
Review article

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Sensitivity to nonsteroidal anti-inflammatory drugs

Jennifer Altamura Namazy, MD and Ronald A. Simon, MD

Background: Aspirin can provoke reactions ranging from respiratory to cutaneous in susceptible individuals. There has been particular attention looking at the role of cyclo-oxygenase enzymes 1 and 2 and their role in aspirin-exacerbated respiratory disease.

Objective: Patients who present with a spectrum of allergic and pseudoallergic reactions to aspirin pose a special challenge for the physician. This article discusses proposed classification system, clinical manifestations, pathogenesis of disease, and current treatment options of aspirin-related disease.

Data Sources: Relevant articles in the medical literature were derived from searching the MEDLINE database with key terms *aspirin-sensitive asthma*, *cyclo-oxygenase enzymes 1 and 2*. Sources also include review articles, randomized control trials, and standard textbooks of allergy and immunology.

Results: Aspirin-exacerbated respiratory disease remains a complex, heterogenous disease with varied clinical presentations. There have been many advances in trying to elucidate the pathogenesis of this disease. The classification system presented will provide greater ease when reading the literature and communicating with one another. Oral aspirin challenge remains the diagnostic test of choice for both respiratory and cutaneous reactions. Aspirin desensitization is an option for those with refractory respiratory disease or who require aspirin for other medical conditions.

Conclusions: This review discusses the challenges in classification, diagnosis, and treatment of those patients with a sensitivity to aspirin. Special attention is made to the possible mechanisms mediating disease progression and how specific therapies, such as leukotriene modifiers, may be helpful.

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INTRODUCTION

Aspirin, or acetylsalicylic acid (ASA), the first nonsteroidal anti-inflammatory drug (NSAID), has been used for more than 100 years by individuals around the world for its analgesic, anti-inflammatory, and platelet inhibitory properties.¹ Within the past 40 years a variety of NSAIDs have been introduced. Both ASA and NSAIDs are generally well tolerated; however, there are various side effects which can be life-threatening. Through their effects on the enzyme, cyclo-oxygenase 1 (COX-1), gastritis and peptic ulcer disease are frequent side effects. Other adverse effects include, among others: hepatitis, erythema multiforme, anemia, hepatotoxicity, interstitial nephritis, toxic epidermal necrolysis, and Stevens Johnson syndrome. Several types of pseudoallergic and allergic reactions to ASA and NSAIDs have been described. Many of these reactions are dependent on their effects on COX-1 enzyme inhibition. Various terms have been used to describe the respiratory reactions to NSAIDs,

including ASA intolerance, ASA idiosyncrasy, pseudoallergic reactions, or ASA sensitivity. This article will use the new classification as recently published by Stevenson et al² in an editorial in September 2001 as the framework for discussing sensitivity to ASA/NSAIDs.

As more physicians become aware of ASA-associated disease there has been a tendency in some to advise their asthmatic patients to avoid ASA and all other NSAIDs for fear of a potentially dangerous adverse reaction. This has led to unnecessary avoidance of these medications. To complicate matters further, the introduction of new NSAIDs which inhibit cyclo-oxygenase 2 enzyme (COX-2) have raised the question of cross-reactivity. These issues will be addressed in this article as well.

ASA-EXACERBATED RESPIRATORY DISEASE (AERD)

Samter was the first to describe the classic triad of asthma, rhinitis/nasal polyps, and ASA sensitivity. This description has become more complicated over the years, and most recently, has been expanded to include chronic sinusitis. It is important to remember that respiratory disease, not ASA sensitivity, is the underlying problem. In those patients with

Division of Allergy, Asthma and Immunology, Scripps Clinic, La Jolla, California.

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AERD, avoiding ASA and NSAIDs does not change the course of respiratory inflammation, which once it begins, progresses over time.

AERD, which is virtually only seen in adulthood, has a prevalence, which is variable. Giraldo et al³ noted that 5% of hospitalized adult asthmatic patients reported a past history of ASA-induced respiratory reactions. In 1972, the Scripps Clinic and Research Foundation found 9% of challenged adult asthmatic patients to be ASA-sensitive. The prevalence of ASA sensitivity in asthmatic patients with associated rhinitis or nasal polyps increases this number significantly to 30 to 40%.⁴

The prevalence of ASA-sensitive asthma also seems to be higher in females. Of 300 ASA-sensitive asthmatic patients referred to Scripps Clinic from 1995 to 2001, 174 (58%) were female and 126 (42%) were male.

Typically, ASA respiratory disease affects adults between 20 and 40 years of age. In the Scripps Clinic study from 1995 to 2001, nasal polyps or asthma first developed in these patients around the age of 34. In the European Network study of ASA-induced asthma, persistent rhinitis appeared at a mean age of 29.7 years followed by the development of asthma symptoms.⁵

Respiratory inflammation frequently precedes the development of ASA and NSAID-induced reactions. These patients, previously in good health, typically relate a story of developing an ordinary upper respiratory infection. However, the clinical course is different from past upper respiratory infections in that it appears to persist and, in some cases, develops into a pansinusitis with nasal polyps.

Roentgenographic abnormalities range from mucoperiosteal thickening to complete opacification of the sinuses. At Scripps Clinic between 1991 and 1997, 234 patients with AERD were referred for ASA desensitization. Two hundred patients were proven by challenge to be ASA-sensitive. Previous sinus computed tomography (CT) scans were not available for six patients; however, in the remaining 194 patients, 96% (187 patients) had abnormal sinus radiographs or CT scans.⁶ Inflammation may be limited to upper respiratory tract, but more likely, lower respiratory tract inflammation develops as well.

There are no in vitro tests to measure ASA sensitivity. The physician should be suspicious of an asthmatic patient with nasal polyps and chronic pansinusitis. It is important to remember, however, that the majority of the patients with this clinical presentation will never have reactions to ASA or NSAIDs. Most of these patients in fact have an immunoglobulin (Ig)E-mediated rhinitis with sensitivity to dust mites and, in some cases, sulfites. Conversely, there are those patients with symptoms which appear idiopathic in nature. It is important to watch these patients because they may develop AERD in the future.

DETECTION OF ASA/NSAID SENSITIVITY

Patients with ASA/NSAID-induced asthma/rhinitis, urticaria, angioedema, or anaphylaxis can not be identified with any

known in vitro test. Because of this limitation, the only way to definitively make the diagnosis is through provocative challenge testing. ASA challenges include oral, bronchial, or nasal routes.

In the United States, only oral ASA challenges are available. Physicians conducting these challenges should be experienced in their proper use and be prepared to aggressively treat reactions. Reactions include not only severe bronchospastic and nasal reactions, but also cutaneous, gastrointestinal, or vascular effects.

The more irritable the tracheobronchial tree, the more severe the bronchospastic reaction to ASA challenge. Therefore, oral and inhaled corticosteroids, intranasal corticosteroids, theophylline, and long-acting bronchodilators should be continued at the time of oral challenges. Discontinuing these medications may lead to worsening of patient's asthma and subsequent decline in lung function. In these situations, ASA challenges can not be safely and accurately performed. Despite continuing theophylline and intranasal and inhaled corticosteroids, ASA- and NSAID-induced respiratory reactions still occur.⁷ Antileukotriene modifiers such as zileuton and montelukast can block bronchospastic responses during oral ASA challenges, but often do not inhibit ASA-induced respiratory tract reactions.^{8,9}

There are some medications, however, which should be discontinued 24 hours before challenge. These include anticholinergics, antihistamines, cromolyn, and short-acting inhaled β -agonists. Simultaneous use of anticholinergics and short-acting β -agonists may lead to false-positive reactions.¹⁰ After the effect of the medication disappears, the immediate decline in lung function might be misinterpreted as a true reaction. Antihistamines can block upper respiratory tract reactions to ASA, which will interfere with the accuracy of clinical evaluation.¹¹ Cromolyn has minor inhibitory effects on the severity of the respiratory reaction induced by ASA, but pretreatment with cromolyn delays the onset of ASA-induced asthmatic reactions.¹²

At Scripps Clinic, the following oral ASA challenge protocol was developed and modified (Table 1). ASA oral challenges are conducted over 3 days. All patients receive 30 mg of ASA as their first dose. Very few patients react to 30 mg of ASA. Depending on the patient's history, they may be advanced by 15- or 30-mg doses at 3-hour intervals for a total of three doses. Therefore, individualization of doses is en-

Table 1. ASA Oral Challenge Protocol at Scripps Clinic

Time	Day 1	Day 2	Day 3
8 AM	Placebo	15–30 mg	150 mg
11 AM	Placebo	45–60 mg	325 mg
2 PM	Placebo	100 mg	650 mg

FEV₁, every hour for 3 hours after each dose.

Placebo day: FEV₁ baseline or first AM value >70% predicted.

First, AM FEV₁ value should be within $\pm$ 5% from placebo.

FEV₁ values should not change (i.e. <15%) during 9-hour placebo challenges.

couraged. A maximum of three doses are given per day. If 650 mg is administered without reaction and the patient is not taking >10 mg of prednisone or a leukotriene (LT) modifier drug, the challenge test is determined to be negative.

The onset of reactions after ASA ingestion occurs between 15 minutes and 1 hour. Respiratory reactions last 1 to 24 hours after the start of reactions. After the reaction begins, it is reversed with appropriate treatment and subsequent ASA challenges are suspended for that day. Respiratory tract signs and symptoms, which commonly occur during positive oral ASA and NSAID challenges, include nasal congestion, anosmia, and, in some, asthma exacerbation. Pleskow et al¹³ performed oral ASA challenges in 50 individuals thought to have ASA-sensitive asthma. Of these individuals, 12% experienced primarily or exclusively upper respiratory reactions during standard oral ASA challenges. Looking more closely at this population of patients, Lumry et al,¹⁴ in a followup study selected 19 patients with naso-ocular responses without asthma (as evidenced by negative methacholine challenges) to at least one prospective oral ASA challenge. The provoking dosages of ASA were between 30 and 650 mg. These dosages are similar to those reported for ASA-induced concurrent naso-ocular and asthmatic responses. Desensitization of the naso-ocular response to ASA was achieved in all 19 of these patients. ASA desensitization and continuous administration of ASA appeared to improve the nasal symptoms in 76% patients. This group is representative of a distinct, albeit rare, subgroup of all patients with AERD.

Challenges for ASA-induced urticaria and angioedema follow the same protocol. However, in patients with chronic idiopathic urticaria, discontinuing antihistamine a day or two before the oral challenge often results in a flare of urticaria, which may coincide with but be unrelated to the drug challenge. As those with active urticaria (at the time of challenge) have a much higher prevalence of ASA sensitivity, antihistamines should be tapered to the lowest effective dose.¹⁵ Most patients react to doses of ASA between 325 and 650 mg, and the reaction time from ASA ingestion to onset of hives is generally longer. Therefore, challenge protocol is usually adjusted to begin with doses of 150 mg of ASA and increasing to 325 and 650 mg.

Drug challenge for anaphylaxis carries a certain risk. There are reports of oral challenges performed for ASA/NSAID-induced anaphylactic reactions.¹⁶ However, indications for these are limited. In those patients who have not taken an NSAID since their initial reaction, challenging with a structurally different NSAID and noting no reaction to the second NSAID is the preferred strategy.^{17,18} If a cross-reactive NSAID has been taken in the interim, then these patients are not at risk for anaphylaxis, but are at risk for urticaria/angioedema. For those patients requiring ASA for a specific medical condition, oral challenges may be performed. Small doses of 3 to 10 mg of ASA are given initially and should be conducted in an intensive care unit. If the challenge is positive, rapid desensitization with ASA can be completed.^{18,19}

INHALATION CHALLENGE WITH ASA-LYSINE

Although not available in the United States, inhalation challenge is routinely performed in other parts of the world and deserves mention. Bianco et al²⁰ first introduced inhalation challenge with ASA-lysine in 1977. The onset of respiratory reaction with inhalation challenge is commonly less than 30 minutes and bronchospasm is easily reversed with an inhaled β -agonist. Therefore, each increasing concentration can be delivered at 30-minute intervals.²¹ This appears more convenient and allows the test to be performed in an outpatient setting.

Then why have we not adopted this type of ASA challenge in the United States? First, the test *substrate* is unavailable in the United States. In addition, Dahlen and Zetterstrom²¹ performed a study comparing oral and bronchial inhalation ASA challenges in 22 patients. Both routes accurately detected bronchospastic reactions. Inhalation challenge produced limited and short bronchospastic reactions. Two of 22 patients experienced only naso-ocular reactions in the oral challenge group and no patients in the bronchial challenge group. This is not surprising as there is no direct naso-ocular contact in bronchial challenges. Oral ASA challenges approximate more closely real-life challenges with ASA/NSAIDs.

Another type of ASA challenge is the nasal inhalation challenge with ASA-lysine. ASA-lysine can induce local swelling of the nasal membranes in AERD asthmatic patients. The study is limited, however, by limited sensitivity when compared with oral or inhalation provocation testing. Still, the test provides a rapid and safe means of confirming the diagnosis when positive.

ASA DESENSITIZATION AND CROSS-DESENSITIZATION

The first ASA desensitization for an episode of anaphylaxis was reported in 1922 by Widal et al.²² Desensitization is used in its broadest sense, as IgE-mediated mechanisms have not been established for ASA respiratory sensitivity. Historically, desensitization has been viewed as repeated exposure to injected antigens, leading to the reduction of IgE-mediated reactions.

In 1977, Bianco et al²⁰ induced "tolerance" to inhaled ASA-lysine after repeated inhalations in ASA-sensitive asthmatic patients. In 1980, Stevenson et al²³ reported two ASA-sensitive asthmatic patients who became refractory to ASA after single-blind, oral challenges with ASA, both patients, after desensitization, experienced improvement in respiratory disease while taking daily doses of ASA.

A state of tolerance can be induced and maintained by ASA desensitization. This process includes administration of small incremental doses of ASA over 2 to 3 days until 400 to 650 mg of ASA is tolerated. Thereafter, ASA can be administered daily to maintain desensitization, between doses of 80 and 325 mg. After desensitization, the desensitized state persists for 2 to 5 days.²⁴ During this refractory period, NSAIDs may be taken with relative safety. Stevenson et al²⁵ compared clinical outcomes after 1 to 6 years of daily ASA

treatment. They found that patients who remain on maintenance therapy at doses of 325 to 650 mg, twice daily, usually respond with improvement of respiratory symptoms.

From a practical standpoint, those patients with a history of arthritis, rheumatic diseases, or those patients who require antiplatelet therapy may be desensitized to ASA and then take daily ASA indefinitely; or the patient can be switched to any cross-reacting NSAID as long as ASA or the NSAID is continued daily.

NSAIDs, which preferentially inhibit COX-1 *in vitro*, cross-react with ASA upon first exposure to the new NSAID. Those NSAIDs which inhibit COX-1 with the least concentration require the smallest doses of NSAIDs in cross-reacting with ASA.²⁶ Further, cross-desensitization between ASA and any of the NSAIDs that inhibit COX-1 occurs routinely.

Acetaminophen is a weak inhibitor of COX-1 and therefore poses a challenge in determining element of cross-reactivity. Acetaminophen partially cross-reacts with ASA in patients with AERD, but only when high doses are administered. Delaney²⁷ challenged ASA-sensitive asthmatic patients with 1,000 mg acetaminophen and found that 28% of patients developed respiratory reactions. Similarly, in a large study by Settiple and Stevenson,²⁸ they challenged 50 ASA-sensitive asthmatic patients with 1,000 mg and then 1,500 mg acetaminophen. They found that 34% of the subjects developed respiratory reactions. However, 650 mg acetaminophen appears safe in ASA-sensitive asthmatic patients and can be recommended for analgesia and antipyresis.

Chemicals, dyes, and additives, such as azo and non-azo dyes, sulfites, and hydrocortisone succinate, have been reported to cross-react with ASA. However, their compounds have not been shown to inhibit COX-1. Azo dyes, frequently found in coloring for food, drinks, drugs, and cosmetics, have been reported to induce bronchospasm. However, more recent studies have shown that azo intolerance is rare among ASA-sensitive asthmatic patients.²⁷⁻²⁹ Reports of severe bronchospasm within minutes of receiving hydrocortisone IV led to a study by Feigenbaum et al³⁰ who found only 1 of 44 ASA-sensitive asthmatic patients reacted to both hydrocortisone succinate and methylprednisone succinate. Re-administration of hydrocortisone succinate after ASA desensitization continued to induce a respiratory reaction in this patient. This suggests a coincidental IgE-mediated reaction rather than cross-reactivity with ASA.

The recent development of highly selective COX-2 inhibitors, such as rofecoxib and celecoxib, has reduced many of the adverse side effects commonly seen with COX-1 inhibitors. Theoretically, these drugs should not cross-react with ASA or those COX-1 NSAIDs. A recent double-blind placebo controlled study from Stevenson and Simon³¹ at the Scripps Clinic, in 60 (now 100 by personal communication) patients with demonstrated ASA sensitivity, none had reacted to rofecoxib at therapeutic doses. A recent study by the same group, now in submission, found similar results with celecoxib.

INFLAMMATORY CELLS OF AERD

In 1971, Vane³² discovered the shared pharmacologic effects of ASA and NSAIDs on inhibition of COX enzymes in the metabolic cascade of arachidonic acid metabolism. The COX enzymes exist in at least two isoforms, COX-1 and COX-2. COX-1 is expressed in most mammalian cells. COX-2 is induced during inflammation.

Both mast cells and eosinophils synthesize arachidonic acid products. All biochemical events related to AERD appear to occur in mast cells of nasal and bronchial mucosa. Along with eosinophils, they are important cells in inducing ongoing inflammation. Both types of cells have been observed in nasal cytograms and nasal tissue biopsy from ASA-sensitive asthmatic patients.³³ Sladek et al³⁴ analyzed bronchoalveolar lavage fluid from ASA-sensitive asthmatic patients and found elevation in number of eosinophils and eosinophil cationic protein when compared with controls. Yamashita et al³⁵ found numerous eosinophils and degranulated mast cells in immunohistochemically stained polyp tissue of ASA-sensitive asthmatic patients. Neutrophils and macrophages, which also synthesize arachidonic acid products, are found in lavage fluid from both ASA-sensitive and ASA-tolerant asthmatic patients. The fact that they are not increased in ASA-sensitive asthmatic patients does not exclude their participation in AERD.

In 1980, Samuelsson et al³⁶ reported that a second metabolic pathway for arachidonic acid metabolism was also involved in inflammation. This pathway involves 5-lipoxygenase enzyme induction of LT synthesis. LTs (LTC₄, D₄, E₄) are potent mediators of chemotaxis of eosinophils, increased vascular permeability, mucus gland secretion, and bronchoconstriction. Interestingly, as the COX pathway is blocked, there is preferential diversion to the 5-lipoxygenase pathway.

There is evidence that ASA-sensitive asthmatic patients produce higher amounts of arachidonate products. Sladek et al³⁴ measured higher concentrations of LTC₄ and thromboxane (TXB₄) in bronchial lavage fluid taken from ASA-sensitive asthmatic patients before ASA-lysine challenge. Christie et al³⁷ and Smith et al³⁸ reported higher urinary LTE₄ and TXB₂ in ASA-sensitive asthmatic patients when compared with controls. This suggests that even before ASA challenge, ASA-sensitive asthmatic patients produce more LTs and prostanoids.

What stimulates and propagates such an inflammatory response? Szczeklik³⁹ has suggested that AERD is the result of a chronic or latent viral infection of the respiratory tract with activation of T lymphocytes, secretion of cytokines, followed by recruitment, activation, and stimulation of inflammatory cells.

PATHOGENESIS OF ASA RESPIRATORY REACTIONS

Clinical presentation of reactions to ASA and other NSAIDs are reminiscent of immediate hypersensitivity reactions. However, an antigen-antibody mechanism has never been demonstrated in AERD.

Based on the cross-reactivity of AERD patients to structurally distinct NSAIDs upon first exposure, it is thought that initiation of ASA-induced reactions is not based on antigen-antibody reactions but by the inhibition in respiratory cells of intracellular COX enzymes.⁴⁰ In vitro studies have shown that there may be a difference in function of COX enzymes when comparing ASA-sensitive asthmatic and ASA tolerant patients.⁴¹ This may be an explanation as to why more reactions are not seen with ASA exposure.

A crucial event in the pathogenesis of ASA-induced respiratory reaction occurs as ASA/NSAIDs rapidly bind COX-1. There is a subsequent decrease in the synthesis of COX products such as prostaglandin (PG)E₂. Under normal circumstances, PGE₂ inhibits 5-lipoxygenase. Without the modulating effects of PGE₂, the 5-lipoxygenase pathway is preferentially stimulated and there is an increase in the production of LTs. Upregulated cysteinyl (cys)LT1 receptors augment the effects of LTs and are considered major mediators in ASA-induced asthmatic reactions.⁴²

It is thus not surprising that most patients with ASA-sensitive asthma excrete two- to 10-fold higher amounts if LTE₄ is in their urine than asthmatic patients who are tolerant to ASA. Christie et al³⁷ found after oral challenge in ASA-sensitive asthmatic patients, there was a significant elevation in urinary LTE₄. Several studies have also shown elevated LTC₄ and histamine in nasal lavage fluid after oral ASA challenge. Similar findings have been reported in studies of the lower respiratory tract. Sladek et al³⁴ obtained bronchial lavage fluid after ASA inhalation challenges in ASA-sensitive asthmatic patients. The fluid contained elevated levels of LTC₄ and histamine.

It remains unclear why there is a subset of patients who are ASA-sensitive and why there is an overproduction of LTs in those with the disease. As mentioned earlier, the modulating effect of PGE₂ on 5-lipoxygenase is an essential target in the development of ASA respiratory disease. Sestini et al⁴³ pre-treated ASA-sensitive asthmatic patients with PGE₂ by inhalation before ASA inhalation challenge. No reactions were reported. In addition, urinary LTE₄ did not increase.

During ASA desensitization, there is continued inhibition of COX-1 as well as phospholipase A2. This leads to a

decrease in synthesis of LTs and prostanoids. In addition, cysLT1 receptors are downregulated, further blunting the effects of available LTs. Studies have shown during acute desensitization, there is a slight decrease in TXB₂ and LTB₄. In contrast, during chronic desensitization, LTB₄ synthesis declines substantially.^{44,45}

CLASSIFICATION SYSTEM

In an editorial, Stevenson et al² offers a classification system of allergic and pseudoallergic reactions to ASA and NSAIDs (Table 2). Current literature is filled with descriptive terms describing various reactions to ASA and NSAIDs. This runs the risk of leading to confusion when reading the literature and communicating with one another. Therefore, it is important to review the proposed classification when discussing ASA/NSAID sensitivity. The following not only provides a description of reactions but also comments on the effectiveness of desensitization with each presentation.

NSAID-Induced Asthma and Rhinitis

NSAID-induced asthma and rhinitis describes those patients with AERD who, after ingesting ASA or NSAIDs, develop upper and/or lower respiratory tract symptoms including rhinorrhea, nasal congestion, laryngospasm, and bronchospasm. These reactions tend to be dose-dependent, in that smaller doses of ASA or NSAIDs may not induce a significant reaction, whereas a larger and possibly therapeutic dose may induce severe reactions. ASA desensitization, as it is outlined in the text and performed today, is appropriate for individuals with this type of presentation.

NSAID-Induced Urticaria/Angioedema

There are patients with a history of chronic urticaria who develop an exacerbation of urticaria with or without angioedema after ingestion of ASA or NSAIDs. The prevalence of this phenomenon is between 21 and 30%.^{46–48} The mechanism involved is attributable to inhibition of COX-1 enzyme. Dose-dependency and degree of activity appear to play a role. Mathison et al⁴⁷ found that approximately 70% of patients who had active urticaria at the time of challenge reacted to ASA. There are no in vitro tests with which to identify patients with ASA-induced urticaria. Therefore, oral ASA

Table 2. Classification of Allergic and Pseudoallergic Reactions to ASA and NSAIDs

Description of reactions	Underlying disease	Cross-reactions first exposure	Current terminology
NSAID-induced rhinitis and asthma	Asthma/nasal polyps/sinusitis	Yes	Intolerance, ASA-induced, sensitivity
NSAID-induced urticaria/angioedema	Chronic idiopathic urticaria	Yes	Acute/chronic urticaria, angioedema
Single drug-induced urticaria/angioedema	None	No	Acute urticaria/angioedema
Multiple drug-induced urticaria/angioedema	None	Yes	Acute urticaria
Single drug-induced anaphylaxis	None	No	Anaphylactoid
Single drug or NSAID-induced blended reaction	Asthma, rhinitis urticaria, or none	No or yes	Asthma & urticaria

Modified from Stevenson D et al.²

challenges are the only way to identify ASA-induced cutaneous reactions. Avoidance of ASA or NSAIDs in these patients may eliminate acute flares of urticaria associated with ASA/NSAID ingestion; however, the course of their chronic disease is unchanged.

Mathison et al⁴⁷ reported six patients with ASA-sensitive chronic urticaria who experienced transient desensitization. However, three additional patients were challenged since that study, and continuation of ASA was associated with escalating urticaria/angioedema in all nine patients, precluding completion of long-term desensitization. Therefore, long-term ASA desensitization does not appear to be a treatment option for individuals with NSAID-induced urticaria/angioedema.⁴⁹

Single Drug-Induced Urticaria/Angioedema

In some patients without underlying risk factors, ingestion of ASA or NSAIDs induces either acute urticaria or angioedema. These patients commonly react to only one NSAID or to ASA. The likely mechanism involved is IgE-mediated. Previous sensitization to a specific drug occurs and after two or more exposures, an anaphylactic reaction may occur. It is important to understand that cross-reactivity between these drugs is unusual. Therefore, if a patient presents with acute, presumably IgE-mediated urticaria, there is a chance that further exposure of the individual to the same agent may induce anaphylaxis.

Theoretically, if this is an IgE-mediated process, desensitization is possible although unnecessary, as starting an alternative NSAID is more practical.

Multiple Drug-Induced Urticaria/Angioedema

There are those rare patients without underlying risk factors who develop urticaria/angioedema after ingestion of more than one NSAID. Interestingly, some of these patients develop chronic idiopathic urticaria at a later date. Again, as above, the likely mechanism is attributable to inhibition of COX-1 enzyme.

There are no published data regarding desensitization in this group of individuals. If these patients do not have chronic urticaria, it may be possible to desensitize them. Alternatively, COX-2 medications may be given. Although they may not be tolerated, the cross-reactivity is no higher than 30%.³¹

Single NSAID-Induced Anaphylaxis

Similar to the previous classification individuals with this presentation appear to have an IgE-mediated, single drug-induced reaction. Again, these patients can be challenged with other structurally different NSAIDs without harmful effect. In a retrospective study of 266 subjects brought to an emergency room with anaphylaxis, 52 patients (20%) were suspected of single drug-induced anaphylaxis. Approximately half of the episodes were caused by ASA or one of the NSAIDs.⁵⁰ Interestingly, there is a report of celecoxib-induced anaphylaxis.⁵¹ This specific COX-2 inhibitor does not cross-react with ASA or other COX-1 NSAIDs. Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions. There are reports in the literature of those

rare individuals who develop anaphylactoid reactions to more than one of the NSAIDs.

As was discussed in the section *Single drug-induced urticaria/angioedema*, these patients may be desensitized; however, treating with an alternative NSAID is more practical.

Single Drug or NSAID-Induced Blended Reaction

In essence, this type of reaction does not fit into any of the previously described reactions and was included to ensure accurate classification.

Other Rare Presentations

Aseptic meningitis. The mechanism of aseptic meningitis has not been elucidated. However, specific IgG and immune complexes, which have been measured in intrathecal fluid during reactions, may play a role.⁵² Activated lymphocyte-mediated response to ibuprofen has been documented in vitro and may explain this reaction.⁵³ It is a diagnosis of exclusion, because bacterial, viral, and autoimmune meningitis must be excluded. Patients typically present with fever, nausea, abdominal pain, arthralgias, and/or rash within hours of NSAID ingestion. All signs and symptoms typically resolve after discontinuation of the NSAID in question. The four NSAIDs reported to cause aseptic meningitis include ibuprofen, sulindac, tolmetin, and naproxen, but not ASA.^{52,53}

Hypersensitivity pneumonitis. Rarely, patients present with NSAID-induced cough, fever, pulmonary infiltrates, and eosinophilia.⁵⁴ The clinical course includes rapid resolution of infiltrates over several weeks with the use of systemic steroids. It appears to be an immune reaction; either delayed hypersensitivity or IgE-mediated. In 1983 Nader and Schillaci⁵⁵ induced typical pulmonary infiltrates and eosinophilia in patients within 24 hours of challenge with naproxen. Lung biopsies of infiltrates revealed interstitial lymphocytes and eosinophils. Subsequently, there have been three other controlled oral challenges with naproxen in sensitive patients with similar responses.⁵⁶⁻⁵⁸ Hypersensitivity pneumonitis has been described for a number of different NSAIDs but not for ASA.

TREATMENT

Education of the patient with ASA-induced disease is very important. Avoidance of ASA and all cross-reacting NSAIDs prevents respiratory and urticarial cross-reacting events in previously sensitized patients. However, avoidance of only the specific inciting NSAID or ASA is important in preventing a recurrence of acute urticarial reactions, anaphylaxis, aseptic meningitis, and hypersensitivity pneumonitis. In patients with single NSAID-induced urticaria, some blended reactions, anaphylaxis, hypersensitivity pneumonitis, and aseptic meningitis, it is not necessary to avoid dissimilar NSAIDs. For those patients who are cross-reactive, the patient should receive a list of drugs that are contraindicated and reaction potential of these drugs.

Patients with ASA-sensitive asthma can take acetaminophen for analgesic or antipyretic properties. However, a cross-reaction was reported after ingestion of 1,000 to 1,500 mg of acetaminophen in patients with ASA-sensitive asth-

ma.⁵⁹ Patients can also take drugs with no activity or weak activity such as: sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextropropoxyphene.⁴⁰ Selective COX-2 inhibitors are safe for patients with ASA-sensitive asthma because COX-1 will continue to produce PGE₂.

AERD is ongoing inflammation of both the upper and lower respiratory tract. Therefore, a major goal in controlling ASA disease is to reduce this inflammation. Prevention of nasal polyp formation, sinusitis, and worsening asthma are important goals. Many patients require bursts of oral corticosteroids.

If LTs are responsible for most of the respiratory reactions seen in ASA-sensitive asthma, then theoretically preventing synthesis of LTs may modify these reactions. Recently, the anti-LT drugs have been introduced as treatment of ASA-sensitive asthma. These drugs act by inhibiting synthesis of LTs by blocking 5-lipoxygenase or by blocking the cysLT receptors. Several early studies have shown that pretreatment with LT modifiers attenuates nasal and bronchial reactions in ASA-sensitive asthmatic patients. However, these studies were using minimal provoking doses of ASA. More recent studies using escalating doses of ASA showed that approximately half of subjects experienced breakthrough asthmatic responses.^{8,9} This may indicate that LT modifiers are incomplete in their blockade or alternative mediators may be involved in ASA-induced respiratory reactions. For the most part, treating with a 5-lipoxygenase inhibitor provides only partial control of symptoms.

However, a recent Swedish-Polish study⁶⁰ of 40 patients with ASA-sensitive asthma found that treatment with zileuton provided acute and chronic improvement of pulmonary function measurements. This is thought to be because of its bronchodilating effects. In patients treated with LT receptor antagonists, such as montelukast, variable responses may be seen. In a study by Kuna et al,⁶¹ montelukast was given to 80 patients with ASA-sensitive asthma who were not controlled with inhaled or oral steroids. After 4 weeks patients had improvement in pulmonary function as measured by forced expiratory volume in 1 second (FEV₁), less nocturnal asthma symptoms, more asthma-free days, and improvement in quality of life. However, the effects of treating ASA-sensitive asthmatic patients are, overall, moderate at best and no different than those seen in non-ASA-sensitive asthmatic patients.

There is an alternative to treating patients with ASA-sensitive asthma. Through desensitization, ASA tolerance can be induced and maintained. Selection of patients for ASA desensitization therapy should include all AERD patients, except those whose disease is controlled with topical corticosteroids, and LT modifier drugs. Also, ideal candidates are those patients with recurrent or chronic sinusitis and nasal polyps. In some cases "triple therapy" including 5-lipoxygenase inhibitor, cysLT receptor antagonist, and desensitization are required.

CONCLUSION

The last 2 decades have provided many advances into understanding the pathogenesis of AERD. The discovery of the many important mediating properties of the LT modifiers has allowed further work into finding appropriate treatment opportunities. It is evident that much more research is needed and expected in this area. ASA sensitivity remains a complex, heterogeneous disease with many clinical manifestations. Proper classification of reactions to ASA and NSAIDs will enable more accurate understanding of the literature. Without in vitro tests to determine patients at risk, making a definitive diagnosis becomes an even more laborious process.

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Requests for reprints should be addressed to:
Jennifer Namazy, MD
Scripps Clinic
Division of Allergy, Asthma and Immunology
10666 North Torrey Pines Road, 205W
La Jolla, CA 92037
E-mail: janamazy@yahoo.com

CME Examination

1–5, Namazy JA and Simon RA. 2002;89:542–550.

CME Test Questions

1. During ASA challenge, asthma maintenance medications that should NOT be discontinued are:
 - a. Long-acting bronchodilators.
 - b. Short-acting bronchodilators.
 - c. Antihistamines.
 - d. Cromolyn.
 - e. None of the above.
2. The prevalence of AERD in adult asthmatics is in the range of:
 - a. 0–5%.
 - b. 5–10%.
 - c. 10–20%.
 - d. >20%.
 - e. >40%.
3. After ASA desensitization, the desensitized state persists for:
 - a. 0–2 days.
 - b. 2–5 days.
 - c. 5–10 days.
 - d. 10–20 days.
 - e. Indefinitely.
4. An essential prostanoid involved in AERD is PGE₂ and its effects on:
 - a. COX-1.
 - b. 5-Lipoxygenase.
 - c. COX-2.
 - d. Phospholipase A₂.
 - e. LTC₄ synthase.
5. A patient presents with history of recurrent sinusitis, asthma having experienced nasal congestion, rhinorrhea, and wheezing 40 minutes after two doses of ASA. According to the new proposed classification system, this patient has:
 - a. NSAID-induced rhinitis/asthma.
 - b. ASA-induced rhinitis/asthma.
 - c. ASA sensitivity.
 - d. ASA intolerance.
 - e. None of the above.

Answers found on page 605