

Statement of the Spanish Society of Allergology and Clinical Immunology on Provocation Tests With Aspirin/Nonsteroidal Anti-inflammatory Drugs

Izquierdo-Domínguez A^{1,2}, Bobolea I³, Doña I^{4,5}, Campo P^{4,5}, Segura C⁶, Ortega N⁷, González R⁸, Delgado J⁶, Torres MJ^{4,5}, Dordal MT⁹, on behalf of the SEIC Rhinoconjunctivitis Committee

¹Allergy Service, Consorci Sanitari de Terrassa, Barcelona, Spain

²Allergy Unit, Clínica Diagonal, Barcelona, Spain

³Allergy Section, Servei de Pneumologia i Alergia Respiratòria, Hospital Clínic, Barcelona, Spain

⁴Allergy Unit, Hospital Regional Universitario de Málaga, Málaga, Spain

⁵Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA, Málaga, Spain

⁶UGC Alergología, Hospital Universitario Virgen Macarena, Sevilla, Spain

⁷Allergy Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

⁸Allergy Service, Hospital Universitario de Canarias, Tenerife, Spain

⁹Allergy Unit, Servei de Medicina Interna, Hospital Universitari de Bellvitge, Barcelona, Spain

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■ Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used throughout the world. They are frequently involved in hypersensitivity reactions, which range from local or mild reactions to systemic and severe reactions. Consequently, it is necessary to perform an exhaustive study of patients in order to make an accurate diagnosis, search for safe procedures in the case of severe reactions, and identify alternative treatment options. Various guidelines and protocols address the management of hypersensitivity to NSAIDs, although these vary widely from country to country. The Committees of Asthma, Rhinoconjunctivitis, and Drug Allergy of the Spanish Society of Allergy and Clinical Immunology (SEIC) propose the present position statement on available options for provocation testing with aspirin/NSAIDs. This document is the fruit of an exhaustive review of current evidence and is based on recent publications addressing the diagnosis of patients with hypersensitivity to NSAIDs and on a consensus-oriented discussion among a group of experts from the SEIC. The main objective was to draft an easy-to-read, practical guideline for health care professionals in specialist areas who assess and manage patients with suspected hypersensitivity to NSAIDs. Furthermore, indications, contraindications, and procedures for oral, bronchial, and nasal provocation tests with aspirin/NSAIDs have been updated.

Key words: AERD. Aspirin. NSAID. NERD. Aspirin provocation test.

■ Resumen

Los antiinflamatorios no esteroideos (AINE) son medicamentos ampliamente utilizados a nivel mundial y frecuentemente implicados en reacciones de hipersensibilidad que pueden comprender desde reacciones locales y/o leves a reacciones sistémicas y graves. La complejidad del diagnóstico ante la falta de pruebas cutáneas o de laboratorio estandarizadas y/o validadas, hace que en muchos casos debamos realizar pruebas de provocación de alto riesgo. Por ello, es necesario un exhaustivo estudio de estos pacientes en los que tienen gran importancia el correcto diagnóstico y la búsqueda de procedimientos más seguros ante pacientes con reacciones graves, así como también la búsqueda de opciones alternativas de tratamientos antiinflamatorios.

Actualmente existen diversas guías y protocolos de actuación que describen el manejo de la hipersensibilidad a los AINE aunque con importante variabilidad entre diferentes países. Desde los distintos comités de Asma, Rinoconjuntivitis y Alergia a Fármacos de la Sociedad Española de Alergología e Inmunología Clínica (SEIC) proponemos un documento de posicionamiento sobre las opciones en las pruebas de provocación con aspirina/ AINE. Este documento es el resultado de una revisión exhaustiva de la evidencia actual, basada en publicaciones recientes sobre el diagnóstico de pacientes con hipersensibilidad a AINE, y de la discusión consensuada de un grupo de expertos de la SEIC. El objetivo fundamental ha sido elaborar una guía práctica de fácil lectura dirigida a profesionales sanitarios de atención especializada implicados en el estudio y manejo de pacientes con sospecha de hipersensibilidad a AINE. Además, se ha realizado una actualización sobre las indicaciones, contraindicaciones y procedimientos de las pruebas de provocación oral, bronquial y nasal con aspirina/AINE.

Palabras clave: EREA. Aspirina. AINE. NERD. Provocación con aspirina.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) induce a wide range of adverse reactions associated with their pharmacological properties. NSAIDs are the drugs most frequently involved in hypersensitivity reactions [1,2]. Aspirin (acetylsalicylic acid) was the first synthetic compound marketed with antipyretic, analgesic, and anti-inflammatory activity. Dozens of compounds with similar activity were subsequently developed, all of them capable of inducing hypersensitivity reactions in susceptible persons. The reactions vary according to their latency period (immediate or delayed), organ involved (skin, respiratory tract, other), and severity (from rhinitis to bronchospasm, exanthema or urticaria, and anaphylaxis) [3].

Diagnosis of hypersensitivity reactions is complex because we do not have skin tests or in vitro tests that are sufficiently reliable or standardized. Consequently, in most cases we must perform provocation tests.

The objective of the present position statement is to set out a practical guideline on the performance of oral, bronchial, and nasal provocation tests in patients with suspected hypersensitivity to NSAIDs.

Therefore, the members of the respective Asthma, Rhinoconjunctivitis, and Drug Allergy Committees of SEAIC held face-to-face and online meetings to harmonize working criteria. Group leaders were then chosen to review the data. A systematic methodology was followed to obtain data sources and draft content. The literature search strategy was based on the following key words: *allergy to aspirin/NSAIDs, hypersensitivity, L-ASA, bronchial challenge test, oral and nasal challenge test*. The searches were performed based on the OVID Medline, EMBASE, and Cochrane Review databases using Boolean operators. The scientific assays selected were evaluated in terms of their quality and risk of error following the criteria of the Oxford Centre for Evidence-based Medicine [<http://www.cebm.net/index.aspx=1025>]. Our research identified a total of 458 studies. Only studies in English were included. Finally, 104 papers were eligible for systematic review.

2. Classification of Hypersensitivity Reactions to NSAIDs

Hypersensitivity reactions to NSAIDs can be classified into 2 key groups based on their underlying mechanism: (1) allergic reactions mediated by specific immunological mechanisms (selective hypersensitivity, immunoglobulin [Ig] E in immediate reactions or T cells in delayed reactions), in which patients present reactions to a single NSAID or several NSAIDs of the same chemical group; and (2) hypersensitivity reactions not mediated by a specific immunological mechanism (the most common), in which the mechanism is associated with the enzyme cyclo-oxygenase (COX)-1, with the result that the patient reacts to various NSAIDs belonging to different chemical groups [3]. In this case, inhibition of COX-1 leads to an increase in the expression of specific proinflammatory mediators such as cysteinyl-leukotrienes (cys-LT) and prostaglandin [PG] D₂ and a decrease in the expression of other

bronchoprotective agents such as PGE₂, thus generating an imbalance that eventually triggers symptoms (bronchospasm, nasal symptoms, skin symptoms) [4].

2.1. Allergic Reactions to NSAIDs

These are selective reactions induced by a single NSAID or several NSAIDs belonging to the same chemical group, with no cross-reactivity between groups. They are COX-independent and are classified into 2 groups:

- a) Immediate reactions, which usually appear in <4-5 hours. The most frequent symptoms are urticaria/angioedema or anaphylaxis.
- b) Nonimmediate reactions, which generally appear 24-48 hours after administration of the drug and manifest as skin symptoms (generalized exanthema, fixed drug eruption), involvement of other organs (eg, hypersensitivity pneumonitis or aseptic meningitis), or severe adverse cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug-induced hypersensitivity syndrome).

2.2. Hypersensitivity reactions to NSAIDs not mediated by a specific immunological mechanism

These are the most common type and result from cross-reactivity between different NSAIDs that are not structurally related [5]. According to the position statement published by the European Academy of Allergy and Clinical Immunology [3], these reactions can be classified into 3 groups:

- a) NSAIDs-exacerbated respiratory disease (NERD), which manifests mainly as bronchial obstruction, dyspnea, cough, wheezing, nasal congestion, sneezing and rhinorrhea. NERD affects patients with underlying chronic respiratory disease of the lower and/or upper airways (asthma/chronic rhinosinusitis with/without sinonasal polyposis [CRSwNP/CRSwoNP]).
- b) NSAIDs-exacerbated cutaneous disease (NECD), which manifests as urticaria and/or angioedema that affects patients with a history of spontaneous chronic urticaria.
- c) NSAIDs-induced urticaria/angioedema (NIUA), which manifests as urticaria and/or angioedema in persons with no history of spontaneous chronic urticaria or underlying respiratory disease. These patients are generally atopic and sensitized mainly to house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*). The most characteristic manifestation is palpebral angioedema [6].

3. Pathophysiology

Hypersensitivity reactions to NSAIDs are caused by various pathogenic mechanisms (see above).

Allergic reactions are not associated with COX-1 inhibition, and patients show good tolerance to NSAIDs from other groups, including potent COX-1 inhibitors. Symptoms are associated with production of specific IgE in terms of symptoms, reaction time (generally <1 hour), and reaction to a specific NSAID or several NSAIDs from

the same pharmacological group, with good tolerance to the rest. This IgE-mediated mechanism has been proven with pyrazolones [7,8] and, in some cases, with paracetamol [9], although skin test or in vitro test results are only occasionally positive with other drugs [10]. In delayed organ-specific and cutaneous reactions, sensitization to drugs is mediated by specific T CD4⁺ and CD8⁺ lymphocytes [11]. This mechanism has been reported in sporadic cases with pyrazolones and aryl acetic and propionic acid agents [5,12,13].

Nonimmune hypersensitivity reactions have received the most attention, especially in patients with asthma and urticaria/angioedema. Blockade of COX and, more specifically, its constitutive isoform COX-1, in susceptible individuals seems to play a key role in hypersensitivity reactions to NSAIDs [14].

The main biological activity of NSAIDs is that of inhibiting production of inflammatory mediators resulting from metabolism of arachidonic acid (AA). AA is metabolized via 3 pathways for production of inflammatory mediators: (1) via the enzyme COX, leading to production of PG; (2) via 5-lipoxygenase (5-LOX), leading to the production of leukotrienes (LT); and (3) via 12-lipoxygenase (12-LOX), leading to production of 12-hydroxyeicosatetraenoic acid (12-HETE) and lipoxins [15].

In most cells, except for platelets and endothelial cells, PGE₂ is the main product of COX-1 and COX-2. When synthesis of PGE₂ is suppressed by inhibition of COX-1 in epithelial and inflammatory cells in the airways, the negative feedback effect on 5-LOX disappears, and, consequently, a large quantity of cys-LT is synthesized and released. In parallel, the density of cys-LT receptors increases on bronchial smooth muscle, vascular endothelial cells, eosinophils, and sinonasal and bronchial epithelial cells, thus amplifying the pharmacological and proinflammatory effects of these eicosanoids [16]. Therefore, a sudden decrease in synthesis of PGE₂ seems to be the main precipitating event in overproduction of LT, with the subsequent reaction in the respiratory tract. In fact, exogenous inhalation of PGE₂ prevents the bronchoconstriction caused by aspirin and inhibits urinary excretion of cys-LT [17].

In patients with CRSwNP who are hypersensitive to NSAIDs, expression of the type 2 receptor of PGE₂ in the mucosa [18] and in polyp samples is diminished [19]. Therefore, abnormal receptor expression in these patients could reduce the antiproliferative and anti-inflammatory capacity of PGE₂. Similarly, production of PGE₂ by bronchial fibroblasts in asthmatics who are hypersensitive to NSAIDs is also less pronounced than in tolerant asthmatics [4]. In addition, production of 9 α ,11 β -PGF₂, a metabolite of PGD₂, is excessive, with higher levels of the metabolite and more frequent bronchial symptoms in the serum of patients with NERD than in patients with nasal symptoms only [20].

As for LTs, in patients with NERD, inhibition of COX is associated with increased synthesis and release of cys-LT, with the base form containing 2 to 10-fold more LTE₄ in urine than in aspirin-tolerant asthmatics [21]. Exposure to aspirin in patients with NERD leads to very significantly increased secretion of LTE₄ in urine [22] and in both the sinonasal mucosa [23] and the bronchial mucosa [24]. A recent meta-analysis showed that LTE₄ in urine can be considered a marker of NERD and potentially useful as a clinical test for identifying the risk of hypersensitivity to NSAIDs in patients with asthma [25].

In summary, there are specific differences between patients with NERD and aspirin-tolerant asthmatics with respect to the levels of most eicosanoids. The pathogenic mechanisms of NERD seem to be associated with a complex imbalance in AA, more specifically with the metabolism of prostanoids and cys-LT. Such dysregulations in the degradation of AA are genetically determined. Hypersensitivity to NSAIDs and its clinical manifestations are the result of an interaction between genetic and environmental factors.

Although NECD is the most frequent form of hypersensitivity to NSAIDs, most genetic studies have focused on NERD; therefore, the studies generally have a limited number of patients. Furthermore, most studies have focused on polymorphisms associated with the metabolic pathway of AA, and 3 genome-wide association studies have been published [26]. The polymorphism of the LTC₄ synthase gene (-444A>C) has been associated with a greater risk of NERD [27] and increased expression of the gene in eosinophils, bronchial mucosa, and nasal mucosa. However, this association has not been confirmed in American or Asian populations [26]. Similarly, increased expression of -444A>C has been reported in patients with NERD [28], although not in Spanish patients with NECD [29]. Furthermore, 2 variants in the COX-1 genes (rs5789 and rs10306135) were recently shown to be associated with NERD [30].

These phenomena have received less attention in patients with cutaneous manifestations. In patients with NECD, excretion of LTE₄ in urine is more pronounced after oral provocation with aspirin than in tolerant patients with chronic urticaria, whose extension is associated with levels of LTE₄ in urine [31]. However, a different pattern has been found for eicosanoids in patients with NECD: nasal lavage after specific provocation with lysine-aspirin did not reveal an increase in PGD₂, LTD₄, or LTE₄, which did increase in patients with NERD [32].

4. Classification of Controlled Provocation Tests With Aspirin

Given that the underlying mechanism of a reaction is not immunological, but rather a consequence of inhibition of COX-1, skin testing is of no use in cases of hypersensitivity reactions to multiple NSAIDs. In most cases, controlled exposure will be necessary to ensure an appropriate diagnosis.

Before starting a provocation test, it is necessary to determine whether the patient is likely to have selective allergy or hypersensitivity to multiple NSAIDs; therefore, we must know whether 1 or several NSAIDs are involved. In addition to enabling us to predict the underlying pathogenic mechanism, this information helps us to design an action plan. Therefore, it is very important to ensure that the clinical history is as accurate as possible.

Depending on the route of administration, we can distinguish between 4 types of provocation test: oral, bronchial (inhaled), nasal, and intravenous. Only the first 3 are used in daily clinical practice. Intravenous provocation testing is used exclusively in Japan [33].

Controlled oral provocation testing with aspirin is considered the "gold standard" for diagnosis of hypersensitivity

to NSAIDs [34]. However, it is very time-consuming, and potential systemic reactions can prove very severe, especially in patients with NERD, in whom the risk of severe bronchospasm has led to the development of techniques that are less likely to cause a systemic reaction. These include bronchial provocation testing and nasal provocation testing, which are faster and safer and prove particularly useful when oral challenge testing is contraindicated.

4.1. Oral Provocation Testing With Aspirin

4.1.1. Introduction

Controlled oral provocation testing is the main tool for diagnosis and the only unanimously accepted diagnostic method that makes it possible to identify patients with exclusively cutaneous symptoms [34].

4.1.2. Indications

The indications are well established: (1) for confirming or ruling out a diagnosis of hypersensitivity to the culprit drug in patients for whom there are no other conclusive allergology tests; and (2) provocation with a drug other than that which produced the reaction, generally aspirin, in order to confirm or rule out cross-reactivity between NSAIDs [34].

Additional indications include the following [34,35]:

- a) Providing a safe alternative therapy in cases of confirmed hypersensitivity.
- b) The need to perform desensitization to aspirin for therapeutic purposes.
- c) The study of real prevalence of sensitization to aspirin.
- d) Investigation of the underlying basic pathogenic mechanisms in this type of reaction.

Despite these indications, performance of controlled provocation tests is highly controversial. Some authors recommend them, whereas others do not, since they believe that the risk of triggering severe anaphylactic reactions is high. Therefore, it seems reasonable to evaluate the individual patient carefully before performing an oral provocation test [35,36].

4.1.3. Contraindications

The main contraindications are as follows [34,36]:

- a) Patients with severe or unstable respiratory disease (FEV₁ varying by more than 20%).
- b) A history of anaphylactic reaction may be a contraindication for performance of oral provocation testing with the drug involved.
- c) Organ-specific conditions (hepatitis, meningitis) and severe cutaneous reactions (this group does not include maculopapular rash or fixed drug eruption).
- d) Patients who do not sign the informed consent to undergo provocation testing.
- e) Patients with a respiratory infection or uncontrolled chronic condition, such as asthma or urticaria.
- f) Patients with psychiatric disorders that affect performance of the oral provocation test.
- g) Patients with a disease in which NSAIDs and/or epinephrine are contraindicated and patients who cannot interrupt treatment with betablockers to undergo the test (relative contraindication).

4.1.4. Methodology

- *Preparation:* The test should be performed under the supervision of experienced health professionals and at centers with the necessary equipment to treat

Table 1. Recommendations for Interrupting Treatment That May Interfere With the Performance of Oral Provocation Tests With Aspirin and Bronchial/Nasal Challenge Tests With Lysine-Aspirin [33,48]

Oral Provocation Test and Bronchial Challenge Test		Nasal Provocation Test
<i>Medication</i>	<i>Time of avoidance before oral exposure to aspirin</i>	<i>Time of avoidance before nasal exposure to lysine-aspirin</i>
Oral/topical antihistamines	3 d	48 h or 1-2 wk depending on the drug/4-5 days
Leukotriene receptor antagonists	7 d	
Oral corticosteroids	If the patient is receiving regular treatment with oral corticosteroids, the dose should not exceed 10 mg of prednisolone or equivalent	2-3 wk
Intranasal/inhaled corticosteroids	Maintain the lowest dose possible in a stable fashion throughout the provocation test	48-72 h/suspension is not necessary
Long-acting beta-agonists	24-48 h	
Short-acting beta-agonists	6-8 h	
Long-acting anticholinergics	7 d	
Monoclonal antibodies (omalizumab especially)	5 half-lives of the drug (6 mo in the case of omalizumab)	
Nasal decongestants (in general)		2 d
Tricyclic antidepressants/reserpine or clonidine-type antihypertensive agents		3 wk/3 wk

severe systemic reactions [33,34,37-39]. The patient must sign a written informed consent document before undergoing the test [33,39,40] and must be stable, with well-controlled asthma (baseline FEV₁ must be at least 60%-70% of predicted and more than 1.5 L [absolute]) [33,34]. It has been suggested that LT receptor antagonists, corticosteroids (inhaled and oral), long-acting β_2 -agonists and long-acting muscarinic antagonists reduce the risk of bronchospasm in oral and bronchial provocation testing without altering naso-ocular reactions [41-44]. Moreover, new evidence shows that omalizumab reduces or eliminates aspirin intolerance in treated patients [45,46]. Although no data are available to date, new biologicals targeting anti-IL-5/IL-5 receptors might also modify the results of aspirin provocation testing [47]; therefore, we believe that aspirin provocation tests should either not be performed or be carefully interpreted in patients receiving biologicals. In summary, and in line with current European guidelines, this document recommends avoiding some drugs before performing the tests [36,48] (see also Table 1).

- *Procedure:* The oral provocation test should be performed in a simple-blind, placebo-controlled fashion, although it should be double-blind in situations where psychological aspects play a role [39]. Both aspirin and placebo are administered in gel capsules; these should be identical in appearance if possible. The capsules should be prepared by the hospital pharmacy in order to prevent subjective interpretations by the patient [33]. Patients should be monitored continuously (baseline and at 30- to 60-minute intervals), and symptoms, FEV₁, arterial blood pressure, heart rate, and peak nasal inspiratory flow (PNIF) should be recorded. Other methods of objective evaluation of nasal obstruction that can be used include active anterior rhinomanometry and acoustic rhinometry [37,39]. The option of inserting a venous line can be evaluated in specific cases [33,37].

On the first day of the test, we administer 3 capsules of placebo at intervals of 90-120 minutes. FEV₁ should not vary by more than 15% during the test; if it does, the patient's

condition is considered unstable, resulting in suspension of the test. On the second and third days, we administer increasing doses of aspirin until signs or symptoms indicative of a reaction appear (positive provocation) or the maximum dose of aspirin is reached (negative provocation) [37]. The doses and intervals at which the capsules are administered vary from study to study (Table 2). If the patient has a history of severe reaction to aspirin or other NSAIDs or has a high risk of bronchial reaction during exposure (previous history of visiting the emergency department for asthma and/or baseline FEV₁ <80%), then the test should be started with lower doses of aspirin [33,49] (Table 2). As for the intervals between doses, most studies indicate that the capsules should be administered at intervals of 90 and 180 minutes [33,38,40]. However, it has been suggested that intervals of 60 minutes are safe in patients who experience immediate reactions to NSAIDs [50]. There have been no extensive evaluations of whether protocols with shorter intervals between doses are associated with more severe reactions, since the observation time was not sufficiently long to enable identification of a reaction before the following dose was administered. In protocols with intervals of 180 minutes, the reactions appear a mean of 102 minutes after a mean cumulative dose of aspirin of 68 mg [49,51]. However, when the interval is 60 minutes, the reactions appear a mean of 50 minutes after a mean cumulative dose of 157 mg of aspirin [50].

4.1.5. Interpretation of the results

We must determine whether there are bronchial symptoms (bronchospasm, chest tightness, wheezing), nasal symptoms (rhinorrhea, nasal congestion), ocular symptoms (tearing, conjunctival injection), cutaneous symptoms (edema, erythema, urticarial), or other symptoms (nausea, abdominal pain). A positive result in an oral provocation test, which should be interrupted immediately, is defined as the appearance of 1 or more of the following signs/symptoms [33,37]:

- a) Decrease in FEV₁ >20% over baseline value.
- b) Objective signs and symptoms of respiratory reaction (rhinorrhea, nasal congestion, sneezing fits, wheezing,

Table 2. Protocols for Oral Provocation Testing With Aspirin

Protocol	Interval Between Doses, min	Dose of Aspirin, mg
Scripps Clinic [38]	180	1st day: 20-40, 40-60, 60-100 ^a 2nd day: 100-160, 160-325, 325
Aspirin Desensitization Joint Task Force [40]	90	20.25, 40.5, 81, 162.5, 325
University of Texas Southwestern [33]	60	40, 81, 120, 162, 325 ^b
EAACI guideline [33]	90-120	27, 44, 117, 312, 500 ^c
Spanish Society of Allergy and Clinical Immunology Guideline [34]	180	1st day: 50-100 2st day: 250-500

^aIf the patient has a history of attending the emergency department for asthma and/or baseline FEV₁, the first test should be with the lowest dose possible of aspirin (20 or 30 mg).

^bIf the patient has a history of serious reactions to nonsteroidal anti-inflammatory drugs, the protocol should be started with 20 mg 60 minutes before the dose of 40 mg.

^cIf the patient has a history of severe reaction to aspirin or other nonsteroidal anti-inflammatory drugs, divide the first dose of aspirin (27 mg) into 2 doses (10 mg and 17 mg), which should be administered at an interval of 90-120 minutes.

tearing, cough, chest tightening, stridor, dysphonia) or extrabronchial symptoms (angioedema, wheals, erythema, abdominal pain, nausea, vomiting), even if FEV₁ does not decrease >20% over baseline.

In patients with NERD, most positive oral provocation tests (90%-98%) include naso-ocular reaction, and 35%-90% of cases bronchial reaction [49,50,52,53]. Gastrointestinal, cutaneous, and laryngeal symptoms appear in 23%, 10%, and 8% of cases, respectively [52]. Hypotension has been reported sporadically [43,54].

The result of an oral provocation test is defined as negative when the maximum cumulative dose of aspirin is reached without signs, symptoms, or reaction and with no decrease in FEV₁ >20% over baseline.

4.1.6. Complications and their management

The severity of a previous NSAID-induced reaction reported by the patient cannot predict the reaction observed during oral provocation testing with aspirin, which is generally milder [52]. Severe bronchial reactions (defined as a decrease in FEV₁ >30% over baseline) have been associated with the following factors:

- Unstable asthma during the provocation test [55].
- Not taking LT receptor antagonists during the provocation test [49].
- Severe asthma (baseline FEV₁ <80% predicted and history of visits to the emergency department for asthma) [49].
- Elevated levels of LTE₄ in urine [55] (test not available in daily clinical practice) [49].
- Age at the time of the oral provocation test (30-40 years) [49].
- Less than 10 years since the last reaction [49].

If 3 or more of these factors are present, the risk of a moderate to severe reaction during the provocation test with aspirin is 43% [49]. In the case of a positive reaction, treatment should be administered early. Naso-ocular reactions should be treated with oral and topical antihistamines, mast cell stabilizers, and nasal decongestants. Bronchial reactions should be treated with short-acting β₂-agonists until FEV₁ returns to 90% of baseline. Oral or parenteral corticosteroids should be administered in the case of more severe reactions. Laryngeal reactions should be managed with nebulized or intramuscular epinephrine. Cutaneous symptoms should be managed with oral or parenteral H₁ antihistamines, and gastrointestinal symptoms with oral or intravenous H₂ antihistamines [54]. Anaphylactic reactions must be managed with intramuscular epinephrine and according to the protocol recommended by current guidelines [54,56-58].

4.1.7. Special situations

– *Pediatric patients*: NSAIDs are the most commonly prescribed drugs in pediatric medicine, whether as antipyretic, anti-inflammatory, or analgesic agents. Therefore, it is necessary to make the correct diagnosis in the case of suspected hypersensitivity reaction. Diagnosis in children is complex, since childhood fever is caused by both bacterial and viral infections, which can progress with cutaneous symptoms that mimic an

allergic reaction. A study performed in Spain showed that specific nonimmunological reactions are the most common in children. Ibuprofen is the most frequently involved drug, angioedema the most frequently reported condition, and controlled oral provocation the most reliable diagnostic method [59]. In pediatric patients, prescription of authorized drugs is limited by the patient's age. Paracetamol is the preferred oral antipyretic agent, and high-dose ibuprofen and paracetamol the preferred anti-inflammatory/analgesic agents. Other authorized drugs include naproxen, diclofenac, metamizole, and indomethacin. Meloxicam has also been used in children aged 2-12 years and is authorized for use in patients with rheumatic conditions such as juvenile rheumatoid arthritis. Treatment with aspirin has become considerably less frequent in recent years [59] owing to reports of Reye syndrome. Notwithstanding, even though aspirin is not recommended as an antipyretic drug, it does continue to be used as a pediatric antiplatelet drug or for the treatment of other diseases, such as Kawasaki syndrome [60].

Few parenteral NSAIDs have been authorized for use in children in Spain. With the exception of dipyron and paracetamol, the remaining injectable intravenous solutions have not been assessed in children or in adolescents. Therefore, the safety and efficacy profile has not been established, and the drug cannot be recommended as such on the summary of product characteristics, although dexketoprofen/ trometamol, for example, is prescribed [61].

As is the case in adults, diagnostic algorithms based solely on the clinical history have low positive and negative predictive values, are of little worth, and can never replace an allergology work-up consisting of skin tests (when a selective reaction is suspected) and controlled oral provocation, which is considered the gold standard [62].

Indications and contraindications, as well as the methodology and techniques used in controlled oral provocation tests in adults, can almost be generalized to children, with some slight variations. As in adults, there are several protocols, which differ in the following respects:

- The dosage used.
- The number of doses administered: most authors reach the total cumulative dose in 4 steps [36], although this number could be lower if the reaction is not very indicative.
- The interval between doses. This is generally set at 30 minutes, although some authors increase the dose gradually every 60-90 minutes until they reach the total cumulative dose, which is adjusted for age and weight [36,63-65].

The drug is most commonly administered as a syrup or suspension. The criteria for a positive result are similar to those applied for adults.

– *Pregnancy*: Analgesics are one of the most commonly used drug types during pregnancy, and paracetamol is the drug of choice for mild to moderate pain. NSAIDs should be used with caution, especially during the last trimester [66,67]. Most authors consider pregnancy a contraindication for oral provocation testing with NSAIDs. However, in specific situations, such as the immediate need for antiplatelet medication, a

provocation test may be necessary after evaluating the cost-benefit ratio. The United States Food and Drug Administration classifies aspirin at antiplatelet doses (75-162 mg/d) as category D for pregnancy, and treatment should only be administered in specific cases after evaluation of the cost-benefit ratio [68]. In cases where antiplatelet medication is fully indicated during pregnancy, such as in antiphospholipid syndrome, the patient should be desensitized to aspirin after taking all necessary precautions: admission to an intensive care unit and presence of a multidisciplinary team (allergologist, anesthetist, gynecologist, and, on occasion, neonatologist) [69,70].

- Other diseases: In other risk situations, such as kidney failure, heart disease, and liver disease, controlled oral provocation testing should be considered a high-risk procedure and performed on an individual basis only after considering the risk-benefit ratio.

4.2. Bronchial Provocation Testing With Lysine-Aspirin

4.2.1. Introduction

Oral provocation testing has been compared with bronchial provocation testing in 3 studies [71-73]. The results reported were similar. Both methods have the same specificity (around 93%), although oral provocation is more sensitive (89% vs 77%) [71]. 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 obtain the definitive diagnosis [33].

4.2.2. Indications

Patients over 18 years with suspicion of NERD who present with bronchial symptoms after taking NSAIDs.

4.2.3. Contraindications

The contraindications are basically those of spirometry itself (eg. recent surgery, aneurisms) as well as severe or poorly controlled asthma during the previous month, severe diseases (heart, digestive, liver, or kidney), respiratory infection during the 4 weeks before the provocation test, pregnancy, and treatment with betablockers.

4.2.4. Methodology

- *Preparation* [33,36]: The patient must sign a written informed consent document before undergoing bronchial provocation. The patient's usual medication should be stopped (Table 1).
- *Procedure*: Bronchial provocation is performed with lysine-aspirin, a salt of aspirin that is more water-soluble than aspirin (40% vs 0.3%), less irritant, and better tolerated for inhalation. The technique was first described in 1977 by Bianco et al [74] and then modified by Phillips et al in 1989 [75]. The current protocol is based on a modified Philips method [33]. It can be performed by means of continuous inhalation at incremental volumes with a constant output [76] or intermittent breathing through a nebulizer connected to an electronic dosimeter (eg, Me-Far or Spira-Electro 2) [77].

Table 3. Protocol for Inhaled Provocation Testing With Lysine-Aspirin Using a Dosimeter [33]

Concentration of Lysine-Aspirin, mg/mL	No. of Inhalations	Dose of Lysine-Aspirin Inhaled, mg	Cumulative Dose of 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

Bronchial provocation testing is performed on an outpatient basis. The technique is carried out by suitably trained nursing staff under the supervision of the allergologist. According to the recommendations of current clinical guidelines, the medication necessary to treat potential reactions must be at hand (short-acting β_2 -agonists and anticholinergic drugs, inhaled and systemic corticosteroids, epinephrine, antihistamines, nasal vasoconstrictors).

The test is started with baseline spirometry to verify that FEV₁ is >70% predicted and >1.5 L. The test cannot be performed if this requirement is not fulfilled.

The patient first receives 5 inhalations of the control diluent (physiologic saline 0.9%). Spirometry is repeated at 10 minutes. A decrease of >10% in FEV₁ is considered a sign of airway instability that could generate a false-positive result; therefore, the test should be postponed. If FEV₁ does not decrease by more than 10% over baseline, the test continues and the FEV₁ recorded with the diluent is the reference value.

Fresh lysine-aspirin solutions (Inyesprin, Aristo Pharma Iberia, S.L.) are prepared immediately before the test (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 and 45 mg/mL. Consecutive doses of lysine-aspirin are inhaled every 30 minutes, and spirometry and peak expiratory flow (PEF) values are measured at 10, 20, and 30 minutes after each dose (Table 3).

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 at 1 hour and 2 hours after the test. The patient subsequently records PEF every 2 hours at home, except while sleeping, until 24 hours after the test, when he/she returns to the clinic with the PEF recording.

4.2.5. Interpretation of the results

The criteria for a positive bronchial provocation are as follows [33,73,78]:

- Immediate reaction with bronchospasm and decrease in FEV₁ \geq 20%.

- b) Immediate reaction with a 15-20% decrease in FEV₁, as well as extra-bronchial symptoms (sneezing, naso-ocular pruritus, nasal congestion, runny nose, conjunctival reddening and pruritus, tearing, and palpebral angioedema).
- c) Dual reaction: immediate and late reaction.
- d) Exclusively late reaction (late decrease in PEF \geq 20%, between 4 and 24 hours after the provocation test).

The result of the bronchial provocation is considered negative if the maximum dose is reached with no decrease in FEV₁ or PEF \geq 20% up to the 24 hours following the end of the test. In order to clarify the diagnosis in this case, oral provocation with aspirin is scheduled after an interval of at least 7 days [33,36,39].

4.2.6. Complications and management

- a) Bronchospasm must be treated with nebulized salbutamol, as needed, in order to relieve symptoms.
- b) Nasal obstruction can be treated with a topical nasal decongestant (eg, oxymetazoline). If untreated, nasal obstruction can lead to trapping of secretions and severe headache. Nasal symptoms can also be managed with oral antihistamines.
- c) Ocular symptoms can be treated with oral antihistamines.
- d) Laryngospasm must be treated with intramuscular epinephrine.

4.2.7. Special situations:

Pediatric patients: Bronchial provocation is contraindicated in patients aged under 18 years; therefore, when NERD is suspected, diagnosis must be confirmed based on oral provocation with aspirin, as set out in the corresponding section of this consensus document.

4.3. Nasal Provocation Test With Lysine-Aspirin

4.3.1. Introduction

While a large number of studies have addressed the standardization of oral and bronchial provocation testing with aspirin, fewer studies have analyzed nasal provocation, despite the fact that it is a safe alternative to oral provocation and bronchial provocation in the assessment of patients with hypersensitivity to NSAIDs. Nasal provocation testing was implemented in daily clinical practice at the end of the 1970s and 1990s, both for provocation tests with allergens/drugs and for the study of the response to treatment, as well as for study 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 [79-89]. The diagnostic usefulness of nasal provocation and bronchial provocation compared with oral provocation is summarized in Table 4.

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 increased airflow resistance. Airflow resistance can be measured objectively using 2 techniques: rhinomanometry (RNM) and acoustic rhinometry (ARM) (see below). In addition, the patient's symptoms can be evaluated subjectively during nasal provocation test using a visual analog scale and symptom scores (rhinorrhea, sneezing, nasal obstruction, and pruritus).

One of the main limitations of this diagnostic method results from its low sensitivity and, therefore, its low negative predictive value. Therefore, a history that is suggestive of NERD and a negative result in a nasal provocation test with lysine-aspirin still require confirmatory oral provocation.

However, if we consider the yield of this approach and its ability to identify conjunctival symptoms, it should be considered the method of choice in patients who report analgesic-induced naso-ocular symptoms.

4.3.2. Indications

Nasal provocation is indicated in the study of patients with suspected NERD and, more specifically, in those whose concomitant conditions prevent them from undergoing oral or bronchial provocation as, for instance, in patients with FEV₁ <70% (see above).

4.3.3. Contraindications

Nasal provocation should not be performed in the following cases:

- Massive nasal polyposis
- Perforated septum
- Autoimmune diseases (eg, Wegener disease, Churg-Strauss syndrome)
- Immunodeficiency
- Pregnancy
- Uncontrolled severe asthma
- Concomitant respiratory infection
- Age under 5 years

4.3.4. Methodology

4.3.4.1. Preparation (preconditions)

- i. Patient-related conditions
 - The patient must sign a written informed consent document before undergoing nasal provocation.
 - The patient must be asymptomatic, that is, if the patient also has another type of rhinitis such as allergic or infectious rhinitis, then 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. The test should be postponed

Table 4. Diagnostic Yield of Challenge Tests With Aspirin

Type of Test	Sensitivity	Specificity	Negative Predictive Value
Oral	89%	93%	77%
Bronchial	77%	93%	64%
Nasal	80%	90%	78%

until at least 2–4 weeks after an exacerbation of allergic or infectious rhinitis [82,84,85].

- The patient must also be free of respiratory symptoms, with no asthma exacerbations or bronchial infections in the previous month at the time of the test. Forced spirometry is always recommended before and after nasal provocation in order to evaluate lung function.
- The patient should avoid smoking and alcohol during the 24–48 hours before the test.
- The provocation should be postponed for 6–8 weeks after nasal surgery [84].
- Where possible, avoid performing nasal provocation during pregnancy.
- Nasal provocation is not recommended in patients with a perforated septum or total nasal obstruction, since objective evaluation of nasal obstruction is very difficult and interpretation of the results more complicated.
- Any medication that can modify the nasal response must be discontinued before the test (Table 1).

ii. Room-related conditions

- Temperature and humidity must be maintained at a constant temperature of 20°C to 22°C with humidity of 40%–60%. Temperatures above 35°C with a high degree of humidity (80%–90%) can alter the immediate response owing to diminished release of histamine and the vascular/neural response [90].
- The patient must be acclimated (20–30 minutes in the room) in order to avoid nonspecific reactions 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 (eg, tobacco smoke, pollution, spicy food, coffee, exercise).

iii. Conditions related to the staff who carry out the test

- Appropriate knowledge of the test methodology.
- Appropriate knowledge of the technique that will be used to evaluate the results, eg, RNM or ARM.
- Knowledge of and access to the necessary therapeutic measures in the case of a positive result.

4.3.4.2. Procedure

The most widely used approach today is instillation of 0.1 mL of lysine-aspirin at the head of the inferior turbinate with a syringe, pipette, or dropper. Lysine-aspirin is not available in the USA, where nasal provocation is performed using intranasal ketorolac [33,91]. Experience with ketorolac has been reported by Quiralte-Castillo et al [92].

A micropipette is preferred. Doses of lysine-aspirin vary according to the study and are detailed below.

Objective evaluation is usually by active anterior RNM (AARNM) or ARM. RNM enables simultaneous measurement of flow and pressure variations in air current crossing the nostrils during the different phases of respiration. For evaluation of nasal permeability, AARNM with a facemask and computerized recording of pressure, flow and resistance is recommended as the optimal test in daily clinical practice [93,94].

The doses of lysine-aspirin used in nasal provocation with AARNM vary according to the protocol: 20 mg as the

maximum cumulative aspirin-equivalent dose [95], a single aspirin-equivalent dose of 14 mg [96,97], and 4 progressive concentrations (5, 25, 50, and 100 mg/mL), with a total cumulative aspirin-equivalent dose of 18 mg [98]. The cumulative dose used is critical for the yield of the test, since low doses do not enable sufficient analytical values to be reached [96], whereas doses above 30 mg of aspirin are irritant and, therefore, invalidate interpretation of the results [97].

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 and reproducible and requires only minimal cooperation from the patient. Therefore, it is easy to use with children. It is well standardized for the demonstration of changes in the permeability of the nasal mucosa.

Measurements are made at different time points depending on the method used [33,98]. Therefore, we must perform a measurement at baseline, 30 minutes after administration of the diluent, and at 15, 30, 60, and 90 minutes after administration of lysine-aspirin. Diluent (0.9% NaCl) is administered beforehand in order to rule out nasal hyperreactivity. We then administer 29 mg of lysine-aspirin 100 µL (equivalent to 16 mg of aspirin) to the inferior turbinate of each nostril using an Eppendorf pipette [99,100].

4.3.5. Interpretation

Nasal provocation with lysine-aspirin performed using ARM is considered positive when nasal cavity volume at 12 cm decreases by 25% with respect to the postdiluent value [98,99]. 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 clinical symptoms (subjective values) by means of the visual analog scale (see above) and symptom scores. A positive result is defined as an increase of 30% of airflow resistance [90,99,101].

The reference values obtained using AARNM are not fully agreed upon, and a certain degree of variability is accepted as a result of differences in the devices used, age, weight, and the racial-ethnic characteristics of the study population [93,94,100,101]. A minimum 100% increase is accepted as a criterion for positivity [87,101,102].

4.3.6. Complications and management

If the result of the nasal provocation test is positive, a topical or systemic antihistamine should be administered depending on the intensity of the symptoms. While systemic reactions are extremely rare, any that occur should be treated as stated in the section on oral provocation.

Lastly, the reappearance of nasal symptoms, especially obstruction, at 3 to 12 hours after nasal provocation should be interpreted as a delayed reaction [88]. The patient should be informed of this possibility, and measures must be taken to ensure that appropriate treatment is available for control of symptoms. The criteria for evaluating a delayed nasal response are not as well established as those for bronchial response. Although the immediate response is easy to demonstrate, symptom scoring is not sufficient in the case of a delayed reaction.

4.3.7. Special situations

ARM is easy to perform and reproducible. It requires little cooperation from the patient, thus making it especially useful for children. In addition, it is not affected by rhinorrhea or nasal obstruction. However, ARM cannot be performed in cases of perforated septum. No international consensus regimens have been drafted for nasal provocation. Therefore, criteria for positivity, methodologies, and the preparations used in nasal provocation testing vary depending on the study. Irrespective of these limitations, nasal provocation is a very useful clinical and research tool in nasal disease and for the study of patients with NERD [102,103].

4.4. Ocular provocation with aspirin

Ocular symptoms in hypersensitivity reactions to NSAIDs in NERD are unusual and have not been sufficiently documented to date. An exhaustive review of the literature revealed that no publications have explored the possibility of performing provocation tests with aspirin or other NSAIDs (eg, lysine-aspirin, ketorolac) directly on the conjunctiva in humans [104].

5. Conclusions

Diagnosis of hypersensitivity to NSAIDs is of great importance for the patient and for the health system. The patient must know not only the NSAIDs to be avoided, but also those that he/she can tolerate. Therefore, provocation tests have become an essential diagnostic tool.

Ideally, priority should be given to nasal and bronchial provocation in patients with NERD (depending on the availability of the technique and the level of knowledge and experience of the treatment team). However, a negative result should be followed by an oral provocation, since this has a higher negative predictive value.

In the case of NECD, neither nasal provocation testing nor bronchial provocation testing appears to be of use. Therefore, oral provocation should be performed.

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Conflicts of Interest

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- **Adriana Izquierdo-Domínguez**
- E-mail: adrianaeizquierdo@hotmail.com