3 to 35%, depending on the severity of the disease and on whether the diagnosis is based on the clinical history alone or on confirmatory tests [2–4]. As specific and sensitive in vitro tests are still not available, a definite diagnosis of AIA relies on the use of an aspirin challenge. Oral challenge with ASA is still considered the ‘gold standard’, but it can precipitate life-threatening reactions, and thus only a limited number of units have acquired

experience and expertise in its use [5, 6]. The ASA bronchial provocation test is safer than the oral test, but it still has a low risk of severe episodes of bronchospasm. Furthermore, neither the oral nor the bronchial test can be used in patients with moderate-to-severe bronchial obstruction [forced expiratory volume in 1 s (FEV₁) <70%] [7, 8]. For all these reasons, safer alternative methods to oral and bronchial challenge tests are needed to extend the use of confirmatory tests for AIA in respiratory and allergy units reluctant to implement oral and bronchial tests in the diagnosis of NSAID intolerance. The nasal challenge test with lysine-ASA (L-ASA) has demonstrated good specificity and sensitivity (94 and 73%, respectively), as well as an excellent security profile [8, 9]. Most studies, however, have been performed for research purposes on a limited number of patients, and the clinical findings and tolerability of the test in routine clinical practice have scarcely been reported. The aim of this study is to describe clinical features and safety aspects of positive L-ASA nasal challenge tests in patients with AIA, carried out in the context of normal clinical practice.

Material and Methods

Subjects

Seventy-two asthmatic patients with AIA and a positive confirmatory L-ASA nasal test were recruited. Their mean $\pm$ SD age was 47.9 $\pm$ 14.5 years and 79% were women. All subjects refrained from using any medication (antihistamines, intranasal corticosteroids and montelukast (1 week) or systemic corticosteroids (4 weeks) prior to and during the study and none of them had recently suffered an asthma exacerbation or a respiratory tract infection within the 4 weeks prior to the challenge [7]. The baseline values of FEV₁ were (87.0 $\pm$ 11.8%; range: 45–102% of predicted). In 22 patients, the FEV₁ was lower than 70% of predicted. Subjects gave their informed consent prior to the study, as is customary in challenges performed in regular clinical practice.

Study Design

Nasal response was evaluated objectively by acoustic rhinometry (AcR) and nasal nitric oxide (nNO) and subjectively by a total nasal symptom score (TNSS) and a visual analogical scale (VAS). Nasal congestion, nasal itching, sneezing, and rhinorrhea were evaluated using a Likert scale [from absent (0) to severe (3) (TNSS)] and from 0 to 10 in VAS. Nasal response was measured at 30 min after diluent and at 15, 30, 60 and 90 min after L-ASA challenge (table 1).

Nasal Challenge

The nasal challenge test with L-ASA (Aspisol®; Bayer, Germany; 900 mg of L-ASA equivalent to 500 mg of ASA) was performed according to the method described previously [8, 10]. Briefly, all subjects were challenged with L-ASA diluent (0.9% NaCl) prior to L-ASA to rule out any unspecific nasal reactivity.

Table 1. L-ASA nasal challenge schedule

	Likert scale	Symptoms VAS	Acoustic rhinometry	nNO	Pulmonary functions test
Baseline	×	×	×	×	×
Diluent					
30 min	×	×	×	×	
L-ASA					
15 min	×	×	×	×	
30 min	×	×	×	×	
60 min	×	×	×	×	
90 min	×	×	×	×	×

Then, 29 mg of L-ASA solution (equivalent to 16 mg of ASA) was applied to each inferior turbinate with an Eppendorf pipette. A challenge was considered positive when nasal volume at 12 cm (Vol₀₋₁₂) decreased by at least 25% as compared with post-NaCl challenge volume. Lung function was assessed by maximal forced flow spirometry, performed in all patients before and after the nasal challenge.

Acoustic Rhinometry

Nasal volumes were measured by AcR (Acoustic rhinometer SER 2000 RhinoMetrics, Lynge, Denmark). All AcR measurements were repeated 3 times and then averaged to ensure the reproducibility of the results. All measurements were performed in both the right and left nasal cavities. Nasal volume was evaluated using a standardized method between the nasal inlet and the 12th centimeter (Vol₀₋₁₂) [11]. We also evaluated volumes between the 2nd and 5th centimeters (Vol₂₋₅) because the main changes in the nasal mucosa occur in this segment, due to its great vascularization [12, 13].

Nitric Oxide Measurements

nNO measurements were performed by chemiluminescence (SIR, System N6008 NO tracer, Madrid, Spain) following a standardized method; they were repeated 3 times and then averaged in order to ensure the reproducibility of the results [14].

Statistics

The statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) for descriptive statistics: The Wilcoxon signed-rank test and the Mann-Whitney U test were used to compare related and unrelated variables, respectively.

The correlation between measurements of nasal volumes within 0 and 12 cm and those within 2 and 5 cm was evaluated by measuring the κ -coefficient.

Results

According to a previous study, a decrease in nasal volume (Vol₀₋₁₂) greater than 25% is the criterion that allows an L-ASA challenge to be considered positive (11). This

decrease was detected in 20% of the patients at 15 min, an additional 36% were positive at 30 min, 18% at 60 min, and the remaining 26% at 90 min (fig. 1). All in all, most patients (74%) showed a decrease in nasal volume greater than 25% at 60 min, matching with the greatest decrease in volume.

Although evaluation of the nasal volume from the tip of the nostril and 12 cm back (Vol_{0-12}) is commonly used to assess changes in nasal patency, it has been suggested that the measurement of nasal volume within 2 and 5 cm (Vol_{2-5}), which is more reproducible, could improve the ability of the method to detect mucosal changes after an L-ASA challenge [12, 13]. As expected, the decreases in nasal volumes measured with the two methods change in parallel. We found that the results with the two methods were highly concordant (κ 0.72).

Nasal congestion and rhinorrhea, evaluated by the Likert scale and VAS, were the most important symptoms, with nasal congestion being the most relevant when nasal challenge reached the level of positivity ($p < 0.05$). No differences between nasal congestion and rhinorrhea scores were observed at any time except at 60 min, when nasal congestion was the most important symptom ($p < 0.05$), matching up with the greatest decrease in volume. Itching and sneezing were the least relevant symptoms

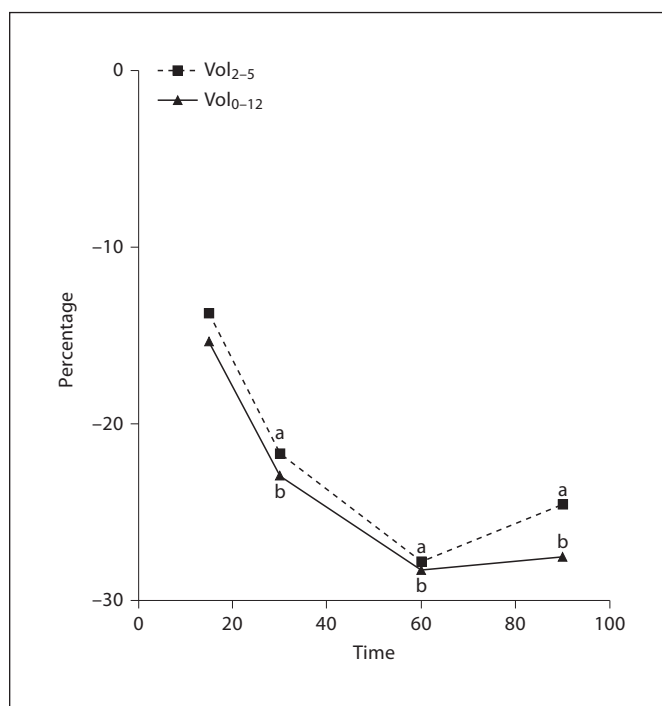
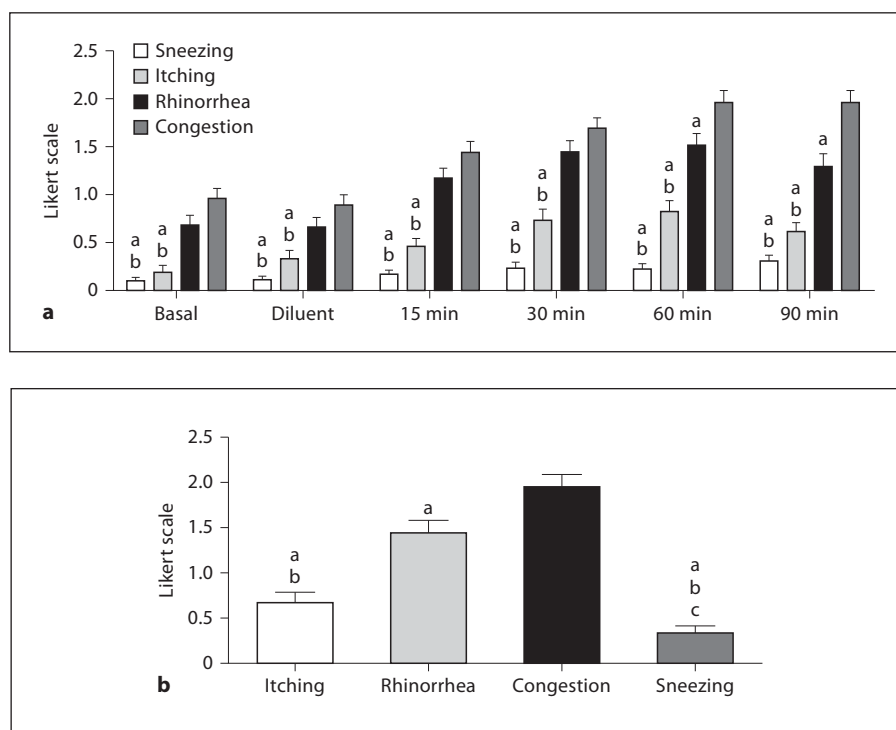


Fig. 1. Volume decrease (%) in Vol_{2-5} and Vol_{0-12} . Differences in volume decrease in Vol_{2-5} between diluent at 30, 60 and 90 min (^a $p < 0.05$). Differences in volume decrease in Vol_{0-12} between diluent at 30, 60 and 90 min (^b $p < 0.05$).

Fig. 2. a L-ASA nasal challenge symptom score (Likert scale). Differences between nasal congestion and sneezing (^a $p < 0.001$) and itching (^a $p < 0.001$) at any time and rhinorrhea at 60 and 90 min (^a $p < 0.05$) are statistically significant. Differences between rhinorrhea and sneezing and itching are statistically significant (^b $p < 0.05$). **b** Symptoms (Likert scale) when nasal challenge is positive. Differences between congestion values (Likert scale) and itching, rhinorrhea and sneezing are statistically significant (^a $p < 0.05$) when nasal challenge is positive. Differences between rhinorrhea (Likert scale) and itching and sneezing (^b $p < 0.05$) are statistically significant. Differences between itching values (Likert scale) and sneezing are statistically significant (^c $p < 0.05$).



($p < 0.05$ vs. rhinorrhea or congestion) (fig. 2a, b). When the weight of each symptom was balanced with respect to the total composite symptoms score, nasal congestion accounted for 51% of symptoms, followed by rhinorrhea (32%), nasal itching (12%) and sneezing (5%).

nNO levels decreased progressively (with no statistical significance compared with diluent levels) and the lowest level was observed at 60 min, matching up with the greatest decrease in nasal volume and severity of symptoms (essentially nasal congestion).

L-ASA challenge did not elicit any respiratory or systemic reaction (urticaria, facial flush, angioedema). There were no differences between baseline FEV₁ values (87.0 ± 11.8 ; range: 45–102%) and those obtained at the end of the test (86.8 ± 11.8 ; range: 47–108%).

Discussion

The main findings of our study are: (1) nasal congestion and rhinorrhea are the most relevant symptoms; (2) the test takes less than 2 h to confirm the suspected diagnosis of AIA; (3) L-ASA challenge can be performed in all patients, even those suffering from severe nasal obstruction due to the presence of nasal polyposis, and (4) L-ASA challenge is very safe and can be used in patients with moderate-to-severe bronchial obstruction.

Nasal congestion and rhinorrhea are the most important and severe symptoms reported following L-ASA nasal challenge in AIA patients, representing 51 and 32%, respectively, of total symptoms. In contrast, nasal itching (12%) and sneezing (5%) have a very limited impact on the evaluation of the nasal response to L-ASA in AIA. These findings concur with those previously reported by other authors [8, 10]. Although the assessment of itching and sneezing has been included in various studies and guidelines [7, 9, 10, 15], their contribution to the confirmation of aspirin intolerance is almost irrelevant.

Nasal challenge positive criteria were detected within 90 min after L-ASA intranasal instillation. These data are consistent with those of other authors [8, 15–17], who found positive responses within 10 and 110 min (mostly around 60 min) that lasted at least 1 h on average. Nasal dynamics in response to L-ASA present differential characteristics, with a slower evolution and delayed start and end compared with nasal allergen challenges [18]. Although guidelines [7] recommend evaluating the nasal response every 10 min, our results suggest that measurements recorded at intervals of 30 min could be sufficient to establish the diagnosis of as-

pirin intolerance without any risk of losing positive patients.

The performance of oral and bronchial tests usually requires many hours of observation, significantly increasing the cost and inconvenience of the study. In contrast, the short time needed to perform the L-ASA nasal challenge test represents a major improvement in the cost/benefit of the diagnostic procedure while significantly reducing the inconvenience usually caused to patients by oral and bronchial tests.

AcR is a safe, easy and reliable technique with demonstrated accuracy in the evaluation of the volume of nasal cavities in several diseases, even in those with reduced nasal volumes, such as chronic rhinosinusitis with nasal polyposis [19–24]. Patients with AIA present an increased prevalence of chronic rhinosinusitis/nasal polyposis [10, 25] and some techniques, such as rhinomanometry and nasal inspiratory peak flow (NIPF), are difficult to perform due to the low flow rates generated in patients with severe nasal obstruction. Several authors have reported that rhinomanometry/NIPF failed to evaluate L-ASA challenge response in up to 20% of selected patients [10, 17, 26]. AcR does not have this limitation, and all patients in our study could be evaluated, including those with massive nasal polyps. Our observations suggest that AcR is more convenient than other techniques for measuring changes in nasal flow, such as rhinomanometry/NIPF, in the assessment of the nasal response to L-ASA in the diagnosis of AIA [8, 15, 16, 27]. However, a number of factors can lead to measurement variations when AcR is used. The presence of pathological spaces such perforation of the nasal septum leads to abnormal recordings. AcR is also more expensive than such techniques as rhinomanometry and PNIF.

The cut-off criterion for a positive L-ASA challenge controlled by AcR was defined by Casadevall et al. [8] as a decrease in nasal volume of between 0 and 12 cm (Vol_{0–12}) greater than 25%. Nasal volume of between 2 and 5 cm (Vol_{2–5}) contains the most vascularized area, and therefore mucosal changes induced by inflammatory responses might be detected more accurately by evaluating this area [12, 13]. In our study, however, the L-ASA nasal challenge test assessed by both Vol_{0–12} and Vol_{2–5} showed similar results. Kupczyk et al. [16] used Vol_{2–5} evaluation in nasal challenge with L-ASA, and concluded that AcR has limited sensitivity in detecting mucosal changes, but they used a low L-ASA dose (15 vs. 29 mg in our study), which could explain the low rate of positive challenges in patients with AIA confirmed by oral challenge.

nNO values progressively decreased in concordance with the reduction in nasal volume and the increase in symptom score. nNO is assumed to be continuously produced by the ciliated cells of the paranasal sinuses and nasal mucosa, and to diffuse through the ostiomeatal complex to the nasal cavity [28]. Patients with a positive nasal challenge are thought, however, to have an inflamed nasal mucosa and, thus, high nNO levels [29, 30]. These apparently controversial results are explained by the blockade of the ostiomeatal complex, and the consequent inability of newly generated NO to reach the nasal cavity [31]. This phenomenon has been described in several inflammatory nasosinus diseases, such as chronic rhinosinusitis, with or without nasal polyps [24, 32].

In our study, no systemic reactions were noticed and FEV₁ which was recorded before and after the nasal challenge test, did not show any significant difference. Our results contrast with those of Pawlowicz et al. [33], who observed a significant fall in FEV₁ in all the patients they evaluated. Most authors have reported only a few mild reactions, however, thus demonstrating the high safety profile of the nasal challenge test with L-ASA [7, 8, 10, 16, 34].

In conclusion, nasal congestion is the most important clinical feature present in positive nasal challenge with L-ASA in AIA patients. AcR is a safe, rapid and reliable tool in the evaluation of nasal obstruction. For all these reasons, we consider nasal challenge with L-ASA, objectively assessed by AcR, a very useful diagnostic tool in AIA patients.

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