

Cross-Reactive Reactions to Nonsteroidal Anti-Inflammatory Drugs

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Abstract: *Introduction:* Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequent causes of adverse drug reactions, particularly in patients with asthma and chronic idiopathic urticaria. Many subjects report cutaneous and/or respiratory symptoms and, less frequently, anaphylactic shock after the administration of one (single-reactors) or different (cross-reactors) drugs of this class.

Diagnosis: There are no reliable cutaneous or *in vitro* tests which allow NSAID hypersensitivity to be identified in patients with cross-reactive reactions; therefore, the challenge test is considered the "gold standard" for establishing or excluding a diagnosis of NSAID hypersensitivity in such patients.

Management: Culprit drugs should always be avoided by patients with suspected or well-established multiple hypersensitivity to NSAIDs. The therapeutic options range from the administration of alternative drugs – such as weak cyclooxygenase (COX)-1 inhibitors and/or preferential or highly selective COX-2 inhibitors to desensitization to the culprit ones.

Conclusion: In patients with different NSAID-induced reactions, the challenge test with both culprit drugs and alternative ones is the only method to establish a reliable diagnosis of NSAID hypersensitivity and to find some alternative therapeutic options, respectively. In specific cases, drug desensitization can also be performed. However, further studies are required to improve management of such patients.

Key Words: Nonsteroidal anti-inflammatory drugs, cross-reactivity, hypersensitivity, challenge test, desensitization.

GENERAL CONCEPTS

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid (ASA) and pyrazolone derivatives, are among the most common causes of adverse drug reactions. In addition to frequent gastrointestinal effects, NSAID hypersensitivity reactions represent a serious but often underestimated problem.

The prevalence of ASA hypersensitivity (AH) in the general population ranges from 0.6% to 2.5% [1]. No ethnic differences have been reported. Some predisposing factors have been identified in atopy, female gender, young adulthood, a genetic background, and an increased use of NSAIDs for the relief of acute pain, as well as a history of chronic idiopathic urticaria (CIU), asthma, nasal polyps, and/or chronic rhinitis. In particular, with regard to the populations studied and the diagnostic methods used, AH occurs in approximately 21% to 30% of patients with CIU, 2% to 23% of asthmatics, 14% to 22% of patients with nasal polyps, and 0.7% to 1.4% of subjects with chronic rhinitis [1].

Clinical manifestations may affect the skin and/or the respiratory tract with urticaria/angioedema and/or asthma/rhinitis, respectively; in rare cases, anaphylaxis occurs. Subjects may report symptoms after the administration of one

(single reactors) or different (cross-reactors) drugs of this class.

CLINICAL MANIFESTATIONS

Stevenson *et al.* [2] classified hypersensitivity reactions to ASA and NSAIDs in 6 categories. Cross-reactive reactions to NSAIDs are present in the following four:

- 1) NSAID-induced asthma/rhinitis in patients with ASA-exacerbated respiratory disease (AERD) who, after ingesting ASA or NSAID, develop upper and/or lower respiratory tract symptoms including rhinorrhea, nasal congestion, laryngospasm, and bronchospasm. These reactions tend to be dose-dependent; in effect, smaller doses of ASA or NSAIDs may not induce a significant reaction, whereas a larger and possibly therapeutic dose may induce severe reactions.
- 2) NSAID-induced urticaria/angioedema in patients with CIU. Urticaria with or without angioedema connected with NSAIDs that inhibit the constitutive isoform of the cyclooxygenase (COX)-1 enzyme affects approximately one-third of such patients when it is under control [3] and up to two-thirds when the disease is active. No previous exposure to NSAIDs is necessary for the reaction to occur.
- 3) Different drug-induced urticaria/angioedema. Acute urticaria and/or angioedema may also occur in individuals without underlying risk factors, such as CIU, within a

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few minutes and up to 24 hours after ingestion of different NSAIDs. The most frequent reaction is facial angioedema, followed by urticaria [4]. These reactions occur with a frequency much lower than that observed among patients with CIU. In effect, Settupane *et al.* [5] found that, after excluding subjects with recurrent urticaria, hay fever and chronic chest diseases, the prevalence of urticaria and angioedema in the general population was 0.3%.

- 4) **NSAID-induced mixed reactions.** These are characterized by urticaria and/or angioedema plus respiratory symptoms (bronchospasm, cough, rhinorrhea, hoarseness) associated with the administration of different NSAIDs. In a study by Sánchez-Borges *et al.* [6], 47 (33.8%) of 139 consecutive NSAID-sensitive subjects presented this mixed pattern, which can also occur in children. Indeed, the same group [7] classified 37 (86%) of 43 children with NSAID hypersensitivity as cross-reactors.

With regard to the pathogenic mechanism, cross-reactive reactions to NSAIDs are mediated by a pharmacological mechanism. NSAIDs, such as ASA, pirazolones, indomethacin, diclofenac, ketoprofen, ibuprofen, piroxicam, etc., inhibit COX-1, and thus reduce protective prostaglandin (PG)_{E2}, as well as increase the unrestrained synthesis of cysteinyl-leukotrienes (Cys-LTs) and the release of mediators such as PGD₂ from mast cells. This mechanism, which is well-established in ASA-induced asthma [8], has also been recently supported by biochemical observation in ASA-induced urticaria [9-11].

In addition, Asero [12-14] reported that a very high percentage (86%) of patients with urticaria/angioedema induced by different NSAIDs presented positive skin reactions to intradermal testing with autologous plasma – which is more sensitive than the autologous serum skin test – and that some of them developed CIU at a later date. The mechanism involved in this disorder is probably related to increased thrombin generation, as has been observed in patients with CIU.

Although much research has been performed in order to improve diagnostic methods, there are no fully validated allergologic tests for evaluating subjects with cross-reactive reactions to NSAIDs; therefore, the challenge test is considered the "gold standard" for establishing or excluding a diagnosis of NSAID hypersensitivity in such patients. Culprit drugs should be avoided by sensitive patients. Therapeutic options range from the administration of alternative drugs to desensitization to the culprit ones.

As far as alternative drugs are concerned, paracetamol is a weak inhibitor of COX-1 and COX-2 (the induced isoform) and acts prevalently on a third, distinct COX isoform (COX-3). At very high concentrations, it inhibits COX-1 making cross-reactivity with ASA and other COX-1-inhibiting NSAIDs infrequent when standard therapeutic doses of the drug (650 mg or less) are used [4,15-19]. Nimesulide and meloxicam are preferential inhibitors of COX-2, and can safely be administered to NSAID-sensitive patients [19-30]. The newer NSAIDs, such as celecoxib, parecoxib, and etoricoxib, which selectively inhibit COX-2 without affecting the arachidonic acid metabolism, show very low cross-reactivity

and can be considered good alternatives for patients with hypersensitivity to nonselective NSAIDs [8,26,31-45]. However, selective COX-2 inhibitors may provoke hypersensitivity reactions in a minority of patients, particularly in those with cutaneous reactions, with a frequency ranging from 2.5% for etoricoxib [35,37,38] to 4.1% for celecoxib [26,33-36].

With regard to desensitization, it may be performed in ASA-sensitive patients who specifically require this treatment, such as those with a coronary artery disease (CAD), antiphospholipid syndrome (APS) during pregnancy, or AERD [46-54]. However, this approach seems to be less successful in cases of CIU.

New diagnostic markers and therapeutic options might come from analysis of the genetic background of this heterogeneous disease. Some studies have shown associations of ASA-induced asthma (AIA) and urticaria (AIU) with several HLA alleles (-DPB1 0301 and DRB1 1302 in AIA and -DQB1 0609 in AIU) [55], and single nucleotide polymorphisms in genes encoding enzymes (LTC₄ Synthase in AIA and AIU and Cys-LT Receptors only in AIA) [56] involved in arachidonic acid metabolism.

DIAGNOSIS

Challenge Tests

As previously noted, the challenge test is considered the "gold standard" for establishing or excluding the diagnosis of NSAID hypersensitivity in patients with cross-reactive reactions. If positive, this test reproduces both allergic and non-allergic hypersensitivity symptoms, and, in case of a negative response, it allows the diagnosis of hypersensitivity to the NSAID concerned to be ruled out.

In patients with reactions to more than one NSAID, it is advisable to perform the first challenge with the suspected NSAID with the lowest capability of inhibiting COX-1, and in case of negative results, administer the other suspected compounds in the order of the increasing capability of inhibition of COX-1 [4, 55]. Recently, Quiralte *et al.* [57] performed a total of 697 challenges in 223 subjects with histories of hypersensitivity reactions to NSAIDs. The order of the different drugs administered to each patient was as follows: celecoxib, meloxicam, paracetamol, piroxicam, diclofenac, dipyrrone, ibuprofen, and ASA. Each patient underwent challenges with the first drug not involved in a previous reaction. In case of negative results, challenges with the next drug were carried out.

In patients with symptoms induced by a single NSAID, challenges with strong COX-1 inhibitors (e.g., ketoprofen) other than responsible ones are useful for detecting any cross-reactors. Using this approach, the unnecessary exclusion of potentially useful NSAIDs can be avoided [16, 17].

According to the EAACI/GA²LEN guidelines [58], subjects should be challenged under single-blind, placebo-controlled conditions. They should be in a stable clinical condition; in particular, subjects with asthma should have a baseline forced expiratory volume in 1 second (FEV₁) at least 70% of the predicted value and those with urticaria should be without any skin eruptions at least 1-2 weeks be-

fore the test. If regular treatment is required, patients could continue their therapy, including oral corticosteroids in doses not exceeding 10 mg of prednisone per day. Other medications should be withdrawn according to the guidelines.

In order to diagnose NSAID-induced bronchial asthma/rhinosinusitis, bronchial or nasal challenges should be used first, because they are less harmful than oral ones. In case of negative results of the former, however, oral challenges can be used, as they should always be in patients with cutaneous symptoms.

With regard to ASA, oral challenges are carried out during two consecutive days, administering on the first day 3-4 capsules of placebo and on the second day exponentially increasing doses of ASA (27, 44, 117, and 312 mg; in certain cases, an additional 500 mg may be administered) at 1.5-2 hour intervals, up to a cumulative dose of 500 mg (1000 mg, in certain cases) of ASA.

The oral ASA challenge (OAC) is relatively safe, even in patients who report respiratory reactions to full therapeutic doses of ASA or other NSAIDs that were severe enough to warrant immediate medical care. Williams *et al.* [59] found that, although many patients with AERD report having sought such care for ASA- or other NSAID-induced asthmatic reactions, only a minority of these patients (10%) respond to the OAC with severe ones ($\geq 30\%$ decrease in FEV_1). Furthermore, study results support the hypothesis that pretreatment with asthma controller therapy, including LT receptor antagonists (LTARs), contributes to the overall safety of OACs.

Challenge protocols for NSAIDs other than ASA are available in the literature [4,16-29,31-43,57,60,61]. In our practice, we initially administer 1/100 of the therapeutic dose, then 1/10, and finally the full dose [39,42]. The time interval between doses is either 1 hour in case of a previous immediate reaction (i.e., occurring less than 1 hour after drug administration) or 3-7 days (depending on the time interval between drug intake and adverse reaction) in case of previous nonimmediate reactions (i.e., occurring more than 1 hour after the last drug administration).

As far as nasal and bronchial challenges are concerned, detailed protocols are described in the aforementioned guidelines.

Monitoring of respiratory and/or cutaneous symptoms, as well as of FEV_1 and/or nasal flow and volumes, throughout the challenge procedure and for several hours after the last dose of NSAID or placebo is necessary.

The challenge procedure is interrupted if any reactions (respiratory, cutaneous, or other) develop, as well as if a decrease in FEV_1 ($\geq 20\%$ of baseline), total nasal flow value at 12 cm ($\geq 25\%$ of baseline), or bilateral inspiratory nasal flow ($\geq 40\%$ of baseline) occurs.

With regard to urticarial eruptions, their severity can be assessed by the Urticaria Severity Index (USI, scale: 0-6), with 0 indicating no eruptions and pruritus and 6 indicating intense or large confluent areas of wheals and severe pruritus.

According to the aforementioned guidelines [58], the sensitivity and specificity of ASA challenge tests are respec-

tively 89% and 93% for the oral challenge, 77% and 93% for the bronchial one, and 80-86.7% and 92.5-95.7% for the nasal challenge.

Recently, Dursun *et al.* [62] found that the probability of a positive OAC was 42% in patients without prior exposure to ASA or other NSAIDs and 86% in those with a history of ASA/NSAID-associated asthma attacks. Cross-reactors had an 89% probability of having a positive OAC, while single reactors had an 80% one ($P = .04$). Mild or moderate prior reactions were associated, respectively, with 84% and 80% positive OACs, whereas 100% of the patients with severe prior reactions had positive OACs ($P = .007$). In addition, they found that an age of less than 40 years and a poor sense of smell significantly increased the probability of a positive OAC, whereas, unlike what had been previously observed [1], gender, atopy, number of sinus infections per year, and number of sinus surgical procedures were not associated with positive OACs.

In Vitro Testing

There are no reliable *in vitro* tests allowing patients with NSAID hypersensitivity to be identified [63]. Sanz *et al.* [64] evaluated 60 patients with NSAID-associated symptoms by performing a new test, which combines detection with a flow cytometric technique of basophil activation and the ELISA of sulfido-LTs released in the cell supernatant (CAST). Using this test, a hypersensitivity to ASA and/or other NSAIDs was diagnosed in 73.3% of the 60 patients; the specificity was 71.4%.

Recently, Rodríguez-Trabado *et al.* [65] performed the basophil activation test – using a flow colorimetric cytometry and double staining with the monoclonal antibodies anti-IgE and anti-CD63 – in 43 patients with immediate reactions to one or more NSAIDs and 29 controls. Specificity and sensitivity were 100% and 42.85%, respectively. The positive and negative predictive values were 100% and 53.84%, respectively.

However, further studies are needed in order to fully establish the sensitivity and specificity of this method.

In addition, the assay of urinary levels of LTE_4 might be a useful tool in monitoring patients who undergo challenges with suspect NSAIDs. In 2 studies [9,31], patients with NSAID-induced bronchospasm or NSAID-exacerbated CIU presented elevated urinary levels of LTE_4 , which further increased after positive challenges with ASA or naproxen.

Kowalski *et al.* [66] also assessed the diagnostic value of ASA-induced 15-hydroxyeicosatetraenoic acid (15-HETE) generation measurement to identify ASA-sensitive patients. Incubation of peripheral blood leukocytes from 43 ASA-sensitive patients with asthma and rhinosinusitis, 35 ASA-tolerant asthmatics, and 17 healthy control subjects with 200 μ M ASA resulted in an increased 15-HETE generation only in the first group. This ASA-sensitive patient identification test (ASPI test) showed a sensitivity of 83% and a specificity of 82%; the positive and negative predictive values were 0.79 and 0.86, respectively.

However, further studies are needed in large samples of ASA-sensitive patients, including those with cutaneous

symptoms, in order to confirm the high sensitivity and specificity of this test.

MANAGEMENT OF PATIENTS WITH CROSS-REACTIVE NSAID HYPERSENSITIVITY

Avoidance of Culprit Drugs and Administration of Alternative Ones

Culprit drugs should always be avoided by patients with well-established multiple hypersensitivity to NSAIDs, as well as by those who are unable to undergo an allergologic diagnostic procedure (e.g., the challenge test is contraindicated in case of a history of severe reactions). In order to identify an alternative treatment for pain and inflammation that can safely be administered in such patients, a single-blind placebo-controlled tolerance test may be performed in the hospital setting with weak COX-1 inhibitors (i.e., paracetamol at low doses) and/or preferential (nimesulide and meloxicam) or highly selective (celecoxib, etoricoxib, and parecoxib) COX-2 inhibitors [2,67,68].

According to literature data, the tolerability rate of these alternative compounds in patients with NSAID hypersensitivity reactions ranges from 89.4% for paracetamol to 100% for parecoxib [paracetamol: 4,16-19; nimesulide: 19-22; meloxicam: 22-29; celecoxib: 26,31-36; etoricoxib: 35,37-41; parecoxib: 42,43] (Table 1). Most of these studies did not specify the number of cross-reactors. Moreover, there are discrepancies among the different studies regarding the challenge doses and samples assessed. With regard to patients, in some studies NSAID hypersensitivity was diagnosed on the basis of positive histories and positive responses to challenges with the suspect compounds, while in others only on the basis of positive histories.

In conclusion, weak COX-1 inhibitors, as well as preferential and highly selective COX-2 inhibitors, can be safe alternatives in cross-reactors. However, medically supervised challenges are advisable before prescribing these drugs to such patients. In highly sensitive ones, if a tolerance test with a COX-2 inhibitor is positive, a second one, more selective, may be administered; if this is again unsuccessful, all NSAIDs should be avoided [67].

It is essential that patients receive a list containing the contraindicated drugs, as well as the tolerated ones.

Desensitization

ASA or NSAID desensitization consists in a gradually increasing exposure to the responsible drugs in sensitive patients with no alternative medications in order to avoid hypersensitivity reactions [46-49]. Although the mechanism of desensitization is unknown, in most NSAID-sensitive patients, tolerance can be achieved and maintained safely by this approach, which is less successful in cases of CIU. Candidates for desensitization are especially patients with CAD and females with APS during pregnancy, who specifically require treatment with ASA, as well as subjects with AERD.

Recently, Rossini *et al.* [50] successfully desensitized 23 out of 26 patients with histories of ASA-induced respiratory or cutaneous symptoms and CAD requiring coronary stent implantation. The desensitization procedure involved the oral administration of 6 sequential doses of ASA (1, 5, 10, 20, 40, and 100 mg) over 5.5 hours without the use of corticosteroids or antihistamines. At the 1-year follow-up, all patients tolerated ASA.

In a study by Wong *et al.* [51], 9 out of 11 patients with histories of ASA- and/or ibuprofen-induced urticaria and/or angioedema (9 of whom also had CAD) were successfully desensitized to ASA with a rapid oral protocol; 10 patients were pre-treated with antihistamines, one patient also received prednisone. The two patients who failed suffered from urticaria and/or angioedema, which occurred in the absence of NSAIDs. Starting doses ranged from 0.1 to 10 mg and were administered at 15-30 minute intervals. Doses were individualized for each patient, but followed this general sequence: 0.1, 0.3, 1, 3, 10, 20, 40, 81, 162, and 325 mg. Desensitized patients continued taking ASA for periods ranging from 1 to 24 months without adverse effects.

A rapid oral challenge-desensitization to ASA was performed in 4 pregnant women with APS and ASA sensitivity (manifested with cutaneous reactions in 3 subjects and asthmatic ones in one) [52]. Desensitization was performed during pregnancy in 3 patients and before the next pregnancy in the fourth, using increasing doses of ASA (0.1-125 mg) over a 24-hour period.

As far as ARDS is concerned, desensitization is performed in patients with recurrent nasal polyps that can not be controlled with polypectomy or sinus surgery, patients affected by AIA requiring long-term high-dose systemic corti-

Table 1. Tolerability of Alternative Compounds in NSAID-Sensitive Patients

Compounds	References	Total No. of Patients	Total No. of Cross-Reactors [References]*	No. of Tolerating Patients (%)
Paracetamol	[4,16-19]	236	98 [4,16-18]	211 (89.4)
Nimesulide	[19-22]	1,275	42 [22]	1,182 (92.7)
Meloxicam	[22-29]	635	213 [22,23,26,27,29]	612 (96.4)
Celecoxib	[26,31-36]	316	219 [26,31-36]	303 (95.9)
Etoricoxib	[35,37-41]	354	183 [35,38-41]	345 (97.5)
Parecoxib	[42,43]	101	40 [42,43]	101 (100)

* The remaining studies did not specify the number of patients who had reacted to more than one NSAID.

costeroids to control their disease, and patients whose asthma or rhinosinusitis is not optimally treated with inhaled corticosteroids or drugs interfering with the LT pathway [53]. With regard to the optimal dosage of daily ASA after desensitization, most studies used 650 mg twice daily. However, a recent study [54] demonstrated that 325 mg of ASA twice daily, administered after a 1-month period of therapy with 650 mg twice daily, is fairly equivalent in terms of clinical efficacy, with fewer side effects.

Management of NSAID Sensitive Patients with CIU

About 30% of patients with CIU experience flares of urticaria and/or angioedema after ingesting either ASA or NSAIDs [69]. NSAID hypersensitivity in patients with CIU is dose-dependent and is accentuated when the urticaria is in an active phase. It is not clear whether the sensitivity remits or continues after resolution of the urticaria, but it seems likely to decrease in most patients [70]. In CIU patients, diagnostic challenge tests could be incorrectly interpreted because of false positive reactions due to independent flare-ups of the underlying disease [67,69].

As a general rule, ASA and COX-1 inhibitors should be avoided in patients with CIU. In the vast majority of them, highly selective COX-2 inhibitors are well tolerated and can be safely used.

There is an increasing literature on the efficacy and safety of LTRAs, taken alone or in conjunction with antihistamines, in ASA-sensitive CIU patients, as well as in those with AERD [71-74].

In patients with imperative indications for ASA, desensitization can be tried. However, long-term ASA desensitization does not appear to be a treatment option for individuals with ASA-sensitive CIU.

The efficacy of anticoagulant therapy in a patient with CIU and NSAID-induced exacerbations of his disease was recently demonstrated. This can probably be explained by a downregulation of some adhesion molecules that are important in the pathogenesis of both manifestations [75].

CONCLUSION

A great amount of research has been undertaken to develop an adequate *in vitro* test in order to diagnose NSAID-induced hypersensitivity reactions, but, at present, all these tests are considered supplementary diagnostic tools. Therefore, the challenge test is considered the "gold standard" for establishing or excluding the diagnosis of NSAID hypersensitivity.

In case of a suspected or well-established multiple hypersensitivity to NSAIDs, culprit drugs should always be avoided. The therapeutic options range from the administration of alternative drugs (such as weak COX-1 inhibitors and/or preferential or highly selective COX-2 inhibitors) to desensitization to the culprit NSAIDs.

In patients with CIU, the aforementioned rules are valid, even if desensitization has demonstrated a lack of efficacy.

Finally, analysis of the genetic background of these heterogeneous NSAID-induced reactions might lead to new diagnostic and therapeutic options.

ABBREVIATIONS

AERD	=	ASA-exacerbated respiratory disease
AH	=	ASA hypersensitivity
AIA	=	ASA-induced asthma
AIU	=	ASA-induced urticaria
APS	=	Antiphospholipid syndrome
ASA	=	Acetylsalicylic acid
ASPItTest	=	ASA-sensitive patient identification test
CAD	=	Coronary artery disease
CAST	=	Cellular allergen stimulation test
CIU	=	Chronic idiopathic urticaria
Cys	=	Cysteinyl
COX	=	Cyclooxygenase
ELISA	=	Enzyme-linked immunosorbent assay
FEV ₁	=	Forced expiratory volume in 1 second
HETE	=	Hydroxyeicosatetraenoic acid
HLA	=	Human leukocyte antigen
IgE	=	Immunoglobulin E
LT	=	Leukotriene
LTRA	=	LT receptor antagonist
mg	=	Milligram
microM	=	Micromole
NSAID	=	Nonsteroidal anti-inflammatory drug
OAC	=	Oral ASA challenge
PG	=	Prostaglandin

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