

Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs



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KEYWORDS

• Nonsteroidal anti-inflammatory drugs • Hypersensitivity • Clinical diagnosis
• Allergic • Nonallergic • Management

KEY POINTS

- Nonsteroidal anti-inflammatory drugs are the most frequent drugs involved in hypersensitivity drug reactions.
- The mechanisms involved can be specific (immunologic), whether mediated by immunoglobulin E or T cells or by activation of pathways that release vasoactive mediators.
- Five major well-defined clinical entities are currently recognized, although overlapping may exist.
- The diagnosis is mostly based on clinical history and a drug-provocation test.
- Management consists of drug eviction, providing alternatives such as paracetamol and cyclooxygenase-2 inhibitors and, when needed, desensitization.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the medicines most frequently prescribed worldwide, many of which are available over the counter.¹ NSAIDs induce a wide variety of adverse reactions that are classified as type A (predictable and usually related to the effects of the drug) and type B (unpredictable and related to the individual response).² This review deals with type B drug hypersensitivity reactions (DHR), mediated by immunologic (allergic) or nonspecific pharmacologic mechanisms (nonallergic).³ NSAIDs are of great concern because they are the drugs most commonly involved in DHR.^{4–7}

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CLASSIFICATION

NSAIDs have different chemical structures that share the capacity for inhibiting cyclooxygenase (COX) enzymes (COX-1 and COX-2) (Table 1). The mechanism for inducing DHR is related to the release of vasoactive mediators (histamine, prostaglandins, and sulfidopeptide leukotrienes [LTs])⁵ or is due to their recognition as xenobiotics, inducing immunoglobulin E (IgE) or T-cell responses.⁴

The authors use the nomenclature for DHR proposed by the European Academy of Allergy and Clinical Immunology (EAACI),³ based on the timing of reactions (acute or delayed), clinical pattern of symptoms (respiratory and/or cutaneous and/or anaphylaxis), and the presence or absence of cross-tolerance to other chemically unrelated NSAIDs.^{5,6} Cross-reactive types (1, 2, and 3) involve nonallergic mechanisms while single-drug-induced types (4 and 5) involve allergic, putative IgE, and T-cell-mediated mechanisms (Table 2).^{8–10} In addition, the presence of underlying chronic inflammatory disease of the skin (chronic spontaneous urticaria [CSU]) and of the respiratory tract (asthma/chronic rhinosinusitis [CRS]) should be considered. This phenotype-based classification allows the use of a simple history-based algorithm for diagnosis (Fig. 1) and indicates putative underlying mechanisms.⁷

EPIDEMIOLOGY

NSAIDs are usually reported to be the second most important group of drugs involved in DHRs after antibiotics, although recent studies indicate that they are in fact the principal group.^{11–13} The prevalence of self-reported DHR to NSAIDs has been shown to be 1.9%, with acetylsalicylic acid (ASA; aspirin) and ibuprofen being the most frequent

Table 1 Examples of NSAIDs according to capacity for COX enzyme inhibition			
Nonselective COX inhibitors	Salicylic acid derivatives	Acetylsalicylic acid	
	Indoleacetic acids	Indomethacin	
	Heteroaryl acetic acids	Diclofenac	
	Arylpropionic acids	Ibuprofen	
	Enolic acids	Piroxicam	
	Para-aminophenol derivatives	Paracetamol	
	Alkanones	Nabumetone	
	Anthranilic acids	Mefenamic acid	
Selective COX-2 inhibitors	Diaryl-substituted pyrazoles	Celecoxib	

From Cornejo-García JA, Blanca-Lopez N, Doña I, et al. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs. *Curr Drug Metab* 2009;10:973; with permission.

Table 2
Type of reactions and clinical manifestations induced by NSAIDs

Type of Reaction	Clinical Manifestation	Timing of Reaction	Underlying Disease	Cross-Reactivity	Putative Mechanism
NSAID-exacerbated respiratory disease	Bronchial obstruction, dyspnea, and/or nasal congestion/rhinorrhea	Acute (usually immediate to several hours after exposure)	Asthma/rhinosinusitis	Cross-reactive	Nonallergic COX-1 inhibition
NSAID-exacerbated cutaneous disease	Wheals and/or angioedema		Chronic urticaria		COX-1 inhibition
NSAID-induced urticaria/angioedema	Wheals and/or angioedema		No underlying chronic diseases		Unknown, probably COX-1 inhibition
Single NSAID-induced urticaria/angioedema or anaphylaxis	Wheals/angioedema/anaphylaxis		No underlying chronic diseases	Not cross-reactive	Allergic IgE mediated
Single NSAID-induced delayed reactions	Various symptoms and organs involved (eg, fixed drug eruption, SJS/TEN, nephritis)	Delayed onset (usually more than 24 h after exposure)	No underlying chronic diseases		T-cell mediated

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

From Kowalski ML, Asero R, Baybek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013;68:1221; with permission.

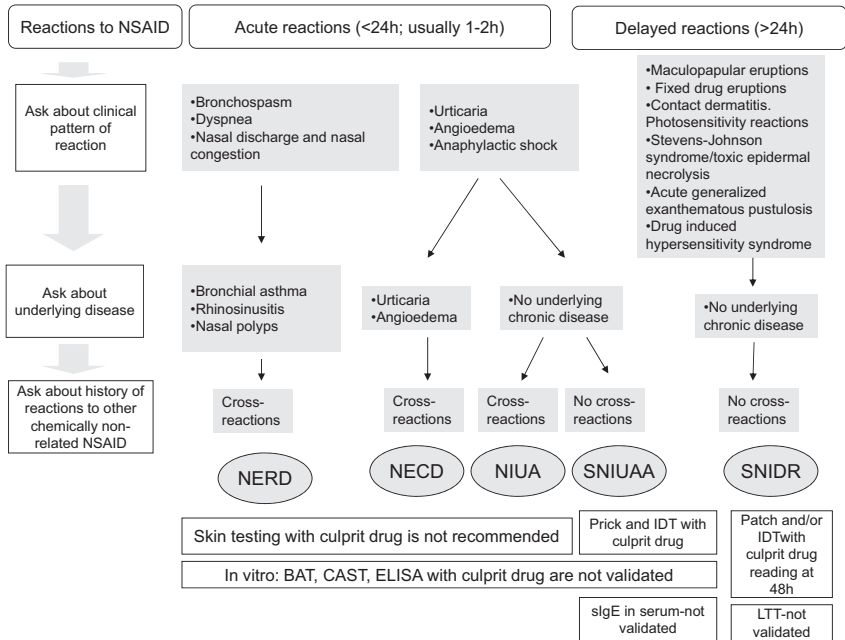


Fig. 1. Five major groups of clinical entities induced by NSAIDs with a practical approach for their identification. BAT, basophil activation test; CAST, cellular allergy stimulation test; ELISA, enzyme-linked immunosorbent assay; IDT, intradermal test; LTT, lymphocyte transformation test; NECD, NSAID-exacerbated cutaneous disease; NERD, NSAID-exacerbated respiratory disease; NIUA, NSAID-induced urticaria/angioedema; slgE, specific IgE; SNIDR, single NSAID-induced delayed reactions; SNIUAA, single NSAID-induced urticaria/angioedema or anaphylaxis. (From Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013;68:1228; with permission.)

culprits.¹⁴ The prevalence of NSAID DHRs in the general population ranges from 0.6% to 5.7%, depending on the population studied, the type of reaction, and the criteria used for diagnosis.¹⁵ In fact, 55% of all patients labeled as NSAID-hypersensitive according to their clinical history tolerated NSAIDs following drug-provocation testing (DPT).¹⁴

Considering the different entities, the prevalence of NSAID-exacerbated respiratory disease (NERD) varies from 4.3% to 20%.^{16–18} The presence of CRS with nasal polyps, severe asthma, and female gender are all associated with higher prevalence.^{19,20} Moreover, a history of CRS and nasal polyposis are independent predictors for NERD.²¹ Although this entity has been more extensively studied, the most frequent DHRs are those involving the skin,²² appearing in 0.07% to 0.3% of the general population.^{23,24} NSAIDs may be an aggravating factor for 10% to 30% of patients with CSU,⁶ and this effect is dose-dependent and related to CSU activity. This entity is known as NSAID-exacerbated cutaneous disease (NECD). Finally, NSAID-induced urticaria/angioedema (NIUA) affects up to 60% of all patients with DHR to NSAIDs.²²

The prevalence of immunologically mediated DHR to NSAIDs ranges from 0.1% to 3.6% of subjects treated with NSAIDs,^{25,26} and represents up to 30% of all NSAID-induced DHRs in Spain.²² Single-NSAID-induced urticarial/angioedema or anaphylaxis (SNIUAA) is the most frequent entity after NIUA, with pyrazolones, ibuprofen, diclofenac, ASA, and paracetamol the NSAIDs most often involved.^{8,27–29} In a

population-based case-cohort study, penicillins, analgesics, and NSAIDs were the drugs with the highest relative risk of inducing anaphylaxis.²⁵ However, SNIUAA seems to have decreased in the last decade, probably because of the lower consumption of pyrazolones.¹⁰ The prevalence of single NSAID-induced delayed hypersensitivity reactions (SNIDR) is not known, the most frequently reported being exanthemas, fixed drug eruptions, contact dermatitis, and photosensitivity reactions. NSAIDs can also induce severe organ-specific (eg, cutaneous, kidney, liver) allergic reactions.

PATHOPHYSIOLOGY

As proposed by Szczeklik and colleagues,³⁰ the mechanism of NERD is not immunologic, but related to COX inhibition and prostaglandin synthesis. In fact, only NSAIDs that are strong or moderate inhibitors of COX-1 (an enzyme that converts arachidonic acid [AA] to prostaglandins and thromboxanes) can induce these reactions, whereas selective COX-2 inhibitors are well tolerated. Inhibition of COX-1 by ASA or other NSAIDs, in conjunction with an intrinsic regulatory defect (probably prostaglandin E deficiency), triggers a biochemical cascade involving the generation of LTs and the release of mast-cell-derived and eosinophil-derived mediators.³¹ Intrinsic abnormalities of basal AA metabolism are characteristic of NERD and include the impaired generation of protective prostaglandin E₂ and lipoxins, downregulation of COX-2 and E-prostanoid receptor subtype 2 accompanied by overproduction of LTs, and increased expression of LT receptor 1.^{32–34} More recently, it has been documented that platelet-adherent leukocyte interaction may drive the production of LTs in these patients.³⁵ The pathogenesis of chronic eosinophilic inflammation in the airway mucosa and in nasal polyps in NERD patients does not result from an exposure to NSAIDs, but may be related to underlying AA metabolism abnormalities; the role of viral infections or *Staphylococcus aureus* enterotoxin have also been suggested (Fig. 2).^{36,37}

Because cross-responses also exist in NECD, a mechanism similar to that of NERD has been proposed.³⁸ There are similarities in the eicosanoid profile, with an increase in urine LT E₄ excretion associated with the clinical manifestations.³⁹ A further indication is the protective effect of LT-receptor antagonists.^{40,41} Whether this can be also applied to NIUA is a matter of debate that needs further research.⁴²

For selective DHRs, the time interval between NSAID administration and the appearance of symptoms suggest mechanisms mediated by IgE (SNIUAA) or T cells (SNIDR).^{43,44}

GENETICS

Previous studies of the genetic basis of NSAID hypersensitivity have consisted in the evaluation of single-nucleotide polymorphisms (SNPs). Most studies have included patients with NERD, following a candidate gene approach based on biological plausibility,^{45,46} and associations have been found for SNPs in genes related to LT synthesis/receptors^{47–52} and prostaglandin and thromboxane pathways.^{53–55} The number of variants analyzed is limited, and the associations inconsistently replicated. Regarding NIUA, 3 SNPs in genes coding for members of the AA pathway (rs7220870 in *ALOX15*, rs8004654 in *PTGDR*, and rs320095 in *CYSLTR1*) were found to be associated in 2 unrelated Spanish populations.⁵⁶ The potential participation of other pathways in NIUA has been highlighted by the association with the missense polymorphism rs10156191 in diamine oxidase, a key enzyme in histamine homeostasis.⁵⁷

Genome-wide association studies (GWAS) represent an alternative to candidate gene approaches, with the first study conducted in a Korean population of NERD

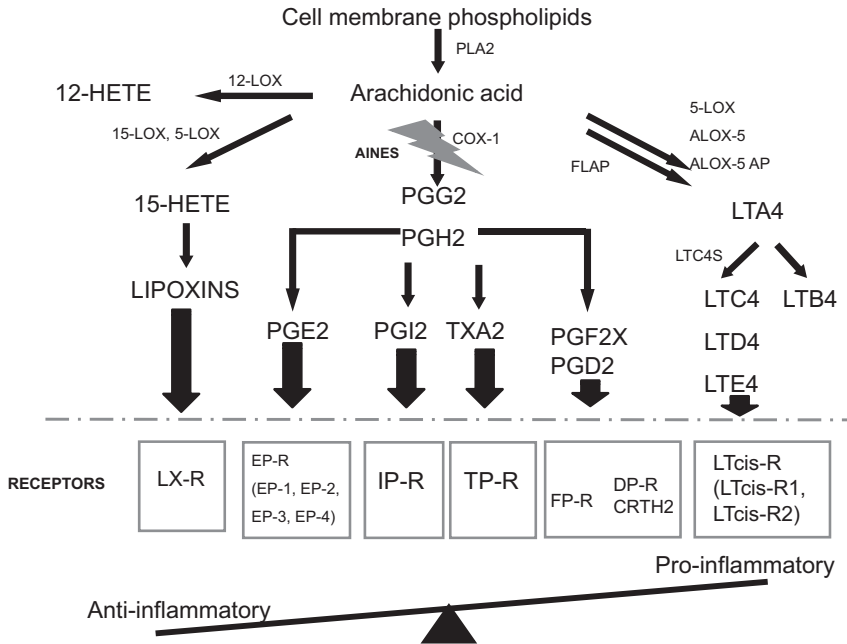


Fig. 2. Prostaglandin-leukotriene cascade with the different messengers and their receptors. ALOX-5 (arachidonate 5-lipoxygenase), ALOX-5 AP (5-lipoxygenase-activating protein), COX-1 (cyclooxygenase-1), CRTH2 (chemoattractant receptor-homologous molecule expressed on T helper type 2 cells, a second prostaglandin D2 receptor), DP-R (prostaglandin D receptor), EP-R (prostaglandin E receptor), EP-1 (prostaglandin E2 receptor subtype 1), EP-2 (prostaglandin E2 receptor subtype 2), EP-3 (prostaglandin E2 receptor subtype 3), EP-4 (prostaglandin E2 receptor subtype 4), FLAP (5-lipoxygenase-activating protein), FP-R (prostaglandin F receptor), IP-R (prostaglandin I receptor), LTA₄ (leukotriene A₄), LTC₄S (leukotriene C₄ synthase), LTC₄ (leukotriene C₄), LTB₄ (leukotriene B₄), LTD₄ (leukotriene D₄), LTE₄ (leukotriene E₄), LTCis-R (cysteinyl leukotriene receptor), LTCis-R1 (cysteinyl leukotriene receptor 1), LTCis-R2 (cysteinyl leukotriene receptor 2), LX-R (lipoxin receptor), PLA2 (phospholipase A₂), PGG₂ (prostaglandin G₂), PGH₂ (prostaglandin H₂), PGE₂ (prostaglandin E₂), PGI₂ (prostaglandin I₂), PGF₂X (prostaglandin F₂X), PGD₂ (prostaglandin D₂), TP-R (thromboxane receptor), TXA₂ (thromboxane A₂), 5-LOX (5-lipoxygenase), 12-HETE (12-hydroxyeicosatetraenoic acid), 12-LOX (12-lipoxygenase), 15-HETE (12-hydroxyeicosatetraenoic acid), 15-LOX (15-lipoxygenase).

patients.⁵⁸ The nonsynonymous variant rs7572857 (Gly74Ser) in the centrosomal protein of the 68-kDa gene (*CEP68*) was associated with changes in forced expiratory volume in 1 second (FEV₁).⁵⁸ In another study, the rs1042151 (Met105Val) SNP in the *HLA-DPB1* gene showed the most significant association with NERD susceptibility.⁵⁹ However, the role of human leukocyte antigen (HLA) alleles in hypersensitivity to NSAIDs needs further clarification. Concerning NIUA, a recent article comparing 2 ethnically distinct populations found suggestive associations after meta-analysis (*HLF*, *RAD51L1*, *COL24A1*, *GaINAc-T13*, and *FBXL7*), some of which are related to second-messenger pathways.⁶⁰

Despite recent research into the genetics of hypersensitivity to NSAIDs, the effects of gene variants cannot fully explain disease susceptibility. An important issue is missing heritability and the contribution of rare variants, which cannot be identified by current GWAS technologies. Further studies should integrate data from the 1000

Genomes Project, deep sequencing, and transcriptomics. This approach will enhance the understanding of the underlying mechanisms and improve the management of these patients.

CLINICAL MANIFESTATIONS

This section describes the 5 major clinical entities recognized in the new nomenclature proposed by EAACI.⁶

NSAID-Exacerbated Respiratory Disease

In a subset of patients with asthma, NSAIDs induce symptoms such as bronchoconstriction, usually accompanied by rhinorrhea and/or nasal congestion, within 2 hours after drug exposure.^{61,62} Classically “the aspirin tetrad” consists of CRS, complicated by polyps, severe bronchial asthma, and cross-intolerance to other NSAIDs.

Although NERD presents a heterogeneous phenotype, patients usually suffer from a moderate or severe form of asthma requiring chronic treatment with moderate to high doses of inhaled glucocorticosteroids, and associated with a high risk of exacerbation.⁶³ Almost all patients have nasal and sinus symptoms related to polypoid hypertrophy of the mucosa of the nasal cavity and paranasal sinuses.⁶⁴ The course of CRS is protracted with recurrence after polypectomy.

NSAID-Exacerbated Cutaneous Disease

Subjects with CSU may develop wheals and/or angioedema after administration of NSAIDs.⁶⁵ As with NERD, the response is related to the potency of COX-1 inhibition and also to the basal activity of the CSU.⁶⁶ Symptoms usually appear in a time interval of 1 to 6 hours, although this can vary from a few minutes to many hours. The morphology of the lesions is variable, from erythematous plaques to confluent and migratory wheals, which can be accompanied by angioedema. Although there are no prospective studies on the evolution of NECD, CSU may subside and patients can become tolerant to NSAIDs.⁶⁷ As with CSU,⁶⁸ the association between atopy, allergic rhinitis, bronchial asthma, and NECD is not clear,^{67–69} and further studies are required.

NSAID-Induced Urticaria/Angioedema

NIUA refers to the presence of urticaria and/or angioedema after the intake of different NSAIDs in patients without underlying CSU, with symptoms subsiding following drug withdrawal. Symptoms usually vary from mild to moderate, although anaphylaxis can occur.²² Severity and persistence of symptoms may be related to a prolonged metabolism of histamine.⁵⁷ The association of urticaria/angioedema or isolated angioedema is more common than in NECD.⁶⁸ The time interval between NSAID intake and the appearance of symptoms is usually less than 1 hour, but can extend to 6 hours or longer.²²

Although there is some debate as to whether these patients can convert to NECD over time,⁶⁸ a recent study has shown that after 12 years of follow-up the percentage of subjects developing CSU was not different from patients with SNIUAA or healthy controls.⁶⁹

NIUA shows a strong association with atopy, particularly sensitization to house dust mite allergens,^{22,70–72} which is strongest for younger patients with angioedema.¹³ Concerning food allergy, some preliminary data in adults have shown that the prevalence is not higher than in controls.⁷³ However, more studies need to be conducted for a better definition of these associations.

Single NSAID-Induced Urticaria/Angioedema or Anaphylaxis

This entity consists of anaphylaxis, urticaria, and/or angioedema appearing soon after the intake of a single NSAID (usually within 1 hour), with good tolerance to other NSAIDs including strong COX-1 inhibitors.⁸ SNIUAA have been reported to occur in up to 30% of all cases of hypersensitivity reactions to NSAIDs in a Spanish cohort.²² The drugs more frequently involved are pyrazolone derivatives, followed by ibuprofen, diclofenac, ASA, and paracetamol.^{74–84} These culprits may vary from country to country according to patterns of prescription and consumption.⁸ A retrospective evaluation of hospitalizations in allergy services in the Netherlands found that 17% of hospitalizations were related to NSAID hypersensitivity, 30% of which were attributed to diclofenac, and the most common reaction was anaphylaxis.⁷⁵

Single NSAID-Induced Delayed Hypersensitivity Reactions

These reactions are the least frequent and include a wide range of entities affecting mainly the skin, such as exanthema and fixed drug eruption. In some instances they are accompanied by fever or the involvement of other organs. The most frequent exanthemas are maculopapular, and are most often triggered by ibuprofen and naproxen⁸⁵ in addition to pirazolones.^{86,87} The type of urticarial reaction is difficult to distinguish from those occurring in acute reactions.^{85,88} Contact dermatitis and photosensitivity are common, and most often triggered by ketoprofen and diclofenac.^{89–92} Fixed drug eruption and acute generalized exanthematous pustulosis may also occur.^{93–96} Severe reactions such as Stevens-Johnson syndrome or Lyell syndrome are infrequent.⁹⁷

SNIDRs are induced by a single NSAID, and the patient will show good tolerance to other chemically unrelated NSAIDs. These reactions have a delayed onset, 24 hours or more after exposure, and are mediated by a specific T-cell mechanism.^{66,98}

MIXED REACTIONS

Mixed reactions occur when patients with a clinical history of respiratory symptoms also develop extrapulmonary manifestations such as urticaria, angioedema, stomach-ache, and, in some instances, full anaphylaxis.^{20,26,99} In addition, 10% of the patients with NECD may develop airway manifestations.¹⁰⁰ In terms of prevalence, in one study in Spain, patients with manifestations involving both the skin and the airways represented 18% of all nonallergic NSAID hypersensitivity patients, making mixed reactions the second most frequent entity after NIUA.²²

Mixed reactions can be confused with SNIUAA whereby several organs may be involved, including both skin and respiratory airways. The time course of the initiation of symptoms, which is faster in SNIUAA, may suggest whether a true IgE-mediated response is being dealt with.⁷ Confusion may also occur when both airway and skin manifestations are present, but only the latter is induced by NSAIDs, as occurs in asthmatic or rhinitis patients who develop urticaria after NSAID administration despite no worsening of respiratory symptoms.¹⁰¹

INTERACTIONS

It is well known that in some instances, patients with food allergy may develop anaphylaxis if they have previously taken NSAIDs; this situation arises with both inhalant and food allergens. Sánchez-Borges and colleagues^{102,103} have reported that systemic reactions for patients with food allergy contaminated with mites may occur if they simultaneously take NSAIDs. The reason for this interaction is complex, although it has been proposed that *Dermatophagoides pteronyssinus* and

Dermatophagoides farinae can inhibit COX-1 activity¹⁰² or favor the release of LTs.¹⁰⁴ Further investigations have been suggested.¹⁰⁵

Other studies have shown the influence of NSAIDs on mast-cell activation after food and/or exercise.^{106,107} A possible explanation is that ASA may upregulate the allergic response to food allergens.¹⁰⁸ Another proposal is that ASA and potentially other NSAIDs may increase the gastrointestinal permeability, leading to an increase in the general circulation of the allergen components and thus facilitating the systemic response.^{107,109}

Interactions between NSAIDs and hormonal factors may also occur. For example, premenstrual urticaria or anaphylaxis may occur following NSAID intake in patients with an otherwise good tolerance.^{110,111} The mechanism for this association is as yet unknown.

DIAGNOSTIC APPROACH

The diagnosis of NSAID hypersensitivity is based on clinical history, which is essential to establishing whether a patient reacts to multiple NSAIDs (nonallergic) or a single drug (allergic). For nonallergic patients neither skin nor laboratory tests are of value; however, for patients experiencing allergic reactions, skin tests and some in vitro tests can be of benefit, albeit with limitations.

The reliability of clinical history depends on several variables, including type and duration of symptoms, time interval between drug intake and appearance of symptoms, response to treatment, and, possibly, the time interval between the reported adverse drug reaction and the allergologic examination.^{5-7,22}

Skin Testing

The usefulness of skin testing with certain drugs, such as pyrazolones, has been reported in SNIUAA, although sensitivity is not optimal and the risk of systemic responses exists.¹¹² Skin testing with aspirin polylysine has not been able to show the presence of IgE antibodies^{113,114} and has led to negative results with diclofenac.

In SNIDR, although skin tests have not been sufficiently standardized for clinical practice, they can be useful. Patch testing can confirm drug imputability, especially with noninjectable NSAIDs and for contact dermatitis. Photopatch tests are indicated for NSAID-induced photoallergic or phototoxic reactions.¹¹⁵ Intradermal skin test with delayed reading at 24 to 48 hours has been mainly used for pyrazolones.⁸⁶

In Vitro Tests

Although specific IgE antibodies have been reported in patients with SNIUAA to ASA,¹¹⁶ ibuprofen,¹¹⁷ propyphenazone,²⁸ and diclofenac¹¹⁸ by individual study groups, commercial immunoassays are not available. With ASA, a prototype for detecting specific IgE antibodies has been reported using 2 different conjugation procedures.¹¹⁶ Studies with the pyrazolone derivative propyphenazone conjugated with human serum albumin have shown the presence of specific IgE antibodies by both enzyme-linked immunosorbent assay and immunoblotting.²⁸

The basophil activation test has been considered to be a reasonable method when reactions are mediated by IgE, with sensitivity for pyrazolones exceeding 50% and 90% specificity.²⁹ Although this sensitivity is not optimal, it provides a good alternative, especially in severe reactions. This test has also been used for evaluating NSAID cross-reactivity, with heterogeneous results in the sensitivity and, more importantly, very low specificity because of the high rate of false-positive responses.^{119,120} Some investigators reported the value of this test in subjects with immediate reactions.^{121,122}

Similar problems exist for other tests such as the cellular leukotriene release assay, the clinical application of which has yet to be validated.¹⁹ Further studies are necessary to determine the role of other basophil markers or even other cells involved in the pathogenesis of NSAID hypersensitivity.

Aspirin specifically triggers 15-hydroxyeicosatetraenoic acid (15-HETE) generation in nasal polyp epithelial cells and peripheral blood leukocytes (PBL) from NERD patients, which suggests the presence of a specific abnormality of the 15-lipoxygenase pathway in these patients.¹²³ Accordingly, measurement of 15-HETE release from PBL following in vitro ASA challenge has been proposed for confirmation of a clinical history-based diagnosis in NERD patients, but more studies are needed to confirm the discriminative value of this test.

Drug-Provocation Test

A DPT can be used to confirm the diagnosis when there are no alternatives, or can be used to find a safe NSAID once the diagnosis has been confirmed. This latter approach is used to identify selective responders and provide safe alternatives, usually COX-2 inhibitors and weak COX-1 inhibitors in those with nonallergic hypersensitivity. This procedure must be performed by experienced personnel in a clinical setting where a rapid and adequate treatment can be administered if needed. Several protocols exist with different time intervals and total cumulative dose. If the DPT is performed with different NSAIDs, an interval of at least 1 week between each drug administration should be considered.^{5,6}

A DPT should follow existing guidelines.^{5,6} This procedure is not risk-free, and is contraindicated in patients with a FEV₁ lower than 1.5 L or a FEV₁ variability with placebo greater than 20%, pregnancy, infectious diseases, psychiatric disorders, uncontrolled asthma, severe cutaneous reactions such as Stevens-Johnson syndrome or Lyell syndrome, anaphylactic shock, and organ-specific reactions.

For nonimmunologic reactions (NERD, NECD, and NIUA), clinical history may be consistent enough to establish the diagnosis. In NERD, oral ASA challenge is the gold standard to confirm the diagnosis,⁴² with local intranasal or bronchial provocation with lysine-ASA used as alternatives.¹²⁴ For NECD, oral ASA challenge may also be needed, but the response may be related to the activity of the CSU.

DPT is the only available method for diagnosing patients with nonimmunologic reactions with skin symptoms (NECD and NIUA).^{125,126} If a patient has developed a reaction with 2 or 1 NSAIDs, an ASA DPT should be considered to establish the diagnosis.^{22,125} If the DPT is positive and tolerance to paracetamol or COX-2 inhibitors is not known, a DPT with these drugs must be also considered.¹²⁶ There are several cases whereby NIUA is manifested as anaphylactic reactions, and caution must be exercised.

In patients with a suspicion of immunologically mediated reactions, the first approach is to look for history of tolerance to other strong COX-1 inhibitors. If this is not known, a DPT with another, chemically nonrelated strong COX-1 inhibitor should be performed, and if this is positive, subjects are considered cross-intolerants and therefore the selective response is ruled out. This procedure is contraindicated in severe reactions such as Stevens-Johnson syndrome and Lyell syndrome.

TREATMENT

Patients with nonallergic hypersensitivity require comprehensive management, which includes education on NSAID avoidance and the use of alternative drugs.^{5,6}

In NERD patients, ASA tolerance can be induced by repeated administration of increasing oral doses of ASA, a procedure known as desensitization. Once a patient

can tolerate 600 mg of ASA he or she is considered desensitized and can then take this drug on a daily basis indefinitely, without further adverse respiratory reactions.¹²⁷ Of interest, the ASA-tolerance state can be also achieved without provoking symptoms, by a slow, gradual increase in ASA dosing (silent desensitization).¹²⁸ Administration of ASA (300–1300 mg/d) after desensitization results in improvements in both upper and lower airway symptoms, and may lead to a significant reduction in hospitalization, emergency room visits, or the need for nasal/sinus surgery.^{129–131} The clinical benefit, which is usually seen within the first weeks after desensitization, can be maintained during several years of treatment with ASA.^{6,132} However, not all NERD patients demonstrate an improvement in the clinical course of the airway disease following ASA after desensitization, and an a priori identification of those patients who would benefit from ASA treatment is not possible at this stage of clinical practice. Further understanding of the mechanism of ASA desensitization may allow for more effective selection of patients benefiting from such treatment.¹³³ Desensitization to ASA may be also achieved in patients with other forms of hypersensitivity to NSAIDs (eg, NIUA), and has been used at lower doses (ranging from 75 to 150 mg) for chronic treatment with ASA of coronary heart disease or rheumatoid diseases in NSAID-hypersensitive patients.

In patients with allergic hypersensitivity, the treatment recommended is avoidance of the culprit NSAID and those chemically related. Patients can tolerate other non-chemically-related NSAIDs independently of the COX-1 inhibitory capacity.

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