

Clinical Management of Patients with a History of Urticaria/Angioedema Induced by Multiple NSAIDs: An Expert Panel Review

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Key Words

NSAID • Urticaria • Cross-reactivity • Oral challenge tests • COX-1 • COX-2 • Nonsteroidal anti-inflammatory drug hypersensitivity

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most frequent causes of drug-induced urticaria/angioedema worldwide. Recent review articles have classified patients experiencing NSAID-induced urticaria/angioedema into different categories, including single reactors, multiple reactors, and multiple reactors with underlying chronic urticaria. Each of these categories requires a different clinical approach. The present article, written by a panel of experts, reports the main recommendations for the practical clinical management of patients with a history of urticaria/angioedema induced by multiple NSAID based on current knowledge.

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Introduction

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 nonsteroidal anti-inflammatory drugs (NSAIDs) [1–3]. This subset of chronic urticaria patients generally reacts to drugs exerting an inhibitory effect on the COX-1 enzyme and tolerates selective COX-2 inhibitors [4–6]. It is possible that these patients show a specific genetic profile [7–9] although more studies are needed to clearly establish this. Differently from chronic urticaria patients, the existence of otherwise normal subjects with multiple NSAID hypersensitivity (defined as two or more 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 until recently. 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 hypersensitivity found that a not negligible percentage reacted to compounds that were chemically distinct from the offending

Table 1. Classification of the most commonly employed NSAIDs according to their inhibitory effect on COX isoenzymes

		COX-1 inhibition [42]
COX-1/COX-2 inhibitors	Arylacetic acids (indomethacin, etodolac, sulindac, diclofenac, tolmetin) Fenamates (meclofenamate, mefenamic acid) PAD (ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen) Piroxicam Pyrazolones (phenylbutazone, oxyphenbutazone, feprazone, noramidopyrine) Pyrrolo-pyrrole (ketorolac) Salicylates (aspirin, diflunisal, salsalate)	Ketorolac 100% Flurbiprofen 96% Aspirin 92% Ketoprofen 91% Ibuprofen 88% Naproxen 85% Indomethacin 83% Tolmetin 83% Fenoprofen 80% Meclofenamate 73% Piroxicam 70% Sulindac 68% Diclofenac 66% Etodolac 28%
Weak COX-1/COX-2 inhibitors	Paracetamol	
Preferential COX-2 inhibitors	Meloxicam, nimesulide	Nimesulide 40% Meloxicam 28%
Selective COX-2 inhibitors	Coxibs (celecoxib, etoricoxib, rofecoxib, etc.)	Celecoxib 60% Rofecoxib 18%
PAD = Propionic acid derivatives.		

ones and that were, hence, expected to be tolerated [10–17]. In one study, 36% out of 261 subjects with a history of NSAID-induced urticaria, but without spontaneous chronic urticaria, were finally found to have multiple NSAID hypersensitivity (multiple NSAID reactors) based on their clinical history and oral tolerance test results [18]. In a very recent study by Doña et al. [19], 76% of 659 otherwise normal NSAID-sensitive subjects were found to be cross-reactive to chemically unrelated NSAIDs.

Remarks on Pathogenesis

In most studies, similarly to patients with AERD (aspirin-exacerbated respiratory disease), in patients with acute urticaria induced by distinct NSAIDs (both with and without underlying chronic urticaria) cross-reactions occurred mainly among COX-1-inhibiting drugs [15, 20], whereas drugs exerting little effect on the COX-1 enzyme (e.g. nimesulide, paracetamol, meloxicam, and coxibs) [6, 12, 13, 21–29] as well as NSAIDs characterized by different mechanisms of action (floctafenine) or opiate agonists with analgesic activity (e.g. tramadol) [4, 11, 13,

17] are generally well tolerated. These observations, although obtained in part in patients with underlying chronic urticaria, clearly suggest that COX-1 inhibition plays a pathogenic role in subjects with multiple NSAID cutaneous hypersensitivity. The role played by cys-LTs as mediators of aspirin-exacerbated urticaria in some patients with spontaneous chronic urticaria could be hypothesized on the basis of preliminary studies reporting a protective role by leukotriene receptor antagonists [30, 31]; further, one study showed the presence of common eicosanoid alterations in aspirin reactors with underlying urticaria and asthma [32]. Whether the same mechanism is involved in otherwise normal patients with multiple NSAID reactivity has not been established yet. However, the fact that a variable proportion of these patients ends up with chronic urticaria supports a similarity in the pathogenesis [33]. A classification of the most important NSAIDs according to their inhibitory effect on COX isoenzymes is shown in table 1.

Interestingly, several studies have found an association between multiple NSAID hypersensitivity in otherwise normal subjects and atopic status [12, 14, 15, 17, 19, 34].

Table 2. Proposed classification of hypersensitivity reactions induced by NSAIDs

Types of allergic/hypersensitivity reactions	Underlying disorder	NSAID cross-reaction
1 Aspirin-exacerbated respiratory disease	Asthma/sinusitis/polypsis	Yes
2 Aspirin-exacerbated cutaneous disease	Chronic urticaria	Yes
3 Multiple reactivity to NSAIDs (in some cases preceding chronic urticaria)	None	Yes
4 Immediate selective responder (possibly IgE mediated)	None	No
5 Delayed selective responder (T cell mediated)	None	No

Classification of NSAID-Induced Hypersensitivity Reactions

In 2001, Stevenson et al. [35] proposed a classification of hypersensitivity reactions induced by NSAIDs that includes 6 distinct categories of patients. This panel believes that such a classification can be further simplified following the recent EAACI/ENDA/GA2LEN review ([36]; table 2). Interestingly, skin reactions are present in 4 out of 5 categories.

Diagnostic Workup Step by Step

Aim of the Diagnostic Workup

In view of the possible distinct pathogenesis underlying multiple or single NSAID hypersensitivity, it is essential to establish whether the patient is a mono- or a multi-NSAID reactor.

Validating Clinical History

Patients should be thoroughly interviewed about their reactions to NSAIDs. Two factors in the patient's history have to be considered: reliability and the number of reportedly offending drugs.

Reliability (Does Clinical History Unequivocally Suggest NSAID Hypersensitivity?)

In drug hypersensitivity reactions, the reliability of the clinical history depends on a number of variables, including the type and duration of clinical symptoms, the time interval between drug intake and the appearance of symptoms, response to treatment, and possibly the time interval between the reported adverse drug reaction and the allergologic examination.

Two situations may occur:

Doubtful History of NSAID Reactions. If the clinical history is not reliable (e.g. if the patient took several drugs at the same time, and/or if he/she is not able to recall ex-

actly the offending compound, which is often the case when adverse reactions occurred years before) a confirmative drug provocation test with the reportedly offending drug is warranted. This might hold true also in patients reporting hypersensitivity to more than one chemically distinct NSAID, as in a recent study more than three fourths of the patients reporting NSAID intolerance were able to tolerate the reportedly offending drugs upon challenge; in that study, NSAID hypersensitivity (i.e. a positive challenge) was associated with a younger age, a history of immediate reactions, male gender, and a time interval <1 year from the adverse reaction [37]. However, thorough history taking is always essential, as in another study on both single and multiple NSAID reactors the large majority of subjects with a history of reactions to multiple, chemically unrelated NSAIDs reacted on subsequent challenge with the offending drugs [38]. In case of a doubtful history of multiple reactions, the diagnostic approach is still a matter of debate. Some experts suggest that challenges should start with the drug exerting the lowest COX-1-inhibiting effect followed, in case of a negative response to this drug, by the culprit drug occupying the following rank (in terms of low COX-1-inhibiting effect). Obviously, a positive response upon the first challenge would completely validate the clinical history and confirm the diagnosis of NSAID hypersensitivity. Alternatively, others suggest a first challenge with aspirin (if aspirin is not among the culprit drugs) in order to validate the clinical history and, in case of a negative response, to move on challenging the reportedly culprit drug in order to confirm the hypersensitivity.

The Clinical History Is Clear-Cut. A clinical history can be considered unequivocal if the adverse reaction occurred within 6 h after the intake of a single drug exactly recalled by the patient or recorded by a physician or an emergency department staff, or if two or more reactions to the same or distinct NSAIDs taken in different times are reported. In this case, the need to perform confirmative provocation tests with the reportedly offending

drug(s) is a matter of debate [22, 37, 38]. Many researchers believe that in these cases provocations are not warranted for the following reasons:

- a clear positive clinical history is in most cases associated with positive confirmative provocation, particularly in subjects reporting hypersensitivity reactions to more than one NSAID [22, 38];
- challenges with the putative offending drug might cause severe, even life-threatening adverse reactions;
- an alternative drug which is equally effective, but chemically distinct, probably exists and should be sought.

For the management of patients reporting an unequivocal clinical history see below.

Number of Reportedly Offending Drugs

Two cases may occur:

Unequivocal History of Urticaria/Angioedema Caused by One Identified Single NSAID and Tolerance to Other NSAID Unknown. A subject like this should be challenged first with a chemically distinct and stronger COX-1 inhibitor (e.g. diclofenac, piroxicam, naproxen, aspirin, etc.) as this is the only way to establish whether he/she is really monosensitized (i.e. 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 hypersensitivity. In these patients, starting challenge tests with drugs exerting little inhibition on COX-1 (e.g. nimesulide, paracetamol, meloxicam) is not recommended as the anti-inflammatory and/or analgesic activity of such substances is, in most cases, inferior to that of nonselective COX inhibitors and not sufficient to adequately control chronic inflammatory disorders, such as arthritis. If the alternative COX-1 enzyme-inhibiting drug is tolerated, the patient is diagnosed as having single drug hypersensitivity and no further tests are needed. In contrast, the occurrence of a reaction to the challenged drug suggests multiple NSAID hypersensitivity. Some recent studies clearly address these aspects. In one study [39] only 28/117 (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 historically offending NSAIDs; 5 of these 28 (18%) patients also failed to tolerate NSAID exerting little or no inhibitory activity on the COX-1 enzyme on subsequent oral challenges. The same proportion of aspirin reactors among otherwise normal subjects with a history of single NSAID intolerance was detected in a subsequent report [40]. In another study of 40 otherwise normal subjects with a history of acute ur-

ticaria following the ingestion of aspirin, 24 (60%) patients did not tolerate ketoprofen on single blind placebo-controlled oral challenges [41]. One interesting observation coming from these studies is that patients with a history of aspirin-induced urticaria seem more prone to develop multiple NSAID hypersensitivity than patients with a history of urticaria induced by other NSAIDs (60 vs. 24%) [41]. This finding is in keeping with the observation that both multiple and single NSAID reactors with a history of aspirin-induced urticaria seem at a higher risk for chronic urticaria than patients with a history of single intolerance to NSAIDs other than aspirin [34].

Unequivocal History of Urticaria/Angioedema following the Ingestion of Two or More Chemically Unrelated NSAIDs (in Patients with or without Chronic Urticaria). This patient should be classified as a multiple NSAID reactor and challenged with drugs exerting little or no inhibitory effect on the COX-1 isoenzyme [42]. Two or more episodes with at least two chemically unrelated drugs should be considered enough for the diagnosis in the majority of cases [38].

Tolerance Tests with NSAIDs in Multiple Reactors

Multiple NSAID reactors (diagnosed by a clinical history or by proper drug provocation tests, as indicated above) should undergo further oral tolerance tests with drugs exerting little or no inhibitory activity on the COX-1 enzyme (e.g. nimesulide, coxibs, paracetamol, meloxicam, tramadol) in order to detect compounds to be safely used in everyday life. These drugs show different pharmacological effects, with paracetamol being mainly analgesic and antipyretic, coxibs anti-inflammatory drugs, and tramadol an analgesic active on CNS. Thus, it is suggested that patients be challenged with all three of them. Nimesulide is also an anti-inflammatory drug but its use is declining in most countries due to reported severe adverse effects. Similarly, most coxibs have been withdrawn from the market due to severe cardiovascular side effects.

How to Perform Oral Challenges with NSAIDs

Several protocols have been proposed and employed over the years. Based on the available literature, the most commonly followed one is based on the oral administration of one fourth and three fourths of a normal therapeutic dose 1 hour apart in a single blind fashion, keeping the patient under observation for 2 h after the last administra-

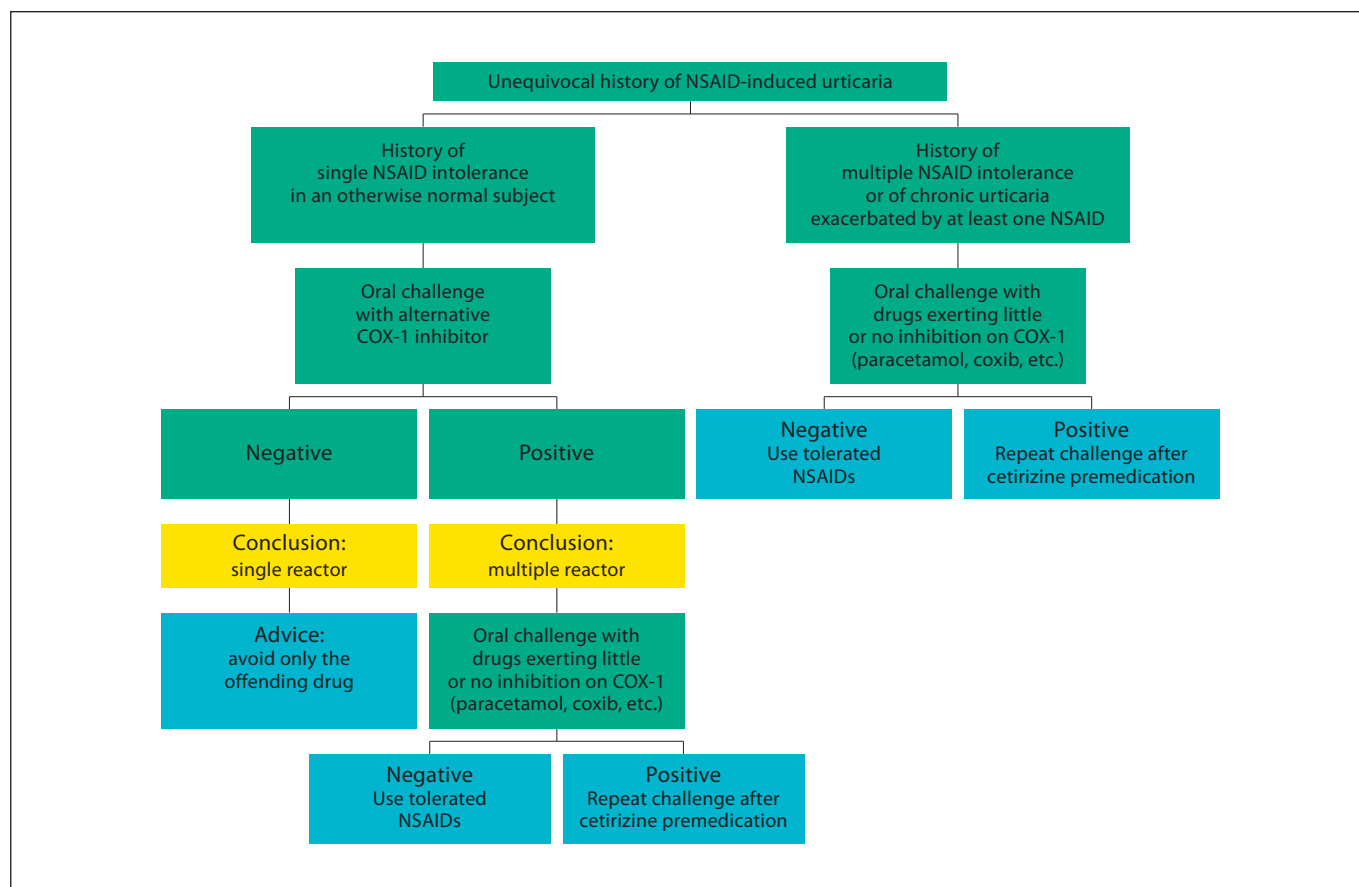


Fig. 1. Diagnostic workup of patients intolerant to NSAID.

Table 3. Some currently available NSAIDs used as alternative drugs for oral challenges and doses given in subjects with a history of NSAID hypersensitivity

Drug challenged	Patient history	First provocative dose	Last provocative dose	Reference
Paracetamol	Single and multiple reactors	10–125 (500) ^a	100–500	12–14, 17–19, 38, 46
Nimesulide	Single and multiple reactors	5–50 (100) ^a	50–100	12, 13, 17, 18, 23, 38, 46
Piroxicam	Single and multiple reactors	5–10	15–20	14, 19, 20
Diclofenac	Single and multiple reactors	12.5–25	25–50	14, 19
Dipyrrone	Multiple reactors	10–50	250–300	14, 19
Mefenamic acid	Single and multiple reactors	50	250	14
Ibuprofen	Multiple reactors	150	300	19
Ketoprofen	Single and multiple reactors	10–20	50–60	14, 40
Indomethacin	Multiple reactors	10	20	19
Aspirin	Single and multiple reactors	10–125	250–500	14, 16, 19, 39, 40
Etoricoxib	Multiple reactors	22.5–30 (90) ^a	60–67.2	6, 45, 49–51
Meloxicam	Single and multiple reactors	1.87–7.5	5.63–7.5	23, 28

^a These drugs were given as a single provocative dose in patients premedicated with cetirizine [46].

tion [13, 28]. Although in some cases adverse reactions may be more delayed, such a protocol fits for most patients, is not too time consuming, and is sufficiently safe. However, it should be considered that according to the severity of symptoms reported by the patients the starting dose as well as subsequent incremental doses may be lower, and more steps may be necessary to reach the goal of a normal therapeutic dose [19]. Since in rare cases adverse reactions may be delayed, some authors suggest giving a full therapeutic dose of the drug after an interval of 24 h for 2 consecutive days in order to ascertain tolerance beyond any doubt [19, 43]. A summary of the most commonly used challenge doses is shown in table 3.

Interpreting the Results of Oral Challenges

It is essential that the drug used during the challenge test can induce unequivocal symptoms in order to produce a positive result. In doubtful cases, patients should be re-challenged to confirm that the reaction is truly due to the drug being tested. The second challenge should be performed at least 1 week after the first one to avoid the refractory period that generally follows positive reactions [44].

The suggested diagnostic workup is shown in figure 1. Patients with a history of NSAID-induced anaphylaxis should be managed exactly like patients reporting urticaria/angioedema caused by a single NSAID (i.e. avoid challenging with the offending drug), maybe starting challenges with alternative drugs using reduced doses. In this sense, the proposed algorithm simplifies that previously suggested by Sanchez-Borges et al. [45].

Management of Patients Who React to Alternative NSAIDs

A proportion of multiple NSAID reactors will not even tolerate drugs exerting little or no inhibition on COX-1 (i.e. paracetamol, coxibs, nimesulide, tramadol, etc.) [43, 46]. Managing these subjects may be a problem, particularly if they suffer from chronic arthritis or other conditions that require anti-inflammatory or anti-febrile treatments. As reported in a recent study, premedication with a second-generation, nonsedating antihistamine such as cetirizine at the licensed dose could be effective in preventing the skin reactions induced by weak COX-1 inhibitors in most cases [46]. These observations open new opportunities for such patients but further studies are needed to confirm the validity of this approach.

How Reliable Are Negative Oral Challenge Tests in the Long Term?

The long-term tolerance of alternative drugs that have been tolerated on oral challenge has been investigated by some studies. Although more studies are probably needed to establish this definitively, available data suggest that the tolerance ascertained in the clinical setting is frequently long-lasting [13, 47, 48].

Summary

- This study examined multiple NSAID hypersensitivity in otherwise normal subjects.

Facts

- Multiple NSAID hypersensitivity may occur in otherwise normal subjects.
- Inhibition of COX-1 by NSAIDs seems to play a key role in the pathogenesis of cross-reactivity.

Objective

- To distinguish between subjects with single or multiple NSAID hypersensitivity. To this end, challenge tests with alternative NSAIDs may be warranted.

Recommendations

- A thorough interview is essential to decide on the subsequent diagnostic workup.
- If the history suggests multiple NSAID hypersensitivity, it is necessary to start challenge tests with alternative drugs exerting little or no COX-1 inhibition (unless tolerance to these drugs is already reported).
- If the history suggests single NSAID hypersensitivity, it is necessary to start challenge tests with a distinct COX-1 inhibitor with a potency at least equal to the drug that induced the adverse reaction.
- If the history is unclear, a confirmative challenge with the reportedly offending drug may be warranted.

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