Chapter

Clinical Phenotypes in NSAID-Induced Urticaria/Angioedema

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Abstract

The skin clinical phenotypes of nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity (NH) are very heterogeneous with several syndromes after NSAID intake, which include different symptoms, different organ involvement and different associated concomitant diseases and possibly different underlying pathophysiology and mechanisms. Making a correct diagnosis in NH is an exciting journey for any allergist. Thus, to classify these diseases properly will be pivotal for appropriate diagnostic and management strategy. Treatment modalities are depending on the clinical phenotypes of NH and they will embrace for each patient: the avoidance of culprit NSAID, the finding of well-tolerated NSAID and in certain cases, desensitization procedures when the NSAID treatment was absolutely needed as well as the control of associated diseases such as spontaneous chronic urticarial or allergic respiratory diseases. This review updates the recent evidence of classification, diagnostic strategies, and management of skin NSAID hypersensitivity reactions.

Keywords: NSAID hypersensitivity, urticaria, angioedema, single-blind placebo-controlled oral challenge, management

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are one of the most commonly used drugs worldwide. NSAIDs are a major cause of hypersensitivity reactions, and they suppose up to half the cases of adverse reactions evaluated in a tertiary allergy unit [1]. Adverse reactions to NSAIDs account for 12% to 29.6% of all adverse reactions in hospital admissions. Most adverse reactions to NSAIDs belong to type A, which are dose-dependent and predictable from their pharmacological actions. Common type A reactions include gastrointestinal bleeding and acute kidney injury. Type B reactions, also known as NSAID hypersensitivity (NH) reactions, account for 8.4% to 18.3% of total adverse reactions to NSAID [2]. NSAIDs are a large and chemically heterogeneous group of drugs that inhibit the enzyme cyclooxygenase (COX) 1 and 2 isoforms, an so block the production of prostaglandins from arachidonic acid.

NSAIDs are typically divided into groups based on their chemical structure and selectivity for blocking COX-2: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen, dexketoprofen),

acetic acids (diclofenac, indomethacin, aceclofenac, tolmetin), enolic acids (meloxicam, piroxicam), anthranilic acids (meclofenamate, mefenamic acid, niflumic acid), naphthylalanine (nabumetone), pyrazolones (metamizole, propyfenazone) and selective COX-2 inhibitors (celecoxib, etoricoxib).

Several distinct clinical syndromes are described regarding NH, most often manifested as respiratory reactions (e.g, bronchospasm and nasoocular reaction), urticaria/angioedema or systemic anaphylaxis. NH often appears in patients who also suffer certain concomitant diseases, such as chronic rhinosinusitis with nasal polyps and bronchial asthma or spontaneous chronic urticaria. Both, the type of reaction after NSAID exposure and the concomitant associated disease are critical to classify the NH [3]. The focus of this chapter will provide an overview on all the aspects of skin NSAID hypersensitivity immediate reactions, from clinical symptoms to leading practical recommendations with respect to diagnosis and management.

2. A working classification of skin NSAID hypersensitivity based on clinical phenotypes

Controlled oral challenge is the only definitive way to diagnose the reactions caused by NSAIDs. These challenge-proven immediate responses are a wide group of disorders that includes respiratory, cutaneous and anaphylaxis reactions [1, 3].

The mechanisms of NH are unknown, but two general hypotheses have been proposed [4]. The first one, an enzymatic activity inhibition of at least the cyclooxygenase-1 (COX-1) isoform that may inhibit the prostaglandin synthesis and thus deregulate the 5-lipooxygenase pathway, with cys-leukotriene hyperproduction in some susceptible patients. All NSAIDs that inhibit the COX-1 isoform could precipitate the reaction. For this reason, cross-reactivity among COX-1 inhibitor NSAIDs can be demonstrated in all patients with respiratory reactions and in most patients with urticaria/angioedema reactions (multiple reactors) [1, 3, 4]. The second mechanism can be applied only to a small subset of patients with NSAID hypersensitivity, as those with systemic anaphylaxis [4]. We have previously demonstrated that patients with NSAIDs-induced systemic anaphylaxis can react only to one specific NSAIDs and tolerate other COX-1 inhibitor NSAIDs in controlled oral challenges. Up to 1/3 of patients with NSAID induced systemic anaphylaxis might present immediate acute urticarial previous to anaphylactic episode when taken a specific NSAID (selective reactors) [3–5].

At least, three subsets of these patients with NH may have an associated underlying disease: in fact, around 10 percent of patients with chronic rhinosinusitis with nasal polyps and moderate-to-severe asthma and 30 percent of those with chronic urticaria/angioedema may present a nasoocular/asthmatic or urticarial reaction after NSAID exposure at some times in their lives, respectively [6]. Some clinical phenotypes of skin NSAID hypersensitivity are also definitely associated with allergic respiratory disease [3, 7].

Therefore, the diagnostic approach determines very different clusters of patients [3, 8]. Those who present clinical reactivity between different NSAIDs (multiple reactors) versus those who develop a reaction exclusively to a specific NSAID (selective reactors), and secondly, those in whom there is a very defined concomitant associated disease from the clinical and biological point of view. NSAID exposure exacerbates these diseases, determining a clinical reaction. However, the NSAID withdrawal does not determine a notable modification of the natural history of the disease, which often must continue to be treated despite the avoidance of NSAID [8].

Therefore, the NSAID reaction is an epiphenomenon that together with other clinical features constitutes what we have called the clinical phenotype (formerly called the NSAID-reaction complex) [1, 3]. This classification based on clinical phenotypes is a real and practical approach in the daily clinic, which will allow us to make the best appropriate diagnostic and therapeutic decisions.

3. The skin clinical phenotypes of NSAID hypersensitivity

The skin reactions are the most prevalent clinical phenotypes in patients with NSAID hypersensitivity. We have described at least 5 clinical phenotypes of immediate-type of skin NSAID hypersensitivity: [3, 7] NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (NIUA), two clinical phenotypes (NSAID induced isolated periorbital angioedema and NSAID induced recall urticarial) which are present exclusively in patients with respiratory allergy, mainly house dust mites; and a single NSAID induced urticaria/angioedema/anaphylaxis (SNIUAA) (**Table 1**). The last mentioned is probably an IgE-mediated allergy. The remaining phenotypes do not have an immunological pathophysiology, but are caused by inhibiting COX-1 resulting in an imbalance in eicosanoid mediators, as above outlined.

3.1 The NSAID-exacerbated cutaneous disease

Patients with NECD suffer from spontaneous chronic urticaria and/or angioedema (CSU) and experience a worsening of these symptoms after NSAID intake. Most reactions appear between 1 to 12 hours after administering NSAID and last several days until the reaction is controlled with supplemental doses of antihistamines and/or corticosteroids. In up to 30 percent of cases facial, neck and hand angioedema may occur during the clinical exacerbation; an isolated angioedema is rarely a possible manifestation of NECD. Approximately 30% of patients with chronic spontaneous urticaria present exacerbations of their disease after NSAID exposure throughout their lives [1, 3–5, 8]. A positive correlation between the basal CSU activity disease and the possibility of a NSAID challenge reaction have been described in NECD patients [8].

NSAID reactivity pattern	Clinical form	Associated underlying diseases
Cross-reactive syndromes	NSAID-exacerbated cutaneous disease	Spontaneous chronic urticaria/angioedema
	NSAID-induced urticarial/angioedema	
	NSAID-induced isolated periorbital angioedema	Allergic respiratory diseases
		Oral mite anaphylaxis
	NSAID- induced recall urticaria	Allergic respiratory diseases treated with subcutaneous allergen immunotherapy
Selective syndromes	Urticaria/systemic anaphylaxis	

Table 1.
Skin clinical phenotypes of NSAID hypersensitivity.

Since CSU is often a self-limiting disease within months to years, NECD can potentially remit with the resolution of CSU. However, NECD patients seem to have a distinct phenotype compared with NSAID-tolerant CSU patients: the latter have a shorter duration of CSU and less often have angioedema when compared with NECD patients [9].

3.2 NSAID-induced urticaria/angioedema

Patients with NSAID-induced urticaria and/or angioedema (NIUA) do not have spontaneous urticaria and/or angioedema, but only the reactions develop after the NSAID intake. NIUA is a multiple NSAID hypersensitivity syndrome and there is cross-reactivity between chemically unrelated NSAIDs. Since patients often start to avoid NSAIDs after their first reaction, this cross-reactivity might not always be clear. Patients can report isolated urticaria, angioedema or a combination of both. A small proportion of patients with NIUA developed chronic spontaneous urticaria after 10 year- period of follow-up [10]. So, there is a certain degree of interrelationship between both phenotypes, NECD and NIUA, and possibly in some patients they represent different stages of the same disease.

All patients with NECD and NIUA show a pattern of multiple reactivity between NSAID, dependent on the level of *in vitro* inhibition potency of COX –1 isoform (**Table 2**).

3.3 Isolated periorbital angioedema (iPA), or the infanto-juvenile form of NH

This type of reaction usually affects children and young people, with an onset in the first or second decade of life in more than 80% of cases and, in all cases, an associated respiratory allergy is detected, mostly caused by mites, suggesting a close relationship with aspirin exacerbated respiratory disease (AERD) with which they share not only the concomitant disease, but also the pattern of multiple reactivity among NSAID [3, 6].

Category	Drug	Doses
Placebo	Lactose	
Highly selective COX-2 inhibitor	Celecoxib	50, 100, 200 [a]
	Etoricoxib	30, 60 [a]
Preferential COX-2 inhibitor	Meloxicam	7.5, 15 mg [a]
Weak, non-discriminatory COX-1/COX-2 inhibitor	Paracetamol	100, 250, 500, 1000 mg [a]
Potent, non-discriminatory COX-1/COX-2 inhibitor	Diclofenac	25, 50 mg [b]
	Ibuprofen	50, 150, 250, 600 mg [a, d]
	Metamizole	10, 50, 125, 250, 575 mg [a, e]
	Acetylsalycilic acid	50, 100, 250, 500 mg [c, f]

Drugs were administered in an opaque capsule at the following intervals between each dose: [a]60 minutes, [b]120 minutes and [c]180 minutes. [d]Three doses, [e]four doses or [f]two doses were administered on the first day, and [d, e]one dose or [f]two other doses on the second day.

Table 2.
NSAIDs and doses used for single-blind, placebo controlled oral challenge.

Within this group of patients and in close relationship with the atopic phenomenon, a new syndrome has been described: the systemic anaphylaxis triggered by ingestion of food contaminated by mites (NSAIDs sensitivity mite-ingestion reaction syndrome or also recently called oral mite anaphylaxis) [11, 12]. Most of the patients presented common clinical characteristics: they had respiratory allergy to mites, presented mostly periorbital angioedema and presented anaphylactic episodes of variable severity in relation to the ingestion of food made with cereal flour (wheat, oat and corn), without any evidence of food allergy during the clinical study. 87% of the study group presented intolerance to aspirin, contrasting with the frequency of less than 2% that we observed in the population of patients allergic to domestic dust mites. This meant that an atopic aspirin intolerant was up to 300 times more likely to suffer a severe reaction from ingestion of mites than a tolerant patient. Microscopic analysis of the flour revealed extreme contamination of the flour by *Dermatophagoides farinae* and other mites of the Acaridae family (specifically *Tyreophagus entomophagus* and *Suidasia medinensis*). At present, the cause of the association of aspirin intolerance with systemic reactions by ingestion of food contaminated by mites is unknown.

3.4 NSAID-induced recall urticaria

Recall urticaria (RU) is a rare biologic phenomenon characterized by the existence of hives only in the previously injected site when the patient is exposed again from another source. The most common example are patients who have received previously subcutaneous allergen immunotherapy (sq AIT) and present focal skin reaction at the sites of previous allergens injection when a new kind of allergen shot was administered or after heavy ambiental exposure to the allergen [13].

We recently described a patient with allergic respiratory disease who underwent sq. AIT to house dust mites after a 5 year-period. Two years after allergen immunotherapy discontinuation, patient first experienced an immediate local urticarial reaction with multiple hives at previous sq. AIT injection sites after metamizole and ibuprofen intake. SBPCOC with ibuprofen and aspirin was performed and elicited multiples hives in a circumscribed area in both arms, although a controlled challenge with celecoxib was negative.

In our patient, the symptoms were elicited by different NSAIDs (Ibuprofen, metamizol and aspirin) which resembles the pattern of patients with skin cross-reactive phenotypes of NSAID hypersensitivity. This suggests that the enzymatic inhibition of COX type I isoform could play a role in the development of this specific reaction. The tolerance of highly selective COX type 2 inhibitors such as celecoxib in our patient reinforces this hypothesis. However, the nature of the relationship between COX-1 inhibition and the local immunological trace of mite remains largely unknown. This phenomenon might be a new phenotype of skin NSAID hypersensitivity which would appear in those patients with respiratory allergy treated with sq. AIT [7].

3.5 Selective acute urticaria/angioedema and anaphylaxis

The existence of underlying diseases is common in NECD, NIUA and IPA. However, there is another phenotype of otherwise healthy patients, (i.e. without any concomitant disease associated) who experience immediate reactions of urticarial or anaphylactic type after the administration of a specific NSAID [1, 3–5, 8].

Up to 15% of patients with NSAID-induced urticaria present a selective pattern of sensitivity to NSAIDs, [8] with a predominance of certain NSAID groups, such as

those derived from the pyrazole group (metamizole) followed in order of frequency by ibuprofen, diclofenac and paracetamol, A selective pattern involves SBPCOC tolerance to other NSAIDs not involved in the clinical reaction, including those that are potent inhibitors of COX isoform 1.

Immediate systemic reactions present clinical and biological features that are compatible with a possible immunological mechanism: they are generally anaphylactic, selective and, on certain occasions, can be associated with positive skin tests that can be read immediately (such as metamizole) [14].

Recently, Doña et el have described some patients who may develop immediate reactions to several NSAIDs but tolerate ASA (the NSAIDs-multiple selective immediate reaction phenotype). Patients usually present with a biselective or triselective pattern: they presented different episodes of anaphylaxis to ibuprofen and diclofenac while tolerate an aspirin challenge or developing hypersensitivity reactions to three non chemically related NSAIDs [1].

Although the selective form is the most frequent clinical form of NSAID anaphylaxis (96%), a small subgroup of patients with phenotypes associated with multiple reactivity can present an anaphylactic reaction during SBPCOC. Patients with NIUA and exceptionally periorbital angioedema may present with a systemic reaction after administration of a potent COX-1 inhibitor NSAID. In rare cases, the systemic reaction may be a clinical phenotype in itself, with patients exhibiting this clinical response to any exposure to NSAID [3].

4. Diagnostic strategy in skin reactions to NSAID

The main tools that allow us to deal with cutaneous reactions to NSAIDs are the clinical history and controlled re-exposure to NSAIDs in a hospital setting [3]. The careful and complete review of clinical reactions to NSAID is essential before any challenge procedure and allows us to provisionally classify the patient with NH, while the latter, the SBPCOC, definitively assigns the patient to a specific phenotype. Our objective is to offer the best analgesic, anti-inflammatory or antiplatelet alternatives in the event that the patient tolerates the NSAID without reaction.

4.1 To classify, to classify, to classify...always

The clinical history is the basic method of temporarily assigning the patient to a specific clinical phenotype. The phenotypic classification of any patient with a possible NH (**Table 1**) will be the first (and the most important) diagnostic step in the investigation of these types of reactions. Properly classifying NH will help us to choose safest diagnostic approach for each patient [1, 3–5, 8].

The first key element to classify these patients will be the time elapsed between the administration of NSAID and the beginning of the reaction. The so-called latency time allow us to differentiate the reactions in: immediate (less than 24 hours, usually between 1 and 2 hours) and delayed reactions (over 24 hours). Secondly, we will have to evaluate the clinical manifestations of the reaction (respiratory, cutaneous or systemic), the NSAID involved, the route of administration and the reason why the drug was prescribed, as well as the coexistence of associated concomitant diseases (chronic rhinosinusitis with nasosinusal polyposis, bronchial asthma, spontaneous chronic urticaria or allergic respiratory disease). Thirdly, we will have to determine the NSAID tolerated previously and after the reaction. This will allow us to make a first historical approach to NSAID reactivity status: multiple

reactor with reactivity among non-chemically related NSAIDs (**Table 3**) or selective reactor with sensitivity to a single NSAID with tolerance to at least one potent COX-1 inhibitor NSAID (**Table 4**).

Therefore, the classification of patients based on clinical phenotypes is critical in addressing diagnostic and therapeutic strategies in these patients. The identification of comorbidities such as chronic spontaneous urticaria, allergic respiratory disease or reactions to mite-contaminated cereal flour-based foods are key clinical elements that might define a phenotype and predict in most cases multiple reactivity to different groups of NSAIDs. The worsening of spontaneous chronic urticaria after NSAID administration and the development of the reaction within 1 to 6 hours of NSAID administration are common clinical features that can be referred up in most patients with skin-type reactions.

In a percentage of cases, clinical information on reactivity status is limited, either because the patient has had only a single reaction with a single NSAID or because of the impossibility of determining each of the NSAIDs involved in the patient's lifetime reactions. In these cases, determining this status is essential to approach a therapeutic plan. The only way to determine the reactivity status is through SBPCDC with NSAIDs that have differential inhibition against each of isoforms COX-1 and COX-2. However, we could collect in the clinical history some findings that may allow us to identify a multiple or selective reactor status (**Tables 3** and **4**). In general, a NSAID highly selective for COX-2 inhibition, such as a COXIb, will be better tolerated than a potent COX 1–2 inhibitor in patients who are multiple reactors. The degree of COX inhibition is directly proportional to the probability of reaction and the intensity of its clinical manifestations [1, 3–5, 8]. In the case of a selective reactor, all COX-1 inhibitor NSAIDs will be tolerated, except the one involved in the historical reaction (or those which are chemically related).

• Urticaria/angioedema which appear between 1 to 6 hours to NSAID intake
• Bilateral periorbital angioedema after NSAID intake in children
• Nasoocular and/or asthmatic reaction after NSAID intake
• Historical reactions to other non-chemically related NSAID
• Chronic rhinosinusitis with nasal polyps
• Moderate-to-severe bronchial asthma
• Spontaneous chronic urticaria
• Inducible (dermographism, cholinergic) chronic urticaria
• Allergic respiratory disease to house dust mites
• Systemic reaction after flour-based food ingestion

Table 3.
Clinical findings suggesting a NSAID multiple reactor.

• Urticaria which appear within 1 h to NSAID intake
• Inmediate Systemic anaphylaxis after NSAID administration
• Historical tolerance to other non-chemically potent COX-1 inhibitor NSAID
• No concomitant associated diseases

Table 4.
Clinical findings suggesting a selective reactor status.

4.2 Principles to design the best controlled oral challenge for each clinical phenotype

The fundamental objectives of SBPCOC is threefold: **first**, to determine the clinical syndrome associated with the reaction after administration of the NSAID. In the case of systemic anaphylaxis due to an NSAID, the use of the NSAID involved during the clinical reaction is completely contraindicated. **Second**, determine the tolerance pattern to NSAIDs in an individual patient. A negative SBPCOC will determine the NSAID reintroduction of the treatment in the patient with NH. The stratification of NSAID according to their inhibitory potency of each of the COX1 and COX2 isoenzymes determines the likelihood of reaction and therefore the order of administration of NSAIDs during SBPCOC [15]. Thus, for example, in a patient with diclofenac and ibuprofen-induced NIUA, a SBPCOC with celecoxib or etoricoxib is highly likely to be tolerated (and therefore included in the self-care plan for patient management) while an SBPCOC with another strong COX-1 inhibitor NSAID is highly likely to induce a reaction, diagnose the patient, and determine a multiple pattern of reactivity. And **third** and finally, it allows us to initiate a desensitization procedure in patients with immediate respiratory or cutaneous reactions requiring a desensitization procedure that determines the introduction of an NSAID for anti-inflammatory or antiaggregant treatment if necessary. Desensitization is a procedure which will be discussed later and which determines a temporary state of tolerance while the administration of the NSAID persists.

4.2.1 SBPCOC with NSAID in patients with cross-reactive skin reactions

The approach to patients with the various phenotypes of cross-reactive skin reactions (NECD, NIUA, IPA and NIRU) is very similar. We always have to bear in mind that these patients seek our advice because they lack analgesic and anti-inflammatory alternative strategy, and their fundamental objective is to find an alternative that will solve their underlying disease without inducing a reaction. Therefore, the stratification of SBPCOC with NSAIDs plays an essential role in these cases, since it is directly related to a potential positive response during the challenge [15]. In virtually all cases these patients tolerate COXiB. Even in the rare cases where they do not tolerate a given COXiB, it is essential to expose them to another COXiB as it can be otherwise tolerated [16].

NSAIDs, which are COX2 inhibitors, but which inhibit COX-1 in a dose-dependent manner, such as meloxicam, would be the next alternative to propose in these patients. Paracetamol, a weak COX-1 and COX-2 inhibitor, is generally tolerated at the time of the clinical history by most patients. Its analgesic potential, but the absence of anti-inflammatory effects, is what finally decides the patient to go to the allergist looking for more appropriate alternatives. The use of potent COX1 and COX2 inhibitors, such as aspirin, ibuprofen, metamizole or diclofenac necessarily determine a reaction and therefore a diagnosis in this type of reaction [3, 8, 15].

4.2.2 SBPCOC with NSAID in patients with selective urticaria and anaphylaxis

The existence of an NSAID-induced anaphylaxis predicts the existence of a selective pattern that in many cases can already be detected in the clinical history, because the patient has tolerance to other non-chemically related NSAIDs. In a study of patients with NSAID anaphylaxis we have demonstrated that patients tolerated with impunity any NSAID, if we avoided the historically implicated NSAID or other chemically related NSAIDs during the SBPC [3]. In the group of patients with pyrazolone (metamizole, propyfenazone) anaphylaxis in Spain, skin tests (prick

test at 400 mg/mL and ID at 4 mg/mL) are extremely useful tools to detect an IgE-mediated allergy to these drugs. A positive metamizole skin test will always determine a safe SBPCDC if another non-pyrazolone NSAID is used during challenge. With other NSAIDs, in my experience, skin tests have extremely low sensitivity.

4.2.3 Treating reactions during SBPCOC

NSAID challenges always pose a certain risk, depending on the phenotype of the patient. Therefore, these challenges should be performed by experienced specialized nurses and allergists with the appropriate resources and access to emergency medical and intensive care.

4.3 The single-blind, placebo controlled oral challenge with NSAID: how do we do it?

The SBPCOC with NSAID is the gold standard for the diagnosis of skin NH. SBPCOC is indicated in 3 main scenarios: 1) to confirm/discard if the NSAID involved in the reaction is responsible (especially in those cases where the history is not very suggestive of a reaction to NSAID); 2) To confirm/exclude multiple reactivity among potent COX-1 inhibitors with another NSAID, usually aspirin; and 3) to identify potential alternative NSAIDs that are well tolerated by the patients.

However, there are several clinical situations in which it is contraindicated: If there is severe or uncontrolled bronchial asthma, active spontaneous urticaria/angioedema, pregnancy, active infection, and a recent vaccination ($\leq$ 1 week) and uncontrolled psychiatric disorders. Relative contraindications are also the use of beta-blockers or ACE-inhibitors.

We propose an order of administration of NSAIDs trying to stratify them according to the in vitro potency of COX-1 and COX-2 inhibition (**Table 2**) [3, 14]. This risk stratification management makes us start with, some of the selective COX-2 inhibitors (etoricoxib and celecoxib). Later, if there is no clinical response, the preferential COX-2 NSAIDs are continued (with a dose-dependent inhibitory effect on COX-1, as was the case with meloxicam). Thirdly, if there is no clinical response, a weak NSAID inhibiting both isoforms (e.g. paracetamol) will be administered; to continue, finally, with the potent COX-1 and COX-2 inhibitors.

Stratification of NSAIDs according to their COX-1 inhibition potency allows, to generate effective alternatives that these patients can take if the response during SBPCOC is negative; and to confirm the pattern of reactivity between NSAIDs that allows us to classify clinical phenotypes appropriately.

In the case of NECD the ideal is to carry out the study in a period of remission of chronic spontaneous urticaria. If this is not possible, we will titrate the treatment with antihistamines until the minimum effective control dose is achieved and then perform the SBPCOC. A complete withdrawal of all anti-histamines may determine a high rate of false positives in this subset of patients with NH [8].

The existence of NSAID anaphylaxis contraindicates the use of that specific NSAID or other structurally related one during SBPCOC [3, 8]. However, this type of reaction presents a selective pattern of sensitivity to NSAID, and even those with high COX-1 inhibition potency can be taken with impunity.

5. The management of skin NSAID hypersensitivity

The management of skin reactions to NSAIDs will aim to educate the patient on which drugs to avoid and to provide written therapeutic advice on which

alternatives to NSAIDs are potentially safe, after having tested adequate tolerance to them through SBPCOC.

Depending on the diagnosis and outcome of the SBPCOC, the patient can be advised to avoid only the culprit or all NSAID. Then, there might be a need to investigate the safety of other alternative analgesics. Selective COX-2 inhibitors are often a safe alternative, especially in cross-reactive patients who can tolerate acetaminophen. So, below 5% of patients with skin NH reacted to a selective COX-2 inhibitor [17, 18]. Even in those cases with a COXiB reaction, it is possible that the patient may tolerate other COXib without reaction and therefore an second challenge with an alternative COXIb must be performed [16].

Early presentations of periorbital angioedema as key features of cross-reactive reactions to NSAIDs in an atopic children also precluded the use of potent COX-1 inhibitor NSAID. Paracetamol is often well tolerated in these patients. The use of a cyclooxygenase-2-specific medication may not be feasible in this population, and limits options for other medical antiinflammatory treatment. However, Loh et al. have recently demonstrated that etoricoxib can be used as a safe alternative in older children (mean age 13,5 years) with hypersensitivity to multiple antipyretics [19].

Patient with selective urticaria or systemic anaphylaxis presents a selective pattern of sensitivity to NSAID, and even those with high COX-1 inhibition potency, but non chemically related, can be tolerated [3, 5].

Desensitization with aspirin is recommended by clinical guidelines only in patients with aspirin exacerbated respiratory disease and in cases of NECD or NIUA, in which it is strictly necessary to administer any NSAID as an anti-aggregate, anti-inflammatory or analgesic treatment [20]. The desensitization procedure consists of administering progressively increasing doses of aspirin until a reaction is provoked which is as controllable as possible, with the aim of inducing a post-reaction refractory period and which we will use to reach the therapeutic dose, culminating the desensitization process after the administration of a dose of aspirin (or other NSAID) without a reaction.

Rossini et al. have published a multicenter, prospective study that demonstrates that a rapid standardized desensitization protocol in patients with aspirin hypersensitivity undergoing coronary angiography is safe and effective, irrespective of the type of NH which have the patients. A low-dose aspirin could be safely continued without reaction in all patients throughout the next year [20].

6. Conclusions

We have clinically characterized a large population of patients with skin NSAID-induced reactions by means of controlled oral challenges, and we have proposed a working classification of these clinical entities, which can be recognized through the distinct clinical features and the challenge results. Skin NSAID hypersensitivity have showed at least 5 well-defined clinical phenotypes. This classification based on clinical phenotypes is a real and practical approach in the daily clinic, which will allow us to make the best-appropriated diagnostic and therapeutic decisions.

Conflict of interest

The authors declare no conflict of interest.

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