An Overview of Nonsteroidal Antiinflammatory Drug Reactions

Kristen M. Walters, MD, Katharine M. Woessner, MD*

KEYWORDS

- Nonsteroidal antiinflammatory drugs (NSAIDs) • NSAID-induced asthma
- NSAID-induced urticaria • NSAID reactions • NSAID hypersensitivity
- Aspirin intolerance • Drug allergy

KEY POINTS

- Adverse reactions owing to ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) can manifest as an array of symptoms, from mild gastrointestinal upset up to life-threatening anaphylaxis.
- NSAID-induced hypersensitivity may be divided into immunologic and nonimmunologic reactions and should be differentiated from the predictable side effects of the drug.
- The pathophysiology underlying hypersensitivity reactions is related to cyclooxygenase-1 inhibition (nonimmunologic type) or typical IgE-mediated reactions (immunologic type).
- Although difficult, it is imperative to appropriately diagnosis and categorize the type of NSAID-induced reaction so that the affected patient may be managed effectively.

INTRODUCTION

Since the introduction of the first nonsteroidal antiinflammatory drug (NSAID) to medical practice in the late 1800s, NSAIDs, including aspirin (ASA), have become one of the most commonly used class of drugs in the world. It is estimated that more than 20 million people in the United States use an NSAID on a consistent basis,[1] and this number is steadily increasing owing to our aging population and subsequent treatment of various inflammatory and cardiovascular conditions. Consequently, the number of adverse reactions owing to NSAID ingestion have paralleled the increase in NSAID use and may account for up to 10% of preventable drug-related hospital admissions.[2] These reactions vary in severity, from mild gastrointestinal (GI) or cutaneous symptoms, to severe life-threatening anaphylaxis.

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Department of Allergy, Asthma & Immunology, Scripps Clinic, 3811 Valley Centre Drive, San Diego, CA 92130, USA
* Corresponding author.
E-mail address: Woessner.katharine@scrippshealth.org

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The ability to distinguish between a suspected, but unwanted, side effect of a medication and a true hypersensitivity reaction is paramount but frequently met with challenge. In addition to the wide range of symptoms that characterize these reactions, they are often accompanied by abnormal immunologic and/or nonimmunologic processes, which can further complicate the clinician's ability to diagnose and manage NSAID-induced reactions.

Over the years, several classification schemes have been proposed to assist the clinician in identifying and understanding the different forms of NSAID hypersensitivity reactions. In this review, these classification strategies will be used to provide the reader with an in-depth overview of the clinical presentation and management of both immunologic and nonimmunologic NSAID reactions.

MECHANISM AND CLASSIFICATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

It is well-understood that NSAIDs, including ASA, share a common pharmacologic method of action via the inhibition of cyclooxygenase (COX) enzymes. The inhibition of COX leads to altered arachidonic acid metabolism and decreased formation of prostaglandins, prostacyclin, and thromboxanes (**Fig. 1**).[3] Two isoforms of COX have been described, COX-1 and COX-2:

- *COX-1*: Often referred to as the "housekeeping" enzyme owing to its role in maintaining various protective cellular functions, such as the integrity of gastric mucosa, platelet aggregation, and renal function, via production of prostanoids.[4] It is constitutively expressed by most human cell types.
- *COX-2*: Expression is primarily induced in response to inflammatory or mitogenic stimuli (eg, interleukin-1, endotoxin), and inhibited by glucocorticoids. It is constitutively expressed in specific cell types with physiologic roles in reproduction, bone reabsorption, renal function, and neurotransmission.[5] There exists a potential association between COX-2 and adverse cardiovascular outcomes, but this remains to be fully elucidated.[6,7]

The strength of enzyme inhibition is known to vary among the different NSAIDs and explains their ability to generate different levels of clinical effectiveness, side effects, and hypersensitivity reactions.

In general, NSAIDs that inhibit COX-1 are considered to be "cross-reactive" with ASA (eg, ibuprofen, naproxen, ketorolac). NSAIDs that inhibit both COX isoforms are considered "nonselective." Highly selective COX-2 inhibitors have a 200- to 300-fold selectivity for COX-2 at approved therapeutic doses. The 4 broad categories of COX inhibition are listed as follows (**Box 1**):

- Highly selective COX-1 inhibitors
- Weakly selective COX-1 inhibitors
- Preferentially selective COX-2 inhibitors
- Highly selective COX-2 inhibitors

Despite all NSAIDs sharing a similar mechanism of action, it is important to note that they demonstrate differences in their chemical structure (**Table 1**). This enables certain NSAIDs to have antigenic activity and elicit a drug-specific immunologic response. It is vital that the clinician has a sound understanding of the pharmacologic properties of NSAIDs, including their mechanisms of action and degree of COX-1/COX-2 selectivity and chemical structure, to appropriately diagnose and efficiently manage any NSAID-induced reaction.