

Clinical Management of Adult Patients with a History of Nonsteroidal Anti-Inflammatory Drug–Induced Urticaria/Angioedema: Update

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In the large majority of previous studies, patients with a history of acute urticaria induced by nonsteroidal anti-inflammatory drugs (NSAIDs) seeking safe alternative drugs have undergone tolerance tests uniquely with compounds exerting little or no inhibitory effect on the cyclooxygenase 1 enzyme. In light of recently published studies, however, this approach seems inadequate and should be changed. The present article critically reviews the clinical management of patients presenting with a history of urticaria induced by a single NSAID or multiple NSAIDs and suggests a simple, updated diagnostic algorithm that may assist clinicians in correctly classifying their patients.

Key words: aspirin, drug allergy, nonsteroidal anti-inflammatory drug, urticaria

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drug class in the world. Their widespread use, further increased by the fact that, in many countries, some very popular compounds, such as acetylsalicylic acid (ASA), propionic acid derivatives, or paracetamol (acetaminophen), are present in over-the-counter drugs, is certainly the main cause for the increasing number of adverse reactions induced by these drugs that has been recorded worldwide. Although NSAIDs are generally well tolerated, they may induce a large spectrum of adverse reactions, some of which are potentially fatal. The most common adverse reactions linked to their inhibitory effects on the cyclooxygenase 1 (COX-1) enzyme are gastritis and peptic ulcers. Other adverse reactions include hepatitis and liver toxicity, anemia, interstitial nephritis, erythema multiforme, toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, and (cutaneous and/or respiratory) immediate allergic and pseudoallergic reactions. The term *pseudoallergic* defines reactions characterized by clinical symptoms that suggest an immune pathogenesis but for which there

is no evidence of an immune-mediated mechanism.¹ Most pseudoallergic reactions to NSAIDs are presently considered to be associated with their inhibitory effects on the COX-1 enzyme. Urticaria/angioedema is the most common adverse reaction induced by NSAIDs seen by allergologists and probably represents the most frequent drug-induced skin disorder; it has been estimated that it occurs in 0.1 to 0.3% of subjects exposed to NSAIDs.^{2,3}

One has to keep in mind that most patients presenting with an unequivocal history of urticaria (with or without angioedema) following the ingestion of NSAIDs are, reasonably, already convinced that they cannot take the offending drug any more. Invariably, their question is "What can I take in case of headache, pain, or fever?" The present article focuses on the clinical management of patients with NSAID-induced urticaria/angioedema in view of recently published literature. The present review was written on the basis of a literature search carried out using *PubMed/MEDLINE*. Articles dealing with NSAID-induced urticaria published during the last 25 years were considered.

Multiple- versus Single-NSAID Intolerance

Multiple-NSAID Intolerance

It is well known that up to 30% of patients with chronic urticaria experience flares of hives following the ingestion of aspirin or chemically unrelated NSAIDs^{4–6}; in general,

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offending drugs exert an inhibitory effect on the COX-1 enzyme. Unlike immunoglobulin (Ig)E-mediated hypersensitivity, this kind of intolerance frequently occurs on the first administration of a certain drug and parallels the clinical activity of the underlying chronic urticaria; drugs that induced severe skin reactions during a phase of moderate activity of the disease may be tolerated during a subsequent phase of remission.

Differently from chronic urticaria patients, the possible existence of otherwise normal subjects with multiple-NSAID intolerance (defined as several distinct episodes of acute urticaria following the ingestion of chemically unrelated NSAIDs in the absence of any episode of spontaneous urticaria) has been a matter of debate for a long time. The 1998 edition of the most authoritative textbook of allergology still stated that “after earlier exposure to a specific ASA or NSAID, otherwise normal-appearing individuals may develop urticaria, angioedema, or anaphylaxis on re-exposure to the same drug. In this type of reaction, cross-reactivity between ASA and NSAIDs does not occur.”⁷ However, during the last two decades, a number of clinical studies assessing the tolerance to alternative NSAIDs in normal subjects with a history of single-NSAID intolerance found that some of them reacted to compounds that were chemically distinct from the offending ones and that were, hence, expected to be tolerated.^{8–15} Further, in one study specifically aiming to clarify this point, 36% of 261 subjects without chronic urticaria were finally found to have multiple-NSAID intolerance on the basis of the clinical history and oral tolerance test results.¹⁶ Interestingly, and similarly to patients with aspirin-exacerbated respiratory disease (AERD), in patients with acute urticaria induced by distinct NSAIDs (both with and without chronic urticaria), cross-reactions occurred mainly among COX-1-inhibiting drugs,^{13,17} whereas drugs exerting little effect on the COX-1 enzyme (eg, nimesulide, paracetamol, COX-2 inhibitors)^{10,11,18–24} and NSAIDs characterized by different mechanisms of actions (floctafenine, paracetamol) or opiate agonists with analgesic activity (eg, tramadol)^{9,11,15,25} were generally well tolerated. These observations clearly suggested that COX-1 inhibition plays a pathogenic role in immediate pseudoallergic skin reactions induced by NSAIDs. COX blockade “deviates” arachidonic acid metabolism toward the 5-lipoxygenase pathway, and this eventually results in the production of cystinyl leukotrienes (Cys-LTs = LTC₄, LTD₄, LTE₄). Cys-LTs are potent mediators of inflammatory processes, and there is some evidence that they may act as mediators in urticaria. Their intradermal injection elicits a wheal and

flare reaction either in chronic urticaria patients or in normal subjects,²⁶ and on a molar basis, Cys-LTs are 100 times more potent than histamine in inducing wheal and flare reactions. Recent studies showed that both chronic urticaria patients with NSAID intolerance and patients with AERD are characterized by elevated baseline urinary LTE₄ levels and found that such levels are markedly increased by aspirin administration.^{27,28} The central role played by Cys-LTs as mediators of aspirin-induced urticaria (and probably of multiple-NSAID reactivity without chronic urticaria) is indirectly confirmed by studies showing a protective role by leukotriene receptor antagonists.^{29,30} Interestingly, several studies found an association between multiple-NSAID intolerance in otherwise normal subjects and atopic status.^{10,12,13,15}

Single-NSAID Intolerance

Intolerance to single NSAIDs has been reported by several studies. Offending drugs include pyrazolones,^{24,31,32} paracetamol,^{33–38} aspirin,³⁹ ketorolac,⁴⁰ nimesulide,⁴¹ and celecoxib.^{42,43} It has been inferred that in a proportion of these cases, the pathogenesis is really IgE mediated, as sometimes suggested by positive skin tests with the offending compounds. Moreover, a genetic proneness to NSAID-induced anaphylactic reactions seems to exist.⁴⁴ In patients with single-NSAID intolerance, cross-reactions may occur within the same chemical family but not between chemically distinct drugs, and this type of reaction never occurs on first exposition. However, the possibility that reactions to single NSAIDs are COX-1 mediated also cannot be ruled out. These patients might for some reason show a different threshold or different gene polymorphisms and develop multiple-NSAID intolerance at a later date. In effect, in a previous study, approximately 35% of otherwise normal patients with a history of urticaria induced by a single NSAID developed chronic urticaria 1 to 10 years after the adverse drug reaction,⁴⁵ suggesting that chronic urticaria might remain in a state of latency for years, with NSAID intolerance as the only sign of its presence.

New Classification of Immediate Allergic and Pseudoallergic NSAID-Induced Reactions

Based on the studies reported above, in 2001, Stevenson and colleagues proposed a novel classification of allergic and pseudoallergic reactions induced by NSAIDs that includes six distinct categories of patients (Table 1).⁴⁶ Interestingly, skin reactions (urticaria/angioedema) are

Table 1. Classification of Allergic and Pseudoallergic Reactions Induced by Nonsteroidal Anti-Inflammatory Drugs

	Type of Allergic/Pseudoallergic Reactions	Underlying Disorder	Cross-Reaction/Reaction on First Exposure
1	Asthma and rhinitis exacerbated by NSAID	Asthma/sinusitis/polyposis	Yes
2	Urticaria/angioedema exacerbated by NSAID	Chronic urticaria	Yes
3	Urticaria/angioedema from single NSAID	None	No
4	Acute urticaria/angioedema from multiple NSAIDs	None	Yes
5	Anaphylaxis from single NSAID	None	No
6	Blended respiratory/cutaneous reaction from one or more NSAIDs	Asthma/rhinitis/polyposis or none	Yes or No

NSAID = nonsteroidal anti-inflammatory drug.

present in five of six categories. This classification was subsequently adopted in the last edition of the treatise *Allergy: Principles and Practice*.⁴⁷ Notably, the difference between type 2 and type 4 multiple-NSAID intolerance is based uniquely on the presence or absence of chronic urticaria as an underlying disorder. Recent studies seem to abolish even this distinction as

1. type 4 subjects show an extremely high prevalence of positive reactions on an autologous serum skin test,⁴⁸ a typical feature of patients with autoreactive chronic urticaria. A positive autologous serum skin test has been associated with circulating IgG autoantibodies specific for IgE or for the high-affinity IgE receptor FcεRI, present on basophils and mast cells⁴⁹
2. approximately 35% of otherwise normal patients with a history of single- or multiple-NSAID intolerance (urticaria) develop chronic urticaria 1 to 10 years after the adverse drug reaction⁴⁵

Diagnostic Workup

In view of the possible distinct pathogenesis underlying multiple- or single-NSAID reactivity, the most important clinical point to establish is whether the patient presenting with a history of NSAID-induced urticaria/angioedema is a monoreactor or a multireactor. To this end, both a thorough interview and oral challenge tests with properly chosen alternative substances are essential. A classification of the most important NSAIDs according to their inhibitory effect on COX isoenzymes is shown in Table 2.

A confirmative provocation test with the reported offending drug is not warranted for the following reasons:

1. In monosensitized patients with IgE-mediated hypersensitivity, the challenge test might cause severe, even life-threatening adverse reactions.

2. In the clinical practice, the offending drug can, in most instances, be substituted with a number of equally effective but chemically distinct compounds.

In patients with a history of urticaria/angioedema caused by a single COX-1 inhibitor (eg, diclofenac, piroxicam, naproxen, aspirin), tolerance tests should start with a chemically distinct COX-1 inhibitor. There are several reasons why these patients should be challenged first with another nonselective COX inhibitor rather than with a selective COX-2 inhibitor. First, this is the only way to establish whether the patient is really monosensitized (ie, if the patient may take any NSAID other than the offending one) or if the reported reaction represents the first sign of a multiple-NSAID intolerance. Second, the long-term use of COX inhibitors has been associated with

Table 2. Classification of the Most Commonly Employed NSAIDs According to Their Inhibitory Effect on COX Isoenzymes

COX-1/COX-2 inhibitors
Salicylates (aspirin, diflunisal, salsalate)
Oxicams (piroxicam)
PAD (ibuprofen, naproxen, ketoprofen, fenpropfen, flurbiprofen)
Arylacetic acids (indomethacin, etodolac, sulindac, diclofenac, tolmetin)
Fenamates (meclofenamate, mefenamic acid)
Pyrolopyrrole (ketorolac)
Pyrazolones (phenylbutazone, oxyphenbutazone, feprazone, noramidopyrine)
Weak COX-1/COX-2 inhibitors
Paracetamol
Preferential COX-2 inhibitors
Nimesulide, meloxicam
Selective COX-2 inhibitors
Coxibs (eg, etoricoxib, rofecoxib, celecoxib)

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; PAD = propionic acid derivatives.

an increase in cardiovascular events,⁵⁰ and this has brought about the withdrawal of most of them from the market; presently, the only surviving drug of this class is etoricoxib, which is, however, under examination by governmental drug agencies. Similarly, floctafenine was withdrawn from the market some years ago. As a consequence, the spectrum of NSAIDs exerting little or no inhibitory activity on COX-1 is presently very limited, including only nimesulide, paracetamol, and meloxicam. Third, the anti-inflammatory and/or analgesic activity of these remaining substances (nimesulide, paracetamol, meloxicam) is, in most cases, inferior to nonselective COX inhibitors and not sufficient to control adequately chronic inflammatory disorders, such as arthritis.

If the alternative COX-1 enzyme-inhibiting drug is tolerated, the patient is diagnosed as having single-drug intolerance, and no further tests are needed. In contrast, intolerance to the challenged drug suggests multiple-NSAID intolerance, and further challenges with drugs exerting little or no inhibitory activity on the COX-1 enzyme (eg, nimesulide, coxibs, paracetamol, tramadol) should be performed to detect at least some tolerated drugs. Two very recent studies clearly address these aspects. In the first one, only 28 of 117 (24%) otherwise normal subjects with a history of acute urticaria induced by a single NSAID other than aspirin did not tolerate aspirin on single-blind, placebo-controlled oral challenges, with no differences between patients reactive to different NSAIDs; 5 of these 28 (18%) subjects also did not tolerate NSAIDs exerting little or no inhibitory activity on the COX-1 enzyme on subsequent oral challenges.⁵¹ In the second study, of 40 otherwise normal subjects with a history of acute urticaria following the ingestion of aspirin, 24 (60%) did not tolerate ketoprofen on single-blind, placebo-controlled oral challenges.⁵² On subsequent challenges, 3 of 8 (37%) ketoprofen reactors did not tolerate nimesulide. Three ketoprofen reactors reported the onset of spontaneous recurrent urticaria 1 to 3 years after the challenge tests. The choice of aspirin and ketoprofen as challenged substances in these two studies is based on their ranking among the strongest COX-1 inhibitors.⁵³ These two studies show that oral challenges with alternative COX-1 inhibitors are essential to establish whether subjects with a history of urticaria induced by a single NSAID are really single-NSAID reactors; in these subjects, weak COX-1 inhibitors should be challenged subsequently only in the case of multiple-NSAID intolerance. One further interesting observation coming from these studies is that patients with a history of aspirin-induced urticaria seem more prone to develop multiple-NSAID intolerance than patients with a history of urticaria

induced by another NSAID (60% vs 24%). This finding is in keeping with the observations of another study that both multiple- and single-NSAID reactors with a history of aspirin-induced urticaria seem at higher risk of chronic urticaria than patients with a history of single intolerance to NSAIDs other than aspirin.⁴⁵

Patients already presenting with a history of multiple-NSAID intolerance, with or without underlying chronic urticaria, should directly undergo oral tolerance tests with drugs exerting little or no COX-1 inhibition.⁵³

In patients with chronic urticaria, a state of moderate activity of the underlying disease will probably avoid false-negative results. In these patients, it is also essential that the challenged drug induces an unequivocal exacerbation of underlying urticaria to produce a positive result. In doubtful cases, patients with active urticaria should be challenged a second time to confirm that any reaction or exacerbation is truly due to the drug being tested.

Finally, in patients with a history of an allergic or anaphylactic reaction to ASA who need aspirin as a prophylactic treatment for coronary artery disease or for angioplasty or stent procedures, the safest procedure is probably to give alternative prophylactic substances, such as indobufen, ticlopidine, clopidogrel, or dipyridamole.

The suggested diagnostic workup is shown in Figure 1. Since evidence that patients with a history of NSAID-induced anaphylaxis may cross-react to chemically unrelated NSAIDs is lacking, such patients should be managed exactly as those with a history of urticaria induced by a single NSAID. In this sense, the proposed algorithm simplifies that previously suggested by Sanchez-Borges and colleagues.⁵⁴

Oral Tolerance/Provocation Tests

Practically, oral tolerance/provocation challenges are carried out, giving patients increasing doses of the drug under consideration until the therapeutic dose is reached. In general, based on previous studies from this allergy centre,^{14–16,41,51,52} two doses per substance (corresponding to one-quarter and three-quarters of a therapeutic dose) given at 1-hour intervals seem to be a safe, convenient, and sensitive way to detect multiple-NSAID intolerance. Patients should be kept under observation for at least 1.5 hours after the last provocative⁵⁵ dose as most adverse reactions occur within this short time. In otherwise normal subjects (ie, patients without a history of chronic urticaria), oral tolerance tests can be carried out in an open fashion. In subjects with chronic urticaria, it might be necessary to carry out these tests in a single-blind,

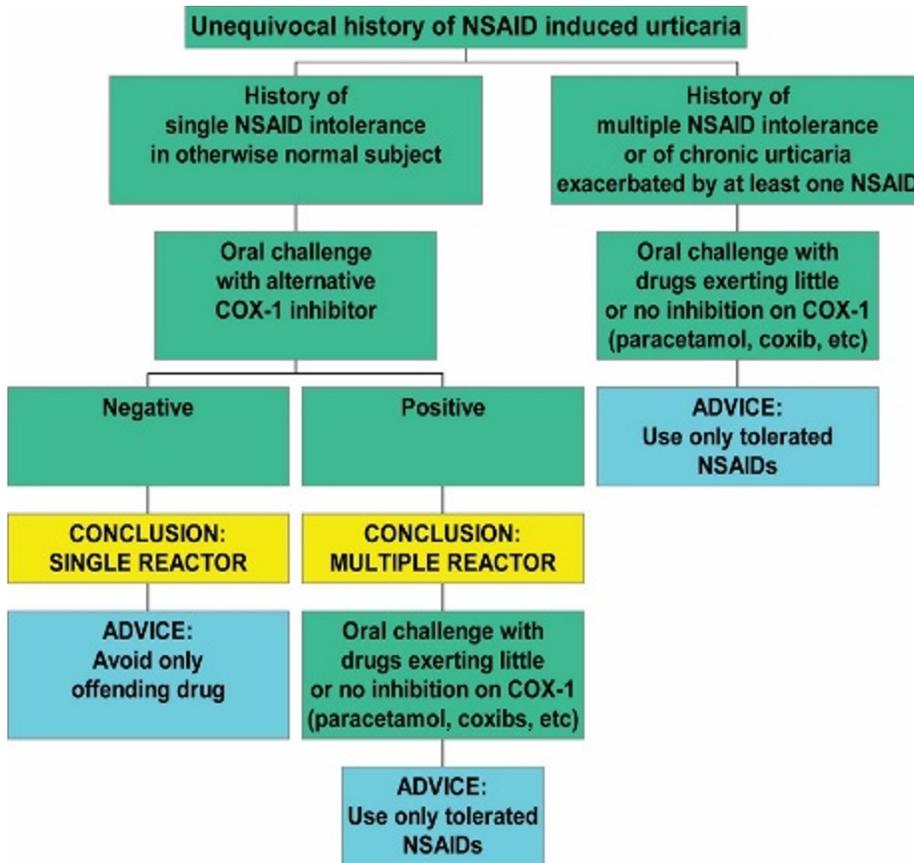


Figure 1. Diagnostic workup in patients intolerant to nonsteroidal anti-inflammatory drugs (NSAID). COX = cyclooxygenase.

placebo-controlled manner. Only the appearance of unequivocal urticaria/angioedema should be considered a positive response.

Conclusion

In the absence of reliable *in vivo* and *in vitro* tests, oral challenge tests remain the only way to assess tolerance or intolerance to specific NSAIDs in subjects with a history of urticaria induced by these substances and, hence, to respond satisfactorily to patients' requests and needs. Progress in the knowledge of the pathogenesis of immediate allergic and pseudoallergic reactions induced by NSAIDs, along with the observations coming from recent studies of oral challenges with alternative anti-inflammatory drugs, has led to a simplification of our approach to patients with a history of NSAID-induced urticaria.

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