Aspirin and Nonsteroidal Antiinflammatory Drugs Hypersensitivity and Management

Brian Modena, MD, Andrew A. White, MD*, Katharine M. Woessner, MD

KEYWORDS

• Aspirin • Nonsteroidal antiinflammatory drugs • Chronic spontaneous urticaria
• Aspirin-exacerbated respiratory disease • Desensitization • Oral challenge

KEY POINTS

- Hypersensitivity reactions to aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) are common, and the allergist must carefully elicit the history when these drugs could be the cause.
- Desensitization protocols are an option for most causes of hypersensitivity reactions. Oral challenges can be equally useful to identify safe alternatives.
- Cyclooxygenase-2–specific medications are often well-tolerated in the NSAID- or aspirin-allergic patient.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are a group of pharmaceuticals primarily used for analgesic purposes with the exception of acetylsalicylic acid (aspirin [ASA]) whose primary use is for its antiplatelet effect. The availability of these medications over the counter, combined with their often first-line use in most types of pain and fever, make them one of the most popular classes of medications used worldwide. The use of ASA for primary and secondary prevention of cardiovascular disease significantly increases the global use of this medication class. In 2005, 19.3% of adult Americans took ASA daily or every other day.[1] Although the prevalence of hypersensitivity to NSAIDs may be low, the sheer volume of use and exposure makes

The authors have nothing to disclose.
Division of Allergy, Asthma and Immunology, Scripps Clinic, 3811 Valley Centre Drive, S99, San Diego, CA 92130, USA
* Corresponding author.
E-mail address: White.andrew@scrippshealth.org

Immunol Allergy Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.iac.2017.07.008 **immunology.theclinics.com**

consultation to the allergist for a reaction to one of these medications a relatively common occurrence.

The existence of several types of hypersensitivity reactions can make the approach to these patients somewhat challenging. Yet, hypersensitivity reactions can be most effectively compartmentalized into pharmacologic (secondary to cyclooxygenase-1 [COX-1] inhibition) or a specific (likely IgE) mediated effect. The presence of reactions to more than one structurally dissimilar NSAID will greatly inform the clinician to the presence of a COX-1 based hypersensitivity reaction.

Several specific reaction phenotypes have been described[2] and will are outlined below, and discussed throughout the article in finer detail.

1. *NSAID-exacerbated cutaneous disease (NECD)*: Sensitivity to all COX-1–inhibiting NSAIDs in the setting of active chronic spontaneous urticaria (pharmacologic effect of COX-1 inhibition).
2. *NSAID-induced urticaria/angioedema (NIUA)*: These patients have no underlying chronic urticaria, but experience cutaneous symptoms with all COX-1–inhibiting NSAIDs.
3. *Single NIUA, anaphylaxis, or both*: Patients experience cutaneous or systemic anaphylactic reactions isolated to a single NSAID.
4. *ASA-exacerbated respiratory disease (AERD)*: A complex pharmacologic effect of COX-1 inhibition leading to primary respiratory hypersensitivity reactions. This occurs with all COX-1–inhibiting NSAIDs.
5. *Non–mast cell–related* (drug rash with eosinophilia and systemic symptoms, aseptic meningitis etc): These involve immune reactions do not depend on mast cell involvement and will not be specifically addressed further.

As would be true for any consultation for a drug allergy, the differentiation of immunologic hypersensitivity from adverse drug effect becomes paramount. NSAIDs are well-known for effects on the gastrointestinal tract. These reactions can vary from annoying to severe, with severe gastritis potentially being inaccurately labeled as an "allergy" in the electronic health record.[3]

NONSTEROIDAL ANTIINFLAMMATORY DRUG HYPERSENSITIVITY ENDOTYPES AND MECHANISMS

ASA had been in clinical use since 1899 when Bayer began marketing it. Yet, it was not until John Vane published the first study of prostaglandin inhibition by ASA in 1971[4] that the pharmacology of NSAIDs became defined. The ensuing decades saw significant progress to the point we are today with numerous COX-1 and COX-2 selective agents on the market. Nonspecific NSAIDs can have action at both COX-1 and COX-2. COX-1 has a constitutive "housekeeping" function in endothelium, kidney, and stomach as well as other locations.[5] Yet, it most likely that the benefits of the NSAID class are related to the effect on COX-2, which is an inducible enzyme at the site of inflammation. COX-2 inhibition can decrease localized prostaglandin formation therefore improving pain and swelling. It is now felt likely the most common side effects of NSAIDs (gastritis, increased thrombosis potential, etc) are related to the NSAID effects on COX-1.

One potential pitfall for the clinician might be to dichotomize this class of drugs into COX-1 versus COX-2 inhibitors. Although this fits into the general paradigm of hypersensitivity reaction phenotypes that can be seen, it also may be overly simplified. A better understanding of NSAID function in and around COX-1 and COX-2 might help to inform reaction phenotypes that do not also fit into a classic pattern. In that