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Respiratory Exposure Tests in Aspirin Exacerbated Respiratory Disease

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Abstract

Purpose of review Controlled oral provocation test with aspirin is considered the "gold standard" for diagnosing hypersensitivity to NSAIDs (non-steroid anti-inflammatory drugs). Newer techniques of respiratory exposure tests, bronchial and nasal respectively, have been nonetheless developed, as they are safer, less likely to cause a systemic reaction, and less time-consuming than the oral provocation test with aspirin (acetyl-salicylic acid). These tests are also particularly useful when oral challenge testing is contraindicated. The aim of this paper is to review and update the detailed protocols of bronchial and nasal challenges with lysine-aspirin, a salt of acetyl-salicylic acid, more soluble and less irritative.
Recent findings Current guidelines recommend standardized protocols for nasal, and especially bronchial challenge with lysine-aspirin, in patients with suspected N-ERD (NSAID-exacerbated respiratory disease).
Summary Nasal and bronchial tests are useful and safe, nonetheless not that sensible as oral aspirin challenge for the diagnosis of N-ERD. So, in cases of high suspicion and negative respiratory tests, an oral challenge should be performed before ruling out the diagnosis. These techniques should be performed by trained personnel in specialized allergy clinics. Further consensus on nasal test protocol and interpretation is still needed.

Introduction

Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) can be classified into 2 groups according to the involved mechanism:

•Allergic reactions, mediated by specific immunological mechanisms: selective hypersensitivity immunoglobulin E-mediated in immediate reactions and T cell-mediated in delayed reactions. Patients present reactions to a single NSAID or several NSAIDs of the same chemical group.
•Hypersensitivity reactions, not mediated by a specific immunological mechanism: the mechanism is associated with the enzyme cyclo-oxygenase (COX)-1. In these reactions, patients react to various NSAID belonging to different chemical groups [1••]. The inhibition of COX-1 leads to an increase in the expression of specific proinflammatory mediators such as cysteinyl-leukotrienes (cys-LT) and prostaglandin (PG) D_2 and a decrease in the expression of other bronchoprotective agents such as PGE_2. The generated imbalance eventually triggers symptoms such as bronchospasm, rhinitis, and/or urticaria/angioedema [2]. These are the most common hypersensitivity type reactions and result from cross-reactivity between different NSAIDs that are not structurally related [3].

These reactions are dose-dependent and can be classified into 3 groups, according to the position statement published by the European Academy of Allergy and Clinical Immunology [1••]:

a.NSAID-exacerbated respiratory disease (N-ERD): patients with underlying chronic respiratory disease of the lower (asthma) and/or upper airways (chronic rhinosinusitis with [CRSwNP] or without [CRSsNP] nasal polyps), who exhibit bronchial obstruction, dyspnea, cough, wheezing, nasal congestion, sneezing, and/or rhinorrhea when exposed to a NSAID.
b.NSAID-exacerbated cutaneous disease (NECD): patients with a history of spontaneous chronic urticaria-manifest urticaria and/or angioedema when exposed to a NSAID.
c.NSAID-induced urticaria/angioedema (NIUA): patients with no history of spontaneous chronic urticaria nor underlying respiratory disease, who develop urticaria and/or angioedema, most characteristically palpebral angioedema. These patients are generally atopic and sensitized mainly to house dust mite [4].
In most cases of hypersensitivity reactions to multiple NSAID, controlled exposure will be necessary to ensure the diagnosis, as skin testing or other immunological in vitro tests are of no use.

Classification of respiratory exposure tests

There are 4 types of provocation, challenge, or exposure tests, depending on the route of administration: oral, intravenous, and respiratory exposure tests: bronchial or nasal challenge, respectively. Intravenous provocation testing is used exclusively in Japan and usually not in daily clinical practice [5•].

Controlled oral provocation testing with aspirin is considered the "gold standard" for diagnosis of hypersensitivity to NSAIDs [6]. Newer techniques of respiratory exposure tests, bronchial or nasal respectively, are the aim of this review. They have been developed as they are safer, less likely to cause a systemic reaction, and less time-consuming than the oral provocation test. These tests are also particularly useful when oral challenge testing is contraindicated because of asthma severity.

Both tests can be performed in outpatient settings. These techniques should always be carried out by suitable trained nursing staff under the supervision of an experienced allergist; full cardiopulmonary resuscitation must be available on site in order to treat potential severe reactions.

Knowledge of each test methodology and of evaluating the results of spirometry, active anterior rhinomanometry (AARNM), or acoustic rhinometry (ARM), respectively, are required. The medication necessary to treat potential reactions must be at hand (epinephrine, inhaled short-acting β_2-agonists and anticholinergics, inhaled/intranasal and systemic corticosteroids, oral and systemic antihistamines, and nasal decongestant).

As in any medical procedure, the patient must sign a written informed consent before undergoing bronchial or nasal provocation tests.

The patient's usual medication should be reviewed and stopped, if necessary, in order not to interfere with the test results (specified below in each procedure).

Specific procedure: bronchial provocation testing with lysine-aspirin

Introduction

As oral provocation testing is considered the gold standard for diagnosis, it has been compared with bronchial provocation testing in 3 studies [7, 8, 9•]. The results reported were similar. Both methods have the same specificity, around 93%, although oral provocation is more sensitive (89% vs 77%) and the negative predictive value was higher with the oral provocation test [7] (Table 1).

Therefore, as the negative predictive value of bronchial testing is lower, a negative result should be followed by an oral provocation test in order to reach the definitive diagnosis [1••, 5•, 9•].

Indications

Patients over 18 years of age with suspected N-ERD, presenting with bronchial symptoms after taking NSAID.

Table 1. Diagnostic value of challenge tests with aspirin and lysine-aspirin [7, 37]

Challenge test	Sensitivity	Specificity	Negative predictive value
Oral	89%	93%	77%
Bronchial	77%	93%	64%
Nasal	80%	92.5%	89.2%

Contraindications [1, 5, 10, 11]

- Patients who do not sign the informed consent to undergo the test.
- Pregnancy.
- Treatment with betablockers.
- Severe or poorly controlled asthma during the previous month.
- Respiratory infection during the 4 weeks before the provocation test.
- Those of spirometry itself: recent abdominal surgery, aneurisms, recent ocular surgery, myocardial infarct, hemoptysis, chest pain (angor, pneumothorax, trauma).
- Baseline spirometry: $FEV_1 < 70\%$ predicted and < 1.5 L.

Methodology

Preparation [5, 9, 10]

Bronchial provocation test should preferably be performed in the morning. Patients should be advised not to consume spicy foods or caffeine drinks and avoid intense exercise before the test. The patients should also avoid smoking and alcohol intake during the 24 previous hours.

Room conditions: when the spirometer is calibrated first thing in the morning, temperature, atmospheric pressure, and humidity must be registered according to the manufacturer's instructions [11].

The following drugs should be discontinued in patients in order not to interfere with the test as follows [5•, 12, 13]:

- Oral antihistamines for 3 days.
- Leukotriene receptor antagonists for 7 days.
- Long-acting agonists for 24–48 h.
- Short-acting agonists for 6–8 h.
- Long-acting anticholinergics for 7 days.
- Inhaled corticosteroids could be maintained at the lowest dose possible.
- If the patient is receiving regular treatment with oral corticosteroids, the dose should not exceed 10 mg of prednisolone or equivalent.

Procedure

Bronchial provocation is performed with lysine-aspirin, a salt of acetylsalicylic acid that is more water-soluble (40% vs 0.3%), less irritating, and better tolerated via inhalation. The technique was first described in 1977 by Bianco et al. [14] and then modified by Philips et al. in 1989 [15]. The current protocol is based on a modified Philips method [5•]. It can be performed by means of continuous inhalation at incremental volumes with a constant output [16], or intermittent breathing through a nebulizer connected to an electronic dosimeter (e.g., Me-Far or Spira-Electro 2) [17].

The test is started with a baseline spirometry aimed to verify that FEV_1 is $> 70\%$ predicted and > 1.5 L.

The patient first receives 5 inhalations of the control diluent (isotonic saline 0.9%). Spirometry is repeated after 10 min. A decrease of > 10% in FEV_1 is considered a sign of airway instability that could generate a false-positive result; therefore, the test should be postponed. If FEV_1 does not decrease by more than 10% over baseline, the test continues and the FEV_1 recorded after the diluent is the reference value.

Fresh lysine-aspirin solutions (Inyesprin©, Aristo Pharma Iberia, S.L.) are prepared immediately before the test, as they remain stable only for 2 h, and should be kept refrigerated (900 mg of lysine-aspirin is equivalent to 500 mg of aspirin). First, 2 vials are diluted with 5 mL of distilled water to produce a solution of 360 mg/mL, which is equivalent to 200 mg/mL of aspirin. Successive dilutions are then made with saline solution 0.9% to obtain concentrations of 180 mg/mL, 90 mg/mL, and 45 mg/mL, respectively.

Consecutive and progressively increasing doses from 45 to 360 mg doses of lysine-aspirin are inhaled every 30 min, and spirometry and peak expiratory flow (PEF) values are measured at 10, 20, and 30 min after each dose (see Table 2).

Once the provocation test is completed, irrespective of whether the result is positive or negative, additional spirometry testing and determination of PEF should be performed in the clinic 1 h and 2 h after the test. The patient subsequently records PEF every 2 h at home, except while sleeping, until 24 h after the test, when he/she returns to the clinic with the PEF recording.

Interpretation of the results

The criteria for a positive bronchial provocation are as follows [5•, 9•, 18]:

a) Immediate reaction with bronchospasm and decrease in $FEV_1 \geq 20\%$ (< 4 h after the test).
b) Immediate reaction with a 15–20% decrease in FEV_1, as well as any of the following extra-bronchial symptoms: sneezing, naso-ocular pruritus, nasal congestion, runny nose, conjunctival erythema and pruritus, tearing, and/or palpebral angioedema.
c) Exclusively late reaction: late decrease in PEF ≥ 20% (between 4 and 24 h after the provocation test).

Table 2. Protocol for inhaled provocation testing with lysine-aspirin using a dosimeter [5•]

Concentration of lysine-aspirin (mg/mL)	No. inhalations	Dose of lysine-aspirin (mg)	Cumulative dose lysine-aspirin (mg)
45	1	0.405	
45	5	2.025	2.43
90	5	4.05	6.48
180	5	8.1	14.58
180	10	16.2	30.78
360	10	32.4	63.18
360	20	64.8	127.98

d) Dual reaction: immediate and late reaction.

The result of the bronchial provocation is considered negative if the maximum dose is reached with no decrease in FEV_1 or PEF ≥ 20% up to the 24 h following the end of the test. In these cases, in order to clarify the diagnosis, oral provocation with aspirin should be scheduled after an interval of at least 7 days, if it is not contraindicated [5•, 10••, 19].

Complications and management

a) Bronchospasm must be treated with nebulized salbutamol and ipratropium bromide, as needed.
b) Nasal obstruction can be treated with an intranasal decongestant to avoid trapping of secretions and severe headache. Nasal symptoms can also be managed with oral and/or intranasal antihistamines.
c) Ocular symptoms can be treated with oral and/or topical antihistamine.
d) Laryngospasm must be treated with intramuscular epinephrine.

If more severe reactions are observed, oral or i.v. corticosteroids should be administered (doses adjusted based on the patient's weight). Anaphylactic reactions require immediate intramuscular injections of epinephrine.

Special situations

Pediatric patients: bronchial provocation is contraindicated in patients aged less than 18 years. In these cases, when N-ERD is suspected, diagnosis must be confirmed based on oral provocation with aspirin or nasal provocation with lysine-aspirin, as explained below.

Specific procedure: nasal provocation test with lysine-aspirin

Introduction

Nasal provocation testing was implemented in daily clinical practice at the end of the 1990s. It is used for provocation tests with allergens or drugs, for the study of response to treatments, and for research studies of the immunology and pathophysiology of the nasal mucosa. Guidelines and consensus statements on the methodology and diagnostic use of nasal provocation have been published [20–30]. The diagnostic usefulness of nasal provocation and bronchial provocation compared with oral provocation is summarized in Table 2. Despite the fact that it is a safe alternative to oral provocation and bronchial provocation in the assessment of patients with hypersensitivity to NSAIDs, fewer studies have analyzed the standardization nasal provocation, if we compare it with oral and bronchial provocation testing with aspirin.

One of the limitations of the nasal provocation test is that there is no single international consensus for it. Therefore, criteria for positivity,

methodologies, and the preparations used in nasal provocation testing vary depending on the study. Nonetheless, nasal provocation is a very useful clinical and research tool in upper airway disease and for the study of patients with N-ERD.

The nasal provocation test involves reproducing a response in the nasal mucosa with controlled exposure to the drug using lysine-aspirin, as in bronchial provocation. The response is characterized by nasal obstruction, rhinorrhea, and edema of the nasal mucosa, with increases airflow resistance and diminishes the intranasal volumes and areas, which are the parameters used to quantify the response.

The main limitation of this diagnostic method though is its low sensitivity and its low negative predictive value. Therefore, a negative nasal challenge should be followed by oral challenge in order to rule out aspirin sensitivity.

Indications

Nasal provocation is indicated in patients with suspected N-ERD, particularly in those of high risk in which bronchial or oral provocation tests are contraindicated, mainly patients with $FEV_1 < 70\%$, and also in children.

Contraindications

Nasal provocation should not be performed in the following cases:

- Patients who do not sign the informed consent to undergo the test.
- Massive nasal polyps or perforated septum: nasal provocation is not recommended in these cases, since objective evaluation of nasal obstruction is very difficult, and interpretation of the results is more complicated.
- Autoimmune diseases (e.g., Wegener disease or GPA, Churg-Strauss syndrome or EGPA).
- Immunodeficiency.
- Pregnancy.
- Uncontrolled severe or poorly controlled asthma: the patient must be free of bronchial symptoms, with no asthma exacerbations within the last 4 weeks.
- Concomitant respiratory infection and in the previous month at the time of the test.
- Age under 5 years.
- Symptomatic rhinitis: the test should be postponed until at least 2–4 weeks after an exacerbation of allergic or infectious rhinitis [23, 25, 26]. In the case of concomitant allergic rhinitis, the test should be performed outside the pollen season or, in the case of perennial allergens, when mild symptoms do not interfere with the results of the test.
- Nasal surgery: the provocation should be postponed for 6–8 weeks after the intervention [25].

Methodology

a. Preparation

- Forced spirometry is always recommended before and after nasal provocation.
- The patient should avoid smoking and alcohol during the 24 h before the test.
- Before the test, oral antihistamines should be interrupted for 48 h to 2 weeks (depending on the drug), intranasal antihistamines for 4–5 days, intranasal corticosteroids for 48–72 h, oral corticosteroids for 2–3 weeks, and nasal decongestants for 2 days.
- Room conditions: temperature and humidity must be maintained constant throughout the whole time of the procedure at a temperature of 20–22 °C, with humidity of 40–60%. Temperatures above 35 °C with a high degree of humidity (80–90%) can alter the immediate response due to diminished release of histamine and the vascular/neural response [31].
- The patient must be acclimated (20–30 min in the same room) in order to avoid nonspecific reactions of the nose to environmental conditions.
- Nasal provocation testing should preferably be performed in the morning in order to avoid the irritant effect of the usual daily stimulants (e.g., tobacco smoke, pollution, spicy food, coffee, exercise as in the bronchial challenge).

b. Procedure

The most widely used approach today is instillation of 0.1 mL (100 µL) of lysine-aspirin on the head of the inferior turbinate, preferably with a micropipette, but also with a syringe, pipette, or dropper, with the patient's head tilted back for 1 min. Intranasal ketorolac has been used by other authors, in some cases because lysine-aspirin is not available in the USA [5•, 32, 33].

The doses of lysine-aspirin used in nasal provocation vary according to the protocol, with 20 mg as the maximum cumulative aspirin-equivalent dose accepted though [34], using either a single dose aspirin-equivalent [35, 36] or progressive concentrations [37]. The cumulative dose is critical for the result of the test, since low doses do not enable sufficient response [35], whereas doses above 30 mg of aspirin are irritating and, therefore, invalidate interpretation of the results [36].

The protocol used in our center is the following: diluent (0.9% NaCl) is administered beforehand in order to rule out nasal hyperreactivity. If a change over 20% compared to baseline values occurs, it implies that the upper airway is hyperreactive and further challenge should not be performed. Then, 29 mg of lysine-aspirin in 100 µL (equivalent to 16 mg of aspirin) is administered to the inferior turbinate of each nostril using an Eppendorf pipette [38, 39]. We perform a measurement at baseline, 30 min after administration of the diluent, and at 15, 30, 60, and 90 min after administration of lysine-aspirin. During nasal challenges, peak flow rate (PEFR) and/or or FEV_1 measurement are taken at the same time points to monitor the bronchial response.

Objective evaluation of the nasal response is usually performed by active anterior rhinomanometry (AARNM) or acoustic rhinometry (ARM), but peak nasal inspiratory flow (PNIF) could be used as an alternative evaluation method.

AARNM enables simultaneous measurement of flow and pressure variations in air current crossing the nostrils during the different phases of respiration. AARNM with a facemask and computerized recording of

pressure, flow, and resistance is recommended as the optimal test in daily clinical practice [40, 41].

ARM is used to evaluate nasal permeability through measurement of areas and volumes in the nasal cavity based on reflection of sound waves through an acoustic rhinometer. It is noninvasive, is reproducible, and requires only minimal cooperation from the patient. It is well standardized for the demonstration of changes in the permeability of the nasal mucosa.

Interpretation

A positive reaction to nasal aspirin challenge is defined as the appearance of nasal symptoms such as rhinorrhea, nasal congestion, and sneezing with increased airflow resistance. The patient's symptoms can be evaluated subjectively using a visual analog scale of symptoms (rhinorrhea, sneezing, nasal obstruction, and pruritus).

Airflow resistance can be measured objectively using 3 techniques: anterior acoustic rhinomanometry (AARNM), acoustic rhinometry (ARM), or peak nasal inspiratory flow (PNIF). The criteria of a positive reaction are not as well defined as in bronchial provocation.

a) Immediate reaction

When using AARNM, a degree of variability is accepted because of differences in the devices used and the characteristics of the study population [39–42]. Usually, a minimum 100% increase in resistance is accepted as a criterion for positivity [28, 41].

When using acoustic rhinometry, it is considered positive a 25% decrease of total nasal flow value at 12 cm, as compared with baseline [37, 38]. Some studies show that the test can be considered positive when there is a fall of 25% in nasal volume at 2–5 cm [99,100]. Values obtained using ARM should also be correlated with subjective values, clinical symptoms, by means of the visual analog scale or VAS (see above) and symptom scores [31, 38].

Alternatively, a positive result can be considered a 40% bilateral drop of inspiratory nasal flow, as compared to baseline value assessed by AARNM or PNIF meter [5•].

b) Dual reaction: reappearance of nasal symptoms, especially obstruction, at 3 to 12 h after nasal provocation [29]. The patient should be informed of this possibility and its treatment.
c) Delayed nasal response: the criteria for evaluating a delayed nasal response are not as well established as those for bronchial response. Symptom scoring is not sufficient in the case of a delayed reaction.

Complications and management

If the result of the nasal provocation test is positive, a topical nasal decongestant and/or intranasal or systemic antihistamines should be

administered, depending on the intensity of the symptoms. In case of severe nasal adverse reactions, oral/systemic corticosteroids should be administered.

Systemic reactions are extremely rare and should be treated as stated in the prior section on bronchial provocation.

Special situations

ARM is easy to perform and reproducible and it is not affected by rhinorrhea or nasal obstruction. It requires little cooperation from the patient, thus making it especially useful for children.

Conclusions

In NSAID-exacerbated respiratory disease (N-ERD), performing challenge tests is necessary. Nasal or bronchial challenge tests with lysine-aspirin are useful and add safety in cases where oral challenge is contraindicated or poses a high risk.

Protocols and diagnostic methods are standardized for bronchial tests; however, further consensus on nasal test protocol and interpretation is needed.

Declarations

Conflict of interest
The authors declare no competing interests.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• Kowalski ML, Agache I, Bavbek S, Bakirtas A, Blanca M, Bochenek G et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)-a EAACI position paper. Allergy. 2019;74(1):28–39.

The latest update of the EAACI on the topic discussed here, based on previous position papers also cited and recommended below (5, 10).

2. Pierzchalska M, Szabó Z, Sanak M, Soja J, Szczeklik A. Deficient prostaglandin E2 production by bronchial

fibroblasts of asthmatic patients, with special reference to aspirin-induced asthma. J Allergy Clin Imunol. 2003;111:1041–8.
3. Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011;41:86–95.
4. Quiralte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to nonsteroidal anti-inflammatory drugs: results of controlled drug challenges in 98 patients. J Allergy Clin Immunol. 1996;98:678–85.
5.• Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. Allergy. 2007; 62:1111–8.
Many of the protocols detailed in this position paper are still valid.
6. Ortega N, Doña I, Moreno E, Audicana MT, Barasona MJ, Berges-Gimeno MP, et al. Practical guidelines for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol. 2014;24:308–23.
7. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. Eur Respir J. 2000;15:863–9.
8. Dahlen B, Zetterstöm O. Comparation of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. Eur Respir J. 1990;3:527–34.
9.• Barranco P, Bobolea I, Larco JI, Prior N, Lopez-Serrano MC, Quirce S. Diagnosis of aspirin-induced asthma combining the bronchial and the oral challenge tests: a preliminary study. J Investig Allergol Clin Immunol. 2009; 19:446–52.
Latest direct comparison of bronchial and oral challenge with aspirin.
10.•• Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal antiinflammatory drugs (NSAIDs) classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. Allergy. 2011; 66:818–29.
Fundamental reading, especially on understanding the classification of the complex NSAIDs-induced reactions.
11. Graham BL, Steenbruggen I, Miller MR et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200(8): e70-e88.
12. Coates AL, Wanger J, Cockcroft DW, Culver BH, Bronchoprovocation Testing Task Force. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Resp J. 2017;49:1601526.
13. Izquierdo Domínguez A, Bobolea I, Doña I, Campo P, Segura C, Ortega N, et al; on Behalf of the SEAIC Rhinoconjunctivitis Committee. Position statement of the Spanish Society of Allergology and Clinical Immunology on provocation tests with aspirin/nonsteroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol. 2020;30(1):1–13.
14. Bianco S, Robuschi M, Petrioni G. Aspirin-induced tolerance in aspirin-induced asthma detected by a new challenge. (IRCS) Med Sci. 1977;5:129–37.
15. Philips GD, Focard R, Holgate ST. Inhaled lysine-aspirin as a bronchoprovocation procedure in aspirin-sensitive asthma. Its repeatability, absence of late-phase reaction and the role of histamine. J Allergy Clin Immunol. 1989;84:232–41.
16. Park HS. Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients. Clin Exp Allergy. 1995;25:38–40.
17. Melillo G, Padovano A, Cocco G, Masi C. Dosimeter inhalation test with lysine acetylsalicylate for the detection of aspirin induced asthma. Ann Allergy. 1993;71:61–3.
18. Melillo G, Balzano G, Bainco S, Dahlén B. Oral and inhalation provocation tests for the diagnosis of aspirin-induced asthma. Report of Interasma Working Group on standardization of inhalation provocation tests in aspirin-induced asthma. Allergy. 2001;56:899–911.
19. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854–63.
20. Bachert C, Gonsior E, Berdel D. Guidelines for the performance of nasal provocations with allergen in upper respiratory tract diseases (Richtlinien für die Durchfürung von nasalen Provokationen mit Allergen bei Erkrangungen der oberen Luftwege) Allergologie. 1990; 13:53–6.
21. Druce HM, Schumacher MJ. Nasal provocation challenge. The Committee on Upper Airway Allergy. J Allergy Clin Immunol. 1990; 86:261–4.
22. Schumacher MJ. Nasal provocation test. Rhinology. 1992;14:242–6.
23. Lund VJ, Aaronson D, Bousquet J, Dahl R, Davies RJ, Durham SR, et al. International consensus report on the diagnosis and management of rhinitis. Int Rhinitis Manage Work Group Allergy. 1994;49:1–34.
24. Melillo G, Bonini S, Cocco G, Davies RJ, de Monchy JGR, Frolund L, et al. EAACI provocation tests with allergens. Report prepared by the European Academy of Allergology and Oral, Bronchial, and Nasal Provocation Tests with Aspirin J Investig Allergol Clin Immunol 2020; Vol. 30(1): 1–13 Clinical Immunology Subcommittee on provocation tests with allergens. Allergy. 1997; 52:1–35.

25. Malm L, Gerth Van Wijk R, Bachert C. Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. Rhinology. 2000;38:1–6.
26. Litvyakova LI, Baraniuk JN. Nasal provocation testing: a review. Ann Allergy Asthma Immunol. 2001;86:355–65.
27. Litvyakova LI, Baraniuk JN. Human nasal allergen provocation for determination of true allergic rhinitis: methods for clinicians. Curr Allergy Asthma Rep. 2002;2:194–202.
28. Gosepath J, Amedee RG, Mann WJ. Nasal provocation testing as an international standard for evaluation of allergic and nonallergic rhinitis. Laryngoscope. 2005;115:512–6.
29. Dordal MT, Lluch-Bernal M, Sánchez MC, Rondón C, Navarro A, Montoro J, et al. SEAIC Rhino conjunctivitis Committee. Allergen-specific nasal provocation testing: review by the rhino conjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. J Investig Allergol Clin Immunol. 2011;21:1–12.
30. Augé J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A, et al. EAACI position paper on the standardization of nasal allergen challenges. Allergy. 2018;73:1597–608.
31. Cimarra M, Robledo T. Aplicación en provocación nasal específica. In: Valero A, Fabra JM, Márquez F, Orus C, Picado C, Sastre J, Sierra JI, editors. Manual de rinomanometría acústica. Barcelona: MRA Médica; 2001. p. 55–63.
32. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon A, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2010;105:130–5.
33. Quiralte-Castillo J, Ávila-Castellano MR, Cimbollek S, Benaixa P, Leguisamo S, Baynova K, et al. Nasal ketorolac challenge using acoustic rhinometry in patients with aspirin-exacerbated respiratory disease. J Investig Allergol Clin Immunol. 2017;27:169–74.
34. Pawlowicz A, Williams WR, Davies BH. Inhalation and nasal challenge in the diagnosis of aspirin induced asthma. Allergy. 1991;46:405–9.
35. González-Pérez R, Vives R, Poza-Guedes P, Campo P, Merchán R, Lozoya C, et al. Nasal provocation test with lysine-aspirin in the diagnosis of NSAIDs intolerance with respiratory symptoms. Allergy. 2001;56:104.
36. González-Pérez R, Vives R, Poza-Guedes P, Merchán R, Cimbollek S, Rodríguez J. Nasal provocation test with lysine-acetylsalicylate in the diagnosis of NSAIDs intolerance with respiratory symptoms. J Allergy Clin Immunol. 2002;109:268–9.
37. Alonso-Llamazares A, Martínez-Cócera C, Domínguez-Ortega J, Robledo-Echarren T, Cimarra-Alvarez M, Mesa del Castillo M. Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). Allergy. 2002;57:632–5.
38. Muñoz-Cano R, Bartra J, Sanchez-Lopez J, Picado C, Bissinger I, Valero A. Acoustic rhinometry and aspirin nasal challenge in the diagnosis of aspirin-intolerant asthma: clinical finding and safety aspects. Int Arch Allergy Immunol. 2013;160:307–12.
39. Uzzaman A, Metcalfe DD, Komarow HD. Acoustic rhinometry in the practice of allergy. Ann Allergy Asthma Immunol. 2006;97:745–51.
40. Clement PAR, Gordts F. Standardisation Committee on Objective Assessment of the Nasal Airway, IRS, and ERS. Consensus report on acoustic rhinometry and rhinomanometry. Rhinology. 2005;43:169–79.
41. Eccles R. A guide to practical aspects of measurement of human nasal airflow by rhinomanometry. Rhinology. 2011;49:2–10.
42. Casadevall J, Ventura PJ, Mullol J, Picado C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. Thorax. 2000;55:921–4.

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