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# CLINICAL MANAGEMENT OF NON-STEROIDAL ANTI-INFLAMMATORY URTICARIA/ANGIOEDEMA PATIENTS

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**Abstract:**

*In the large majority of previous studies, patients with a history of acute urticaria induced by non-steroidal 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, non-steroidal anti-inflammatory drug, urticaria*

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drug class in the world. Their widespread use, more multiplied by the very 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 medication, is definitely the most cause for the increasing range of adverse reactions elicited by this medication that has been recorded worldwide (Brockow, 2012).

Although NSAIDs are typically well tolerated, they may induce a large spectrum of adverse reactions, some of which are potentially fatal. The most common adverse reactions coupled to their repressing effects on the cyclooxygenase one (COX-1) enzyme are inflammation and peptic ulcers. Other adverse reactions include hepatitis and liver toxicity, anemia, interstitial nephritis, erythema multiform, toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, and (cutaneous and/or respiratory) immediate allergic and pseudo-allergic reactions (Gomez et al., 2010).

The term pseudo-allergic defines reactions characterized by clinical symptoms that suggest an immune pathogenesis but for which there is no evidence of an immune-mediated mechanism. The most pseudo-allergic reactions to NSAIDs are presently considered to be associated with their inhibitory effects on the COX-1 enzyme. Urticaria/angioedema is that the most typical adverse reaction induced by NSAIDs seen by allergologists and possibly represents the foremost frequent drug-induced skin disorder; it's been calculable that it happens in 0.1 to 0.3% of subjects exposed to NSAIDs.

One needs to confine mind that almost all patients presenting with an unequivocal history of urticaria (with or while not angioedema) following the bodily process of NSAIDs are, reasonably, already convinced that they cannot take the offending drug any more. Invariably, their question is ''what am i able to take in case of headache, pain, or fever? '' the current article focuses on the clinical management of patients with NSAID-induced urticaria/angioedema in sight of recently revealed literature (Eric, 2006).

The present review was written on the idea of a literature research distributed victimisation PubMed/MEDLINE. Articles addressing NSAID elicited urticaria revealed throughout the last twenty five 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; in general, 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 throughout a section of moderate activity of the disease could also be tolerated throughout a resultant part of remission (Gomez et al., 2010).

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 within the absence of any episode of spontaneous urticaria) has been a matter of discussion for a protracted time. The 1998 edition of the foremost authoritative textbook of medicine still explicit that ''after earlier exposure to a particular ASA or NSAID, otherwise normal appearing individuals may develop urticaria, angioedema, or anaphylaxis on re-exposure to an equivalent drug (Kasperska-Zając et al., 2012).

In this type of reaction, cross-reactivity between ASA and NSAIDs does not occur.'' However, during the last two decades, a number of clinical studies assessing the tolerance to alternative NSAIDs in traditional subjects with a history of single-NSAID intolerance found that a number of them reacted to compounds that were with chemicals distinct from the volatile ones which were, hence, expected to be tolerated (Eric, 2006).

Further, in one study specifically reaching to clarify now, 12 months of 261 subjects while not chronic urticaria were finally found to own multiple-NSAID intolerance on the idea of the clinical history and oral tolerance take a look at results.16 curiously, 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, whereas drugs exerting little effect on the COX-1 enzyme (nimesulide, paracetamol, COX-2 inhibitors) and NSAIDs characterized by different mechanisms of

actions (floctafenine, paracetamol) or opiate agonists with analgesic activity (tramadol) were generally well tolerated. These observations clearly suggested that COX-1 inhibition plays a pathogenic role in immediate pseudo-allergic skin reactions induced by NSAIDs (Gomez et al., 2010).

COX blockade ''deviates'' arachidonic acid metabolism toward the 5-lipoxygenase pathway, and this eventually results in the production of cystinyl leukotrienes (Cys-LTs 5 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, and on a molar basis; Cys-LTs are 100 times more potent than histamine in inducing wheal and flare reactions (Eric, 2006) .

Recent studies showed that each chronic hives patients with non-steroidal anti-inflammatory intolerance and patients with AERD square measure characterised by elevated baseline urinary LTE4 levels and located that such levels are markedly increased by aspirin administration. The central role contend by Cys-LTs as mediators of aspirin-induced urticaria (and most likely of multiple-NSAID reactivity while not chronic urticaria) is indirectly confirmed by studies showing a protecting role by leukotriene receptor antagonists. Interestingly, many studies found associate degree association between multiple-NSAID intolerance in otherwise traditional subjects and atopic standing (Gomez et al., 2010).

**Single-NSAID Intolerance**

Intolerance to single NSAIDs has been according by many studies. Offending drugs include pyrazolones, paracetamol, aspirin, ketorolac, nimesulide, and celecoxib. It has been inferred that during a proportion of those cases, the pathogenesis is actually Ig mediate, as sometimes suggested by positive skin tests with the offending compounds. Moreover, a genetic disposition to NSAID-induced hypersensitivity reaction reactions looks to exist.

In patients with single-NSAID intolerance, cross-reactions could occur among identical chemical family however not between with chemicals distinct medicine, and this type of reaction never occurs on first exposition.

However, the chance that reactions to single NSAIDs are cox-1 mediate additionally cannot be dominated out. These patients would possibly for a few reason show completely different threshold or different cistron polymorphisms and develop multiple-NSAID intolerance at a later date. In effect, in an exceedingly previous study, close to thirty fifth of otherwise traditional patients with a history of **urticaria** iatrogenic by one NSAID developed hronic urticaria one to ten years after the adverse drug reaction, suggesting that chronic urticaria might remain in a state of latency for years, with NSAID intolerance as the only sign of its presence (Kasperska-Zając et al., 2012).

**New Classification of Immediate Allergic and Pseudo-allergic NSAID-Induced Reactions**

Based on the studies reported above, in 2001, Stevenson and colleagues proposed a novel classification of allergic and pseudo-allergic reactions induced by NSAIDs that includes six distinct categories of patients (Table 1).

**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.

Interestingly, skin reactions (urticaria/angioedema) are present in 5 of six classes.This classification was afterward adopted within the last edition of the treatise Allergy: Principles and follow. Notably, the distinction between kind two and kind four multiple-NSAID intolerance relies unambiguously on the presence or absence of chronic urticaria as an underlying disorder. Recent studies appear to get rid of even this distinction as:

1- Type 4 subjects show an extremely high prevalence of positive reactions on an autologous serum skin test, a typical feature of patients with auto-reactive 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 FceRI, present on basophils and mast cells (Eric, 2006).

2. According to the 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 reaction.

**Diagnostic Workup**

In view of the potential distinct pathological process 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 mono-reactor or a multi-reactor. To this finish, both a thorough interview and oral challenge tests with properly chosen alternative substances are essential. A classification of the foremost necessary NSAIDs per their repressive resul t on COX isoenzymes is shown in Table two.

**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, fenprofen, flurbiprofen) |
| Arylacetic acids (indomethacin, etodolac, sulindac, diclofenac, tolmetin) |
| Fenamates (meclofenamate, mefenamic acid) |
| Pyrrolopyrrole (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.

A supportive provocation take a look at with the reported volatile drug isn't secure for the subsequent reasons:

1. In mono-sensitized 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 one cox-1 substance (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 non-selective COX inhibitor rather than with a selective COX-2 inhibitor. First, this is the only way to establish whether the patient is really mono-sensitized (ie, if the patient may take any NSAID other than the offending one) or if the reported reaction represents the primary sign of a multiple-NSAID intolerance. Second, the long-term use of COX inhibitors has been associated with an increase in cardiovascular events, 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 past (Chan, 2006).

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 non-selective COX inhibitors and not sufficient to control adequately chronic inflammatory disorders, such as arthritis (Eric, 2006).

Patients already presenting with a history of multiple nsaid intolerance, with or while not underlying chronic urticaria, ought to directly endure oral tolerance tests with medication exerting very little or no Coxinhibition. In patients with chronic rash, a state of moderate activity of the underlying disease will probably avoid false negative results. In these patients, it's conjointly essential that the challenged drug induces an unequivocal exacerbation of underlying urticaria to provide a positive result. In uncertain cases, patients with active urticaria ought to be challenged a second time to verify that any reaction or exacerbation is really because of the drug being tested (Kasperska-Zając et al., 2012) .

Finally, in patients with a history of an allergic or hypersensitivity reaction reaction to ASA World Health Organization want 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.

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 center, 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 observe multiple-NSAID intolerance. Patients should be kept under observation for at least 1.5 hours after the last provocative dose as most adverse reactions occur within this short time (Kasperska-Zając et al., 2012).

Otherwise traditional 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, placebo-controlled manner. Only the looks of unequivocal urticaria/angioedema ought to be thought of a positive response.

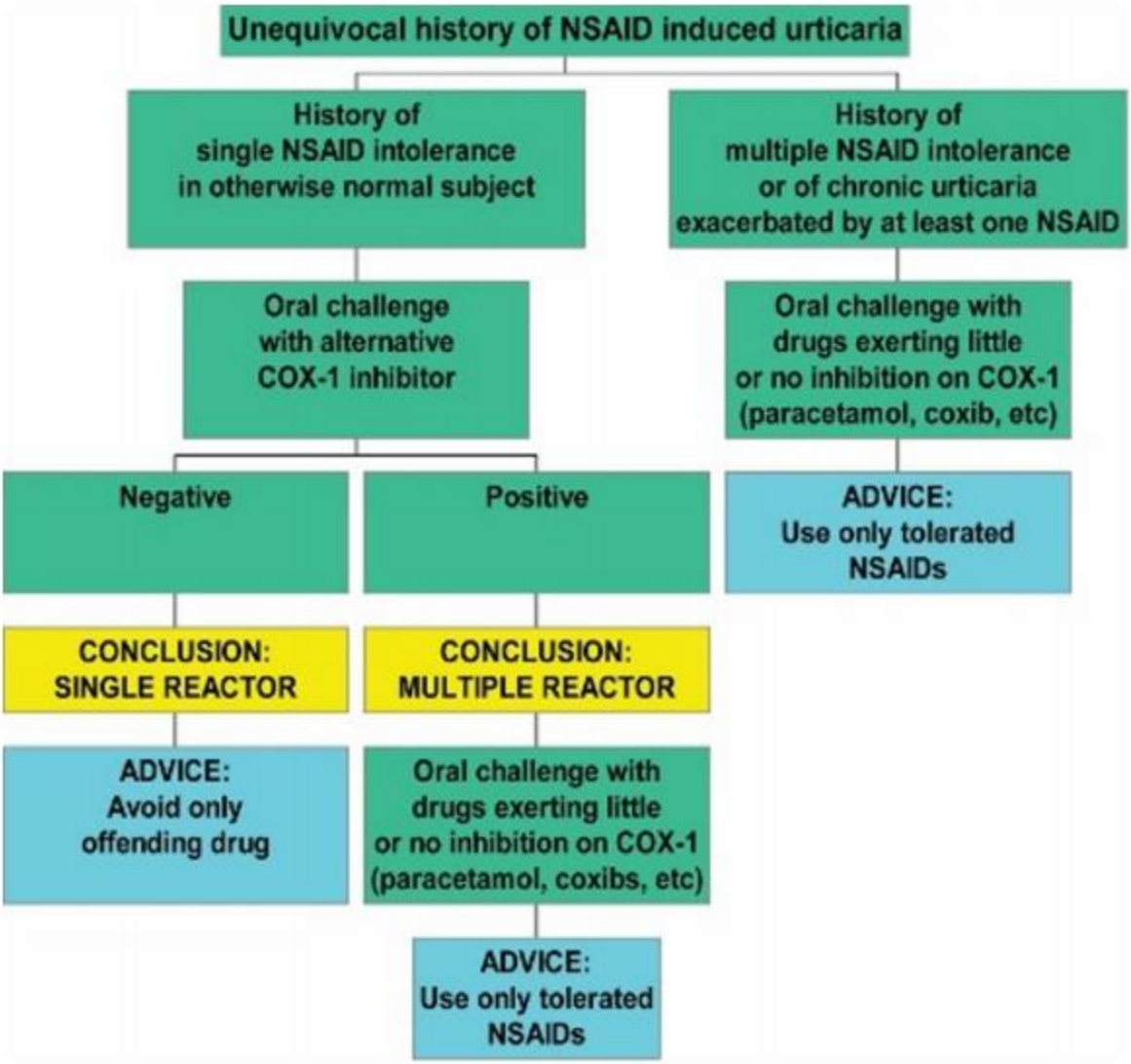


Figure 1

(Source: Kasperska-Zając et al., 2012)

Diagnostic workup in patients intolerant to non-steroidal anti-inflammatory drugs (NSAID). COX 5 cyclooxygenase.

## 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 pseudo-allergic 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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