

Current Knowledge and Management of Hypersensitivity to Aspirin and NSAIDs



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Learning objectives:

1. To identify suspected cases of aspirin-exacerbated respiratory disease (AERD) and other types of aspirin and nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions on the basis of clinical history.
2. To understand when and how to perform diagnostic oral aspirin and NSAID challenges.
3. To appropriately evaluate patients with aspirin and NSAID hypersensitivity and provide disease-specific management and therapeutic options.

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Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most common culprits of drug-induced hypersensitivity reactions, and can lead to a wide array of adverse effects. The accurate and timely diagnosis of aspirin and NSAID-induced hypersensitivity reactions is important for both patient safety and for the initiation of appropriate disease-specific management and treatment. Because there are no reliably validated *in vitro* tests available, aspirin and NSAID challenges

are considered to be the criterion standard for the diagnosis of these hypersensitivity reactions, though in some patients the diagnosis can be made on the basis of a clear clinical history. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:537-45)

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The ingestion of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to an array of adverse effects, which vary from mild gastric irritation induced by predictable pharmacological side effects to severe systemic symptoms and even life-threatening anaphylaxis. Up to 1.9% of the general adult population reports an allergy to NSAIDs,¹ and adverse drug reactions to aspirin and NSAIDs constitute one of the most frequent reasons for consultations to allergy specialists. In fact, as many as 15% of all outpatient allergy referrals are for possible drug allergies, of which 29% are due to NSAID allergies, second only to antibiotic allergies in frequency.² NSAIDs are also a common culprit of severe drug reactions, causing more than half of all cases of drug-induced anaphylaxis,³ and up to 2% of inpatient deaths are linked to an NSAID-induced fatal drug

Abbreviations used

AERD- Aspirin-exacerbated respiratory disease
 AGEP- Acute generalized exanthematous pustulosis
 COX-1- Cyclooxygenase 1
 cysLTs- Cysteinyl leukotrienes
 DRESS- Drug Rash with Eosinophilia and Systemic Symptoms
 LTE₄- Leukotriene E₄
 NSAID- Nonsteroidal anti-inflammatory drug
 PG- Prostaglandin
 SJS- Stevens-Johnson syndrome
 TEN- Toxic epidermal necrolysis

reaction or side effects, of which gastrointestinal hemorrhages account for the majority.⁴

It can be difficult to properly diagnose and manage NSAID hypersensitivity, due in part to the fact that NSAIDs are also commonly associated with dose-related undesirable effects, especially in the gastrointestinal tract, which should be differentiated from true hypersensitivity reactions. In addition, the spectrum of symptoms caused by NSAID-induced hypersensitivity reaction varies widely, and the causative mechanisms are often poorly understood.

CLASSIFICATION OF HYPERSENSITIVITIES TO ASPIRIN AND NSAIDS

A stepwise approach to the diagnosis and clinical classification of aspirin and NSAID hypersensitivities is of practical use to both the clinician and the patient. Depending on the timing, symptoms, and underlying mechanism, several subtypes of NSAID hypersensitivity have been distinguished. Recent internationally collaborative efforts have provided a framework by which reactions can generally be classified into 1 of 5 reaction types (Table 1): 4 with an acute onset (immediate to several hours after drug exposure) and 1 with a delayed onset (more than 24 hours after drug exposure).^{5,6}

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Definition and mechanisms

Aspirin-exacerbated respiratory disease (AERD), which has also been known as Widal syndrome, Samter triad, aspirin-sensitive asthma, and aspirin-induced asthma, is a distinct inflammatory syndrome affecting both the upper and lower airways. It is classically characterized by the triad of asthma, recurrent eosinophilic nasal polyps, and respiratory reactions induced by aspirin and all cyclooxygenase 1 (COX-1) inhibitors. These drug reactions are considered to be pseudoallergic and are universally cross-reactive among all medications that inhibit COX-1. However, exposure to these drugs does not initiate the chronic underlying respiratory inflammation, which persists even if all NSAIDs are avoided, but rather exacerbates clinical manifestations of the disease.

The initial causative trigger of the inflammatory process and the mechanisms that underlie the chronic nature of AERD are not completely understood, but are known to involve aberrations within the arachidonic acid pathway, leading to systemic overproduction of proinflammatory eicosanoids, including cysteinyl leukotrienes (cysLTs)⁷ and prostaglandin (PG)D₂,⁸⁻¹⁰ and underproduction of or diminished response to the anti-inflammatory PGE₂.¹¹⁻¹⁴ Baseline urinary levels of leukotriene E₄ (LTE₄), a marker of systemic cysLT production, are often

5-fold higher in AERD than in aspirin-tolerant patients with asthma, and these levels increase further during the acute NSAID-induced reactions.⁷ In patients with the most severe AERD, baseline levels of urinary PGD₂ metabolites are also elevated compared with aspirin-tolerant controls and rise further during reactions.¹⁰ In addition, baseline levels of urinary LTE₄ and PGD₂ metabolites correlate with the extent of bronchoconstriction that occurs during oral aspirin challenges.^{10,15}

Pathologically, the disease is characterized by extensive eosinophilic inflammation within the sinus and bronchial mucosa,¹⁶ and the presence of degranulated mast cells and an increase in platelet-adherent leukocytes found within the nasal polyps.¹⁷ The primary cellular source of the cysLTs and PGD₂ is likely the mast cell, as parallel elevations in mast cell tryptase and histamine during aspirin challenge suggest mast cell degranulation in patients with AERD.^{9,18,19} However, eosinophils and platelet-adherent neutrophils, which are both found within the nasal polyp tissue in AERD, are also capable of producing cysLTs and may contribute significantly to the leukotriene production.^{16,17}

Clinical manifestations/presentation

AERD is an acquired syndrome with disease onset usually beginning in early adulthood with rhinitis, persistent nasal congestion, and nasal polyposis, followed by the development of asthma and hypersensitivity to COX-1 inhibitors.²⁰ NSAID-induced reactions begin within 30 to 120 minutes of drug ingestion and typically provoke respiratory symptoms in both the upper and lower airways, including increased rhinorrhea, acute nasal congestion, ocular erythema, chest tightness, and bronchoconstriction. In addition to respiratory findings, nearly one-third of patients with AERD develop extrapulmonary symptoms during these reactions, including abdominal pain, nausea, or diarrhea, and cutaneous effects such as flushing or a pruritic macular eruption on the distal extremities.^{10,20,21}

Diagnosis and challenge

Of all the types of aspirin and NSAID hypersensitivities, AERD may be the most common. The prevalence of AERD is 7.2% among adult populations with asthma overall, and it is nearly twice as common (14.9%) in patients with severe asthma.²² Using population estimates from the 2014 National Health Interview Survey Data, there are likely 1.1 million to 1.2 million adults in the United States currently living with AERD. The diagnosis of AERD can often be a clinical one, made after a thorough medical history is taken. Patients who present with the complete triad of adult-onset asthma, recurrent nasal polyposis, and a reliable history of respiratory reactions induced by 1 or more NSAIDs are relatively easy to diagnose and should be picked up quickly by an astute clinician. In general, for patients with asthma, recurrent nasal polyps, and at least 2 previous NSAID-induced respiratory reactions, at least 1 of which was within the last 5 years, we are comfortable making the diagnosis of AERD on the basis of history alone. In these clear-cut cases, no further evaluation is required before proper diagnosis. Additional evidence that can help to further substantiate the diagnosis of AERD, but is not specific for AERD, includes the presence of mild-to-moderate peripheral blood eosinophilia,²³ tissue eosinophils noted on nasal polyp pathology from surgical specimens, and a rapid rate of nasal polyp regrowth after surgery. Respiratory reactions induced by consumption of alcoholic beverages can provide another clue, as 77% to 83% of patients with AERD

TABLE 1. Classification of NSAID-induced hypersensitivity reactions

Timing of reaction	Clinical symptoms	Cross-reactivity within NSAID class	Presence of underlying disease	Putative mechanism
AERD				
Acute	Rhinitis, nasal congestion, bronchoconstriction, asthma exacerbation	Cross-reactive	Asthma/rhinosinusitis/nasal polyps	COX-1 inhibition
Multiple NSAID-exacerbated urticaria/angioedema in patients with underlying cutaneous disease				
Acute	Urticaria/angioedema	Cross-reactive	Chronic urticaria	COX-1 inhibition
Multiple NSAID-induced urticaria/angioedema in otherwise asymptomatic patients				
Acute	Urticaria/angioedema	Cross-reactive	None	Likely COX-1 inhibition
Single NSAID-induced anaphylactic reactions				
Acute	Anaphylaxis, urticaria/angioedema	Single drug-induced	Atopy is common	IgE-mediated
Delayed reactions to NSAIDs				
Delayed	Varied: Fixed drug eruptions, severe bullous skin reactions, maculopapular drug eruptions	Can be single drug-induced or cross-reactive	None	Varied: T-cell-mediated, cytotoxic T cells, natural killer cells, other

report the onset of upper and/or lower respiratory tract symptoms on ingestion of alcohol.^{24,25}

Accurate diagnosis of AERD can allow for disease-tailored therapies, including aspirin desensitization and high-dose daily aspirin therapy, which has been shown to provide a positive long-term therapeutic effect for most patients with AERD.²⁶ However, diagnosis based on history alone can be insufficient, in part because at least 15% of patients with the disease are unaware of their intolerance to NSAIDs and are not alerted to their hypersensitivity until a reaction is induced during a physician-observed provocation test.^{20,21,27} The proper identification of both nasal polyposis and asthma should be relatively straightforward, provided the patient has access to appropriate specialty medical care. The third component of the triad, NSAID hypersensitivity, tends to be the most complicated to tease out and asking the simple question “are you allergic to aspirin or NSAIDs?” may not be enough. We have identified many patients with true AERD who had originally answered “no” to this question and therefore had been improperly undiagnosed or had a significant delay in diagnosis.

These cases usually fall into 1 of 3 categories, and may warrant a provocative challenge:

1. Patients who present with both asthma and nasal polyps, but have not used NSAIDs since the development of their respiratory disease. Although these patients have never experienced an NSAID-induced reaction, in the absence of any recent NSAID exposure, they do not know whether they are currently hypersensitive. A physician-observed provocative challenge is required for diagnosis.
2. Patients who present with both asthma and nasal polyps, but maintain that they occasionally use NSAIDs and have not noted any adverse effects. This lack of perceived reaction is generally due to either (A) pharmacologic blockade of reactions or (B) general insensitivity to reaction symptoms:
 - A. Leukotriene-modifying agents, such as a leukotriene receptor antagonist such as montelukast, or the 5-lipoxygenase inhibitor zileuton, can blunt the clinical manifestations of NSAID-induced reactions to the point that they go unnoticed by the patient.^{28,29} Therefore, for

patients taking one of these agents, we recommend that all leukotriene-modifying medications be stopped for at least 7 days before a physician-observed provocative challenge.

- B. There is also a small subset of patients, often those with the most severe chronic respiratory disease, who just do not seem to have noticed the acutely worsening symptoms that followed NSAID ingestion. For some patients who live with complete nasal obstruction due to massive nasal polyposis, or poor baseline lung function, occasional bouts of worsened nasal congestion or further bronchoconstriction may go unnoticed, and therefore a physician-observed provocative challenge can be helpful.
3. Patients who present with both asthma and nasal polyps, but are taking a daily 81 mg aspirin dose for cardiac protection. In a recent publication, our center highlighted the finding that some patients with AERD apparently tolerated low-dose aspirin, but then after stopping aspirin for at least 10 days, did develop the typical aspirin-induced respiratory symptoms during a provocative oral aspirin challenge. These patients tended to have more mild asthma symptoms, both at baseline and during the aspirin challenge, and patients falling into this category during initial clinical evaluation may necessitate a provocative challenge.³⁰

Provocative challenges

Provocation challenges with aspirin, or occasionally with another COX-1 inhibitor, are the most reliable method to confirm the diagnosis of AERD because there are no validated clinically available *in vitro* diagnostics. Challenge procedures using oral aspirin and/or intranasally administered ketorolac are the most commonly available methods in the United States. Although both inhalational and intravenous testing is performed at several European and Asian centers, these modalities generally require the administration of lysine-aspirin, which is not approved for use in the United States.³¹⁻³³

General requirements for provocative aspirin challenges. Aspirin challenges should be performed under the direct supervision of a physician who is experienced in carrying out provocation tests with aspirin, and the facility must have

emergency resuscitation equipment readily available and constant observation by qualified medical personnel. The outpatient setting is appropriate for most patients with AERD, provided that they are in stable clinical condition, have relatively well-controlled asthma (preferably with a baseline FEV₁ of at least 60%-70% of predicted), are not currently using a β -receptor blocker, and do not have any underlying medical condition that would make management of severe reaction symptoms more difficult. For patients not meeting these criteria, an inpatient challenge may be preferred. Although earlier guidelines had recommended that a peripheral intravenous line be placed before aspirin challenges,^{33,34} safety data have been strong enough that at most major academic centers in the United States that routinely perform these aspirin provocation tests, they are done without a peripheral intravenous line in place.

In order not to blunt the reaction symptoms and risk a false-negative challenge, it is recommended to temporarily discontinue all oral antihistamines and leukotriene modifiers for 1 week before any diagnostic provocative challenge for AERD. In the United States, we generally allow patients to continue inhaled and oral corticosteroids and long-acting bronchodilators. For patients on chronic oral corticosteroids, every effort should be made to reduce to the lowest achievable steroid dose, as 15 mg/d oral prednisone equivalent may prevent the aspirin-induced bronchospasm and nasal symptoms in some patients.³⁵ Any patients on daily low-dose aspirin (81 mg/d for cardiac protection)³⁰ need to stop aspirin for at least 10 days before challenge, ideally after conferring with their treating cardiologist to ensure that an aspirin-free period is safe.

Oral aspirin challenge. Oral aspirin provocation tests are regarded as the criterion standard for diagnosing AERD. There are a number of distinct protocols used, which differ in the doses of aspirin given and the time interval between doses. At the Brigham and Women's Hospital AERD Center, we generally administer a 4-dose challenge protocol with 90-minute intervals between doses, based on commercially available 81-mg and 325-mg aspirin tablets and using a pill cutter to obtain the lower doses.³⁴ Starting early in the morning, we give 40.5 mg of aspirin, followed by 81, 162, and 325 mg. Lung function is measured every 90 minutes before proceeding with dose escalation, and also with any symptoms. A challenge is defined as "positive" if there is a 15% decrease in the FEV₁ from baseline FEV₁ (lower respiratory tract reaction), and/or there is an acute and physician-observable increase in at least 2 of the following: nasal congestion, rhinorrhea, sneezing, nasal or eye itching, or eye redness or tearing (naso-ocular reaction). The development of additional extrapulmonary symptoms, including headache, gastrointestinal discomfort, and skin findings, is recorded, but in the absence of any respiratory symptoms, they are not enough to confirm a diagnosis of AERD. In a challenge setting, once the patient's symptoms have stabilized and are improving, no further doses are administered and patients can be discharged home. If the goal is to achieve desensitization, the dose that provoked the reaction is repeated at this time and the protocol continued until the patient has tolerated 325 mg of aspirin without evidence of worsening respiratory symptoms.

Intranasal challenge with ketorolac. Intranasal provocation testing can be performed with the parenteral form of ketorolac, which is a potent COX inhibitor used for severe pain

and is available in the United States. The reactions provoked by intranasal challenges tend to cause less severe bronchoconstriction than those provoked by oral challenge, and the development of extrapulmonary symptoms in the gastrointestinal tract and skin is also less common.^{36,37} However, the sensitivity of intranasal ketorolac challenges is only 78%,³⁶ which is lower than for oral aspirin challenges. Therefore, a negative response does not fully rule out aspirin hypersensitivity and may need to be followed by an oral aspirin challenge to make a definitive diagnosis.

Management

Avoidance of NSAIDs and use of alternative drugs.

For patients not desensitized to aspirin, careful avoidance of all medications that inhibit COX-1 is of critical importance, and patients need to become adept at reading the active ingredient list for any over-the-counter medications. Acetaminophen is a readily available alternative, but the recommendation for its use in patients with AERD should include a warning, because about one-third of patients with AERD will develop some reaction to acetaminophen doses of 1000 mg or higher. Although these reactions are generally mild, patients should be made aware of the risk.³⁸ Celecoxib, the only selective COX-2 inhibitor currently available in the United States, is nearly always tolerated by patients with AERD,³⁹ though rare reactions in patients sensitive to extremely low doses of aspirin have been reported.⁴⁰

Aspirin desensitization and high-dose aspirin therapy.

Aspirin desensitization and subsequent initiation of daily aspirin therapy is an important tool for the management of AERD. Indications for aspirin desensitization in AERD include recurrent nasal polyps, suboptimal control of asthma or rhinosinusitis despite the use of standard medical therapies, and the need for frequent bursts of systemic corticosteroids to control respiratory or sinus symptoms.³⁴ Multiple prospective studies have now confirmed that treatment with high-dose aspirin will provide most patients with AERD improvement in both upper and lower respiratory tract symptoms, and a reduction in their corticosteroid requirement.^{26,41-44} This procedure may be especially helpful for patients who have required multiple polypectomies due to quickly recurrent nasal polyps, as high-dose aspirin can be particularly effective at slowing the rate of polyp regrowth and reducing the need for repeat sinus surgery.^{45,46} An economic analysis of outpatient aspirin desensitization and high-dose aspirin therapy found it to be a cost-effective therapeutic intervention for patients with moderate-to-severe AERD, even after accounting for the initial cost of the aspirin desensitization procedure.⁴⁷

The optimal daily dosage of aspirin therapy required to control the respiratory symptoms in AERD was investigated in a study of patients taking 325 mg or 650 mg twice daily. The side effect profile was similar for both dosages, and the study found that approximately half the patients experienced adequate symptom control at the lower dose of 325 mg twice daily, and the other half required an increase to 650 mg twice daily for optimal symptom control.⁴⁸ Thus, we recommend that patients begin daily aspirin therapy with 650 mg twice daily for an initial period of 2 months, and subsequently decrease to 325 mg twice daily to determine whether the lower dose can maintain symptom control. Patients for whom the lower dose is not

sufficient to maintain adequate control will notice a gradual worsening of their nasal symptoms within 2 weeks of lowering their aspirin dose, and are instructed to then return to the 650 mg twice daily dosage indefinitely. Patients for whom the lower dose continues to provide benefit could then begin a trial of further decreasing the dosage to only 325 mg once daily, as some patients report that doses down to 325 mg per day maintain sufficient symptom control.⁴⁹

Although nearly all patients with AERD can be successfully desensitized to aspirin, there is a portion of patients who do not derive therapeutic benefit from high-dose aspirin. In a long-term retrospective analysis of 172 patients who initiated aspirin therapy following desensitization, 22% of the patients reported no symptom improvement, or had discontinued aspirin because of side effects.⁴² Unfortunately, we are not yet able to predict which patients will derive benefit from high-dose aspirin, and further investigation is required to establish precise biomarkers and a better understanding of individual AERD phenotypes.

Leukotriene-modifying drugs. Several studies have investigated the efficacy of therapies targeting the leukotriene pathway with either leukotriene receptor antagonists such as montelukast or the 5-lipoxygenase inhibitor zileuton. In a double-blind placebo-controlled study of aspirin-sensitive patients with asthma on inhaled corticosteroids, the addition of montelukast was found to improve lung function and asthma control, though the therapeutic response to montelukast did not correlate with baseline urinary LTE₄ and was approximately equivalent to the response seen in aspirin-tolerant patients with asthma.⁵⁰ The use of montelukast before aspirin desensitization has been shown to reduce the extent of aspirin-induced bronchoconstriction and allows for a safer procedure,^{51,52} and therefore pretreatment with a leukotriene receptor antagonist is generally recommended before aspirin desensitization.

Zileuton, which decreases leukotriene production through blockade of the 5-lipoxygenase enzyme, affords notable clinical benefit to patients with AERD. In a double-blind placebo-controlled study of 40 patients with aspirin-sensitive asthma, zileuton provided acute and chronic improvement in pulmonary function, decreased need for rescue bronchodilator use, and a remarkable return of smell and decrease in rhinorrhea and nasal congestion.⁵³ In a recent questionnaire study evaluating perceived effectiveness of available therapies by 190 patients with AERD, 28% of patients who had tried zileuton found it to be extremely effective, but only 24% of patients had ever been treated with a 5-lipoxygenase inhibitor. In contrast, the vast majority of patients, 88%, had been treated with a leukotriene receptor antagonist, though only 15% of patients had found it to be extremely effective.²⁵ This suggests that zileuton is underprescribed for patients with AERD, and may provide additional benefit.

Biologics (omalizumab, mepolizumab, and dupilumab). There have been several case reports and a prospective study suggesting that omalizumab may improve baseline symptoms in AERD and reduce the severity of aspirin-induced reactions.⁵⁴⁻⁵⁶ Neither the chronic underlying inflammation in AERD nor the aspirin-induced reactions are IgE-mediated, and the mechanism by which omalizumab is effective in AERD may

instead be due to decreased mast cell activation and subsequent decreases in cysLT and PGD₂ production.⁵⁶

Mepolizumab, a humanized anti-IL-5 mAb that was recently approved for severe eosinophilic asthma in the United States, and dupilumab, a fully human anti-IL4R α antibody, have also been studied as treatment options for eosinophilic nasal polyposis and may be helpful in the management of AERD. Mepolizumab achieved a statistically significant reduction in nasal polyp score for more than half of the 20 patients who received it in the study, though only 5 of those 20 patients were aspirin intolerant by history.⁵⁷ Dupilumab also significantly reduced the nasal polyp score and increased sense of smell, though only 6 of the 30 patients were aspirin intolerant.⁵⁸ The use of these new biologics requires further studies in AERD-specific subgroups.

MULTIPLE NSAID-EXACERBATED URTICARIA/ANGIOEDEMA IN PATIENTS WITH UNDERLYING CUTANEOUS DISEASE

Definition and mechanisms

NSAID-induced exacerbations of underlying chronic urticaria and/or angioedema, also known as NSAID-exacerbated urticaria/angioedema or NSAID-exacerbated cutaneous disease, are defined as an increase in the frequency or severity of chronic urticaria and/or angioedema with the use of any COX-1 inhibitor. This is a cross-reactive process whereby exposure to any COX-1 inhibitor worsens the patient's underlying chronic cutaneous disease. The mechanism of this exacerbation of the underlying chronic urticaria and/or angioedema is thought to be related to COX-1 inhibition, the subsequent loss of mast cell-stabilizing prostaglandins (PGE₂), and an acute increase in tryptase release and cysLT production⁵⁹ and is not IgE mediated. A role for autoimmunity, as can be seen in chronic idiopathic urticaria, is postulated because of the presence of positive autologous serum skin test results.⁶⁰

Clinical manifestations/presentation

Between 12% and 30% of adults and children with chronic idiopathic urticaria develop exacerbations of their underlying disease with the use of COX-1 inhibitors.⁶¹⁻⁶³ Hypersensitivity reactions to NSAIDs in this condition are limited to the dermis and subcutaneous structures and occur within minutes to hours of exposure. There is no association with acute upper or lower respiratory tract symptoms, systemic symptoms consistent with anaphylaxis, underlying asthma, rhinosinusitis, or blood eosinophilia.

Diagnosis and challenge

The diagnosis of NSAID-exacerbated urticaria and/or angioedema can often be made by clinical history alone, on the basis of a history of chronic urticaria of more than 6 weeks duration and subsequent exacerbation by the ingestion of a COX-1 inhibitor. An oral challenge to a COX-1 inhibitor such as aspirin performed during a symptom-free period (at least 2 weeks) of their underlying chronic urticaria is the criterion standard to confirm diagnosis. There is no consensus on aspirin dosing for this oral provocation testing, though the same oral challenge protocol used in AERD can also be used in this setting. Our experience and the experience of others is that most patients have a reaction within 1 to 2 hours after a single dose of 325 mg.⁶⁴ No skin or serologic testing is available.

Management

The management of NSAID-exacerbated urticaria and/or angioedema is 3-pronged: (1) management of the underlying chronic urticaria, (2) avoidance of all COX-1 inhibitors, and (3) use of selective COX-2 inhibitors for pain as needed. Success of pretreatment with long-acting H₁ antihistamines 30 minutes before exposure to an NSAID has been reported in some patients.⁶⁵ In this study, better tolerance to lower doses of COX-1 inhibitors with antihistamine pretreatment was shown and may be sufficient to allow for tolerance of 81 mg of aspirin for primary or secondary prevention of myocardial infarction or stroke.⁶⁵ Reactivity to NSAIDs can wane as chronic urticaria resolves and reexposure could be considered at that time. Successful desensitization to aspirin has been reported; however, breakthrough urticaria and/or angioedema is common.⁶⁶

MULTIPLE NSAID-INDUCED URTICARIA/ANGIOEDEMA IN OTHERWISE ASYMPTOMATIC PATIENTS

Definition and mechanisms

Multiple NSAID-induced urticaria and/or angioedema is defined as the development of urticaria and/or angioedema following exposure to any COX-1 inhibitor in patients who have no history of chronic urticaria or angioedema. The putative mechanism is thought to be related to the other cross-reacting NSAID-induced reactions, with the loss of COX-1 activity leading to increased mast cell activation. The role of IgE in this setting is unknown. Research focused on why some cross-reacting NSAID-induced reactions are limited to the skin and others involve the respiratory tract is lacking.

Clinical manifestations/presentation

The development of urticaria and/or angioedema within 1 to 6 hours of the ingestion of an NSAID is typical. Angioedema without concurrent urticaria has been reported.⁶⁷ One large prospective study reported that patients with this condition followed for 10 years developed chronic urticaria and/or angioedema at a rate of approximately 6% and suggested that this rate was similar to the rate in the general population.⁶⁸

Diagnosis and challenge

A history of 2 or more NSAIDs eliciting a cutaneous reaction is considered adequate to make the diagnosis of NSAID-induced urticaria and/or angioedema. If the clinical history is that of a single NSAID-induced reaction not caused by aspirin, aspirin challenge is recommended to confirm the diagnosis because single NSAID-induced hypersensitivity reactions limited to the skin have been reported.⁶⁹ Furthermore, a recent case report identified a patient who developed challenge-proven immediate cutaneous reactions to 3 separate NSAIDs but not to aspirin.⁷⁰ Oral aspirin challenge remains the criterion standard for confirming this diagnosis.

Management

As with multiple NSAID-exacerbated urticaria/angioedema, NSAID avoidance or selective COX-2 inhibitor use is recommended. Successful desensitization to aspirin (9 of 11 patients) using a rapid oral protocol has been reported with durable tolerance of aspirin for up to 2 years.⁷¹

SINGLE NSAID-INDUCED ANAPHYLACTIC REACTIONS

Definition and mechanisms

Anaphylaxis, urticaria, or angioedema can be induced by a single NSAID agent. The current literature on these reactions is limited to individual case reports, except in the case of the pyrazolone class of NSAIDs, which are no longer available in the United States and many other developed nations due to severe side effects of agranulocytosis. These reactions are thought to be IgE-mediated, which has been reported in pyrazolones, but has been difficult to demonstrate in reactions resulting from the other chemical classes of NSAIDs.⁷² Case reports have demonstrated an increase in tryptase during reactions.⁷³ The rapid development of symptoms and lack of cross-reactivity with other inhibitors of COX-1 further support an IgE-mediated mechanism.

Clinical manifestations/presentation

Reactions to single NSAIDs typically occur within minutes to an hour following exposure. Signs and symptoms involving the skin develop quickly and are often accompanied by systemic symptoms including pruritus, bronchospasm, and hypotension.

Diagnosis and challenge

History alone can usually identify the culprit agent and a negative challenge to aspirin or alternative NSAID is helpful to confirm that the reactions are non-cross-reactive.⁶⁹ Although IgE is implicated in these reactions, there have been no large studies of skin testing reagents to validate their use.

Management

Avoidance of the culprit agent and any structurally similar NSAID (Table II) should be strict. An aspirin challenge not only confirms the diagnosis of non-cross-reactivity but also identifies an alternative agent that can be used as needed. In a patient with history of anaphylaxis to a single NSAID, beginning a challenge with 1/100th the target dose of aspirin (eg, 1–3 mg) or lower is recommended. There have been no documented successful desensitizations to the anaphylaxis-inducing culprit NSAID and, given the number of alternative options, a desensitization should be rarely, if ever, attempted.

DELAYED REACTIONS TO NSAIDs

Definition and mechanisms

Although the vast majority of hypersensitivity reactions reported to NSAIDs are immediate, rare delayed reactions to members of the NSAID class have been reported. This category of NSAID-induced hypersensitivity includes reactions that can involve any organ system ranging from cutaneous to systemic reactions occurring after 24 hours or more of exposure. The clinical characteristics and specificity of these reactions to a member of an NSAID class support a T lymphocyte-mediated mechanism.⁷⁴

Clinical manifestations/presentation

The clinical manifestations of delayed NSAID-induced reactions vary widely:

1. Fixed Drug Eruptions—NSAIDs are a common cause of fixed drug eruption, described as 1 or more circular-to-oval erythematous patches that develop following the systemic exposure to a drug and heal with hyperpigmentation.⁷⁵

TABLE II. NSAID classification by chemical structure

Chemical class: Salicyclic acid
Aspirin
Sodium salicylate
Salsalate
Sulfasalazine
Chemical class: Proionic acid
Ibuprofen
Naproxen
Fenoprofen
Flurbiprofen
Ketoprofen
Oxaprozin
Chemical class: Acetic acid
Diclofenac
Etodolac
Ketorolac
Indomethacin
Sulindac
Tolmetin
Nabumetone
Chemical class: Enolic acid
Piroxicam
Meloxicam
Chemical class: Fenamic acid
Mefenamic acid
Chemical class: Selective COX-2 inhibitor
Celecoxib

Reexposure to the culprit agent results in recurrence of the erythematous patch at the site of original presentation, with the possibility of additional patches appearing.

- Severe Bullous Cutaneous Reactions—Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with NSAID use, specifically resulting from the enolic acid class (oxicams) and selective COX-2 inhibitors.^{76,77} Because of the lack of confirmatory testing with these serious cutaneous reactions, many culprits have been identified including potentially aspirin. However, expert opinion is that aspirin does not cause SJS/TEN.^{74,78}
- Maculopapular drug rash—Maculopapular exanthems are the most common delayed cutaneous reaction to NSAIDs. These reactions are typically mild, occur after 1 week of exposure, and resolve with discontinuation of the culprit. Rarely, such exanthems are the first cutaneous manifestation of more serious cutaneous disease.⁷⁷
- Acute Generalized Exanthematous Pustulosis (AGEP)—Aspirin, ibuprofen, and naproxen have been identified in case reports of AGEP.⁷⁹ AGEP is characterized by the development of pustules with fever and leukocytosis that resolves quickly on drug discontinuation.
- Contact Dermatitis—Topical NSAIDs (ketoprofen and etofenamate, which are not available in the United States) are the top 2 most common causes of photo-contact dermatitis in Europe.⁸⁰ They require ultraviolet exposure following cutaneous exposure to elicit a T-cell-mediated erythematous, papulovesicular, pruritic eruption localized to the area of exposure.

- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)—The presence of rash, eosinophilia, fever, lymphadenopathy, and systemic inflammation 2 to 8 weeks following drug initiation is consistent with DRESS. Multiple classes of NSAIDs have been implicated in case reports.

Diagnosis, challenge, and management

Delayed reactions are generally understood not to be cross-reactive, but the strength of this statement varies on the basis of the type of delayed reaction.⁵ Selection of a suitable alternative NSAID will need to be determined case by case. In general, aspirin has either been not reported to cause these delayed reactions or very rarely does and should be considered as an alternative agent if there is a clinical indication for NSAID use. The lack of systematic studies, or even large patient cohorts, of NSAID-induced delayed-type reactions is the primary factor limiting recommendations on performing challenges and management. Use of patch testing to confirm the culprit agent has been reported in cases of fixed drug eruptions, DRESS and AGEP, although the positive and negative predictive value of this testing remains unclear. For SJS/TEN, AGEP, and DRESS, all other testing and challenge is contraindicated.⁸¹ For now, avoidance is the mainstay of management and desensitization has no role.

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