Anaphylactic and Anaphylactoid Reactions to Aspirin and Other NSAIDs

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Aspirin and non-steroidal antiinflammatory drugs (NSAIDs) may cause anaphylactic or anaphylactoid reactions. Constitutively-expressed cyclooxygenase (COX-1) inhibition is likely to be responsible for the cross-reactions and side effects associated with these drugs, as well as the anaphylactoid reactions sometimes seen in aspirin-sensitive respiratory disease. Though anaphylactic and anaphylactoid reactions may be clinically indistinguishable, they involve different mechanisms. Anaphylactic reactions are due to immediate hypersensitivity involving cross-linking of drug-specific IgE. Regardless of COX selectivity pattern, NSAIDs may function as haptens capable of inducing allergic sensitization. Unlike anaphylaxis, anaphylactoid reactions are most likely related to inhibition of COX-1 by NSAIDs. Thus, an anaphylactoid reaction caused by a particular COX-1 inhibiting NSAID will occur with a chemically unrelated NSAID which also inhibits COX-1 enzymes. Selective COX-2 inhibitors appear to be safe in patients with a history of NSAID-related anaphylactoid reactions but can function as haptens, with resulting sensitization and anaphylaxis upon next exposure. This article will discuss the mechanisms, prevalence and population-based studies of anaphylactic and anaphylactoid reactions caused by aspirin and NSAIDs. The evaluation and management of patients suspected of having experienced an anaphylactic or anaphylactoid reaction to aspirin or other NSAIDs will also be reviewed.

Index Entries:
Aspirin; non-steroidal antiinflammatory drugs (NSAID); anaphylaxis; anaphylactoid; cyclooxygenase.
Introduction

Aspirin was first synthesized in 1897 by Felix Hoffman, a chemist employed by the German pharmaceutical company Bayer. In 1899, the Bayer Company launched the first mass marketing campaign for any drug when it promoted aspirin to 30,000 physicians (1). As the first nonsteroidal antiinflammatory drug (NSAID), aspirin has since been used by billions of individuals for its antiinflammatory, anti-pyretic, platelet-inhibitory, and analgesic effects. Since the 1950s, many other NSAIDs have been synthesized. These NSAIDs and aspirin are now among the most widely used drugs in the world. Considering the enormous patient exposure to NSAIDs, the number of side effects and adverse reactions to these drugs is remarkably low. Despite the therapeutic versatility and relative safety of aspirin and other NSAIDs, these drugs occasionally cause toxicity, adverse effects, or allergic and pseudo-allergic reactions, and can induce anaphylactic and anaphylactoid reactions.

The recognized antiinflammatory action of aspirin and NSAIDs is a result of their ability to inhibit cyclooxygenase (COX) enzymes (2). These enzymes exist as two isoforms, constitutively expressed COX-1 and inducibly expressed COX-2. NSAIDs and aspirin differ in their selectivity of inhibition of these isoforms, and can be classified according to this selectivity pattern (3) (Table 1). Some adverse reactions to these drugs are caused by COX-1 inhibition, a pharmacologic characteristic common among all older NSAIDs. Crossreactivity therefore occurs with all NSAIDs that share this COX-1 inhibitory effect (4). Although some adverse reactions are caused by the pattern of COX inhibition, or crossreactivity, some reactions occur after ingesting only one NSAID. Although these patients react to a particular NSAID, they may ingest other COX-inhibiting NSAIDs without an adverse reaction. As presented in the introductory note of this issue, there are six main categories of reactions to NSAIDs that can be categorized depending on the presence or absence of crossreactivity as well as the organ involved in the adverse reaction (5). However, not all reactions can be readily classified into these categories. For instance, a single individual may experience more than one type of reaction either simultaneously (“blended reaction”) or at another time. As with all medications, side effects may vary considerably from person to person. Certainly, these factors make evaluating the patient with a history of NSAID-related adverse reactions challenging. This section focuses on the more serious adverse reactions induced by these drugs—namely, anaphylactic and anaphylactoid reactions.

Mechanisms of Anaphylaxis

Anaphylaxis and anaphylactoid reactions are clinically indistinguishable, but differ in their pathogenic mechanism. Anaphylaxis is a Type I or immediate hypersensitivity reaction to an allergen, in which antigen-specific IgE bound to mast cells and basophils is cross-linked by allergen. This triggers the release of preformed chemical mediators, such as histamine and tryptase, which result in the multi-organ symptoms of anaphylaxis, including flushing, hypotension, bronchospasm, tachycardia, and urticaria. Because this reaction requires the presence of preformed IgE, previous exposure to the allergen is required for subsequent anaphylaxis to occur. Drugs are the most common cause of anaphylaxis, often functioning as hapten to induce an IgE-specific immune reaction (6).

The evidence to date implicates IgE-sensitization as the cause of NSAID-associated anaphylaxis. This is supported by a number of points, including several studies that documented NSAID-specific IgE in single-NSAID reactors (7–9). In 1986, Szczeklik found that all 136 patients who presented with urticaria or anaphylaxis to pyrazolones had positive wheal-and-flare skin reactions to 0.01% dipy-