Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema

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Nonsteroidal anti-inflammatory drug (NSAID)-induced urticarial and angioedema reactions are among the most commonly encountered drug hypersensitivity reactions in clinical practice. Three major clinical phenotypes of NSAID-induced acute skin reactions manifesting with angioedema, urticaria, or both have been distinguished: NSAID-exacerbated cutaneous disease, nonsteroidal anti-inflammatory drug-induced urticaria/angioedema (NIUA), and single NSAID-induced urticaria and angioedema. In some patients clinical history alone might be sufficient to establish the diagnosis of a specific type of NSAID hypersensitivity, whereas in other cases oral provocation challenges are necessary to confirm the diagnosis. Moreover, classification of the type of cutaneous reaction is critical for proper management. For example, in patients with single NSAID-induced reactions, chemically nonrelated COX-1 inhibitors can be safely used. However, there is cross-reactivity between the NSAIDs in patients with NSAID-exacerbated cutaneous disease and NIUA, and thus only use of selective COX-2 inhibitors can replace the culprit drug if the chronic treatment is necessary, although aspirin desensitization will allow for chronic treatment with NSAIDs in some patients with NIUA. In this review we present a practical clinical approach to the patient with NSAID-induced urticaria and angioedema. (*J Allergy Clin Immunol* 2015;136:245-51.)

Key words: Aspirin, angioedema, nonsteroidal anti-inflammatory drugs, urticaria

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are second after antibiotics as the most common cause of drug-induced hypersensitivity reactions, affecting approximately 1% to 3% of the general population. However, in populations such as those with chronic rhinosinusitis, asthma, or chronic urticaria, the prevalence of NSAID hypersensitivity might

Abbreviations used

ASA: Acetylsalicylic acid
NECD: Nonsteroidal anti-inflammatory drug-exacerbated cutaneous disease
NIUA: Nonsteroidal anti-inflammatory drug-induced urticaria/angioedema
NSAID: Nonsteroidal anti-inflammatory drug
SNIUAA: Single nonsteroidal anti-inflammatory drug-induced urticaria/angioedema, anaphylaxis, or both

be even higher, affecting up to 20% to 30%.^{1,2} NSAID hypersensitivity reactions can be associated with multiple symptoms ranging in severity from transient rash to severe anaphylaxis, with the majority of reactions limited to the skin.³⁻⁵ NSAID-induced skin reactions usually develop within hours (rarely within minutes) after drug intake, manifesting as urticarial wheals, angioedema, or erythema multiforme. Less frequently observed are NSAID-triggered delayed skin reactions occurring more than 24 hours after dosing and manifest as either skin-specific (eg, exanthema, fixed drug eruption, toxic epidermal necrolysis, or Stevens-Johnsons syndrome) or other organ-specific manifestations (eg, aseptic meningitis or hypersensitivity pneumonitis).⁶

The purpose of this review is to present a practical clinical approach to the diagnosis and management of cutaneous reactions to aspirin and other NSAIDs.

CLASSIFICATION OF NSAID REACTIONS

The current classification of NSAID hypersensitivity reactions is based on timing, the clinical pattern of symptoms, and the presence or absence of cross-reactivity to other NSAIDs.⁷⁻⁹ An additional criterion is the presence of underlying chronic disease of the skin or respiratory tract, which is typical for some (10 cross-reactive types) but not all (single drug-induced type) reactions (Table I).¹⁰

Using this classification system, a physician can assess the putative pathomechanism of a reaction (allergic or nonallergic) related to the presence or absence of cross-reactivity at an early stage of the diagnostic process.¹¹ In the majority of patients, the mechanism of NSAID-induced skin symptoms occurs through the pharmacologic activity of aspirin and other NSAIDs through inhibition of the COX-1 enzyme. In susceptible subjects COX-1 inhibition results in the activation of inflammatory cells, which generate inflammatory mediators.¹⁰ These patients react to both aspirin and other chemically nonrelated NSAIDs (COX-1 inhibitors), and thus this type of hypersensitivity has been called cross-reactive. In patients with a history of reactions to a single NSAID

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TABLE I. Current classification of aspirin and NSAID-induced reactions⁸

Type of reaction	Clinical manifestation	Timing of reaction	Underlying disease	Cross-reactive	Putative mechanism
NSAID-exacerbated respiratory disease (NERD)	Respiratory	Acute	Asthma/rhinosinusitis	Cross-reactive	COX-1 inhibition
NECD	Cutaneous		Chronic urticaria		COX-1 inhibition
NIUA	Cutaneous		No or atopy		Probably COX-1 inhibition
SNIUAA	Cutaneous/anaphylaxis		No	Non-cross-reactive	IgE mediated
Single NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved	Delayed onset	No		T cell mediated

Types of reactions manifesting primarily as urticaria/angioedema are shown in boldface.

FIG 1. Patient with a history of chronic spontaneous urticaria exacerbated by ibuprofen and paracetamol (NECD) who had acute urticarial lesions 60 minutes after oral challenge with 117 mg of aspirin.

who are otherwise tolerant of other NSAIDs, including aspirin, an immunologic IgE-mediated mechanism can be suspected, and these patients could be called single-drug reactors.

Three major clinical phenotypes of hypersensitivity reactions to aspirin and other NSAIDs manifesting as urticaria, angioedema, or both can be distinguished.

NSAID-EXACERBATED CUTANEOUS DISEASE

Patients with chronic urticaria who experience hypersensitivity reactions to NSAIDs are now identified as having aspirin-exacerbated cutaneous disease or, more precisely, nonsteroidal anti-inflammatory drug-exacerbated cutaneous disease (NECD).⁸

Clinical presentation

Approximately 12% to 30% of patients with chronic spontaneous urticaria will experience an exacerbation of their skin symptoms within minutes to 4 hours when exposed to COX-1-inhibiting NSAIDs (Fig 1).^{12,13} In some patients the sensitivity to NSAIDs might precede the development of chronic urticaria.¹⁴ Analogous to patients with aspirin-exacerbated respiratory disease, they react to all COX-1-inhibiting NSAIDs, and despite the avoidance of NSAIDs, the underlying disease process continues (ie, avoidance of NSAIDs will not lead to resolution of chronic urticaria).¹⁵ On the contrary, the highly selective COX-2 inhibitors are typically well tolerated in this patient population.^{16,17}

Pathogenesis

NECD is the cutaneous corollary of NSAID-exacerbated respiratory disease in that reactions are triggered by NSAIDs with COX-1 inhibitory activity in doses reflecting their *in vitro* inhibitory potency against COX-1 isoenzyme.¹⁸ In patients with NECD, the inhibition of COX-1 enzyme leads to the release of cysteinyl leukotrienes by inflammatory cells.¹⁵

Various inflammatory cells and markers are activated in patients with NECD, leading to the hypersensitivity reaction. At baseline, these patients have increased urinary leukotriene E₄ levels, which are further increased during a positive drug challenge.¹⁹ Additionally, it has been shown that degranulation of basophils in patients with NECD is enhanced.²⁰ A mechanism that might trigger the activation of inflammatory cells is the inhibition of prostaglandin E₂ (PGE₂) synthesis. PGE₂, which acts through the EP2 receptor, stabilizes mast cells, and therefore the abrupt decrease in PGE₂ levels that occurs with COX-1 inhibition might lead to mediator release from inflammatory cells and the development of symptoms in susceptible subjects.²¹ Furthermore, aspirin can increase Syk kinase phosphorylation of the FcεRI signaling complex, facilitating mast cell activation.²² Increased mast cell reactivity might also be related to a genetic predisposition because of a variant of the FcεRIα subunit gene (*FCER1A*–344C>T), which is more common among patients with NECD.²³ Moreover, the role of autoimmunity in these reactions has been postulated²⁴ because a positive autologous serum skin test result²⁵ or autologous plasma skin test result²⁶ can distinguish NECD from single NSAID-induced urticaria/angioedema. To what extent platelets are involved in the pathogenesis of NECD remains to be established.^{27,28}

Diagnosis

The diagnosis of NECD first requires confirmation of the diagnosis of chronic urticaria, which by definition is the spontaneous development of urticaria that has been continuously or intermittently present for at least 6 weeks.²⁹ A careful history can confirm the diagnosis of NECD if the patient has previously reacted to NSAIDs or acetylsalicylic acid (ASA) with exacerbation of their underlying chronic urticaria. An aspirin or other specific NSAID challenge is the gold standard for determination of NECD. A single-blind, placebo-controlled 2-day aspirin challenge can be performed after the patient has been without any skin eruptions for 1 to 2 weeks.³⁰ On day 1, the patient receives a placebo to determine baseline activity, and on day 2, the patient receives escalating doses of ASA (71, 117, 312, and 500 mg) at 1.5- to 2-hour intervals.³¹ Most patients will react to a single

TABLE II. NSAID classes determined by similar chemical structures

Chemical class	Drugs
Salicylic acid derivatives	Aspirin (ASA), sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, olsalazine
Propionic acid derivatives (profens)	Ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen
Acetic acid derivatives	Indomethacin, tolmetin, sulindac, etodolac, ketorolac, diclofenac, aceclofenac, nabumetone
Pyrazolic derivatives (pyrazolones)	Metamizole, phenylbutazone, phenazone, aminophenazone, ampyrone, suxibuzone, sulfamazone, nifhenazone, pyrazolone, propyphenazone
Anthranilic acid derivatives (fenamates)	Mefenamic acid, flufenamic acid, tolfenamic acid
Enolic acid derivatives (oxicams)	Piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam
Para-aminophenol derivatives	Acetaminophen, paracetamol

dose of aspirin between 325 and 650 mg, with at least 1 hour to react after ingestion of aspirin. There is no role for skin testing in the diagnosis of NECD.

NSAID-INDUCED URTICARIA/ANGIOEDEMA

Aspirin and other NSAIDs can also induce urticaria, angioedema, or both in an otherwise healthy subject without a history of pre-existing chronic skin disease (eg, spontaneous urticaria).

Clinical presentation

The skin reaction usually appears within 1 hour of oral drug intake, but in some patients it can develop within 1 to 6 hours. Although in most situations urticaria and angioedema appear simultaneously, NSAID-induced angioedema without urticaria (specifically after ibuprofen and diclofenac) has been seen.³² Concomitant anaphylactic reactions have also been reported.³³ Up to 60% of patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema (NIUA) have atopic diseases (rhinitis and asthma), and positive immediate-type skin test responses to inhalant allergens (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) are common among these patients.^{34,35} Furthermore, NSAID hypersensitivity in patients without a history of chronic urticaria can also manifest as isolated periorbital angioedema.^{32,36,37} Among patients with NSAID-induced isolated periorbital angioedema, sensitization to house dust mite allergen is common as well, suggesting that it might be a subtype of NIUA.^{38,39} Earlier observations have proposed that NIUA can precede the appearance of chronic spontaneous urticaria by years¹⁴; however, a more recent study documented that the percentage of patients with NIUA having chronic spontaneous urticaria is not different from that among healthy control subjects.⁴⁰

Pathogenesis

Patients with NIUA cross-react to chemically nonrelated NSAIDs, and thus a similar mechanism of hypersensitivity related to COX-1 inhibition is proposed. A variant of leukotriene C₄ synthase (*LTC4*–444A>C) doubled the odds ratio for NIUA in one study, although such an association was not found in any other population.^{41,42} Together with another study documenting the association of NIUA with a thromboxane synthase polymorphism (*TBXAS1* rs6962291),⁴³ these data strongly support the COX-1 inhibition–related mechanism of reaction. However, as mentioned above, aeroallergen sensitization is common in patients with NIUA and might even be a prerequisite for the development of NSAID hypersensitivity.^{33,44,45} Thus the role of underlying atopy and IgE-related mechanisms remains to be established.

Diagnosis

A history of skin reactions to at least 2 NSAIDs with different chemical structures in patients without underlying chronic cutaneous disease have been shown to have high sensitivity for the diagnosis of NIUA.^{46,47} If the history is not clear and aspirin was not a culprit drug, an oral challenge with aspirin is recommended to confirm a cross-reactive type of NSAID hypersensitivity and to help differentiate NIUA from single NSAID-induced urticaria/angioedema. As in other cross-reactive types of NSAIDs, hypersensitivity skin testing with a culprit drug or drug-specific IgE in serum are not useful and hence not indicated.

SINGLE NSAID-INDUCED URTICARIA/ANGIOEDEMA, ANAPHYLAXIS, OR BOTH

Wheals, angioedema, and/or anaphylaxis induced by a single NSAID or by 2 or more NSAIDs with similar chemical structures (ie, belonging to the same chemical group; Table II) are typical for this type of NSAID hypersensitivity.⁴⁸

Clinical presentation

The most common symptoms are urticaria and angioedema, but in about one third of patients, anaphylaxis can develop, which could result in death.^{33,49} Symptoms can develop within minutes after drug injection or up to 1 hour after oral intake of the drug. Although almost all NSAIDs are capable of inducing this type of reaction, pyrazolones seem to be the most common triggers of single nonsteroidal anti-inflammatory drug-induced urticaria/angioedema, anaphylaxis, or both (SNIUAA [in countries where the drug is still used]), followed by diclofenac and paracetamol.^{50–52}

Pathogenesis

In the majority of patients, symptoms develop within minutes, typically less than 30 minutes, suggesting an immunologic IgE-related mechanism.⁵³ Patients tolerate chemically nonrelated NSAIDs well, even if they are potent COX-1 inhibitors. In a significant proportion of patients with SNIUAA, IgE specific to a culprit drug can be detected either by means of skin testing or immunoassays in serum.⁴⁸ However, the pathomechanism of these reactions seems to be more complex because hapten modification of human serum albumin by NSAIDs in patients with SNIUAA was found. Moreover, a glucuronide acyl modification of different lysine residues of albumin was reported for diclofenac, ketoprofen, and acetaminophen.^{54,55} *In vitro* prediction of an SNIUAA reaction on this basis is not yet feasible.

Spectrum of symptoms	Urticaria/ angioedema		Urticaria/ angioedema and/or anaphylaxis
Onset of reaction	1hour to 6 hours		Minutes to 1 hour
History of cross-reactivity	Reactions to several Cox-1 inhibitors		Reactions to single NSAID
Underlying chronic disorder	Chronic urticaria	Usually no or atopy	Usually No
Type of reaction	NECD	NIUA	SNIUAA
Putative mechanisms	Non-immunological		Immunological
Skin testing or serum IgE	Not relevant		May be diagnostic
Oral challenge with aspirin	To confirm cross-reactive type		To exclude cross-reactive type
Oral challenge with culprit NSAID	Yes		Not recommended

FIG 2. Diagnosis of urticaria/angioedema induced by NSAIDs.

Diagnosis

These patients usually react to other members of the same drug family and are tolerant of other chemically unrelated NSAIDs (Table II).⁵² The most reliable way to make the diagnosis of SNIUAA and exclude a cross-reactive type would be an oral challenge with aspirin. Tolerance of aspirin confirms a single drug type of hypersensitivity. Because the putative mechanism of SNIUAA involves IgE, skin testing with the culprit drug or identification of serum specific IgE is justified. Positive skin test results have been reported in most patients with a history of reactions to pyrazolone derivatives^{49,50,56}; however, the timing of testing after the reaction might be important because skin test reactivity subsides within a year of the reaction. The reliability of routine skin testing to other NSAIDs (including propionic acid derivatives) has not been documented in systematic studies, and there are no standardized protocols for nonpyrazolone NSAIDs.⁵⁷ The usefulness of drug-specific IgE detection in serum has not been well documented, and immunoassays are not commercially available. Although the diagnostic utility of a basophil activation test has been reported, these tests have not been validated and require further studies.⁵⁸

MIXED REACTIONS

Although the vast majority of NSAID-induced acute (within 24 hours) skin reactions can fall into one of the 3 phenotypes presented by the current classification, some patients can manifest atypical or blended reactions. Approximately 10% of patients with NECD will have respiratory symptoms (bronchoconstriction) resembling the reactions observed in patients with NSAID-exacerbated respiratory disease.⁵⁹ In a study by Doña et al,³³ who

reviewed 384 patients with NSAID-induced skin reactions, concomitant respiratory symptoms were reported by 18.2% of patients with cross-reactive reactions (patients with NIUA) and 4.6% of patients with single-drug reactions (patients with SNIUAA). Association of rhinoconjunctivitis with NSAID-induced skin reactions has been also reported.⁶⁰

DIAGNOSTIC ALGORITHM

Diagnosis of a specific type of hypersensitivity is a prerequisite for proper management of a patient with a history of NSAID hypersensitivity. Based on the current classification, a practical diagnostic algorithm to determine the type of NSAID hypersensitivity has been proposed^{8,61} and can be easily adapted when hypersensitivity is manifested with cutaneous symptoms (urticaria/angioedema, Fig 2). Although a detailed analysis of the patient's history might be sufficient to establish the diagnosis of a specific type of NSAID hypersensitivity, it is associated with relatively low specificity.⁶² In a study by Viola et al,⁶³ as many as 78.8% of patients with a historical reaction to an NSAID tolerated that NSAID in an oral challenge. Thus if the history is not strong, oral provocation challenges might be necessary to avoid overdiagnosis.⁶⁴ Currently, there is limited evidence for the use of *in vitro* testing.

MANAGEMENT

Once the diagnosis of NSAID hypersensitivity has been established, the mainstay of treatment is avoidance of NSAIDs.^{7,65} However, recommendations for management and alternative NSAIDs have to be tailored to a specific type of NSAID hypersensitivity (Table III).⁶⁶

TABLE III. Recommendations for management of patients with NSAID-induced urticaria/angioedema

	NECD	NIUA	SNIUAA
Type of reaction	Cross-reactive	Cross-reactive	Single drug; selective (IgE mediated)
NSAIDs to be avoided	All preferential COX-1 inhibitors	All preferential COX-1 inhibitors	All NSAIDs with similar chemical structure (same chemical class)
NSAIDs recommended	Selective COX-2 inhibitor*	Selective COX-2 inhibitors*	All NSAIDs with different chemical structures (different chemical class)
Aspirin desensitization	Feasible Not recommended	Feasible Recommended if avoidance is not possible (eg, treatment with aspirin in patients with cardiovascular disease)	Not recommended

*Oral office challenge with an alternative NSAID is recommend.

NECD

The highly selective COX-2 inhibitors (celecoxib and etoricoxib) are generally well tolerated in this patient population.¹⁶ There have been rare reports of these patients reacting to the COX-2 inhibitors, and therefore it is recommended that provocation tests for these drugs be performed in a controlled setting to confirm their tolerability.^{13,67} In some patients with NECD, low-dose ASA (81 mg) can be tolerated because it is usually less than the provoking dose. Furthermore, use of leukotriene-modifying drugs might be of benefit in conjunction with standard chronic urticaria management in patients with NECD.⁶⁸

Aspirin desensitization is not recommended in these patients. Although several case reports of successful desensitization have been reported, for the most part, the urticaria becomes intractable with continued attempts at aspirin exposure, leading to failure to achieve a desensitized state.⁶⁹

NIUA

Avoidance of the culprit drug and potentially cross-reactive compounds (COX-1 inhibitors) would usually prevent recurrence of urticaria/angioedema symptoms. However, if chronic intake of aspirin (eg, for cardiovascular disease) or other strong COX-1 inhibitors (eg, for osteoarthritis) is necessary, desensitization to aspirin can be performed because several protocols for desensitization are available.^{61,70,71}

SNIUAA

In a patient with hypersensitivity to a single NSAID (eg, diclofenac, ibuprofen, or ketoprofen), when the culprit drug has been identified, it can be replaced easily by another NSAID with an unrelated chemical structure but similar anti-inflammatory potency (Table II). Desensitization is not recommended.

CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

In susceptible subjects urticaria, angioedema, or both develop after NSAID intake, usually within hours (rarely within minutes). Physicians can follow a simple algorithm based on current classification, leading to diagnosis of the type of NSAID hypersensitivity. Identification of the specific type of hypersensitivity allows for identification of the proper management options. However, because the history of NSAID hypersensitivity is not very specific, in many instances an oral challenge test with the culprit drug might be necessary to confirm the diagnosis or an oral

challenge test with aspirin might be necessary for assessment of cross-tolerance.

It is essential to continue research on the validation of already available *in vitro* tests (eg, immunoassays for drug-specific IgE or basophil activation tests) and on the development of new tests, possibly based on genetic analysis.⁷² Future studies with high-throughput technology should allow for improvement in our understanding of pathomechanisms, better definition of current clinical phenotypes, and potential identification of emerging new phenotypes of NSAID hypersensitivity.^{73,74}

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