GUIDELINES

Practical Guidelines for Diagnosing Hypersensitivity Reactions to Nonsteroidal Anti-inflammatory Drugs

N Ortega,1 I Doña,2 E Moreno,3 MT Audicana,4 MJ Barasona,5 MP Berges-Gimeno,6 N Blanca-Lopez,7 T Lobera,8 A Padial,9 A Rosado,10 MJ Torres2

1Allergy Service, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain
2Allergy Unit, Hospital Regional Universitario de Málaga, Málaga, Spain
3Allergy Service, Hospital Universitario de Salamanca, Salamanca, Spain
4Allergy Service, Santiago Apóstol Hospital, Vitoria-Gasteiz, Spain
5Allergy Service, Reina Sofia University Hospital, Córdoba, Spain
6Allergy Division, Ramon y Cajal University Hospital, Madrid, Spain
7Allergy Service, Infanta Leonor Hospital, Madrid, Spain
8Allergy Service, Centro de Alta Resolución San Millán, Logroño, Spain
9Allergy Service, La Paz Hospital, Madrid, Spain
10Allergy Service, Alcorcón Hospital, Madrid, Spain

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs most frequently involved in hypersensitivity reactions. These reactions include various clinical entities with different mechanisms leading to the release of inflammatory mediators. Characterization of patients based on clinical manifestations and suspected underlying mechanisms is critical for implementation of adequate diagnostic procedures and patient management. Our objectives were to prepare a systematic review of available scientific evidence and to provide general guidelines for the diagnosis and management of patients with hypersensitivity reactions to NSAIDs. We also propose a practical algorithm for the diagnosis of specific types of hypersensitivity to NSAIDs and provide recommendations for the management of hypersensitive patients.


Resumen

Los antiinflamatorios no esteroideos (AINE) es el grupo farmacológico que más frecuentemente ha sido relacionado con las reacciones de hipersensibilidad. Estos cuadros incluyen entidades clínicas muy variadas, producidas por diferentes mecanismos, tanto inmunológicos como no inmunológicos. La caracterización de los pacientes que presentan estas reacciones se fundamenta, en las manifestaciones clínicas y la sospecha del mecanismo subyacente que la ha producido, lo que conduce a la puesta en práctica del procedimiento diagnóstico adecuado y la posterior orientación del paciente. El objetivo de este trabajo es elaborar una revisión sistemática, con las pruebas científicas disponibles, facilitando la directrices generales de diagnóstico y en consecuencia la actitud a tomar en este tipo de pacientes.

Se propone un algoritmo práctico de diagnóstico para cada tipo específico de hipersensibilidad a AINE, así como proporcionar las recomendaciones a seguir en el manejo de los pacientes sensibilizados.

Preface

These guidelines were drafted by a panel of allergy specialists with clinical and research experience from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (Sociedad Española de Alergología e Inmunología Clínica; SEAIC). The panel performed a systematic and independent review of available scientific evidence to provide general guidelines for the diagnosis and management of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). The findings presented in the document are based on the agreement reached between the participants. Applicability in daily practice in our population and the contribution of periodic updates have been taken into account. All the members have declared their conflicts of interest, and external reviewers have critically reviewed the document. All the members have declared their conflicts of interest, and external reviewers have critically reviewed the design and preparation of the consensus guidelines. Our main objective was to achieve as accurate a diagnosis as possible in patients with hypersensitivity to NSAIDs in order to draft appropriate recommendations for patients with hypersensitivity to NSAIDs.

Methods

The participants designed a working protocol based on a number of items to define the key words and the methodology for selecting the publications included in this review. The bibliographic search was performed using electronic databases (MEDLINE and PubMed), electronic libraries (Science Direct, OVID), and a systematic review database (Cochrane Library). Publications were selected from the period comprising January 1980 to July 2013.

The selection took into account the prevalence, pathogenesis, clinical manifestations, diagnosis, and treatment of hypersensitivity to NSAIDs. The key words used were NSAIDs, analgesics, anti-inflammatory, nonsteroidal anti-inflammatory, aspirin, acetylsalicylic acid, urticaria, angioedema, asthma, anaphylaxis, and the specific names of all the NSAIDs, in addition to the key word acetylsalicylic acid (ASA). These words were combined with the terms allergy, hypersensitivity, intolerance, idiosyncrasy, fixed drug eruptions, and selective. We reviewed 323 publications and finally included 195. The inclusion and exclusion criteria depended on the type of article: original research articles and systematic reviews were included; nonsystematic reviews, comments, and other types of article were excluded. We also took the study objective into account: studies examining incidence, prevalence, natural history, clinical manifestations, pathogenesis, clinical manifestations, diagnosis, and treatment were included; studies not addressing NSAID hypersensitivity and other aspects not included in the inclusion category were excluded.

Moreover, the expert panel evaluated the quality of the evidence of the literature search relevant to each type of hypersensitivity. Grades of recommendation were assigned according to the Scottish Intercollegiate Guidelines Network [1]. Wherever evidence was lacking, a consensus was reached among the experts.

Introduction

Definition and Classification

NSAIDs can be classified based on their chemical structure or mechanism of action (Table 1).

Hypersensitivity is currently the most appropriate denomination for unexpected adverse reactions to NSAIDs [2,3]. Depending on the underlying mechanisms, reactions are classified as immunological and nonimmunological [4].

Nonimmunological hypersensitivity reactions to NSAIDs, which were previously termed intolerant or idiosyncratic reactions, are the most frequently reported [5], and their pathogenesis is associated with the mechanism of action of

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Clinical Manifestation</th>
<th>Timing of Reaction</th>
<th>Underlying Disease</th>
<th>Cross-reactivity</th>
<th>Putative Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID-exacerbated respiratory disease</td>
<td>Bronchial obstruction, dyspnea and/or nasal congestion/ rhinorrhea</td>
<td>Acute (usually immediate to several hours after exposure)</td>
<td>Asthma/ rhinosinusitis</td>
<td>Cross-reactive</td>
<td>COX-1 inhibition</td>
</tr>
<tr>
<td>NSAID-exacerbated cutaneous disease</td>
<td>Wheals and/or angioedema</td>
<td></td>
<td>Chronic urticaria</td>
<td></td>
<td>COX-1 inhibition</td>
</tr>
<tr>
<td>NSAID-induced urticaria/angioedema</td>
<td>Wheals and/or angioedema</td>
<td></td>
<td>No underlying chronic diseases</td>
<td>Non-cross-reactive</td>
<td>Unknown, probably COX-1 inhibition</td>
</tr>
<tr>
<td>Single NSAID-induced urticaria/angioedema</td>
<td>Wheals/angioedema/ anaphylaxis</td>
<td></td>
<td></td>
<td></td>
<td>IgE-mediated</td>
</tr>
<tr>
<td>NSAID-induced delayed hypersensitivity reactions</td>
<td>Various symptoms and organs involved (eg, fixed drug eruption, SJS/TEN, nephritis)</td>
<td>Delayed (usually more than 24 hours after exposure)</td>
<td></td>
<td></td>
<td>T-cell–mediated</td>
</tr>
</tbody>
</table>

Abbreviations: COX, cyclo-oxygenase; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Diagnosis of Hypersensitivity to NSAIDs


© 2014 Esmon Publicidad

the NSAIDs, namely, inhibition of the cyclooxygenase enzyme (COX-1). All NSAIDs that inhibit the COX-1 enzyme can induce symptoms, and cross-reactions can occur between them, independently of their chemical structure.

Immunological hypersensitivity reactions to NSAIDs, also known as selective reactions, are limited to 1 NSAID or to a group of NSAIDs with the same chemical structure, although patients can tolerate NSAIDs with a different structure. They are mediated by a specific humoral mechanism (specific IgE antibodies) or a specific cellular mechanism (T effector cells) [6].

In 2001, Stevenson et al [7] drafted a consensus document proposing a classification of hypersensitivity reactions to NSAIDs. The document was the basis for the new document proposed by the European Academy of Allergy and Clinical Immunology, which classified reactions as follows [8]:

1. **Non–immunologically mediated (cross-reactive) hypersensitivity reactions to NSAIDs**
   - Patients have reactions to multiple NSAIDs with different chemical structures.
   - **NSAID-exacerbated respiratory disease (NERD):** NERD is characterized by exacerbations of asthma and/or rhinitis induced by NSAIDs in patients with previous respiratory symptoms (rhinitis, nasal polyps, and/or bronchial asthma).
   - **NSAID-exacerbated cutaneous disease (NECD):** Patients with chronic spontaneous urticaria (CSU) who develop an acute episode or have an exacerbation of urticaria after administration of NSAIDs.
   - **NSAID-induced urticaria/angioedema (NIUA):** NIUA is characterized by the appearance of urticaria and/or angioedema after administration of NSAIDs in patients without undergoing CSU. Reactions are sometimes severe, and patients can even develop systemic symptoms or anaphylaxis.

2. **Immunologically mediated (non–cross-reactive) hypersensitivity reactions to NSAIDs**
   - These reactions are induced by specific NSAIDs with similar chemical structures, although patients can tolerate drugs with a different chemical structure [6].
   - **Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA):** Reactions usually appear less than 1 hour after administration and can take the form of urticaria and/or angioedema and anaphylaxis.

3. **NSAID-induced delayed hypersensitivity reactions (NIDHR):** In these reactions, the interval between drug intake and development of symptoms is greater than 24 hours. However, some patients do not fit in any of the above categories and include those with mixed reactions involving both cutaneous and respiratory symptoms [5,9].

### Epidemiology

NSAIDs are the drugs most frequently involved in hypersensitivity reactions [10], which affect 0.5-1.9% of the general population [11,12]. If reactions with respiratory symptoms are taken into consideration, the prevalence of NSAID hypersensitivity in asthmatic patients is not clear, although it has been reported to range from 4% to 21% [13-15] and can increase to 25.6% in cases with asthma and nasosinusal polyposis [16].

The most frequent reactions are those involving the skin [5], which affect 0.07-0.3% of the general population [17,18]. In patients with underlying CSU, the prevalence of NSAID hypersensitivity can reach 30% [18,19]. The prevalence of NIUA, on the other hand, is unknown, although it has been reported that 36% of patients experience an adverse reaction with skin involvement after taking NSAIDs [20].

The prevalence of immunologically mediated reactions to NSAIDs ranges from 0.1% to 3.6% [21,22]. NSAIDs have been reported to be the most common pharmacological cause of anaphylaxis [23,24] or the second most common [25], since the arylacetic acid and propionic acid groups have a higher risk of inducing an anaphylactic reaction (OR, 19.7) [26]. Pyrazolones frequently induce SNIUAA [27,28]. The prevalence of nonimmediate reactions is unknown, and severe reactions are much less frequent [29].

### Pathogenesis

**NSAID-Exacerbated Respiratory Disease**

NERD is associated with the metabolism of arachidonic acid, overproduction of cysteinyl leukotrienes (CysLT) by the eosinophils or mast cells in the target organ mucosa [30], increased expression of the CysLT receptors in the inflammatory cells of the mucosa [31], and alterations in the metabolism of prostaglandins (PG) [32-35].

Arachidonic acid is metabolized by 2 pathways: the COX pathway, which induces synthesis of PGs, and the lipoxigenase pathway, which induces synthesis of CysLT (Figure 1). There are at least 2 COX isoforms, COX-1 and COX-2. The former is expressed in many tissues and organs, and the latter is induced by proinflammatory stimuli [9]. Classic NSAIDs act on both enzymes, although, in susceptible patients, it is COX-1 blockade that induces a decrease in PGE 

![Figure 1. Metabolism of membrane phospholipids. NSAID indicates nonsteroidal anti-inflammatory drug; COX, cyclo-oxygenase; PG, prostaglandin; LT, leukotriene.](image-url)
NSAID that inhibits COX-1 in all patients only induces an acute increase in CysLT in those with respiratory symptoms. In inflammatory conditions, arachidonic acid is oxidized by 5-lipoxygenase (5-LO) to leukotriene (LT) \( \text{A}_4 \), which is metabolized into the final metabolite \( \text{LTE}_4 \). Baseline levels of CysLT in bronchoalveolar lavage, nasal secretions, blood, and urine are higher in patients with NERD than in asthmatic patients who tolerate ASA and can increase after administration of ASA [37,38]. An increase in cells expressing \( \text{LTC}_4 \)-synthase has been detected in patients with NERD [39-42].

\( \text{PGE}_2 \) induces potent negative feedback in the 5-LO enzyme in many cells. Thus, suppression of \( \text{PGE}_2 \) synthesis by inhibition of COX-1 is accompanied by increased synthesis of CysLT. A parallel increase is observed in CysLT receptors (CysLT-R) in bronchial muscle and endothelial and epithelial cells, as is an increase in the proinflammatory effects of eosinophils and mast cells [31,42]. Increased levels of eosinophil cationic protein and tryptase have also been detected in nasal lavage fluid after a nasal provocation test (NPT) with lystine acetylsalicylate (LAS) in patients with NERD [38]. These observations are reinforced by the fact that previous inhalation of \( \text{PGE}_2 \) completely prevents the bronchospasm induced by ASA and the increased \( \text{LTE}_4 \) levels in urine [43].

Genetic predisposition to NERD has been observed—although a strong association has not been proven—and involves HLA alleles and single-nucleotide polymorphisms in the CysLT receptor 1 gene (CYSLTR1), \( \text{LTC}_4 \)-synthase receptor, transcription factor T-box, \( \text{PGD}_2 \) receptor, and tumor necrosis alfa promoter [44-57]. Nevertheless, the population size and the number of gene variants were limited in most studies, the reported case populations were heterogeneous, and the association found was inconsistently replicated in independent studies [46].

**NSAID-Exacerbated Cutaneous Disease**

As with NERD, the mechanisms involved in NERD seem to be associated with inhibition of COX-1 and overproduction of CysLT. This hypothesis is based on the detection of increased urine \( \text{LTE}_4 \) levels after a drug provocation test (DPT) with ASA in which patients with NERD were compared with patients with CSU and good tolerance [54,55]. Asero [56] suggests a possible association between chronic urticaria, autoimmunity, and NSAID hypersensitivity.

**NSAID-Induced Urticarial/Angioedema**

The mechanism underlying NIUA is unknown. It has been proposed that, similar to NERD and NEC, COX-1 inhibition could be involved in pathogenesis [57]. However, patients with NIUA seem to have a distinctive phenotype: only 12% had a positive response to an NPT with LAS and they showed no significant increase in ECP or in release of tryptase in lavage fluid after an NPT with LAS [38]. Variants related to these pathways can play a role [58], as can variants other than those associated with the metabolism of arachidonic acid [59].

It has also been suggested that, in some cases, NSAID hypersensitivity could precede the onset of chronic urticaria [60], although there are not enough data to clarify this point. A recent study reported that the percentage of patients with NIUA developing CSU was similar to that found for a control group [60], thus showing NIUA to be a well-defined entity that is clearly different from NECED.

**Single NSAID-Induced Urticarial/Angioedema or Anaphylaxis**

The clinical pattern of this reaction, the time interval between drug administration and development of symptoms, and the selectivity of the reaction support an IgE-mediated mechanism. Specific IgE to pyrazolones has been demonstrated by skin and in vitro testing [5,61,66] and with ASA [35], although with other NSAIDs, the detection of specific IgE has only been supported by single-case studies [63].

The drugs that most frequently induce this reaction include pyrazolones [5,9,61,64,65], piroxicam [66], diclofenac [5,21,26,63,67], paracetamol (acetaminophen) [5,68,69], ibuprofen [5,9,12,26], and naproxen [26,70]. Anaphylaxis induced by celecoxib has also been described [71-73]. Finally, associations with HLA-DQ and HLA-DR have been reported in hypersensitivity to pyrazolones [65,74].

**NSAID-Induced Delayed Hypersensitivity Reactions**

Although a T-cell–mediated mechanism seems to be involved in most cases, no studies evaluate the underlying mechanisms in a sufficient number of cases [75]. Pyrazolones, arylacetic acids, and propionic acids are the most frequently involved NSAIDs [5,8,76].

**Characterization of the Clinical Entities**

Hypersensitivity reactions induced by NSAIDs constitute a heterogeneous group of syndromes, in terms of both immunopathogenesis and clinical practice. Several categories can be defined.

**NSAID-Exacerbated Respiratory Disease**

The typical patient is an adult with recurrent episodes of asthma and rhinosinusitis. The disease progresses as persistent rhinitis—with or without polyposis—to asthma that frequently requires systemic corticosteroids to control symptoms. After administration of NSAIDs, patients develop nasal congestion or ocular itching, and nasal hydorrhea that rapidly progress to wheezing in 30 minutes to 3-4 hours. In some cases, the NSAID only induces rhinoconjunctivitis and in others it is accompanied by cutaneous or gastrointestinal symptoms (mixed or blended reactions) [5,39,77-79].

Although these patients were traditionally thought to have nonallergic severe asthma or rhinitis, increasing evidence indicates that a large percentage (34-64%) have a history of atopy and mild symptoms [80-84]. However, in a large series of patients with nasal polyposis, more nonatopic patients had NERD than atopic patients (32.5% vs 21.1%, \( P > .05 \)), and patients with nasal polyposis and NSAID hypersensitivity had a significantly poorer quality of life than those with nasal polyposis only [84].

**NSAID-Exacerbated Cutaneous Disease**

The classic picture involves a patient with CSU that worsens orreactivates after administration of an NSAID. The
Diagnosis of Hypersensitivity to NSAIDs


The intensity of the reaction may change over time, depending on the activity of the CSU, and in some patients it can even resolve [5,9,55,85].

Symptoms usually appear from 1 to 4 hours after administration of the NSAID, although lesions can appear in less than 1 hour or even 24 hours after administration [9]. Progression to systemic symptoms of anaphylaxis is quite infrequent [86].

**NSAID-Induced Urticarial/Angioedema**

Patients with NIUA do not have underlying CSU and present a variable combination of urticaria, angioedema, erythema, or exanthema-like reaction within minutes to 24 hours after the administration of various NSAIDs [75,77].

Atopy is a risk factor and is more frequent in NIUA than in SNIUAA (60% vs 40%) [5,9,77,81,87]. The most significant association reported was sensitization to house dust mites [5,75]. Whether NIUA also occurs with food allergens remains unknown, although preliminary studies indicate that food allergy is not an associated condition [88].

One subgroup with typical symptoms includes patients in the first and second decade of life with respiratory allergy who are sensitized to house dust mites and develop periorbital angioedema after administration of NSAIDs [77,89]. Some of these patients can develop anaphylaxis after ingestion of wheat flour contaminated with mites, although no evidence of food allergy has been reported [90].

Finally, after administration of NSAIDs, some patients develop systemic symptoms accompanied by both cutaneous and respiratory symptoms (blended reactions) [5,75-77]. Up to 30% of patients present hypotension. Pyrazolones, arylocetic acid NSAIDs, and propionic acid NSAIDs are the most frequently involved drugs [26,79,91].

**Single NSAID-Induced Urticarial/Angioedema or Anaphylaxis**

More than 30% of cases of NSAID hypersensitivity involve SNIUAA [5,68]. Clinical symptoms usually appear during the first hour after administration [4] and include generalized urticaria and/or angioedema, which can progress to anaphylaxis and shock [92,93]. Anaphylaxis is the initial manifestation in some cases [61,93].

Subsequent administration of NSAIDs can induce anaphylactic reactions [77,79]. In contrast with cross-reactive patients, no association has been established with atopy [5] or underlying skin diseases [86].

**NSAID-Induced Delayed Hypersensitivity Reactions**

NIDHRs can manifest as cutaneous systems, systemic symptoms, and fever. They can also affect other organs. Onset is from 24 hours to days or weeks after initiation of treatment. The most common manifestations [94] are the following:

- **Maculopapular exanthema**: Maculopapular exanthema is the most common symptom and is caused mainly by ibuprofen, pyrazolones, flurbiprofen, diclofenac, and celecoxib [8,76,95-97].

- **Fixed drug eruption (FDE)**: FDE accounts for 10% of the hypersensitivity reactions induced by drugs, of which NSAIDs are the most frequently involved [98]. FDEs have been described with pyrazolones, piroxicam, paracetamol (acetaminophen), ASA, diflunisal, indomethacin, mafenamic acid, diclofenac, ibuprofen, naproxen, and nimesulide [8,99], and less frequently with COX-2 selective inhibitors [100,101].

- **Delayed urticaria**: Delayed urticaria is similar to that which appears in acute reactions. Ibuprofen is the most frequently involved drug [102].

**Severe cutaneous reactions**: Stevens-Johnson syndrome and toxic epidermal necrolysis induced by NSAIDs are uncommon. The most frequently involved drugs are the oxicams, followed by the pyrazolones and COX-2 selective inhibitors [103,104]. Other severe reactions, such as drug reaction with eosinophilia and systemic symptoms [105] and acute generalized exanthematic pustulosis can be induced by NSAIDs such as ibuprofen, dipyrone, paracetamol, nimesulide, and selective COX-2 inhibitors [106-109].

**Contact and phototype contact dermatitis**: Topical NSAIDs are frequently involved in these reactions, and some can induce severe reactions after systemic administration of the same NSAID (systemic contact dermatitis) [110]. The NSAIDs involved in reactions are ketoprofen, flurbiprofen, ibuprofen, piroxicam, pyrazolones, diclofenac, indomethacin, and etofenamate. Cross-reactivity is common between those from the same chemical family [111].

In photoallergic reactions, the symptoms are similar, but they appear in sun-exposed areas, although they may become generalized and thus affect nonexposed areas [109]. These reactions have been reported with ketoprofen, ibuprofen, piroxicam, diclofenac, and selective COX-2 inhibitors [112,113].

**Organ-specific reactions**: Hypersensitivity pneumonitis has been described with sulindac, ibuprofen, and naproxen [114]. Different types of kidney disease have been described with both COX-1 and selective COX-2 inhibitors [115,116]. Aseptic meningitis has been reported, particularly with ibuprofen, although cases have also been described with naproxen, diclofenac, ketoprofen, piroxicam, indomethacin, and, more recently, with rofecoxib and celecoxib [117].

**Diagnosis**

Currently available methods for diagnosing hypersensitivity reactions to NSAIDs include the clinical history, skin testing, in vitro testing, and DPT.

**Clinical History**

A detailed clinical history is essential for diagnosing hypersensitivity reactions to NSAIDs and must include a description of the symptoms, the time interval between drug administration and the onset of symptoms, the drugs involved, drugs tolerated after the reaction, route of administration, number of episodes, and the underlying diseases, including the one for which the NSAID was prescribed [118]. The clinical history is sufficient when establishing a diagnosis in cases with more than 2 episodes to NSAIDs from different chemical groups (grade of recommendation D) [6,9,118]. NERD in patients with underlying asthma or rhinitis who...
develop respiratory symptoms after administration (grade of recommendation C) [79,119,120], and NECD in patients with CSU who develop urticaria and angioedema after administration (grade of recommendation C) [121].

In patients with 1 or 2 episodes from 2 different NSAID groups for whom tolerance to a more potent COX-1 inhibitor is different from that to the drug involved in the reaction, the diagnosis cannot be established by the clinical history, and more studies are needed (grade of recommendation C).

**Skin Tests**

Skin tests are not valid for evaluating non–immunologically mediated reactions (grade of recommendation D). If the result of skin prick testing is negative in a patient with SNIUAA, then intradermal tests can be used. Most experience is with hypersensitivity to pyrazolone (grade of recommendation C) [61,70,103]. The sensitivity reported ranges widely from 41% for dipyrone [62] to 83% for propyphenazone [61], and specificity is 100% for both these pyrazolones [61,62,93]. Of note, a decrease in skin test sensitivity to pyrazolones has been described in SNIUAA (grade of recommendation C) [62,122].

As for the other NSAIDs, there are single case reports of positive skin test results, mainly with paracetamol and diclofenac (grade of recommendation D) [91,123].

In NIDHR, reading of both intradermal and patch tests at 24-48 hours or more can be useful, although sensitivity and specificity are variable [76,97,124,125] (grade of recommendation D). Patches should be applied to the upper part of the back for 48 hours with readings at 48, 72, and 96 hours, and a reading after 1 week is necessary in some patients. Patch testing on damaged skin can be useful in FDE, and a photopatch test could prove useful in photosensitivity reactions (grade of recommendation D) [126].

**In Vitro Tests**

Several in vitro tests can be used in the diagnosis of hypersensitivity reactions to NSAIDs. Sensitivity and specificity are variable.

**Sulfidoleukotriene release test:** Although this test has been proposed for the diagnosis of non–immunologically and immunologically mediated hypersensitivity reactions to NSAIDs, it does not have sufficient sensitivity and specificity to be recommended for routine diagnosis (grade of recommendation C) [127-131].

**Basophil activation test:** The basophil activation test is based on the determination of basophil activation markers (CD45, CD18, and CD63) using flow cytometry. Data obtained to date have only shown acceptable sensitivity in the case of SNIUAA with specific drugs such as pyrazolones (grade of recommendation C) [62,122,132-135].

**Determination of specific IgE antibodies in serum:** This approach has been proposed for SNIUAA, although its sensitivity is inferior to that of skin testing. The most widely used method is ELISA [61,93,136], mainly for detection of specific IgE to pyrazolones (grade of recommendation C) [61,93,136]. With other NSAIDs, specific IgE antibody detection is limited to single reports (grade of recommendation C) [67,137].

**Lymphocyte transformation test:** The lymphocyte transformation test is based on the capacity of T cells to proliferate after contact with an NSAID to which the patient is sensitized. Although there are few data about its sensitivity and it cannot be recommended as a routine test, the lymphocyte transformation test can prove useful for the diagnosis of NIDHR (grade of recommendation D) [138].

**Drug provocation test:** DPT is considered the gold standard for the diagnosis of hypersensitivity reactions to drugs and is indicated to confirm or exclude the diagnosis when no other test is available and to find an alternative NSAID once the diagnosis is confirmed. In some cases, DPT is not risk-free and is contraindicated in patients with a forced expiratory volume in 1 second (FEV₁) lower than 1.5 L or in whom exposure to placebo leads to >20% variability in FEV₁. It is also contraindicated in the following situations: pregnancy, infectious diseases, psychiatric disorders, uncontrolled asthma, severe cutaneous reactions (eg, toxic epidermal necrolysis), anaphylactic shock, and organ-specific reactions (grade of recommendation C) [139,140].

DPT must be performed by trained personnel in a clinical setting where rapid and adequate treatment can be administered if a reaction occurs. DPT should be performed in a single-blind placebo-controlled manner, although in some cases a double-blind procedure may be necessary. As a general rule, other drugs should be stopped before initiating the DPT, as follows: inhaled short-acting β₂-agonists 8 hours before; long-acting β₂-agonists, theophylline, and tiotropium bromide 24 to 48 hours before; antihistamines 3 days before; and leukotriene antagonists during the previous week.

Depending on the route of administration of the NSAID, the DPT can be nasal, bronchial, and oral.

**Nasal provocation test:** NPT is indicated in patients with symptoms affecting the upper or lower respiratory tract. It is usually safe, except for the occasional appearance of bronchospasm, which is easily treated (grade of recommendation C) [141,142]. NPT is contraindicated in patients with septal perforation and massive nasal polyposis [141]. Sensitivity is lower than in the oral and bronchial provocation tests (grade of recommendation C) [143]. NPT is based on the administration of 28-45 mg of LAS (1800 mg of LAS is equivalent to 1000 mg of ASA). The response is analyzed using a symptom score and active anterior rhinomanometry or acoustic rhinometry [143].

Active anterior rhinomanometry is a commonly used technique. It measures the resistance of the nasal airway, although it cannot be used if the patient has polyps or nasal obstruction. Serial dilutions of LAS are administered with an active anterior rhinomanometry measurement every 10 minutes and spirometry every 20 minutes after administration. A response is considered positive if symptoms appear, nasal resistance increases to >100%, or FEV₁ decreases by >20%. If no response appears, the next dilution is administered until the total cumulative dose is reached. The sensitivity of this method is 80%, and the specificity is 92% (grade of recommendation C) [141,142,144,145].

Acoustic rhinometry is based on acoustic reflection and can be performed in patients with nasal obstruction. A single dose of 25 mg of LAS is administered, and symptoms and nasal volumes are compared with those obtained after administration.
Diagnosis of Hypersensitivity to NSAIDs

Table 2. Doses of the Drugs Used in the Drug Provocation Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, mg</th>
<th>Interval of Administration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoricoxib</td>
<td>60-90</td>
<td>60</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100-200</td>
<td>60</td>
</tr>
<tr>
<td>Paracetamol (acetaminophen)</td>
<td>100-250-500-1000</td>
<td>60</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7.5-15</td>
<td></td>
</tr>
<tr>
<td>Nabumetone</td>
<td>500-1000</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>25-50</td>
<td></td>
</tr>
<tr>
<td>Metamizole (dipyrone)</td>
<td>First day: 50-100-250</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Second day: 575</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>First day: 50-100-200-400</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Second day: 600</td>
<td>180</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>First day: 50-100</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>Second day: 250-500</td>
<td>180</td>
</tr>
</tbody>
</table>

of saline; a response is considered positive when nasal volume decreases by >25%. The sensitivity of the test is 73%-80% and the specificity 94% (grade of recommendation C) [38,146].

Bronchial provocation test: The bronchial provocation test is indicated in patients with bronchial symptoms after intake of NSAIDs. Clinical and spirometric stability should be checked before initiating the test, and the FEV1 must be >80% with no variations >5%. After inhalation of saline, the spirometry test should vary by <10% with respect to baseline values. Doses of LAS are then increased at 30-minute intervals, and FEV1 is measured. If no variations or symptoms appear, the procedure is continued until the maximum dose is reached, although the number of inhalations and dose of LAS depend on the protocol [144,147,148]. The protocol is continued at home with peak-flow determinations during the following 24 hours to detect a delayed reaction [149]. The specificity of the bronchial provocation test is 100%, with a sensitivity of 62%, although it is less dangerous and time-consuming than oral DPT (grade of recommendation C).

Oral provocation test: The oral provocation test is considered the gold standard and is the only available test

Figure 2. Proposed diagnostic algorithm for patients with hypersensitivity reactions to NSAIDs. NSAID, nonsteroidal anti-inflammatory drug; OPT indicates oral provocation test; NPT, nasal provocation test; BPT, bronchial provocation test; NERD, NSAID-exacerbated respiratory disease; NIDHR, NSAID-induced delayed hypersensitivity reactions; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; ASA, acetylsalicylic acid; SNIUAA, single NSAID–induced urticaria/angioedema/anaphylaxis.
Diagnostic Algorithm

The diagnosis of hypersensitivity reaction to NSAIDS is based on symptoms reported in the clinical history and timing. A diagnostic algorithm is proposed in Figure 2, and the methods most often used in each clinical category are shown in Table 3.

Table 3. Methods Recommended for Diagnosis of Hypersensitivity Reactions to NSAIDs

<table>
<thead>
<tr>
<th></th>
<th>Skin Test</th>
<th>In Vitro Test</th>
<th>OPT</th>
<th>NPT/BPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NERD</td>
<td>No</td>
<td>No</td>
<td>Optional</td>
<td>Yes</td>
</tr>
<tr>
<td>NECD</td>
<td>No</td>
<td>No</td>
<td>Optional</td>
<td>No</td>
</tr>
<tr>
<td>NIUA</td>
<td>No</td>
<td>No</td>
<td>&gt;2 NSAIDs: Optional</td>
<td>No</td>
</tr>
<tr>
<td>SNIUAA</td>
<td>Prick/ID</td>
<td>IgE serum BAT</td>
<td>ASA</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild: Culprit</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe: Alternative</td>
<td>No</td>
</tr>
<tr>
<td>NIDHR</td>
<td>ID delayed</td>
<td>Patch test</td>
<td>LTT</td>
<td>Mild: Culprit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe: Alternative</td>
</tr>
</tbody>
</table>

Abbreviations: BAT, basophil activation test; BPT, bronchial provocation test; ID, intradermal; LTT, lymphocyte transformation test; NERD, NSAID-exacerbated cutaneous disease; NIDHR, NSAID-induced delayed hypersensitivity reactions; NERD, NSAID-induced urticaria/angioedema; NPT, nasal provocation test; NSAID, nonsteroidal anti-inflammatory drug; OPT, oral provocation test; SNIUAA, single NSAID-induced urticaria/angioedema/anaphylaxis.

In patients with urticaria and/or angioedema and underlying CSU, 2 options are available. First, if the patient reports reactions with more than 2 NSAIDs from unrelated chemical groups, a diagnosis of NIDHR can be established [121]. In the case of urticaria/angioedema and underlying CSU, 2 options are available. First, if the patient reports reactions with more than 2 NSAIDs from unrelated chemical groups, a diagnosis of NIDHR can be established [121].

Clinical History Indicative of Acute Reactions

Respiratory symptoms
The first approach, if available, is a nasal or bronchial provocation test with LAS, depending on the symptoms reported. If the result is positive, the patient will be diagnosed with NERD. If the result is negative, the diagnosis is based on the consistency of the clinical history. Oral provocation testing with ASA is only recommended if desensitization with ASA is to be performed. Regardless of whether the diagnosis was by clinical history, tolerance of an alternative analgesic (paracetamol) or COX-2 inhibitors should be evaluated using nasal or bronchial provocation testing.

Cutaneous symptoms
In cases with underlying CSU or exacerbation of wheals and angioedema after administration of NSAIDs, NECD can be diagnosed by means of the clinical history. As with NERD, tolerance to alternative analgesics (paracetamol) or COX-2 inhibitors should be assessed.

Nonsuggestive Reaction
In cases of a nonsuggestive reaction, oral provocation testing with the culprit NSAID is the best approach; if the result is negative, the patient will be considered nonallergic. If a reaction appears, oral provocation testing should be performed with either ASA or indomethacin (if ASA is involved). If the result is positive, the diagnosis is NIDHR. If the patient tolerates ASA, then oral provocation testing should be performed with the culprit drug. If the result is positive, the diagnosis is SNIUAA. If pyrazolone is the NSAID involved, skin tests and in vitro tests should be performed beforehand. If tolerance to the culprit NSAID is good, the patient should be considered nonallergic. The decision of whether to administer the culprit drug in this group depends on the type of reaction; testing with the culprit drug is not recommended in patients with anaphylaxis.

Clinical History Indicative of Delayed Reactions
Patch testing should be performed with readings at 48, 72, and 96 hours. A positive response indicates NIDHR; therefore, the culprit NSAID and those belonging to the same chemical family should be avoided.

In patients with negative patch test results, the approach will depend on the severity of the reaction. In severe reactions, oral provocation testing should be performed with an alternative NSAID from a different group; if tolerance is
good, the diagnosis is NIDHR, and the recommendation is to avoid the culprit NSAID and those from a chemically related family. In mild reactions, oral provocation testing should be performed with the culprit NSAID; if the result is negative, the patient is considered nonallergic, and, if positive, oral provocation testing should be performed with ASA or with indomethacin (if ASA is the culprit). In the case of a positive reaction, the diagnosis is NIUA; if negative, it is NIDHR, and the recommendation is to avoid the culprit NSAID and drugs from a chemically related group.

Hypersensitivity Reactions in Children

The drugs that most often induce hypersensitivity reactions in children are ß-lactam antibiotics, followed by NSAIDs [151,152]. In many cases, reactions appear in children who received both types of drug during a viral infection, thus complicating diagnosis, as viral infections can also induce cutaneous symptoms. In general, only a low percentage of children with a history of hypersensitivity reactions to drugs (<10%) are finally confirmed as allergic [153].

The clinical picture is similar to that of adults, although facial angioedema is the most frequent manifestation, especially in cases mediated by a nonimmunological mechanism; the frequency of this symptom increases progressively until the age of 21 years [154-168]. The clinical history has low negative and positive predictive values for diagnosis, the gold standard being DPT, with skin testing proving useful in some cases [159]. Hypersensitivity reactions are confirmed in only 1% to 50% of children with a clinical history of allergy to NSAIDs [156,158], and most are non–immunologically mediated hypersensitivity reactions [155,158,160], with ibuprofen as the most frequently involved drug. Typical symptoms include angioedema, and the reactions are often associated with atopy; DPT is a safe diagnostic method in this population [161]. Once a cross-reactive hypersensitivity reaction is confirmed, the approach is to recommend alternative treatment; reactivity to paracetamol has been shown to range from 0% to 25% [161,163]. In a recent study, all patients tolerated etoricoxib with fewer than 5% reacting to meloxicam. It remains to be determined whether this response can vary over time in this population [164].

Management: Avoidance and Desensitization

Management of patients with hypersensitivity reactions induced by NSAIDs varies according to the underlying mechanism. Patients with immunologically mediated hypersensitivity reactions must avoid the culprit drug and chemically related drugs (grade of recommendation D). In contrast, patients with non–immunologically mediated hypersensitivity reactions must avoid strong COX-1 inhibitors because of the high possibility of cross-reactivity (grade of recommendation C). However, weak COX-1 inhibitors (eg, paracetamol) and preferential COX-2 inhibitors (eg, meloxicam and nimesulide) are safe and can be tolerated by more than 80% of patients (grade of recommendation C) [9,57,165-168]. Selective COX-2 inhibitors are also well tolerated in patients with NERD, and only anecdotal cases have been reported (grade of recommendation B) [169-171]. In contrast, in patients with NECD and NIUA, the percentages of positive responses to COX-2 inhibitors range from 7% to 33% (grade of recommendation D) [169,170,172,173]. It has been reported that the 25% of patients with NIUA have a positive response to selective COX-2 inhibitors if they also have symptoms induced by paracetamol (acetaminophen). Therefore, in patients with non–immunologically mediated hypersensitivity reactions to NSAIDs, tolerance to weak COX-1 and preferential and selective COX-2 inhibitors should be previously assessed in an allergy department (grade of recommendation D).

Desensitization involves daily controlled administration of increasing doses of the NSAID (mainly ASA) in order to reduce and avoid hypersensitivity reactions while the drug is administered. Since desensitization can be lost within 2 to 5 days after interruption, the procedure should be reinitiated if it has been stopped for more than 48 hours. The minimal dose capable of maintaining desensitization is 81 mg of ASA (grade of recommendation C) [174,175]. The procedure is indicated in patients with NERD that can only be controlled with high doses of corticosteroids or who have undergone several nasal polyectomies, as well as in patients requiring ASA or other NSAIDs for treatment of cardiovascular, hematological, or rheumatologic diseases (grade of recommendation C) [176-179]. Less information exists about desensitization in patients with skin symptoms. The procedure is contraindicated in patients with gastroduodenal ulcer, coagulation disorders, and kidney or liver disease. It is also contraindicated during an asthma exacerbation and in patients with severe cutaneous reactions such as Steven-Johnson syndrome or toxic epidermal necrolysis.

Desensitization is a risky procedure that has to be carried out by qualified personnel in an appropriate setting where treatment can be administered if a reaction occurs (grade of recommendation D) [168]. Airway stability is especially important in patients with NERD, who should continue to take asthma medication and initiate antileukotriene treatment 2 to 4 weeks before initiating desensitization [180]. In some patients with skin symptoms, antihistamines and corticosteroids have been used as premedication.

Table 4. Desensitization Protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>ASA: 20-40 mg</th>
<th>ASA: 100-160 mg</th>
<th>ASA: 60-100 mg</th>
<th>ASA: 325 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 AM</td>
<td>Placebo</td>
<td>ASA: 20-40 mg</td>
<td>ASA: 100-160 mg</td>
<td>ASA: 60-100 mg</td>
<td>ASA: 325 mg</td>
</tr>
<tr>
<td>12 AM</td>
<td>Placebo</td>
<td>ASA: 40-60 mg</td>
<td>ASA: 160-325 mg</td>
<td>ASA: 60-100 mg</td>
<td>ASA: 325 mg</td>
</tr>
<tr>
<td>3 PM</td>
<td>Placebo</td>
<td>ASA: 60-100 mg</td>
<td>ASA: 160-325 mg</td>
<td>ASA: 325 mg</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ASA, acetylsalicylic acid.

Procedure in patients with NERD

Different protocols have been described for the oral, intranasal, and bronchial inhaled routes, although the oral route is the most widely used; the procedure is shown in Table 4 [181-184]. The patient should have an intravenous line inserted during the desensitization procedure. Blood pressure and heart rate should be monitored and lung function measured.
before and 30 minutes after each dose. FEV\textsubscript{1} has to be >70% or >1.5 L. Patients with FEV\textsubscript{1} <80% or an exacerbation of their asthma are considered high-risk; consequently, the starting dose must be <20 mg of ASA [179].

If a reaction appears, it should be treated immediately. The next dose can be administered once the patient is stabilized and 3 hours after the last dose. If the reaction persists, the procedure should be stopped and reintiated the following day beginning with the last tolerated dose. If doses are tolerated, the procedure is continued until a dose of 325 mg of ASA is tolerated.

In patients requiring ASA as antiplatelet therapy, the total cumulative dose is lower (100 mg), and doses can be administered at 20-minute intervals with the following schedule: 0.1, 0.2, 1, 3, 10, 25, 50, and 100 mg [185]. If desensitization is performed to treat asthma and nasal polyposis, a dose of 650 mg should be administered twice a day for 1 month; if the patient’s condition improves, the dose will be progressively reduced to 325 mg twice a day [186]. Administration of ASA can change the course of the disease in 25% of cases [187-190], with a marked improvement in symptoms and quality of life [191-193].

Procedure in Patients With NECD and NIUA

Data on desensitization in patients with NECD or NIUA are limited. In one study, 11 patients with NIUA tolerated the desensitization procedure [194]. However, in patients with NECD, desensitization seems to be less effective; in some cases, it is impossible [195].

Procedure in Patients With Immunologically Mediated Hypersensitivity Reactions to NSAIDs

Since these patients develop symptoms with one group of NSAIDs and tolerate others, desensitization is not usually necessary. Desensitization is only indicated in patients with SNIUAA to ASA, and the procedure is the same as that described above. There is less evidence about desensitization in NIDHR.

Acknowledgments

We thank Professors Miguel Blanca and Ignacio Dávila for their in-depth review of our manuscript. We also thank Ian Johnstone for his help with the English language version of the manuscript.

Funding

The authors declare that they received no funding for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

with aspirin hypersensitivity in the adult population of Poland. Allergy. 2003;58:1064-6.


119. Yoshimine F; Hasegawa T; Suzuki E; Terada M; Koya T; Kondo H; Arakawa M; Yoshizawa H; Gejyo F. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. Respirology. 2005;10:477-84.
Diagnosis of Hypersensitivity to NSAIDs


176. White AA, Hope AP, Stevenson DD. Failure to maintain an aspirin-desensitized state in a patient with aspirin-


