Update on hypersensitivity reactions to nonsteroidal anti-inflammatory drugs – Part 1: definitions, pharmacology, epidemiology, pathophysiology, and genetics

Atualização em reações de hipersensibilidade aos anti-inflamatórios não esteroidais – Parte 1: definições, farmacologia, epidemiologia, fisiopatologia e fatores genéticos

Marcelo Vivolo Aun1,2, Rosana Câmara Agondi2, Diogo Costa Lacerda2, Ullissis Pádua Menezes3, Maria Inês Perelló4, Adriana Teixeira Rodrigues5, Ana Carolina D’Onofrio-Silva2, Tânia Maria Gonçalves Gomes6, Luiz Alexandre Ribeiro da-Rocha7, Denise Neiva Santos de Aquino8, Fernanda Casares Marcelino9, Gladys Queiroz7, Maria Fernanda Malaman10, Inês Cristina Camelô-Nunes8, Mara Morelo Rocha Felix11,12,13

ABSTRACT
Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications worldwide and the drugs most frequently associated with the occurrence of hypersensitivity reactions in Latin America. The clinical presentation of the reactions varies widely, which makes them difficult to treat. In this review, we address pharmaceutical aspects of NSAIDs, as well as the definitions, epidemiology, and pathophysiology of hypersensitivity reactions to NSAIDs. Finally, we discuss genetic factors associated with intolerance and allergy to these drugs.

Keywords: Nonsteroidal anti-inflammatory agents, hypersensitivity, pharmacology/pathophysiology, genetics.

RESUMO
Os anti-inflamatórios não esteroidais (AINE) estão entre os medicamentos mais utilizados no mundo e são os fármacos mais frequentemente associados à ocorrência de reações de hipersensibilidade na América Latina. As reações têm grande variabilidade de apresentações clínicas e, consequentemente, com abordagem terapêutica difícil. Nesta revisão, abordamos aspectos farmacológicos dos AINE, bem como as definições, epidemiologia e fisiopatologia das reações de hipersensibilidade aos AINE. Por fim, discutimos aspectos genéticos associados à intolerância e alergia a esses fármacos.

Descritores: Anti-inflamatórios não esteroidais, hipersensibilidade, farmacologia/fisiopatologia, genética.

1. Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein - São Paulo, SP, Brazil.
2. Faculdade de Medicina de Ribeirão Preto (FMUSP), Disciplina de Imunologia Clínica e Alergia - São Paulo, SP, Brazil.
3. Faculdade de Medicina de Ribeirão Preto (FMUSP - Ribeirão Preto), Serviço de Alergia e Imunologia Clínica e Pediátrica - Ribeirão Preto, SP, Brazil.
4. Universidade do Estado do Rio de Janeiro (UERJ), Serviço de Alergia e Imunologia - Rio de Janeiro, RJ, Brazil.
5. Hospital do Servidor Público do Estado de São Paulo (IAMSPE), Serviço de Alergia e Imunologia - São Paulo, SP, Brazil.
6. Hospital Central do Exército (HCE), Ambulatório de Alergia e Imunologia - Rio de Janeiro, RJ, Brazil.
7. Universidade Federal de Pernambuco (UFPE), Centro de Pesquisas em Alergia e Imunologia do Hospital das Clínicas - Recife, PE, Brazil.
8. Universidade Federal de São Paulo (UNIFESP-EPM), Disciplina de Alergia, Imunologia Clínica e Reumatologia - Departamento de Pediatria - São Paulo, SP, Brazil.
9. Hospital Regional da Asa Norte (HRAN), Serviço de Alergia e Imunologia - Brasília, DF, Brazil.
10. Universidade Tiradentes, Faculdade de Medicina - Aracaju, SE, Brazil.
11. Hospital Federal dos Servidores do Estado (HFSE), Setor de Alergia e Imunologia Pediátrica - Rio de Janeiro, RJ, Brazil.
12. Faculdade Souza Marques, Departamento de Pediatria - Rio de Janeiro, RJ, Brazil.
13. Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Departamento de Medicina Geral - Rio de Janeiro, RJ, Brazil.

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Introduction and definitions

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications worldwide, are often seen in prescriptions, and may be sold without prescription. They are used in the treatment of pain, inflammatory processes, and fever. NSAIDs include a varied group of medications that may be classified according to their chemical structure.

NSAIDs have an analgesic, anti-inflammatory, and antipyretic effect resulting from blockade of the cyclooxygenase (COX) enzyme and subsequent inhibition of eicosanoid biosynthesis through the metabolic route of arachidonic acid (AA) cascade. Moreover, NSAIDs promote inhibition of prostanoids, AA derivatives, which would be converted into prostaglandin (PG) G2 (PGG2) and H2 (PGH2) as a result of COX activity. This prevents PGH2 from being metabolized by terminal synthase in biologically active prostanoids. This inhibition leads to a decrease in vasodilation, vascular permeability, pain, and fever produced by PG.

There are at least two COX isoforms. COX-1 is constitutively expressed by specific cells such as platelets and endothelial cells. COX-2, in turn, is inducible by pro-inflammatory mediators in a wide variety of cells. NSAIDs may act in the inhibition of only one COX, or in the inhibition of both.

According to the World Allergy Organization (WAO), the term hypersensitivity may be applied to any reaction that can be reproduced through an initial stimulation. When an individual presents with any reproducible symptom similar to an "allergic" reaction after drug stimulation, it is possible to say that a hypersensitivity drug reaction (HDR) occurred. HDRs may be promoted by specific immunological mechanisms (allergic or immunological HDR) or not (non-allergic or non-immunological HDR).

NSAIDs are one of the main causative agents of HDR. In this group of drugs, there is a remarkably high variety of clinical pictures and pathophysiological mechanisms involved. Consequently, in times of precision medicine, knowing these different scenarios will make it possible to perform the correct management of these patients, especially with regard to future guidance to prevent new reactions, but also to approve medications that would not need to be excluded. In this review, we discuss conceptual, epidemiological, genetic, and pathophysiological aspects of hypersensitivity to NSAIDs.

Mechanism of NSAID pharmacological action

Before 1971, little was known about the NSAID mechanism of action, except that these drugs produced an anti-inflammatory effect different from the anti-inflammatory action of corticosteroids. Many of the biochemical effects of NSAIDs were documented, but theories based on these effects were abandoned. The most reasonable hypothesis that at that time was based on the observation that salicylates could inhibit several proteases. Increased extracellular proteolytic activity was observed in several inflammation models, and this was thought to be responsible for tissue destruction, a typical feature of chronic diseases such as rheumatoid arthritis. NSAIDs are a class of medications used as antipyretic, anti-inflammatory and analgesic agents.

Inflammatory response consists of a vascular reaction and a cell reaction. Many cells are involved in inflammation, such as neutrophils, monocytes, eosinophils, lymphocytes, basophils, platelets, connective tissue cells, including mast cells surrounding blood vessels, connective tissue fibroblasts, local macrophages, and lymphocytes. This inflammatory response may be acute or chronic. The first, characterized by local vasodilation and increased capillary permeability, is a very rapid inflammatory process, because the response is shorter and may last for minutes, hours, or days. The latter, in turn, is characterized by presenting a longer duration and is associated with the presence of lymphocytes and macrophages and with proliferation of blood vessels, fibrosis, and tissue necrosis.

The main NSAID mechanism of action is inhibition of the COX enzyme, or, in a more complete way, of the so-called prostaglandin endoperoxide synthase (PGHS) complex. COX is necessary to convert AA into thromboxanes (TXs), PG, and prostacyclins. The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids. Specifically, TXs play a role in platelet adhesiveness, whereas PGs cause vasodilation, increase hypothalamic temperature set point, and play a role in nociception.

There are two COX isoenzymes: COX-1 and COX-2 (PGHS-1 and PGHS-2, respectively). COX-1 is constitutively expressed in the body and plays a role in the maintenance of gastrointestinal mucosal coating, renal function, and platelet aggregation. COX-2 is not constitutively expressed in the body. Conversely, it is inducibly expressed during an inflammatory response. Most NSAIDs are not selective for one of the isoenzymes and inhibit both COX-1 and COX-2.
However, COX-2-selective NSAIDs (named “coxibs”) aim to inhibit only COX-2, and thus have a different profile of adverse effects. It is important to emphasize that, since COX-1 is the main mediator to ensure gastric mucosal integrity and COX-2 is especially involved in inflammation, COX-2-selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa.\textsuperscript{11,12}

Nevertheless, emerging evidence challenges the theory that COX-2-selective inhibitors are safer. In the early 2000s, there were the first reports of cardiovascular adverse effects associated with COX-2 inhibitors, and subsequent placebo-controlled studies also showed that these inhibitors were related to increased risk of atherothrombotic vascular events.\textsuperscript{13} Moreover, meta-analyses and randomized clinical trials further confirmed these findings, which led the US Food and Drug Administration (FDA)\textsuperscript{14} and, subsequently, other regulatory agencies, such as the Brazilian Health Surveillance Agency (\textit{Agência Nacional de Vigilância Sanitária}, ANVISA), to withdraw approval for several COX-2 inhibitors. In addition to gastrointestinal and cardiovascular complications, the routine use of NSAIDs is also associated with nephrotoxicity and potential renal failure,\textsuperscript{15} along with other transient effects on fluid and electrolyte balance.

The existence of a third COX isoform, named COX-3, has been recently proposed, which, contrary to COX-1 and COX-2, would produce anti-inflammatory chemicals rather than pro-inflammatory prostanoids, a fact that could explain the remission of some chronic inflammatory diseases such as rheumatoid arthritis. COX-3 is expressed in the brain, the spinal cord, and the heart.\textsuperscript{16}

Based on their chemical structure, NSAIDs may be broadly classified into salicylates, aryl and heteroaryl acetic acid derivatives, indole/indene acetic acid derivatives, anthranilates, and oxicams (enol acids) (Figure 1).\textsuperscript{14,18} The general structure of a typical NSAID consists of an acidic moiety (carboxylic acid, enols) attached to a planar aromatic functional group. Salicylates were the first identified NSAIDs following extraction of salicylic acid from willow bark.\textsuperscript{7} They are actually derivatives of 2-hydroxybenzoic acid (salicylic acid). Initially, salicylic acid was medicinally used in the form of sodium salt; later, this compound got replaced therapeutically by the acetylated derivative, acetylsalicylic acid (ASA) or aspirin.

After salicylates, aryl and heteroaryl acetic acid derivatives constitute an important class of NSAIDs. Ibuprofen, ketoprofen, and naproxen are some structural derivatives of aryl and heteroaryl acetic acids which comprise some of the most popular NSAIDs. The next category of NSAIDs is indole or indene acetic acid, which includes popular painkillers, such as indomethacin and sulindac. Moving further, anthranilates are another class of NSAIDs which are N-aryl substituted derivatives of anthranilic acid. Diclofenac, the derivative of 2-aryl acetic acid, is the most widely used anthranilate NSAID, being found in diverse formulations, including pain killer tablets, injections, topical presentations, and fast acting sprays. Mefenamic acid and meclofenamic acid are also derived from anthranilic acid. Finally, there are enol acid derivatives, such as oxicams (tenoxicam, piroxicam, meloxicam) and pyrazolones (dipyrone).\textsuperscript{14,18} The classification of NSAIDs by pharmacological group is synthesized in Figure 1.

**Classification of NSAIDs based on the selectivity of COX isoenzyme**

Bioconversion of AA into inflammatory prostanoids is mediated by COX-1 and COX-2 enzymes, which, in turn, are inhibited by NSAIDs. Almost all the NSAIDs variably inhibit both the COX isoforms at their therapeutic doses. Thus, on the basis of COX selectivity, an inhibitory ratio is determined, which allows a classification of NSAIDs. The inhibitory ratio is based on the COX-1 IC\textsubscript{50}/COX-2 IC\textsubscript{50}. If the ratio is 1, then both the PGHS enzymes are equally inhibited by the concerned NSAID; if the ratio is less than 1, it means that the concerned NSAID is less selective for COX-2 compared to COX-1, and in case of ratio

**Classification of NSAIDs based on chemical groups**

Traditionally NSAIDs were classified on the basis of their chemical characteristics wherein most of the popular NSAIDs are categorized as major derivatives of salicylic acid, acetic acid, enolic acid, anthranilic acid, or propionic acid. However, with the advancement of scientific knowledge, the classification has also been shifted based on their selectivity for inhibiting COX-1 and COX-2 enzymes. In addition, a classification system has also been formulated to categorize NSAIDs on the basis of their half-life. Nevertheless, despite the interclass diversity, their functions are relatively similar.\textsuperscript{17}
<table>
<thead>
<tr>
<th>Pharmacological group</th>
<th>Basic chemical structure</th>
<th>Examples of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salicylic acids</strong></td>
<td><img src="image" alt="Salicylic acids" /></td>
<td>Acetylsalicylic acid (ASA, aspirin), diflunisal, salsalate</td>
</tr>
<tr>
<td><strong>Carbo and heterocyclic acetic acids</strong></td>
<td><img src="image" alt="Carbo and heterocyclic acetic acids" /></td>
<td>Indomethacin, ketorolac, etodolac</td>
</tr>
<tr>
<td><strong>Propionic acids</strong></td>
<td><img src="image" alt="Propionic acids" /></td>
<td>Ibuprofen, ketoprofen, naproxen, flurbiprofen</td>
</tr>
<tr>
<td><strong>Phenylacetic acids</strong></td>
<td><img src="image" alt="Phenylacetic acids" /></td>
<td>Diclofenac, aceclofenac</td>
</tr>
<tr>
<td><strong>Enolic acid derivatives</strong> - Oxicams</td>
<td><img src="image" alt="Enolic acid derivatives" /></td>
<td>Piroxicam, tenoxicam, meloxicam</td>
</tr>
<tr>
<td><strong>Enolic acid derivatives</strong> - Pyrazolones</td>
<td><img src="image" alt="Enolic acid derivatives" /></td>
<td>Dipyrone, phenylbutazone</td>
</tr>
<tr>
<td><strong>Fenamic acids</strong></td>
<td><img src="image" alt="Fenamic acids" /></td>
<td>Mefenamic acid, flufenamic acid, meclofenamate</td>
</tr>
<tr>
<td><strong>Para-aminophenol derivatives</strong></td>
<td><img src="image" alt="Para-aminophenol derivatives" /></td>
<td>Paracetamol (acetaminophen)</td>
</tr>
<tr>
<td><strong>Pyridinic sulfonamide</strong></td>
<td><img src="image" alt="Pyridinic sulfonamide" /></td>
<td>Nimesulide</td>
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<tr>
<td><strong>Naphthyl alkanone</strong></td>
<td><img src="image" alt="Naphthyl alkanone" /></td>
<td>Nabumetone</td>
</tr>
<tr>
<td><strong>Diaryl heterocyclic acids (“coxibs”)</strong></td>
<td><img src="image" alt="Diaryl heterocyclic acids (“coxibs”)" /></td>
<td>Celecoxib, etoricoxib, valdecoxib</td>
</tr>
</tbody>
</table>

**Figure 1**
Classification of non-steroidal anti-inflammatory drugs according to pharmacological group and chemical structure
(modified from Bianca-Lopez N, et al.19)
greater than 1, the NSAID is preferentially selective for COX-2.\textsuperscript{19}

It is presumed that the side effects of NSAIDs, such as gastrointestinal manifestations, are associated with COX-1 inhibition, while therapeutic effect (anti-inflammatory) is correlated with that of COX-2, and often a high level of PG suppression is needed for therapeutic relevance. However, this simplistic view has been questioned recently. In general, NSAIDs are therapeutically employed at doses that generate more than 50% reduction of PG production. In this context, it would be important to check the extent to which COX-1 gets inhibited at the same concentration of NSAID that is required for inhibiting 80% of COX-2 activity. However, in the case of diclofenac, the concentration which inhibits 80% of COX-2 activity can also inhibit almost 70% of COX-1 activity at the same time. So, therapeutic dose (80% inhibition of COX-2) can even lead to toxicity. In this scenario, when relative selectivity varies within a narrow range, other variables, including consumed dose and plasma half-life, should be considered. For example, piroxicam, which has long plasma half-life and is correlated with gastrointestinal toxicity in vivo, did not show notable COX-1 selectivity in the in vitro assay. Hence, it is clear that the relative potency of NSAIDs varies with their dose, concentration, and plasma half-life. Therefore, IC\textsubscript{80} seems to be clinically more relevant in comparing NSAIDs’ inhibitory potencies against COX-1 and COX-2.\textsuperscript{19}

Now, on the basis of the potencies to inhibit COX isoforms, NSAIDs can be divided into four main categories (Table 1): (i) non-selective, complete inhibitors of both COX-1 and COX-2; (ii) complete inhibitors of COX-1 and COX-2, although with specific preference for COX-2; (iii) strong inhibitors of COX-2, although with weak inhibiting action against COX-1; and (iv) weak inhibitors of COX-1 and COX-2.\textsuperscript{19}

However, in terms of kinetics, NSAID interactions with both the COX isoforms can also be used for their classification, which is as follows: freely reversibly interaction (ibuprofen), slowly reversible interaction (indomethacin, diclofenac, celecoxib) and irreversible interaction (aspirin).

Two agents that show some degree of “preferential” COX-2 inhibition are meloxicam and nimesulide. For these compounds, it has been difficult to attribute a relationship of gastrointestinal “safety” when compared to the other conventional NSAIDs, since, despite preferential COX-2 inhibition, the therapeutic doses of these drugs will also result in reduced COX-1 activity.\textsuperscript{19}

### Epidemiology of hypersensitivity reactions to NSAIDs

NSAIDs are widely used worldwide for relief of pain and inflammation and are responsible for 25% of adverse drug reactions, including HR.\textsuperscript{20} NSAIDs, together with beta-lactam antibiotics, are the leading cause of HDRs worldwide.\textsuperscript{21} According to an American study, up to 30% of adults consume pain killers for chronic pain, a percentage that may reach 40% among those older than 65 years, either by prescription or

<table>
<thead>
<tr>
<th>Categories</th>
<th>COX-1 and COX-2 selective inhibition</th>
<th>Name of NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>COX-1 and COX-2</td>
<td>Indomethacin, aspirin, diclofenac, naproxen, ibuprofen</td>
</tr>
<tr>
<td>II</td>
<td>5- to 50-fold selectivity for COX-2</td>
<td>Meloxicam, nimesulide</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 50-fold selectivity for COX-2</td>
<td>Coxibs</td>
</tr>
<tr>
<td>IV</td>
<td>Poor selectivity for COX-1 and COX-2</td>
<td>Sulfasalazine, nabumetone</td>
</tr>
</tbody>
</table>

**COX** = cyclooxygenase, **NSAID** = nonsteroidal anti-inflammatory drug.
self-medication, so that the use of NSAIDs without medical prescription is very common.

In the general population, the prevalence of HR to NSAIDs ranges from 0.5 to 5.7%. Age stratification shows a significant variation with regard to gender, phenotype, and NSAID class involved. Women are the most affected among adults, although this relationship is inverse in childhood, when boys are more affected. In all ages, the most prevalent phenotype is NSAID-induced urticaria/angioedema (NIUA) in patients with no underlying disease. This phenotype accounts for 40% of HRs and for 60% of non-immunological reactions. Within this group, isolated palpebral and/or labial angioedema is the most common presentation in children, with increased prevalence up to young adults, and is often related to atopy and sensitization to aeroallergens. The association of cutaneous with respiratory manifestations characterizes the blended, or mixed, phenotype (30%), considered the second most common both in children (especially in adolescents) and in adults, with manifestations that appear simultaneously or sequentially. The phenotypes characterized by exacerbation of respiratory disease, also known as ASA/NSAID-exacerbated respiratory disease (NERD), or exacerbation of chronic spontaneous urticaria (CSU), known as NSAID-exacerbated cutaneous disease (NECD), are more prevalent in adults, and each one accounts for 8% of total reactions. NERD occurs in up to 20% of individuals with asthma and nasal polyposis. Conversely, the occurrence of NERD (asthma and/or chronic rhinosinusitis and/or polyposis) is rare in pediatric patients. CSU is rare in children, and its exacerbation by NSAIDs (NECD), which fluctuates with periods of disease activity, is less frequent (24%) when compared to adults (up to 40% of those with CSU).

Among patients with non-immunological hypersensitivity (NIUA, NECD and NERD), non-selective or preferential COX-1 inhibitors have a role in inducing reactions. However, even weak COX-1 inhibitors that are preferential or selective COX-2, depending on the dose, are potential triggers, since up to 1/3 of patients may present reactions with paracetamol at doses higher than 1,000 mg.

The class of NSAID involved also varies in frequency according to geographic space and age group. In Americas, NSAIDs are the most prevalent cause of immediate HDR. In Brazil and Latin America, they are the main cause of drug-induced anaphylaxis. Non-immunological anaphylaxis induced by NSAIDs is the most prevalent one, although IgE-mediated reactions were associated with greater severity. Furthermore, dipyrone stands out as one of the most implicated agents in these reactions in Latin America. In the USA, ibuprofen and naproxen lead the ranking, whereas diclofenac is the most prescribed one in the United Kingdom. Considering the pediatric population, o paracetamol and ibuprofen predominate, whereas other NSAIDs (diclofenac, dipyrone, "oxicams," and ASA) increase in parallel with the consumption of new drugs with increased age.

Atopic diseases in adults and children are considered an important risk factor for NSAID hypersensitivity, a fact that may be related to environmental, ethnic, or genetic factors. NIUA is much more frequent among atopic patients sensitized to mites. Regarding NERD, association with atopy is still controversial. Older studies reported that it was less frequent in adults with atopy, but more recent data suggest that up 75% of individuals with NERD have atopy. The participation of cofactors such as infection, food allergy, and physical activity are common in the pediatric population. Infections may act as a co-factor, both in immediate and non-immediate reactions, especially in children, leading to urticaria, angioedema, and maculopapular exanthema not reproducible after oral provocation tests (OPTs).

Selective reactions to a NSAID or a chemically related group, with tolerance to other unrelated groups and ASA, may be immediate and manifest as single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIIUA), a form of immediate immunologic hypersensitivity that occurs less than 1 hour after drug intake (20-30%). The most medication more frequently related to this reaction is dipyrone (methimazole), but selective reactions with paracetamol, diclofenac, and ibuprofen have already been reported. Still within this group, the inclusion of a phenotype of patients with immediate selective reaction to multiple groups with tolerance to ASA was recently suggested.

Non-immediate selective reactions, which occur more than 24 hours after consumption of the NSAID, represent a heterogeneous group of reactions of variable severity and accounting for less than 5% of total reactions. These reactions, also known as single-NSAID-induced delayed hypersensitivity reactions (SNIDR), vary from mild reactions (such as maculopapular exanthema, delayed urticaria, contact
dermatitis or photodermatitis, fixed drug eruption) to the most severe ones, such as hepatitis pneumonitis, nephritis, and the so-called severe drug cutaneous reactions, such as acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalized bullous fixed drug eruption. Maculopapular exanthema, rare in adults, is more frequent in children, in the context of infections, and is often not confirmed by the OPT.25

Pathophysiology of HRs to NSAIDs

HRs associated to NSAIDs are divided into immunological (or allergic) reactions and non-immunological (or non-allergic) reactions. The so-called immunological reactions to NSAIDs involve mechanisms of type I (IgE-mediated) and type IV (T-cell dependent) Gell and Coombs hypersensitivity classification. Up to date there has been no documented strong evidence of type II (cytotoxic) and III (immune complex) reactions. Conversely, non-immunological reactions seem to be associated to potential of COX-1 inhibition by these drugs.2,23

Immunological reactions

Immunological or allergic NSAID-induced reactions may be immediate or on-immediate (delayed). Patients who present these reactions are considered selective reactors, i.e., their reactions are restricted to the causative drug or to others of the same pharmacological class.2,18

In immediate reactions (SNIUAA), symptoms such as urticaria, dyspnea, and anaphylaxis usually result from mast cell degranulation due to binding of the specific IgE to high-affinity IgE receptors present in mast cells. In the first contact with the antigen, there is a polyclonal increase of specific T and B cells and production of specific IgE without causing symptoms. After 5-6 days, the secreted IgE sensitizes mast cells. In the next contact, minutes after the drug was administered, mast cells undergo degranulation, with the release of various mediators, especially histamine, causing symptoms such as urticaria, dyspnea, cough, and anaphylaxis, among others. The development of the reaction does not depend on the administered dose, but it is clear that the intensity of symptoms has a strong association with drug concentration in the body. Among the different classes of NSAIDs, the occurrence of this mechanism is better documented with pyrazolones (e.g.: dipyprone), mainly through skin tests (puncture and intradermal), since in vitro assays have low sensitivity.31

Conversely, delayed reactions (SNIDRs) occur after longer medication use and seem to have some degree of dose-dependency. The activation of TCD4 and/or TCD8 cells is stimulated by drug use, and symptoms (e.g., exanthema) are simply a consequence of the amount of the drug, number of activated T-cells, tissue migration, and intensity of affinity to Toll-like receptor (TLR), innate lymphoid cell receptor, for the peptide-hapten complex/drug.32

Non-immunological reactions

Most NSAIDs perform non-selective inhibition of the COX-1 enzyme. They interfere with AA metabolism, leading to blockade of PG synthesis and to positive regulation of LT pathways, which contributes to several manifestations of HRs to NSAIDs.33 In susceptible individuals, COX-1 inhibition causes AA metabolism disorders, 5-lipoxygenase leukotriene C4 synthase (LTC4S) dysfunction, reduced PGE2, and increased production of cysteinyl leukotriene (CysLT). Reduced levels of PGE2 pathway increase LTC4S pathway response, which enhances CysLT production. Excessive CysLT production leads to vascular extravasation, bronchoconstriction, and excessive mucus secretion, as well as activation of mast cells and eosinophils, which release chemical mediators and cytokines, further increasing systemic inflammation.2,34,35

This is the most common mechanism to explain HRs associated with NSAIDs and includes the phenotypes of NIUA, NECD, NERD, and even the so-called mixed (or blended) reactions, in which individuals develop anaphylaxis after exposure to more than one NSAID of different classes.2,35

NSAIDs that exert a predominant inhibition on COX-1 enzymes, such as ASA, naproxen, and diclofenac, have higher rates of HRs, whereas weak COX-1 inhibitors and COX-2-selective inhibitors are usually better tolerated, with lower probability of HRs.33

The pathophysiological mechanism proposed for non-immunological HRs to NSAIDs (NIUA, NECD and NERD) is summarized in Figure 2.

Genetic aspects

Inhibition of COX-1 activity, the therapeutic target of most NSAIDs, makes it possible to assume
the underlying mechanism for cross-intolerance to NSAIDs of various chemical structures. In this pathway, the polymorphisms in genes that involve COX and lipoxygenase pathways and leads to imbalance between PG and LT have been the focus of most studies, especially in NERD and, more recently, in NIUA.

A Spanish study in patients with NERD revealed a significant association with single nucleotide polymorphisms (SNP) in the prostaglandin-endoperoxide synthase gene 1 (PTGS1) (rs5789 and rs10306135), the first related to decreased enzyme activity, and the latter involved in gene expression regulation. Another study identified, in two different cohorts in Spain, polymorphisms related to PTGS1 rs10306194 and ALOX5 rs28395868 associated with risk of NIUA, whereas the latter polymorphism was also related to respiratory manifestations exacerbated by NSAIDs, bringing hope of a potential genetic biomarker to distinguish the different phenotypes.

A study that analyzed the complete PTGS sequence identified a haplotype in the PTGS1 gene that is over-represented in patients with cross-reactive NSAID hypersensitivity and associated with severely decreased COX-1 enzyme activity in a Spanish population. Such haplotype contains two single nucleotide variations that may be also related to other adverse effects involving decreased enzyme function. However, the identification of variants in the PTGS2 gene (COX-2) was not related to cross-reactivity to NSAIDs, consistent with the tolerance of most patients to COX-2-selective inhibitors. Although the

**Figure 2**
Pathophysiological mechanism of non-immunological hypersensitivity reactions (HR) to acetylsalicylic acid (ASA) and the remaining nonsteroidal anti-inflammatory drugs (NSAIDs), which is based on the pharmacological action of these drugs. The metabolism of arachidonic acid involves actions of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, leading to the synthesis of prostaglandins (PG), prostacyclins, thromboxanes (TX), and leukotrienes (LT). Since the main action of NSAIDs is inhibiting COX, there is a metabolic deviation for the action of LOX and, consequently increased synthesis of cysteinyl leukotriene (Cys-LT). In patients with non-immunological HRs, this accumulation of Cys-LT has a vasodilator action, induces smooth muscle contraction, and eventually cause the symptoms

Adapted from Walters KM, et al.
risk haplotype was present in only a small proportion of patients (5.6%), the strong association observed and the effect of reducing enzyme activity reinforce the hypothesis of potential genetic susceptibility in the investigation of patients with family history of cross-reactive hypersensitivity to NSAIDs.38

The identification of polymorphisms (rs9883222, rs2298954, rs2236944) in the G protein subunit alpha I2 (GNAI2), located in the same haplotype at locus 3p21.31, reflect their influence in the pathological mechanisms of hypersensitivity to NSAIDs, such as LT receptor activation and recruitment of the immune cells involved. This association, identified in genome wide association studies in patients with urticaria/angioedema/anaphylaxis, was replicated in the Spanish population of two different region.39

Few genetic association studies, a useful tool to identify pharmacogenetic targets, were conducted in this area. These studies require large samples, not only to identify low-frequency findings that may have a relevant impact on phenotype, but also to detect disease risk.36 A genetic association study was conducted in a Korean population to investigate genetic susceptibility to aspirin intolerance and identified the CEP68 gene (which codifies the centrosomal protein of 68KDa) as a risk factor in asthmatics. Subsequently, the same study, in a candidate gene approach, related the rs7572857 SNP to the genetic etiology of aspirin intolerance after oral provocation in asthmatics with significant decline in forced expiratory volume in 1 second, especially related to the homozygous AA of rs7572857G >A variant.40

In a study with a population of Spanish ancestry, 17 variants of CEP68 were identified, including rs7572857, in patients with NIUA, 8 of which were also present in patients with respiratory manifestations, NERD, and blended reactions.41 Another study in the Spanish population assessing the CEP68 candidate gene found two intronic variants (rs2241160 and rs2241161) with a significantly association in patients with immediate allergic reaction, selective to a single NSAID (SNIUAA). However, no overlap was observed with genetic variants previously associated with pharmacologically mediated hypersensitivity, pointing to a complex role for this gene and its potential use in the development of biomarkers of clinical utility to diagnose patients at risk.42

A genetic association study in a cohort of Korean asthmatics showed SNPs in 30 regions of the HLA-DPB1 gene that were significantly associated with the risk of NERD, and rs1042151 (Met105Val) was the most important genetic variant.43 In the Asian population, HLA-DPB1*0301 was considered a strong marker of aspirin-intolerant asthma.44 In another Korean study, the HLA-DRB1*1302-HLA-DQB1*0609-DPB1*0201 haplotype revealed to be a potential marker for NSAID-induced cutaneous phenotypes. Furthermore, in an Italian study, HLA-B44 and HLA-Cw4 were positively associated with NECD.36

In this still little explored field, recent findings in a Spanish and Han Chinese population suggest other pathways besides AA metabolism involved in cases of cross intolerance with manifestations of urticaria and angioedema. There may also the influence of genetic variants involved in histamine metabolism, IgE receptors, and activation of cytokines, mast cells, and drug-metabolizing enzymes. It is worth highlighting that most studies were conducted in Asian and European patients and were not replicated in ethnic minority or mixed populations.36

Despite advancements in studies, the discovery of genetic variants that predispose individuals to hypersensitivity to NSAID is still unknown. In addition to the heterogeneity of phenotypes, there are difficulties related to the genetics of complex diseases.26

Conclusions

NSAIDs are both the most used medications worldwide and the most frequently associated with HRs. Knowledge of the pharmacological actions of these drugs, of the epidemiology of HRs, both in Brazil and worldwide, and of the pathophysiological mechanisms and genetic factors involved in these events is essential for allergists-immunologists to provide individualized care to their patients and to act accurately.

References


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Corresponding author:
Marcelo Vivolo Aun
E-mail: marcelovivoloaun@gmail.com