

Nonsteroidal anti-inflammatory drug hypersensitivity: not always an allergy!

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a major cause of hypersensitivity reactions. Several distinct clinical syndromes are described regarding NSAID hypersensitivity. Such a reaction is generally caused by a non-immunological mechanism. In susceptible patients, COX-1 inhibition leads to an imbalance in lipid mediators such as leukotrienes and prostaglandins. It is essential to distinguish multiple nonspecific NSAID hypersensitivity from single NSAID hypersensitivity, since the management of these respective syndromes is essentially different. This review provides an overview on all the aspects of NSAID hypersensitivity reactions, from pathophysiology to clinical symptoms, leading practical recommendations.

KEYWORDS

Acetylsalicylic acid, asthma, drug allergy, hypersensitivity, nonsteroidal anti-inflammatory drugs

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most used drugs worldwide. It is therefore not surprising that they are a major cause of hypersensitivity reactions, accounting for up to 48.7% of drug-related 'allergic' reactions.^{1,3} Various mechanisms are distinguished through which NSAIDs can cause hypersensitivity reactions in humans, all leading to quite similar symptoms making it difficult to determine the cause in a specific patient. Adding to the confusion of clinicians is the different terminology and many abbreviations that are used in the medical literature. This review provides an overview

of the pathophysiology and clinical aspects of NSAID hypersensitivity and ends with practical recommendations.

CASE 1

A 35-year-old male presents to his general practitioner because of alleged reactions to various NSAIDs. He recalls that he had his first reaction about ten years ago consisting of swelling and redness of the eyes shortly after ingestion of ibuprofen. One year ago, swelling of the lips occurred one hour after ingestion of naproxen. Recently, similar symptoms developed three hours after the ingestion of 1000 mg of acetaminophen. His medical history reveals childhood asthma, and mild allergic rhinoconjunctivitis in the spring. He does not take any daily medications. He asks which analgesic he can safely use after an upcoming dentist procedure.

What is the correct diagnosis and what advice should the patient receive?

CASE 2

A 56-year-old male is referred to the Allergy outpatient clinic because of a recent reaction to diclofenac. The patient endured an accident when cycling and had several bruised ribs for which diclofenac 50 mg, three times daily, was prescribed. On the third day, he developed rapidly progressive urticaria, abdominal cramps, and started perspiring heavily, 30 minutes after ingestion of diclofenac. He did not notice any respiratory symptoms. At the Emergency Department, hypotension was found. He has used ibuprofen, diclofenac and acetaminophen in the past without any reactions.

What is the correct diagnosis and what test could aid in this diagnosis?

CASE 3

A 30-year-old woman presents with dyspnoea after taking ibuprofen for a sprained ankle. One hour after the first dose, nasal congestion and dyspnoea occurred. When she presented at the Emergency Department, severe wheezing was noted. The patient did not have a rash or angioedema. She was treated with salbutamol inhalation, intravenous corticosteroids and xylometazoline nose spray. The medical history of the patient revealed constitutional eczema and atopic asthma for which she used high doses of inhaled corticosteroids with a long-acting beta agonist.

What is the correct diagnosis and which analgesics are safe for this patient?

PATHOPHYSIOLOGY OF NSAID HYPERSENSITIVITY

NSAIDs are a large group of drugs that block the enzyme cyclooxygenase (COX), thereby inhibiting the production of prostaglandins from arachidonic acid.⁴ Figure 1 provides an overview of the most used NSAIDs. Arachidonic acid is metabolised by two pathways: the COX pathway, which induces synthesis of prostaglandins, and the lipoxygenase pathway, which induces synthesis of cysteinyl-leukotrienes and thromboxane. There are at least two isoforms of COX. COX-1 is constitutively expressed by specific cells such as thrombocytes and endothelial cells. COX-2 is

inducible by pro-inflammatory mediators in a wide variety of cells.⁴ In susceptible patients, COX-1 blockade leads to a relative increase in cysteine-leukotriene synthesis causing inflammation of the respiratory tract.^{5,6} This is due to a constitutively disrupted balance between pro- and anti-inflammatory prostaglandins and leukotrienes in patients with multiple NSAID hypersensitivity (figure 2). Here, pro-inflammatory cysteinyl-leukotrienes are continually upregulated and the anti-inflammatory prostaglandin E₂ is downregulated.⁷⁻⁹ The latter appears to be a consequence of the downregulation of COX-2.^{6,10} When COX-1 is then blocked by an NSAID, the prostaglandin production is further decreased. This amplifies the pre-existent imbalance in favour of the cysteinyl-leukotrienes, which can induce bronchospasm, vascular leakage, eosinophilic inflammation and mast cell activation.^{9,11,12} Although cysteinyl-leukotrienes appear to play a main role in the mechanism for NSAID-exacerbated respiratory disease (NERD) and NSAID-exacerbated cutaneous disease (NECD), there is evidence for additional

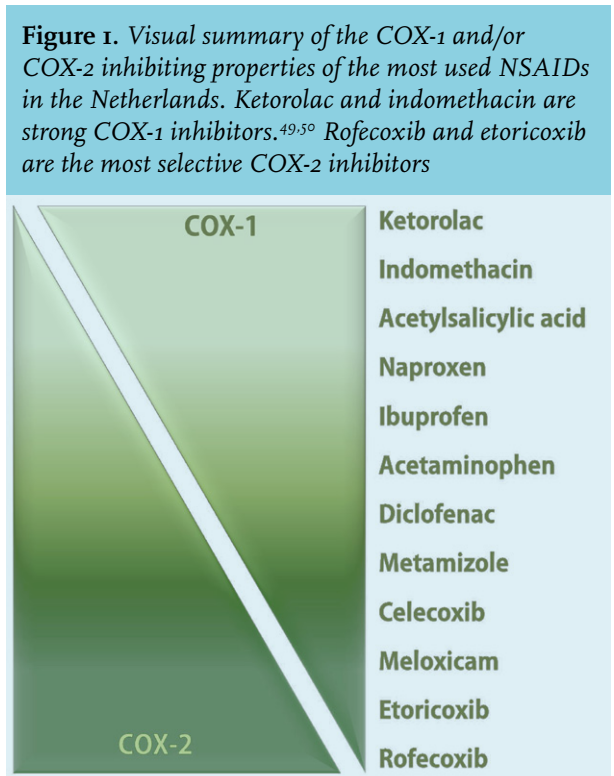
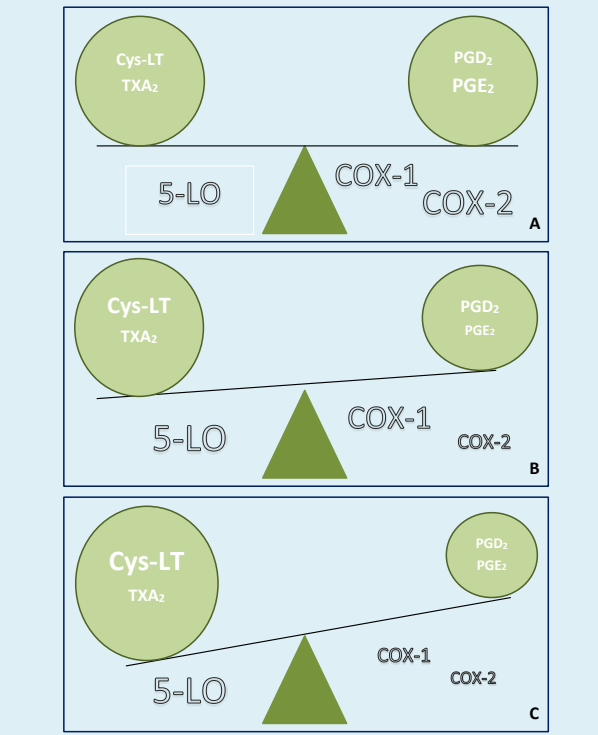


Figure 2. Schematic figure showing the pathophysiology of multiple NSAID hypersensitivity syndrome



The enzymes cyclooxygenase (COX) and 5-lipoxygenase (5-LO) regulate the production of prostaglandins and thromboxane, and leukotrienes, respectively, from arachidonic acid. Under physiological circumstances, pro- and anti-inflammatory eicosanoids are balanced to maintain homeostasis (panel A). In NERD, the levels of pro-inflammatory cysteinyl-leukotrienes (cys-LT) are elevated. Moreover, the levels of the anti-inflammatory prostaglandin E₂ (PGE₂) are decreased due to downregulation of COX-2 (panel B). The use of NSAIDs leads to further imbalance by blocking COX-1, and often also COX-2 (panel C), thereby causing clinical symptoms due to a relative overload of pro-inflammatory cysteinyl-leukotrienes.^{5,6,8}

roles of both TH₁ and TH₂ cells, granulocytes, and thrombocytes.^{11,13,14}

DIFFERENT FORMS OF NSAID HYPERSENSITIVITY

There are four clinical phenotypes of immediate-type NSAID hypersensitivity: NERD, NECD, NSAID induced urticaria/angioedema (NIUA), or single NSAID induced urticaria/angioedema/anaphylaxis (SNIUAA). The last mentioned is a specific, probably IgE-mediated, allergy. The other phenotypes do not have an immunological pathophysiology, but are caused by inhibiting of COX-1 resulting in an imbalance in eicosanoid mediators, as outlined further. The terms *pseudo-allergy* and *intolerance* were commonly used in the past to indicate this type of reaction but are outdated.¹⁵ Next to these immediate-type hypersensitivity syndromes, a delayed-type hypersensitivity syndrome is termed 'single NSAID-induced delayed type reaction' (SNIDR).

NON-IMMUNOLOGICALLY MEDIATED (CROSS-REACTIVE) NSAID INDUCED HYPERSENSITIVITY REACTIONS

NSAID-exacerbated respiratory disease (NERD)

This phenotype is also known as aspirin-exacerbated respiratory disease or the 'acetylsalicylic acid (ASA) triad'.¹⁵ Around 7-14% of adult asthma patients have NERD.^{16,17} Contrary to allergic asthma, NERD commonly starts in early adulthood.¹⁸ It is characterised by refractory polyposis nasi, sinusitis, modest to severe asthma, and hypersensitivity reactions to various types of NSAID with COX-1 inhibiting properties. The asthma is often severe and corticosteroid-dependent. However, not all patients have the full triad, as rhinosinusitis typically precedes asthma by 1-3 years. Consequently, not all patients have clinically overt asthma: they may experience their first 'asthma exacerbation' only after NSAID ingestion.¹⁸ Many patients have anosmia and often need sinus surgery.¹⁴ Ingestion of an NSAID (mainly, but not exclusively, those with strong COX-1 inhibition) will lead to an exacerbation of asthma and/or rhinitis and sometimes also angioedema. The reaction can be delayed for several hours. The mean provoking dose was around 80 mg in different studies; however, reactions are described at doses as low as 10 mg.^{16,19}

NSAID-exacerbated cutaneous disease (NECD)

NECD is actually the cutaneous variant of NERD. Patients with NECD suffer from chronic spontaneous urticaria (CSU) and/or angioedema and experience worsening

of these symptoms after the ingestion of an NSAID.²⁰ Although most reactions include urticaria, isolated angioedema is a possible manifestation of NECD.²¹ The incidence of NECD is estimated to be 12-30% in CSU patients.²² NECD patients did not react to selective COX-2 inhibitors in several studies.^{23,24}

Since CSU is often a self-limiting disease within months to years, NECD can potentially recover 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.²⁵ To our knowledge, there are no comprehensive data on the resolution of NECD.

NSAID-induced urticaria/angioedema (NIUA)

Patients with NIUA do not have spontaneous urticaria and/or angioedema, but only develop them after the ingestion of an NSAID. As with NERD and NECD, NIUA is a multiple NSAID hypersensitivity syndrome and there is cross-reactivity between chemically nonrelated NSAIDs.²² 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. Approximately 60% of all patients with NIUA have concomitant atopic disease, although a hypothesis for a pathophysiological mechanism for this association is lacking.^{22,26} The pathophysiological basis for NIUA appears similar to that of NERD and NECD, as several polymorphisms were detected in genes related to arachidonic acid metabolism.^{27,28} Spanish studies reveal that 62% of NIUA patients spontaneously develop tolerance to NSAIDs after five years. Risk factors for persistent NSAID hypersensitivity are atopy and isolated angioedema.^{29,30} Conversely, 33% of patients with NIUA developed chronic spontaneous urticaria during follow-up.³¹ These patients thus actually had NECD with delayed presentation of the spontaneous urticaria.

IMMUNOLOGICALLY MEDIATED SPECIFIC NSAID HYPERSENSITIVITY REACTIONS

Single NSAID induced urticaria/angioedema or anaphylaxis (SNIUAA)

SNIUAA is biologically and phenotypically distinct from the other NSAID hypersensitivity syndromes. Patients only react to one NSAID or multiple NSAIDs with similar chemical structures. It usually consists of a rapid, systemic anaphylactic reaction, resembling type-I hypersensitivity.^{3,32} Reactions are generally more severe than in the previous syndromes. SNIUAA can also present with isolated urticaria and/or angioedema, although

isolated angioedema is unlikely. The fact that patients with SNIUAA can tolerate other NSAIDs than the culprit drug suggests a sensitisation for a certain epitope in the NSAID in question. Until now, sensitisation tests such as specific IgE measurement and skin testing were often negative.^{3,33} Possibly, there is only a small time window in which specific IgE is detectable, or the reaction might not be IgE mediated at all.³⁴

Single NSAID induced delayed reactions (SNIDR)

SNIDR is a highly heterogeneous group of clinical entities usually occurring within 24-48 hours after the ingestion of an NSAID. The entities range from mild reactions such as a maculopapular rash, to severe allergic syndromes such as acute generalised exanthematous pustulosis or toxic epidermal necrolysis.³⁵ The putative mechanism is T-cell mediated. Due the fact that these reactions can be life-threatening, randomised studies are lacking and the possibility of cross-reactivity has not been elucidated. Because the scope of this review is immediate-type NSAID hypersensitivity reactions, SNIDR will not be discussed further.

DIAGNOSTIC STRATEGIES

All patients with a reaction to an NSAID should be advised to avoid all NSAIDs until more certainty is obtained about cross-reactivity. As outlined previously, SNIUAA typically presents with acute, systemic reactions to the culprit drug, and tolerance to other NSAIDs. However, the clinical symptoms of the above-described hypersensitivity syndromes can overlap, since SNIUAA can also present with isolated urticaria, and patient histories are not always

reliable.³⁶ Furthermore, most patients avoid NSAIDs after their first reaction, and information on clinical cross-reactivity is lacking. Comorbidities can aid in the diagnosis: patients with a history of chronic spontaneous urticaria or a combination of asthma, rhinitis, and nasal polyps are likely to be multiple reactors (*table 1*).

Common allergologic diagnostic procedures are not suitable for NSAID hypersensitivity. The European Academy of Allergy and Clinical Immunology (EAACI) position paper does not recommend skin tests as part of the diagnostic work up.³⁷ Specific IgE and basophil activation tests are not reliable in this context.^{3,15,38} There is also no association between NSAID hypersensitivity and serum tryptase levels.³⁹ Since multiple NSAID reactors have raised levels of prostaglandin D₂ and leukotriene E₄, measurement of these levels might identify persons at risk for NSAID hypersensitivity.^{7,40,41} However, these cannot be used for a final diagnosis.

A provocation challenge remains the gold standard.²² The goal of such a drug challenge can be twofold; it can either establish the diagnosis or identify a safe alternative NSAID. Since ASA is among the strongest COX-1 inhibitors (*figure 1*), this is often used to test for general NSAID hypersensitivity, depending on the patient history and anticipated risk of the provocation challenge itself.⁴² See *figure 3* for a decision model. Contraindications for a provocation challenge are: severe asthma (FEV₁ < 70% of predicted, use of short-acting beta-agonist ≥ 3 times a week, nightly dyspnoea), active spontaneous urticaria/angioedema in the last two weeks, pregnancy, active infection, and a recent vaccination (≤ 1 week). Relative contraindications are the use of beta-blockers or ACE-inhibitors.^{22,43} In order to avoid false-negative results, histamine and leukotriene antagonists need to

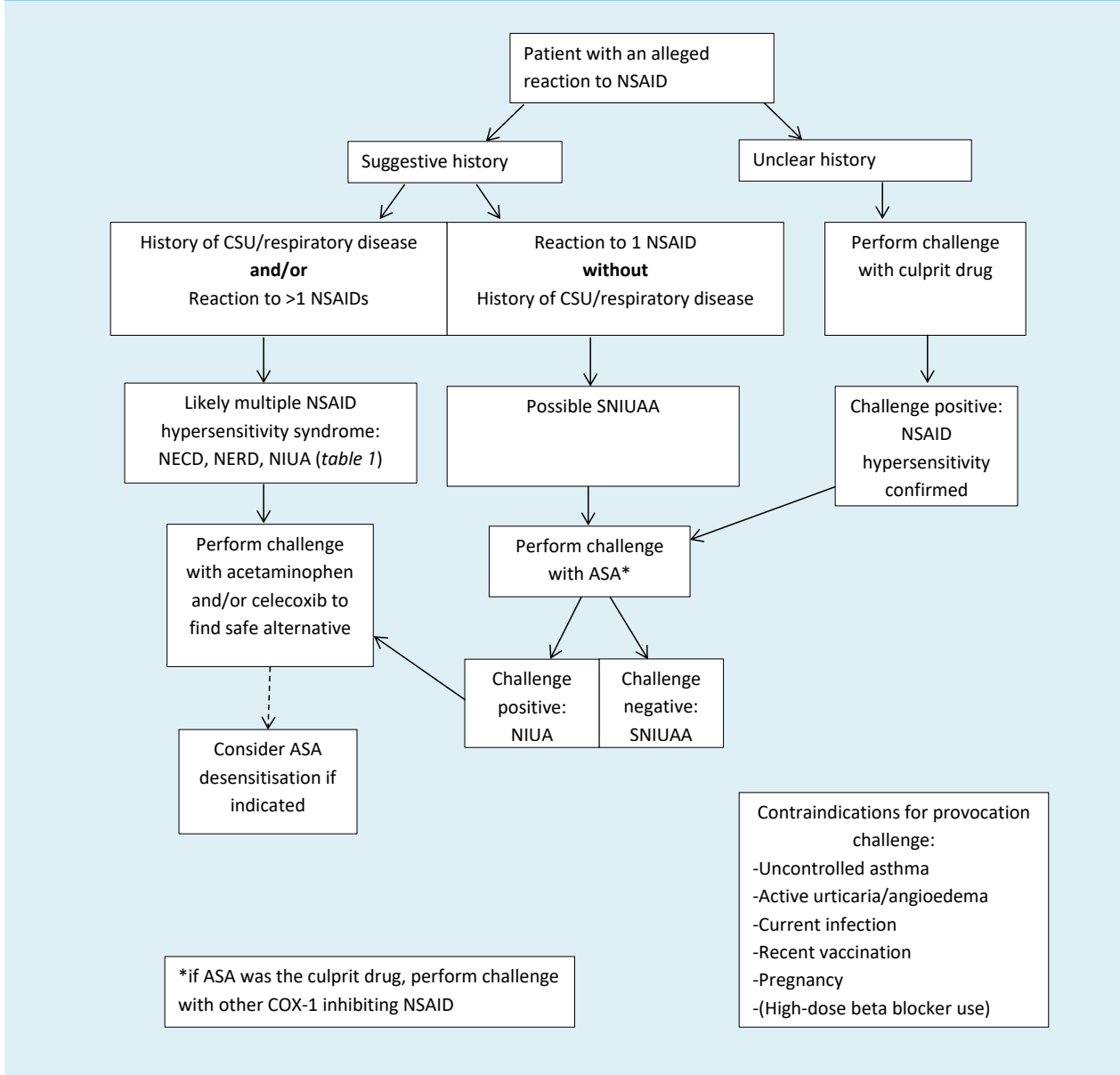
Table 1. Summary of different NSAID hypersensitivity syndromes

Timing of reaction	≤ 24 hours		≤ 2 hours	
Reaction to multiple NSAIDs?	Yes		Yes	No
Type of reaction	Urticaria and/or angioedema		Bronchospasm, nasal congestion, rhinorrhoea	Anaphylaxis*
Underlying disease	None†	Chronic spontaneous urticaria and/or angioedema	Asthma with polyposis nasi, and/or chronic recurring sinusitis	None
Diagnosis	NIUA	NECD	NERD	SNIUAA
Risk of reaction to COX-2 inhibitor ^{23,24}	6%-25%‡	17.4%	0-8.7%	0%
Risk of reaction to acetaminophen ²⁴	12.5%	43.9%	33.3%	0%

NIUA = NSAID-induced urticaria/angioedema ; NECD = NSAID exacerbated cutaneous disease ; NERD = NSAID exacerbated respiratory disease ; SNIUAA = single NSAID induced urticaria/angioedema or anaphylaxis.

*Only urticaria also possible; †Approximately 60% of patients with NIUA have atopic disease; ‡Risk 6% if acetaminophen tolerant, and 25% for patients who also have acetaminophen hypersensitivity.

Figure 3. Flowchart of the decision process regarding the management of a patient who has one or more reported immediate-type reactions to NSAIDs which has raised the suspicion of NSAID hypersensitivity



be discontinued at least three days before the challenge.⁴⁴ Inhalation medication for asthma should be continued for safety reasons. The use of a standardised scoring system and a double-blind, placebo-controlled format can increase the reliability of a drug challenge.⁴⁵ If a patient has a history of multiple NSAID reactions and/or spontaneous urticaria, angioedema or chronic respiratory disease (asthma, rhinitis etc.), the likelihood of multiple NSAID hypersensitivity is very high. A challenge with ASA can in such cases cause cumbersome symptoms or even life-threatening asthma exacerbations. Therefore, it is preferred to directly perform a challenge with an alternative, for instance a specific COX-2 inhibitor, in these patients. When SNIUAA is assumed, it can be

unnecessarily hazardous to challenge the patient with the culprit drug. It is then preferred to perform a challenge with ASA to exclude a multiple NSAID hypersensitivity syndrome. If ASA is tolerated well, the patient is advised to only avoid the culprit NSAID, and other classes will be safe. The patients that present with isolated urticaria after NSAID ingestion without any relevant history are the most difficult to categorise. With the aforementioned strategy, they would first undergo ASA challenge to distinguish between NIUA or SNIUAA. Often, the history is not clear at all, and the first goal is to establish any type of causality between the NSAID ingestion and the reaction. Depending on the severity of the previous reaction, a challenge with the culprit drug can then be performed first. If that

challenge is negative, any type of NSAID hypersensitivity can be excluded. If the challenge to the culprit drug is positive, the Allergist can decide to challenge with ASA to further distinguish between single or multiple NSAID hypersensitivity. Of note, drug challenges always pose a certain risk, depending on the phenotype of the patient, as outlined previously. Therefore, these challenges should be performed by experienced Allergists with the appropriate resources and access to emergency medical care.

AFTER THE DIAGNOSIS: ALTERNATIVE ANALGESICS AND DESENSITISATION

Depending on the diagnosis and outcome of the ASA challenge, the patient can be advised to avoid only the culprit or all NSAIDs. Then, there might be a need to investigate the safety of alternative analgesics. The risk of hypersensitivity reactions to acetaminophen varies between the different subtypes of NSAID hypersensitivity. Numbers between 9.6% and 43.9% have been reported.^{24,46} It is advised to perform a challenge that ends with a sufficiently high dose of acetaminophen (1000 mg) in all patients with multiple NSAID hypersensitivity. Selective COX-2 inhibitors are often a safe alternative, especially in patients who can tolerate acetaminophen. In the latter, only 6% of patients with NIUA reacted to a selective COX-2 inhibitor, and in NERD, the risk was actually zero.^{23,47} It must be noted that the patients in these studies had mild-to-moderate asthma, and the risk of reaction to a COX-2 inhibitor in patients with severe asthma might be higher. Since there are no similar studies among patients with NERD and severe asthma, it is advisable to treat the asthma appropriately before performing any drug challenge. Patients with NECD have the highest risk of cross-reactivity with both acetaminophen and selective COX-2 inhibitors (*table 2*). Thus, an additional challenge with a specific COX-2 inhibitor should be the next step in the evaluation of patients with multiple NSAID hypersensitivity, especially when they have also reacted to acetaminophen. Re-evaluation after five to six years can be considered in patients with NECD or NIUA, because a substantial number develop tolerance to all NSAIDs.^{29,30} Patients with cardiovascular disease are often recommended to use a daily low dose of up to 100 mg ASA, which can cause a problem for multiple NSAID reactors. Fortunately, low doses are often tolerated. If patients do react to these low doses, ASA desensitisation can be attempted. Desensitisation is a procedure aimed at inducing a pharmacological or immunological tolerance to the drug. There is no international standard for this procedure and many different desensitisation schedules are described in the literature. Of course, it is essential that the patient's asthma is well controlled. *Table 2* provides two

possible schedules for desensitisation.⁴⁸ Daily use of ASA after the desensitisation is necessary to maintain tolerance.

CONCLUSIONS

There are several different NSAID hypersensitivity syndromes. The distinction between multiple and single NSAID reactivity is pivotal and can largely be made based on the patient's history. Provocation challenges are the gold standard to confirm NSAID hypersensitivity, or to find safe alternatives. ASA desensitisation is a safe and effective method for patients who have a strict indication.

ANSWERS

Case 1

The reactions to different NSAIDs and the time lag between ingestion and reaction are suggestive of a multiple NSAID hypersensitivity syndrome. Furthermore, the absence of current asthma, sinusitis, rhinitis, nasal polyps or spontaneous urticaria/angioedema argues

Table 2. Examples of acetylsalicylic acid desensitisation schedules

Time (hour)	Dose (mg)	Cumulative dose (mg)
Fast schedule		
08:00	30	30
10:00	60	90
12:00	100	190
14:00	325	515
16:00	650	1165
18:00	End of desensitisation	
Slow schedule		
Day 1:		
8:00	30	30
11:00	60	90
14:00	100	190
17:00	End of day 1	
Day 2		
8:00	150	150
11:00	325	475
14:00	650	1125
17:00	End of desensitisation	

for a diagnosis of NIUA. Up to 25% of patients with NIUA also have hypersensitivity reactions to high-dose acetaminophen (i.e., ≥ 1000 mg) thus it is not surprising that the patient reported reactions to acetaminophen too. A selective COX-2 inhibitor, such as celecoxib, is tolerated in most patients with NIUA. To find out, it was advised to perform an open provocation challenge with celecoxib.

Case 2

This patient had generalised urticaria with hypotension, fulfilling the definition of severe anaphylaxis, rapidly after ingestion of diclofenac. This clinical pattern, combined with the fact that he did not have respiratory disease or CSU, is suggestive of a specific diclofenac allergy (SNIUAA). Because this case is clear-cut, a challenge with diclofenac is not needed to establish the diagnosis. Even in case of a doubtful history, a challenge test with diclofenac should be avoided because of a possible severe reaction during challenge. In this patient a challenge test with ASA is indicated to find out if alternative NSAIDs can be tolerated.

Case 3

It is highly likely that this patient has NERD, because of the combination of respiratory distress with nasal congestion and the medical history of moderately severe asthma. She should be advised to avoid all classic NSAIDs. A challenge with COX-2 would be useful to find out whether this is a safe alternative for her. The risk of hypersensitivity reactions to acetaminophen is negligible for patients with NERD.

DISCLOSURES

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