Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs

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KEYWORDS

• Nonsteroidal anti-inflammatory drugs • Hypersensitivity • Clinical diagnosis • Allergic • Nonallergic • Management

KEY POINTS

- Nonsteroidal anti-inflammatory drugs are the most frequent drugs involved in hypersensitivity drug reactions.
- The mechanisms involved can be specific (immunologic), whether mediated by immunoglobulin E or T cells or by activation of pathways that release vasoactive mediators.
- Five major well-defined clinical entities are currently recognized, although overlapping may exist.
- The diagnosis is mostly based on clinical history and a drug-provocation test.
- Management consists of drug eviction, providing alternatives such as paracetamol and cyclooxygenase-2 inhibitors and, when needed, desensitization.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the medicines most frequently prescribed worldwide, many of which are available over the counter.[1] NSAIDs induce a wide variety of adverse reactions that are classified as type A (predictable and usually related to the effects of the drug) and type B (unpredictable and related to the individual response).[2] This review deals with type B drug hypersensitivity reactions (DHR), mediated by immunologic (allergic) or nonspecific pharmacologic mechanisms (nonallergic).[3] NSAIDs are of great concern because they are the drugs most commonly involved in DHR.[4–7]

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CLASSIFICATION

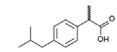
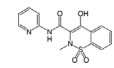
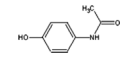
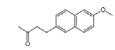
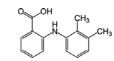
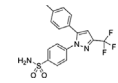
NSAIDs have different chemical structures that share the capacity for inhibiting cyclooxygenase (COX) enzymes (COX-1 and COX-2) (**Table 1**). The mechanism for inducing DHR is related to the release of vasoactive mediators (histamine, prostaglandins, and sulfidopeptide leukotrienes [LTs])[5] or is due to their recognition as xenobiotics, inducing immunoglobulin E (IgE) or T-cell responses.[4]

The authors use the nomenclature for DHR proposed by the European Academy of Allergy and Clinical Immunology (EAACI),[3] based on the timing of reactions (acute or delayed), clinical pattern of symptoms (respiratory and/or cutaneous and/or anaphylaxis), and the presence or absence of cross-tolerance to other chemically unrelated NSAIDs.[5,6] Cross-reactive types (1, 2, and 3) involve nonallergic mechanisms while single-drug–induced types (4 and 5) involve allergic, putative IgE, and T-cell–mediated mechanisms (**Table 2**).[8–10] In addition, the presence of underlying chronic inflammatory disease of the skin (chronic spontaneous urticaria [CSU]) and of the respiratory tract (asthma/chronic rhinosinusitis [CRS]) should be considered. This phenotype-based classification allows the use of a simple history-based algorithm for diagnosis (**Fig. 1**) and indicates putative underlying mechanisms.[7]

EPIDEMIOLOGY

NSAIDs are usually reported to be the second most important group of drugs involved in DHRs after antibiotics, although recent studies indicate that they are in fact the principal group.[11–13] The prevalence of self-reported DHR to NSAIDs has been shown to be 1.9%, with acetylsalicylic acid (ASA; aspirin) and ibuprofen being the most frequent

Table 1
Examples of NSAIDs according to capacity for COX enzyme inhibition

Nonselective COX inhibitors	Salicylic acid derivatives	Acetylsalicylic acid	
	Indoleacetic acids	Indomethacin	
	Heteroaryl acetic acids	Diclofenac	
	Arylpropionic acids	Ibuprofen	
	Enolic acids	Piroxicam	
	Para-aminophenol derivatives	Paracetamol	
	Alkanones	Nabumetone	
	Anthranilic acids	Mefenamic acid	
Selective COX-2 inhibitors	Diaryl-substituted pyrazoles	Celecoxib	

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