

# The multiple faces of nonsteroidal antiinflammatory drug hypersensitivity

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**Summary.** Based on the clinical picture and triggering drugs, allergic and pseudoallergic adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) can be classified in four patterns : respiratory, cutaneous, mixed and systemic. This categorization is useful for the purpose of describing patient populations included in studies about NSAID adverse reactions as well as for the routine management of the patient in the clinical setting.

**Key words:** Non steroidal anti-inflammatory drugs. Urticaria. Angioedema. Asthma. Cysteinil-leukotrienes. Cyclooxygenases.

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recognized among the most frequently used therapeutic agents all over the world, and average consumption has been estimated as high as 80 tablets per person per year [1]. Due to the magnitude of exposure, it is not surprising that NSAIDs are one of the leading causes of adverse reactions to pharmaceutical products in the population.

A common confounding factor in many studies concerning hypersensitivity to NSAIDs is that investigators have included a mixed population of subjects with various clinical manifestations such as respiratory (dyspnea, wheezing, nasal congestion, rhinorrhea, sinusitis), cutaneous (urticaria, angioedema, different types of skin rashes), patients with a mixed picture of respiratory and skin symptoms, or individuals who exhibit systemic manifestations resembling anaphylaxis. This leads the reader to the wrong conclusion that all NSAID-hypersensitive patients suffer from a unique disease.

Recently, Stevenson, Sánchez-Borges and Szczeklik proposed a new system for the classification of allergic

and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes [2]. In this paper we would like to discuss in detail the clinical features of these reactions in an attempt to give clinicians further insights for the better management of patients suffering from them. For the purpose of this article, four clinical patterns will be analyzed: 1) Respiratory 2) Cutaneous 3) Mixed 4) Systemic.

Other hypersensitivity reactions such as cutaneous (fixed eruptions, exfoliative dermatitis, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, erythema nodosum, morbilliform and maculopapular eruptions, allergic and photoallergic contact dermatitis, purpura, vasculitis), neurological (aseptic meningitis), pulmonary (interstitial pneumonitis) or renal (interstitial nephritis) will not be included in this discussion.

## Respiratory Pattern

First described by Widal in 1922 [3], and later on recognized by Samter and Beers [4], the syndrome

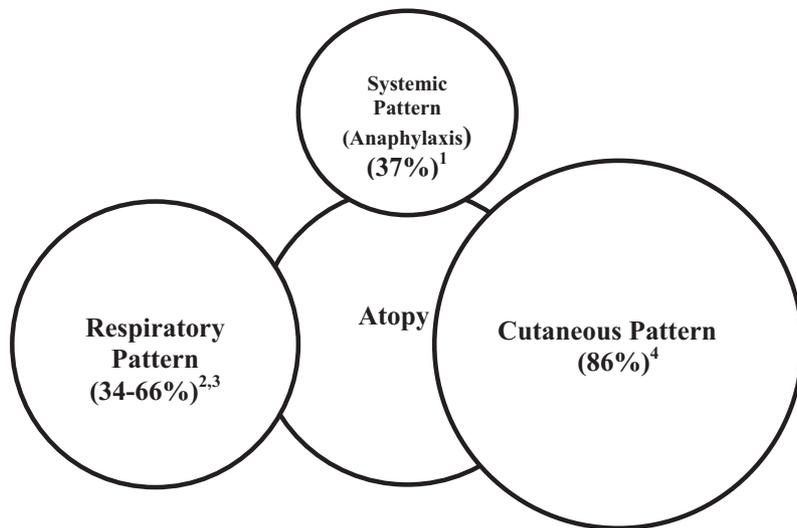


Figure 1. Interrelationship between Atopy and Clinical Patterns of NSAID-induced Hypersensitivity Reactions

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known as aspirin triad (or tetrad), aspirin-induced asthma, aspirin-intolerant asthma or aspirin-exacerbated respiratory disease (AERD) is composed of asthma, rhinosinuitis, nasal polyposis and aspirin sensitivity [5].

Patients experience asthma exacerbations after taking aspirin or other NSAIDs that inhibit cyclooxygenase-1 (COX-1), but the disease progresses independently of drug exposure. Most patients have severe, corticosteroid-dependent asthma and eosinophilic rhinosinuitis associated with nasal polyps. About one third of patients with AERD are atopic (Figure 1). For years it has been brought to our attention that most cases reported in the literature come from the United States of America and Eastern European countries, whereas it is our experience that the condition seems to occur less frequently in Latin American countries such as Venezuela.

The disease is present in about 9.2% of adult asthmatics and in up to 33% of asthmatics who have concomitant chronic sinusitis and nasal polyps. A polymorphism of the gene codifying for LTC<sub>4</sub> synthase has been reported in patients with AERD from Poland [6], but not in those from the United States [7].

The pathogenesis of AERD has been extensively studied and it has been proposed that the main mechanism of NSAID-exacerbated respiratory disease is through inhibition of COX-1 resulting in arachidonic acid metabolism shunting towards the 5-lipoxygenase pathway and increased cysteinil leukotriene synthesis [8]. This theory is supported by the following observations :

- 1) Respiratory reactions are exclusively triggered by drugs that inhibit COX-1, whereas COX-2 specific inhibitors do not induce them in patients with AERD [9-14].
- 2) The induction of airway symptoms correlates with the potency of the drug to inhibit COX-1.
- 3) Inhibitors of leukotriene synthesis and leukotriene receptor antagonists are able to prevent, at least partially, symptoms in AERD patients challenged with aspirin [15,16].
- 4) These patients show increased baseline urinary LTE<sub>4</sub> levels [17] which increase after aspirin challenge [18] and correlate with the severity of respiratory reactions [19].
- 5) Aspirin challenge increases the amount of leukotrienes in nasal and bronchial secretions.

Stevenson and Zuraw have observed that dose-related lower respiratory reactions to aspirin, characterized by bronchospasm, can be reproduced by leukotriene inhalation and blocked by 5-lipoxygenase antagonists or Cys-LT<sub>1</sub>-receptor antagonists but not by antihistamines. On the other hand, upper respiratory reactions to aspirin, including nasal congestion, sneezing, profuse rhinorrhea and ocular injection with conjunctival pruritis would be mediated by both histamine and leukotrienes [20].

The management of patients with AERD includes the avoidance of drugs that inhibit COX-1, topical or systemic corticosteroids, leukotriene modifiers, relief of pain or inflammation either with drugs that do not inhibit

*Table 1.* Management of Patients with Aspirin-Exacerbated Respiratory Disease.

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- Avoidance of cyclooxygenase-1 inhibiting NSAIDs
  - Alternative NSAIDs (weak COX-1 inhibitors) such as acetaminophen, salsalate, dextropropoxyphene, opioids, ergotamine, hyoscine, sodium salicylate, salicylamide, choline-magnesium trisalicylate, floctafenine or COX-2 inhibitors (coxibs) for relief of pain, fever or inflammation
  - High-dose topical (nasal, inhaled) corticosteroids
  - Systemic corticosteroids
  - CysLT1-receptor antagonists (Montelukast, Zafirlukast)  $\pm$  5 - Lipooxygenase inhibitors (Zileuton)
  - Surgery: Sinus drainage, polypectomy
  - Antihistamines
  - Desensitization
  - Future therapies: CysLT2-receptor antagonists?, gene therapy?
- 

or weakly inhibit COX-1 or with COX-2 inhibitors, surgery for sinus complications and polyps and antihistamines (Table 1).

Crossed desensitization with aspirin or other NSAIDs, followed by chronic NSAID administration, is helpful for chronic disease control, although it is lost after few days of omitting the drug [21].

## Cutaneous Pattern

Urticaria and angioedema may be present as minor components of more generalized reactions to NSAIDs and also during aspirin challenges in about 5 % of patients with AERD [20]. On the other hand, cutaneous reactions predominate in patients with the following clinical subpatterns [22]:

- 1) **NSAID-induced urticaria and angioedema** observed in cross-reactor patients with chronic idiopathic urticaria. Up to one third of patients with chronic urticaria experience exacerbations when exposed to NSAIDs that inhibit COX-1 [23] but not to COX-2 inhibitors [24]. This observation suggests that these reactions are mediated through inhibition of COX-1 isoenzyme.
- 2) **Multiple drug-induced urticaria and angioedema** may occur in otherwise normal cross-reactive individuals with acute urticaria and/or angioedema [25]. COX-2 specific inhibitors are also able to induce reactions in NSAID-cross-reactive patients [26,27]. Our studies suggested that the ability of “COX-2 specific” drugs to induce cutaneous reactions in cross-reactive patients might depend on their inhibitory activity

on COX-1 since drugs such as nimesulide, meloxicam and celecoxib can inhibit COX-1 in vitro more effectively than rofecoxib, valdecoxib and etoricoxib [28]. Since celecoxib and valdecoxib, both containing a sulphonamide residue, differed in their ability to induce cutaneous reactions in these patients, we consider unlikely that increased reaction rates to celecoxib are due to sulphonamide allergy [29]. Another reason to consider that these reactions to COX-2 inhibitors are not mediated by IgE antibodies is that our patients had not been previously exposed to coxibs, which makes unlikely that allergic sensitization had occurred.

- 3) **Single drug-induced urticaria and angioedema**, present in individuals who show acute symptoms after exposure to a single drug. The mechanism of this type of reaction is allergic sensitization with the synthesis of IgE antibodies specific for the drug which functions as a hapten. Theoretically any NSAID, including the new inhibitors of COX-2, may produce an immune-mediated reaction [30,31]. For example, there are reports of single-drug reactions to pyrazolones [32], acetaminophen [33], aspirin [34], and ketorolac [35], among others.

Some predisposing factors for NSAID-triggered urticaria and angioedema have been proposed, including atopy [36], female gender, and intermittent NSAID use for relief of acute pain [37]. For unknown reasons (genetic?) most studies regarding urticarial and angioedematous reactions due to aspirin and NSAIDs have been carried out in southern European (especially Italy and Spain) and Latin American countries where large

**Table 2.** Management of Patients with Cutaneous Reactions to NSAIDs.

1. Determine drug pattern from clinical history
2. **Single-reactors:**
  - Oral challenge with chemically unrelated NSAID
  - If negative, proceed with treatment and avoid responsible NSAID
  - If positive, manage as cross-reactor
3. **Cross-reactors:**
  - Alternative NSAIDs (weak COX-1 inhibitors) such as acetaminophen, salsalate, dextropropoxyphene, opioids, ergotamine, hyoscine, sodium salicylate, salicylamide, choline-magnesium trisalicylate, floctafenine

or

  - Oral challenge with COX-2 inhibitor (coxib)
  - If negative, proceed with treatment
  - If positive, try a second, more specific, COX-2 inhibitor
  - If again positive, avoid all NSAIDs

communities from Europe arrived during and after World War II and therefore partially share the same genetic background. Interestingly, no poly-morphism of LTC<sub>4</sub> synthase gene was observed by Torres Galvan et al in Spanish patients with NSAID urticaria and angioedema [38].

In a recent article we have discussed the management of patients with NSAID-induced cutaneous reactions [39]. Briefly, in single-reactor patients a NSAID from a different chemical composition may be used after cautious oral challenge, usually in an outpatient basis, in the office. In cross-reactor individuals, alternative NSAIDs that inhibit weakly COX-1 given in low doses or COX-2 inhibitors (also with tolerance tests) may be utilized (Table 2). Desensitization, successful in patients with AERD, does not seem to work in patients with cutaneous reactions to NSAIDs [21].

### Mixed Pattern

A blended pattern of cutaneous and respiratory symptoms, including urticaria and angioedema plus cough, breathlessness, hoarseness, rhinorrhea, wheezing, tearing and conjunctival itching is observed in about 30 % of our patients during controlled oral challenges.

**Table 3.** Management of Patients with Systemic Reactions to NSAIDs.

#### **Anaphylactoid** (Cross-reactor patients)

- Alternative NSAID (weak COX-1 inhibitors) such as acetaminophen, salsalate, dextropropoxyphene, opioids, ergotamine, hyoscine, sodium salicylate, salicylamide, choline-magnesium trisalicylate, floctafenine

or

- COX-2 inhibitors (coxibs)

#### **Anaphylactic** (Single-reactor patients)

- Avoidance of COX-1 inhibitors
- Oral challenge with unrelated NSAID or COX-2 inhibitor in the intensive care unit, starting with small doses, with iv line in place and drugs (epinephrine, diphenhydramine, ranitidine) and full resuscitation equipment available
- If negative, proceed with treatment
- If positive, avoid all NSAIDs
- Desensitization possible but indicated in only a few cases

Typically, these patients have neither the clinical elements of AERD (chronic severe asthma, sinusitis and nasal polyposis), chronic urticaria nor more generalized manifestations of anaphylaxis.

### Systemic Pattern

In this clinical pattern reactions are characterized by nasal/ocular symptoms, bronchospasm, flushing, urticaria, abdominal pain and more rarely vasomotor collapse. Anaphylactic and anaphylactoid reactions are clinically indistinguishable, but they differ in their pathogenic mechanisms.

Anaphylactic reactions are type 1 immediate hypersensitivity reactions to NSAIDs observed in single-NSAID reactor subjects who tolerate other chemically unrelated NSAIDs. Allergen-specific IgE bound to mast cells and basophils is cross-linked by the drug with cell activation, mediator release and immediate multi-organ

symptoms (flushing, hypotension, bronchospasm, tachycardia, urticaria). Previous exposure to the drug is required for the production of drug-specific IgE antibodies. In order to induce allergic sensitization, NSAIDs are required to function as haptens which bind to carrier proteins. Atopy is a risk factor for anaphylactic reactions to NSAIDs [40].

Some studies have shown that NSAIDs are the second most important cause of drug anaphylaxis after penicillins in hospitalized patients, whereas they are the leading cause in ambulatory patients seen in emergency services [41].

Specific IgE to NSAIDs has been shown by skin tests or in vitro assays for dipyrone [42], and aspirin [43,44], but theoretically any NSAID is capable of functioning as a hapten and induce sensitization.

Reports exist of anaphylaxis to ibuprofen, indomethacin, sulindac, zomepirac, fenoprofen, meclofenamate, naproxen, piroxicam, tolmetin, glafenine, acetaminophen, aspirin, diclofenac, ketorolac and celecoxib [35,37, 45-47].

Anaphylactoid reactions (also called pseudoallergic reactions) resemble the clinical picture of anaphylaxis but are observed in cross-reactor patients and are not mediated by IgE antibodies. They are induced by more than one chemically not related NSAID in the same patient, presumably through inhibition of COX-1.

Extrapulmonary symptoms may be mediated by histamine, since pretreatment with H-1 antihistamines blocks extrapulmonary manifestations but not bronchospasm [48]. The management of patients with systemic reactions caused by NSAIDs is summarized in Table 3.

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