

# Aspirin and NSAID sensitivity

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Adverse reactions to aspirin date back to the turn of the twentieth century [1]. Reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) were recognized soon after indomethacin was introduced in the 1960s [2]. Since then, an entire generation of NSAIDs has been synthesized and introduced into clinical medicine. Additionally, NSAIDs that selectively inhibit cyclo-oxygenase-2 (COX-2) enzymes while sparing COX-1 enzymes were introduced into the US market in the spring of 1999 [3]. All of these medications provide significant benefit to humans but also induce allergic or pseudoallergic reactions in a small subset of patients. This article divides a discussion of these reactions into three separate sections: aspirin and the older NSAIDs, the poor inhibitors of COX-1 and the partially selective COX-2 inhibitors, and the selective COX-2 inhibitors. Drug-induced allergic and pseudoallergic reactions, their known pathogenesis, and their similarities and differences are discussed in detail. Recommendations on how to avoid these reactions, select alternative NSAIDs, and conduct desensitization, when available, are also presented.

## **Aspirin and the cyclo-oxygenase-1–inhibiting nonsteroidal anti-inflammatory drugs**

Since 1896, aspirin has been given to humans to block inflammation and headaches, to provide analgesia, and to lower fever. In the last half-century, additional therapeutic benefits of aspirin treatment have evolved, including the inhibition of platelets, the adjunctive treatment of coronary and other artery shunt placements, the prevention of colon cancer, and the retardation of Alzheimer's disease. Since the 1960s, pharmaceutical companies have synthesized multiple

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Table 1

Cross-reactions between aspirin and other NSAIDs

| Drug and effect                                                                                                            | Generic names               | Brand names          |
|----------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------|
| NSAIDs that preferentially inhibit COX-1 and cross-react with aspirin                                                      | Piroxicam                   | Feldene              |
|                                                                                                                            | Indomethacin                | Indocin              |
|                                                                                                                            | Sulindac                    | Clinoril             |
|                                                                                                                            | Tolmetin                    | Tolectin             |
|                                                                                                                            | Ibuprofen                   | Motrin, Rufen, Advil |
|                                                                                                                            | Naproxen                    | Naprosyn             |
|                                                                                                                            | Naproxen sodium             | Anaprox, Aleve       |
|                                                                                                                            | Fenoprofen                  | Nalfon               |
|                                                                                                                            | Meclofenamate               | Meclomen             |
|                                                                                                                            | Mefenamic acid              | Ponstel              |
|                                                                                                                            | Flurbiprofen                | Ansaid               |
|                                                                                                                            | Diffunisal                  | Dolbid               |
|                                                                                                                            | Ketoprofen                  | Orudis, Oruval       |
|                                                                                                                            | Diclofenac                  | Voltaren, Cataflam   |
|                                                                                                                            | Ketoralac                   | Toradol              |
|                                                                                                                            | Etodolac                    | Lodine               |
|                                                                                                                            | Nabumetone                  | Relafen              |
|                                                                                                                            | Oxaprozin                   | Daypro               |
| NSAIDs that are poor inhibitors of COX-1 and only with higher concentrations of drug; cross-reactions with higher doses    | Acetaminophen (paracetamol) | Tylenol              |
|                                                                                                                            | Salsalate                   | Disalcid             |
| NSAIDs that preferentially inhibit COX-2 but also inhibit COX-1 when higher doses given; cross-reactions with higher doses | Nimesulide                  | Available outside US |
|                                                                                                                            | Meloxicam                   | Mobic                |
| Selective COX-2 inhibitors that do not inhibit COX-1; cross-reactions do not occur                                         | Celecoxib                   | Celebrex             |
|                                                                                                                            | Rofecoxib                   | Vioxx                |
|                                                                                                                            | Valdecoxib                  | Bextra               |

NSAIDs, which are used for analgesia and relief of musculoskeletal pain (Table 1).

Adverse reactions to aspirin that are related to its pharmacologic effects or hypersensitivity reactions include gastritis, peptic ulcerations with or without bleeding, nephritis, hepatitis, erythema multiforme, a variety of blood dyscrasias, and cutaneous and mucosal bleeding from the inhibition of platelets [4,5]. Adverse reactions to NSAIDs include all of the above, except easy bleeding, because NSAIDs only transiently inhibit platelets [6]. Aspirin and the NSAIDs that preferentially inhibit COX-1 can also induce three types of immediate hypersensitivity reactions: bronchospasm with rhinoconjunctivitis, urticaria/angioedema, and anaphylaxis. These three reactions form the central substance of this review (Table 2).

### *Pseudoallergic respiratory reactions*

Aspirin-exacerbated respiratory disease (AERD) [4] is acquired, usually around age 30 years, and consists of intractable inflammation of the nose and sinuses with aggressive formation of nasal polyps, recurrent bouts of purulent

Table 2

Pseudoallergic and allergic reactions to aspirin and NSAIDs and underlying

| Description of reactions                      | Underlying disease                         | Cross-reactions with COX-1 inhibitors |
|-----------------------------------------------|--------------------------------------------|---------------------------------------|
| NSAID-induced rhinitis and asthma             | Rhinitis, nasal, polyps, sinusitis, asthma | Yes                                   |
| NSAID-induced urticaria/angioedema            | Chronic idiopathic urticaria               | Yes                                   |
| Single drug-induced urticaria/angioedema      | None                                       | No                                    |
| Multiple drug-induced urticaria/angioedema    | None                                       | Yes                                   |
| Single drug-induced anaphylaxis               | None                                       | No                                    |
| Single drug or NSAID-induced blended reaction | Asthma, rhinitis, urticaria, or none       | No or yes                             |

sinusitis, and asthma [7]. Aspirin disease can be superimposed on patients who already have allergic rhinitis and asthma or can appear *de novo* without any prior respiratory disease [8]. These patients are indistinguishable from asthmatics with chronic hypertrophic eosinophilic sinusitis and nasal polyps [9] until they experience violent attacks of rhinitis and asthma after ingesting aspirin or the older COX-1–inhibiting NSAIDs. Such attacks routinely occur on first exposure to a new NSAID, making prior allergic sensitization impossible. The reactions consist of rhinorrhea and nasal congestion, paranasal head pain, conjunctivitis, periorbital edema, laryngospasm, and asthma. A minority of patients also experience extrapulmonary systemic symptoms, including flushing, transient hives, abdominal cramping pain, and, rarely, hypotension [10]. With full-strength aspirin (325 or 650 mg), the induced respiratory reactions can be life-threatening [11]. Nevertheless, during oral challenges with aspirin using starting doses of 30 mg of aspirin and usual controller medications, reactions are easy to treat (Table 3). AERD is caused by the overproduction and recruitment of mast cells and eosinophils, which not only synthesize excessive quantities of leukotrienes (LTs) but also overexpress cycLT<sub>1</sub> receptors on their surfaces. During an aspirin/NSAID-induced reaction, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is depleted by the inhibition of COX-1, and unrestrained synthesis of new LTs and release of histamine from mast cells, along with synthesis of PGD<sub>2</sub>, causes the respiratory reactions [12].

### *Pseudoallergic cutaneous reactions*

Chronic idiopathic urticaria (CIU) is an underlying disease that constitutes a major risk factor for aspirin-induced pseudoallergic reactions [13]. Approximately one third of patients with CIU, if their disease is in remission (frequently with antihistamine treatment), experience a flare of urticaria after ingesting aspirin or the older COX-1–inhibiting NSAIDs (see Table 1) [14,15]. In one study, when the urticaria was active, 70% of the patients experienced flares of urticaria during challenges with aspirin [16]. A recent study from Poland [17] demonstrated that patients with CIU had higher levels of serum mast cell tryptase and urinary LTE<sub>4</sub> when compared with healthy control subjects or aspirin-tolerant

Table 3

Oral aspirin challenge in patients with suspected aspirin-exacerbated respiratory disease

| Time  | Dose    |           |            |
|-------|---------|-----------|------------|
|       | Day 1   | Day 2     | Day 3      |
| 7 AM  | Placebo | 30 mg     | 100–150 mg |
| 10 AM | Placebo | 45–60 mg  | 150–325 mg |
| 1 PM  | Placebo | 60–100 mg | 325–650 mg |

Perform challenge as follows:

1. Measure FEV<sub>1</sub> every hour and wait 3 hours between doses.
2. Select advancement from 30 to 45 mg for patients with a history of a severe historical reaction.
3. FEV<sub>1</sub> should be at least 1.5 L to proceed, but >70% of predicted preferred.
4. During placebo day, the FEV<sub>1</sub> should vary by <10%.
5. Reactions can be:
  - Naso-ocular alone
  - naso-ocular plus 15% or greater than decline in FEV<sub>1</sub> (classic reaction)
  - Lower respiratory reaction only (FEV<sub>1</sub> declines by >20%)
  - Laryngospasm with or without first three reactions (flat or notched inspiratory curve)
  - Systemic reaction: hives, flush, gastric pain, hypotension

*Abbreviation:* FEV<sub>1</sub>, forced expiratory volume in 1 second.

urticarial patients. During aspirin-induced urticarial flares, urinary LTE<sub>4</sub> increased significantly above baseline values in patients with CIU. Naproxen-precipitated urticarial attacks occurred in five of the seven patients and induced a further rise in urinary LTs. This study was the first to show that cutaneous mast cells synthesize increased amounts of LTs and release tryptase as a part of the pathology of CIU even before exposure to aspirin. Secondly, both aspirin and a COX-1–inhibiting NSAID (naproxen) induced cutaneous urticarial reactions and simultaneously caused increased excretion of LTE<sub>4</sub> in the urine.

Discontinuing aspirin or NSAIDs does not change the course of CIU, which appears to be driven by unknown factors clearly independent of ingesting aspirin or NSAIDs.

### *Pseudoallergic systemic reactions*

Anaphylactoid reactions to aspirin [18] occur in two situations. First, approximately 20% of patients with AERD release histamine into the systemic circulation during oral aspirin challenges [10,19]. Histamine and perhaps other mast cell products induce most of the target organ responses of anaphylaxis (eg, urticaria, laryngeal edema, gastric cramping pain, hypotension) [20,21]. The release of histamine from mast cells is not IgE dependent but an extension of the cross-reacting respiratory reaction induced by aspirin and the older COX-1–inhibiting NSAIDs [22].

Second, there are rare cases of otherwise normal-appearing humans who experience anaphylactoid reactions shortly after ingesting aspirin and other older NSAIDs [23]. These patients are unusual in that they seem to be normal and specifically do not have AERD or CIU. Because they experience systemic reactions on at least two different occasions to NSAIDs with dissimilar chemical

structures and on first exposure to the offending NSAIDs, it is difficult to explain the mechanism except through COX-1 inhibition with depletion of PGE<sub>2</sub> [18]. This explanation is by no means secure, and other explanations, including direct effects of aspirin and NSAIDs on mast cells or unrecognized prior exposure to both NSAIDs, cannot be ruled out.

Blended reactions to aspirin and the older NSAIDs are difficult to classify, because patients experience urticaria and some shortness of breath. Blended reactions do not seem to be severe enough to reach the definition of true anaphylactoid reactions but neither are they limited to the cutaneous structures.

#### *Probable IgE-mediated reactions to aspirin and nonsteroidal anti-inflammatory drugs*

For IgE-mediated reactions to occur, prior sensitization is essential, and patients only react to the drug to which they have been sensitized. Reactions on first exposure to a drug do not occur unless the drugs share epitopes with each other. Any of the NSAIDs listed in Table 1 are chemically active and readily bind to carrier proteins, functioning as drug haptens.

Unfortunately, assays for detecting specific IgE antibodies directed against drug haptens have been difficult to develop; therefore, specific IgE antibodies to single NSAIDs have only been demonstrated in a few instances [24–28]. Such observations prove that IgE antibodies can be detected in some patients with urticarial and anaphylactic reactions to NSAIDs. The logical implication is that if techniques for measuring IgE antibodies against drug haptens were more advanced, one would be able to detect IgE antibodies in most, if not all, of these patients. Because some specific IgE antibodies to NSAIDs have been demonstrated, and no satisfying alternative mechanism has been discovered, it seems reasonable to conclude that these reactions are probably IgE mediated.

#### *IgE-mediated urticarial/angioedema reactions*

Urticaria is the most common form of IgE-mediated reactions to NSAIDs [13,29]. Prior exposure and sensitization are always required, and cross-reactivity to NSAIDs with chemically distinct structures does not occur. Because the chemical structures of aspirin and individual NSAIDs are so diverse, it is not possible for IgE to recognize more than the NSAID that induced the original sensitization. The only known exception to this fact is that a few NSAIDs have molecular structures that are almost identical. Sulindac, tolmetin, and zomepirac are chemically similar; therefore, they can be recognized by the same IgE antibodies [30,31].

#### *Cross-reacting non-IgE urticaria/angioedema*

With the exception of sulindac, tolmetin, and zomepirac (the last drug being off the market since 1986), if cross-reactions between several of the NSAIDs

occur, one cannot explain the reactions through IgE-dependent mechanisms. In fact, COX-1 inhibition, depletion of PGE<sub>2</sub>, destabilization of cutaneous mast cells from the protective effect of PGE<sub>2</sub>, and discharge of histamine into the skin and soft tissues are the most likely mechanism [13].

In a study reported by Ispano et al (Italy) in 1993 [32], 92 patients who did not have CIU and who appeared to be otherwise normal reported urticarial reactions after ingesting aspirin or an NSAID in the past. These patients underwent 237 challenges with multiple NSAIDs. Of the 92 patients, 10 (11%) reacted to a second or third NSAID in addition to the original NSAID. Eighty-two of 92 patients (89%) were single NSAID reactors and probably experienced IgE-mediated reactions. Sanchez-Borges et al [33] (Venezuela) reported data from 110 patients with a prior history of urticaria associated with ingesting NSAIDs. Of the 110 patients, 82 (74.5%) reacted to more than one NSAID and were classified as cross-reactors. By contrast, Quiralte et al [34] in Spain found that 21 patients with a history of urticarial reactions to aspirin or another NSAID did not react when challenged with a panel of nine other NSAIDs over 9 weeks. These 21 patients were not challenged with the original historical NSAID. In this smaller population, cross-reacting urticaria or angioedema was not observed in any patient.

These conflicting studies are presented to highlight the controversy that exists regarding cross-reactions of NSAIDs in persons who appear to be normal. Some investigators believe that cross-reactions do not occur, except in patients with CIU, and that faulty challenge techniques are responsible for the reports. Others adamantly defend their challenge results. I believe that occasional cross-reactions probably occur in individuals who do not meet the criteria for CIU. It seems likely that inactive CIU patients might be confused with normals and yet still be vulnerable to aspirin/NSAIDs, even if they were not actively urticating at the time of exposure to an NSAID. Country-to-country variation may exist in the vulnerability of certain genetic populations to the effects of aspirin/NSAIDs, particularly because some countries have a higher prevalence than others do. In the United States, my experience is that an urticarial reaction to two structurally unrelated NSAIDs in an individual who otherwise appears to be normal is distinctly unusual.

#### *Probable IgE-mediated anaphylaxis to aspirin or one of the nonsteroidal anti-inflammatory agents*

It is difficult to study this subject definitively because of the appropriate reluctance of investigators to conduct challenge studies to confirm prior associations between the ingestion of drugs and anaphylaxis [18]. Nevertheless, because IgE antibodies to NSAIDs have sometimes been identified, and because challenges with other NSAIDs are routinely negative, these systemic reactions are most likely IgE-mediated reactions to a single NSAID.

Because identifying specific IgE antibodies to the suspect NSAID is not always possible, some allergists call these reactions “anaphylactoid” (not proven

at this moment to be IgE mediated). Nevertheless, because there already is a classification of cross-reacting, COX-1–inhibiting “anaphylactoid reactions” to aspirin/NSAIDs, it might be more useful to use the term *probable IgE mediated* if one finds oneself unable to use the term *IgE mediated* without the identified antibody.

### *Prevalence of anaphylaxis to aspirin and nonsteroidal anti-inflammatory drugs*

Penicillin and its derivatives are the most common drugs to cause anaphylaxis, with NSAIDs responsible for the second most common reactions [35]. In a retrospective study of all emergency room admissions for anaphylaxis from 1985 to 1996 at University Hospital in Florence, Italy, 107 patients were identified as having anaphylaxis (6 patients on two occasions were admitted with anaphylaxis for a total of 113 admissions) [36]. During those same years, there were 153,086 admissions to the same emergency room for all diagnoses; therefore, the prevalence of all forms of anaphylaxis was 113 in 153,086 (0.07%). Anaphylactic reactions to drugs were the most common causes of admissions (52 of 113 episodes or 49%). Of the episodes caused by drugs, 25 of 52 (48%) were caused by antibiotics and 18 of 52 (35%) by NSAIDs. The prevalence of NSAID-induced anaphylaxis admissions was 0.01%.

In an evaluation of 266 patients who presented to an emergency department in the United States, all of the patients were referred to an allergy center for further diagnostic evaluation [37]. Anaphylaxis was caused by a medication in 52 of the 266 patients (20%). Of these 52 patients, 20 reacted to aspirin and 7 to other NSAIDs. More than half of the medications that induced anaphylaxis were aspirin or other NSAIDs. Because the study did not further classify reactions into single-drug or multiple NSAID-induced anaphylaxis, it is impossible to determine whether these reactions were probable anaphylaxis or anaphylactoid reactions. In a recent study of outpatient-diagnosed anaphylaxis, such information is available. A cohort of 432 patients with anaphylaxis referred to an allergy center in Australia were analyzed with respect to the cause of their anaphylactic reactions [38]. Foods caused 61%, stinging insects 20.4%, and medications 8.3% of the reactions. Among the 8.3% of patients (36 of 432), the medications causing the anaphylactic reactions were aspirin alone in eight patients, paracetamol (acetaminophen) alone in one patient, aspirin and paracetamol in one patient, and NSAIDs alone in ten other patients. Of the 36 patients with anaphylaxis caused by drugs, 20 of 36 (55%) reacted to aspirin, acetaminophen, or one NSAID. Furthermore underscoring the unusual prevalence of cross-reactions with aspirin and other NSAIDs was the finding that only 1 of 20 patients (5%) in this study group experienced a “cross-reaction” after aspirin on one occasion and paracetamol on another occasion. Because paracetamol is a poor inhibitor of COX-1, it is unlikely that this patient had a COX-1 cross-reacting reaction. In my experience, a better explanation is that this patient probably formed IgE antibodies to aspirin and paracetamol during prior sensitizations.

## Poor inhibitors of COX-1 and partial inhibitors of COX-2

Poor inhibitors of COX-1 are acetaminophen and salsalate (Table 1). At high concentrations, these analgesic agents inhibit COX-1 and participate in the cross-reactions described in the previous section. They can induce respiratory reactions in patients with AERD and cutaneous reactions in patients with CIU. All of the information previously presented on the older NSAIDs and aspirin also applies to acetaminophen (paracetamol) and salsalate, except for the following points: reactions only occur after high doses of acetaminophen (1000 to 1500 mg) and salsalate (2000 mg), and the reactions are milder than those seen with the older NSAIDs and aspirin [39–41].

### *Probable IgE-mediated reactions to acetaminophen and salsalate*

After prior exposure to these drugs, IgE antibodies can form and participate in urticarial/angioedema reactions or anaphylaxis on next exposure. These IgE-mediated reactions are drug specific and can be severe [42–45].

### *Partial COX-2 inhibitors with inhibition of COX-1 at higher doses of the drugs*

Meloxicam and nimesulide are anti-inflammatory drugs that are used for the treatment of arthritis (see Table 1). Meloxicam is available in the United States, and nimesulide is used in Europe and other parts of the world. These drugs are interesting because they preferentially inhibit COX-2 at lower drug concentrations, but their molecular structure allows them to enter the COX-1 enzyme channel when a high enough concentration of drug is available at the channel entry.

The characteristics of their clinical reactions are identical to acetaminophen and salsalate. Low doses of meloxicam and nimesulide do not induce cross-reactions in persons with AERD or CIU; however, as the doses increase, cross-reactions begin to occur [33,46,47]. As is true for acetaminophen and salsalate, the reactions tend to be mild even at high concentrations of meloxicam and nimesulide [48].

### *Probable IgE-mediated reactions to partial inhibitors of COX-2*

Meloxicam and nimesulide are excellent haptens that can bind to carrier proteins and induce IgE-mediated hypersensitivity reactions [33].

## Selective COX-2 inhibitors

### *Lack of cross-reactions with nonsteroidal anti-inflammatory drugs that inhibit COX-2 in patients with aspirin-exacerbated respiratory disease*

Szczeklik et al [49] challenged 12 patients with AERD with rofecoxib at 12.5 and 25 mg. None of the patients reacted during single blind oral challenges.

Furthermore, urinary  $\text{LTE}_4$  levels did not increase after rofecoxib but did increase during aspirin-induced respiratory reactions. Stevenson and Simon [50] also challenged 60 patients with AERD with 12.5 and then 25 mg of rofecoxib, and none reacted. Martin-Garcia et al [51] challenged 40 patients with AERD with rofecoxib up to 25 mg, and no reactions occurred. To determine whether a higher dose of rofecoxib would cause respiratory reactions in patients with AERD, the author and his colleagues recently challenged 60 patients with 50 mg of rofecoxib. None of the 60 patients reacted to rofecoxib (K.M. Woessner et al, personal communication, February 2004). In all of these studies, 172 patients with AERD have been challenged with rofecoxib without any reactions.

Celecoxib is also an acceptable alternative in patients who have AERD. Yoshida et al [52] challenged 17 patients who had AERD with 200 mg of celecoxib, and none reacted. In a double-blind, placebo-controlled challenge study, Woessner et al [53] did not identify any reactions to 200 mg of celecoxib in 60 patients with AERD. Gyllfors et al [54] recently reported that 32 patients with AERD did not react to celecoxib up to doses of 400 mg. Furthermore, they demonstrated that urinary  $\text{LTE}_4$  levels did not increase after celecoxib challenges, further supporting the notion that celecoxib does not induce reactions or cause increased synthesis of LTs in patients with AERD.

Despite the encouraging data presented previously, the warning label for all three coxibs (rofecoxib, celecoxib, and valdecoxib) states that COX-2 inhibitors should be withheld from patients with AERD or patients who are asthmatic in whom sensitivity to NSAIDs is unknown. Because of this warning label, and unrelated to the science of understanding of the functions of COX-2 inhibitors, the first full therapeutic dose of rofecoxib or celecoxib should be given in the physician's office. Valdecoxib has only recently entered the market. The completion of further challenge studies currently underway is needed before it can be recommend for use in patients with AERD.

#### *Probable lack of cross-reactivity of COX-2 inhibitors in patients with prior urticarial reactions to nonsteroidal anti-inflammatory drugs*

Sufficient studies have been performed to confirm that urticarial reactions to first exposure of rofecoxib and celecoxib are either rare or nonexistent. After sensitization by prior exposure, rofecoxib and celecoxib function as drug haptens and participate in IgE-mediated and other immune reactions. The evidence that COX-2 inhibitors inhibit COX-1 is not persuasive, and cross-reactions between COX-2 inhibitors and aspirin or the older NSAIDs probably do not occur.

Some studies have reported cross-reacting urticarial reactions between COX-2 and COX-1 inhibitors; however, in none of these studies was a second confirmatory challenge using double-blind protocols used to prove the relationship between the suspected COX-2 inhibitor and the urticarial reaction. Furthermore, in the excellent study from Poland mentioned in the section on chronic idiopathic reaction and aspirin, the 18 patients with aspirin-induced urticarial reactions were challenged in a double-blind protocol with rofecoxib (37.5 mg)

and celecoxib (300 mg). None of the 18 patients reacted to either of the COX-2 inhibitors, and urinary LTE<sub>4</sub> levels did not increase. Biochemical support for the theory that COX-2 inhibitors cause increased synthesis of LTs or cross-react with aspirin in patients with CIU does not exist.

In the entire medical literature on rofecoxib and urticaria, 8 of 349 patients (2.2%) with prior urticarial reactions to older NSAIDs have experienced urticaria during rofecoxib challenges [33,55–59]. In only three of these studies did the investigators conclude that rofecoxib induced urticaria [33,55,58]. Even in these studies, it is not entirely clear that urticaria was caused by rofecoxib, because confirmatory double-blind oral challenges were not performed. In addition, it is not clear that first drug exposure to rofecoxib was indeed observed. Asero [55] reported that 4 of 22 (18%) patients with CIU and prior urticarial reactions to NSAIDs also reacted to 25 mg of rofecoxib. In addition, 2 of 12 patients (17%) with prior reactions to NSAIDs but without CIU also had urticaria in association with rofecoxib. Nettis et al [58] reported that 1 of 139 patients (0.7%) had “a few urticarial lesions” on one arm after oral rofecoxib challenge. Sanchez-Borges et al [33] reported that 1 of 24 patients (4%) with prior urticarial reactions to at least two of the older NSAIDs experienced urticaria after challenge with rofecoxib.

Far fewer challenge studies have been performed for celecoxib. In the Sanchez-Borges study [33], 5 of 25 patients (20%) with multiple NSAID sensitivity experienced urticaria after celecoxib. In another study, Garcia-Rodriguez et al [60] found that none of 20 patients with multiple NSAID-induced urticaria reacted to celecoxib. These two studies reported opposite results, but the total number of patients in both studies is too small to reach conclusions.

### *Anaphylaxis to COX-2 inhibitors*

This topic is difficult to study because investigators are appropriately reluctant to challenge patients with NSAIDs that have historically caused a life-threatening reaction. Nevertheless, some information is available, and recommendations can be made. COX-2 inhibitors can sensitize an individual and initiate an IgE-mediated anaphylaxis on next exposure [61].

It is not clear whether a first drug exposure to a selective COX-2 inhibitor can induce an anaphylactoid reaction. Theoretically, based on current knowledge, this is not possible, because the only mechanism available to explain such an event is inhibition of COX-1. A single case report documents three reactions to diclofenac that resembled anaphylaxis [62]. The patient was admitted to the hospital and underwent open challenge with 12.5 mg of rofecoxib. Forty minutes later, the patient had uncontrolled shaking and a drop in blood pressure to 95/55 mm Hg. The pulse rate was not stated, and the patient never had pruritus, hives, or dyspnea. The patient promptly “responded” to adrenalin (although it was given subcutaneously), and the blood pressure quickly returned to normal. A serum tryptase or plasma histamine level was not drawn or reported. Subsequently, the patient took acetaminophen without adverse effect. It was concluded that, “a COX-2 inhibitor is not safe in all persons who have adverse reactions to COX-1

inhibitors.” The implication is that the reported reaction to diclofenac was related to inhibition of COX-1, as opposed to forming specific IgE antibodies, and that the highly selective COX-2 inhibitor (rofecoxib) caused an anaphylactoid reaction by inhibiting COX-1. Such an explanation is unlikely for two reasons. First, if the patient could take doses of acetaminophen that would have any effect on arthritis pain, he would have been exposed to 500 to 1000 mg of acetaminophen every 6 to 8 hours. Acetaminophen at high doses inhibits COX-1, the mechanism invoked by the investigators to explain “cross-reactivity” with rofecoxib, yet this patient had no reaction to acetaminophen. Second, the so-called “anaphylactoid” reaction to rofecoxib could just as well have been a vasovagal reaction in a frightened man undergoing an open challenge with a drug that he believed might cause anaphylaxis. My interpretation of this case is that the original reaction was an IgE-mediated anaphylaxis to diclofenac, whereas the in-hospital “reaction” to rofecoxib was a vasovagal reaction.

### **Strategic approaches to patients who give a history of reactions to aspirin and other nonsteroidal anti-inflammatory drugs**

When patients give a history of a prior reaction to an NSAID, there are three important issues to clarify. The first objective is to explore the details of the historical reaction. It is not unusual for patients to remember a fair amount about their prior reaction, even if it occurred many years ago. Identifying an “allergy-sounding” history is the first step. Patients with “stomach pain” or “easy bruising” did not have an allergic or pseudoallergic reaction to aspirin or one of the NSAIDs. Second, one should look for underlying diseases such as AERD and CIU, wherein COX-1 pseudoallergic reactions are expected. Without these underlying diseases, the patient is more likely to experience a single drug IgE-mediated reaction. The final issue is to identify the reason why the patient needs to take an NSAID now or in the future. For pain and arthritis, the approach should depend on the presence or absence of underlying AERD or CIU. Without those underlying diseases, another COX-1-inhibiting NSAID or a selective COX-2 inhibitor has a low probability of inducing a reaction; therefore, a full-dose oral challenge with another NSAID in the physician’s outpatient office is safe and appropriate. In patients with a history of a severe prior reaction to an NSAID, particularly anaphylaxis, placing an intravenous line before starting the challenge with another NSAID is a reasonable precaution, because rapid injection of diphenhydramine, 50 mg, or ranitidine, 50 mg, can be performed if needed. In patients with underlying AERD or CIU, COX-1-inhibiting NSAIDs are contraindicated; however, selective COX-2 inhibitors are an acceptable alternative. One should always select a COX-2 inhibitor that has never been taken before. I am not convinced that first-dose anaphylactoid reactions have been reported for any of the selective COX-2 inhibitors.

A significant dilemma is the approach to patients with prior histories of aspirin-induced reactions when these patients also have cardiovascular disease.

Because aspirin is a superior inhibitor of platelets, whereas older NSAIDs have transient effects on platelet function, long-term aspirin is the drug of choice for patients with coronary and cerebral artery disease.

In patients with AERD, desensitization to aspirin is routine and is successful 100% of the time (Table 3). In patients with CIU, there is a two in three chance of not flaring the urticaria with introduction of aspirin. Furthermore, aspirin doses that inhibit platelets effectively (81 mg) are frequently below their threshold (325 mg) for inducing urticaria.

For patients who appear to be normal but who give a history of urticaria/angioedema after ingesting aspirin, a challenge with aspirin can be performed in the outpatient department (Table 4). Particularly if the urticaria with aspirin ingestion occurred over 10 years ago, there is a reasonable chance that no reaction to aspirin will occur at this time, because immunologic memory fades. If urticaria does occur, rapid desensitization can be conducted in most cases (Table 4), unless the patient cross-reacts with other COX-1 inhibitors.

For patients who appear to be normal and who give a history of anaphylaxis after taking aspirin, admission to an intensive care unit with cardiology staff in attendance is mandatory. The risk of challenge is substantially increased, because release of histamine during the reaction can induce coronary spasm and arrhythmias or myocardial infarction. Fortunately, such complications are rare, but informed consent must be obtained from the patient before proceeding (Table 4). Rapid aspirin desensitization is usually successful and can be performed safely in the setting of an intensive care unit.

Table 4

Oral challenges with aspirin to detect probable IgE-mediated cutaneous and systemic reactions, which previously occurred after ingestion of aspirin <sup>a</sup>

| Historical reaction types                           | Responses             | Initial dose (mg) | Advanced dose schedule | Interval between challenges (min) | Range of reaction dose (mg) |
|-----------------------------------------------------|-----------------------|-------------------|------------------------|-----------------------------------|-----------------------------|
| Acute urticaria <sup>b</sup><br>(normal individual) | Urticaria/angioedema  | 30                | Doubling               | 30                                | 30–60                       |
| Anaphylaxis <sup>c</sup><br>(normal individual)     | Urticaria anaphylaxis | 10                | Doubling               | 30                                | 20–30                       |

<sup>a</sup> Most patients can be managed by avoiding the NSAID suspected of causing the historical reaction, followed by an oral challenge with another NSAID or aspirin to prove new NSAID acceptance. Such challenges can be conducted in the outpatient office with a full dose of the alternative NSAID.

<sup>b</sup> A prior history of acute urticaria after ingesting aspirin is a special problem if aspirin is required. Many patients with a positive history of aspirin-induced urticaria experience negative challenges to aspirin. Even if aspirin currently causes an urticarial reaction, rapid desensitization can often be achieved and maintained with daily aspirin therapy. Outpatient challenges with an intravenous line in place are acceptable.

<sup>c</sup> Challenge should be performed in an intensive care unit with an intravenous line in place, a cardiologist in attendance, and all available modalities of treatment available. This reserved for patients giving a history of anaphylaxis to aspirin.

## Summary

Cross-reactions to aspirin and the older NSAIDs are a significant problem, with a particularly high prevalence in patients with AERD and CIU. By contrast, cross-reactions to acetaminophen, salsalate, nimesulide, and meloxicam occur only with high doses of these drugs. There is no persuasive evidence that selective COX-2 inhibitors have any effect on COX-1. Not surprisingly, there are no reports of cross-reactions between COX-2 inhibitors and aspirin/NSAIDs in AERD. There are sporadic and rare reports in the literature of cross-reacting urticarial reactions between COX-2 and COX-1 inhibitors. Because none of the studies reporting COX-2 cross-reactions performed a second confirmatory double-blind challenge in their “reactive” patients, one should remain skeptical about the existence of such cross-reactions.

By contrast, all NSAIDs can sensitize and cause IgE-mediated reactions on next exposure; therefore, urticaria/angioedema and anaphylaxis are to be expected in a small number of patients previously sensitized by these drugs.

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