

Adverse Reactions to Aspirin and Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Ronald A. Simon* and Jennifer Namazy

Division of Allergy, Asthma and Immunology, Scripps Clinic, La Jolla, CA 92037

Abstract

Background Aspirin can provoke reactions ranging from respiratory to cutaneous in those susceptible individuals. There has been particular attention looking at the role of cyclooxygenase enzymes 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.

Methods Relevant articles in the medical literature were derived from searching the MEDLINE database. 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 manifold 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 the leukotriene modifiers may be helpful.

Index Entries:

Aspirin-sensitive asthma; cyclooxygenase enzyme 1; cyclooxygenase enzyme 2; asthma; aspirin-exacerbated respiratory disease.

*Author to whom all correspondence and reprint requests should be addressed. E-mail: Rsimon@ScrippsClinic.com

Introduction

Aspirin or acetylsalicylic acid, the first non-steroidal 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. Within the past 40 years a variety of NSAIDs have been introduced. Both aspirin and NSAIDs are generally well-tolerated; however, there are various side effects that can be life-threatening. Through their effects on the enzyme, cyclooxygenase 1 (COX-1), gastritis and peptic ulcer disease are frequent side effects. Other adverse effects include hepatitis, erythema multiforme, anemia, hepatotoxicity, interstitial nephritis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome. Several types of pseudoallergic and allergic reactions to aspirin and NSAIDs have been described (1). Many of these reactions are dependent on their effects on COX-1 inhibition. Various terms have been used to describe the respiratory reactions to NSAIDs, including aspirin intolerance, aspirin idiosyncrasy, pseudo-allergic reactions, or aspirin sensitivity (ASA). As the framework for discussing ASA sensitivity to NSAIDs, this article will utilize the new classification recently proposed by Szczeklik and Stevenson (2). In addition the issues of crossreactivity with COX-2 inhibitors are also discussed.

Aspirin Exacerbated Respiratory Disease (AERD)

Samter was the first to describe the classic triad of asthma, rhinitis/nasal polyps, and ASA. This description has become more complex over the years, and most recently, has been expanded to include chronic sinusitis. It is important to remember that aspirin-respiratory disease, not ASA, is the underlying problem. In those patients with AERD, avoiding aspirin and NSAIDs does not change the course of respiratory inflammation, which progresses over time after it begins.

AERD, which is usually only seen in adulthood, has a variable prevalence. Giraldo et al. (3) noted that 5% of hospitalized adult asthmatics reported a past history of aspirin-induced respiratory reactions. In 1972, the Scripps Clinic and Research Foundation found 9% of challenged adult asthmatics to have ASA. However, this was in a referral population of more severe asthmatics, and therefore this figure is probably greater than in the overall asthmatic population. What is clear is that the prevalence of ASA in asthmatics with associated chronic sinusitis and/or nasal polyps increases this number significantly to 30–40% (4).

The prevalence of ASA in asthma also appears to be higher in females. Of 300 asthmatics with ASA referred to the Scripps Clinic from 1995–2001, 174 (58%) were female and 126 (42%) were male.

Typically, aspirin-respiratory disease has its onset in adults between 20 and 40 yr of age. In the Scripps Clinic study from 1995–2001, nasal polyps or asthma first developed in these patients at approx 34 yr of age. In the European Network study of aspirin-induced asthma (AIA), persistent rhinitis appeared at a mean age of 29.7 yr followed by the development of asthma symptoms (5).

The natural history of AERD indicates that the respiratory-tract inflammation frequently precedes the development of ASA and NSAID-induced reactions. Typically, these patients were previously in good health and relate a story of developing an ordinary upper-respiratory inflammation (URI). However, the clinical course is different than past URIs in that symptoms appear to persist with the development of sinusitis progressing to pansinusitis with nasal polyps and asthma. At some point along this path, when the patient takes a COX-1 inhibitor, the typical AERD reaction occurs.

Roentgenographic abnormalities range from mucoperiosteal thickening to complete opacification of the sinuses. At the Scripps Clinic between 1991 and 1997, 234 patients with AERD were referred for aspirin desensitization. Two

Table 1
Editorial on NSAID Classification

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.D., Sanchez-Borges, M., and Szczeklik, A. (2001), Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes, *Ann Allergy Asthma Immunol.* **87**, 177–180.

hundred patients were proven by challenge to be aspirin-sensitive. Prior 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 the upper respiratory tract, but lower-respiratory-tract inflammation usually develops as well.

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

Aspirin-/NSAID-Induced Cutaneous Reactions

In an editorial (2), Stevenson offers a classification system of allergic and pseudoallergic

reactions to aspirin and NSAIDs (Table 1). Although AERD is a fairly clear-cut syndrome, current literature is filled with different terms describing various reactions to aspirin and NSAIDs. However, the classification (and therefore the terminology) used to describe cutaneous reactions to aspirin/NSAIDs is not as clear when reading the literature. Therefore, it is important to review the proposed classification when discussing ASA and NSAID sensitivity.

NSAID-Induced Asthma and Rhinitis in Asthmatic Patients

Describes those patients with AERD who, after ingesting aspirin or NSAIDs, develop upper- and/or lower-respiratory-tract symptoms including: rhinorrhea, nasal congestion, laryngospasm, and bronchospasm.

These reactions tend to be dose-dependent, because smaller doses of aspirin or NSAIDs may not induce a significant reaction, whereas a larger and possibly therapeutic dose may induce severe reactions.

NSAID-Induced Urticaria/Angioedema in Patients with Chronic Urticaria

There are patients with a history of chronic urticaria who develop an exacerbation of urti-

caria with or without angioedema after ingestion of aspirin or NSAIDs. The prevalence of this phenomenon in patients with chronic urticaria is 21–30% (7–9). The mechanism involved is the result of inhibition of COX-1 enzyme. Dose-dependency and degree of activity appear to play a role. Mathison et al. (8) found that approx 70% of patients who had active urticaria at the time of challenge reacted to aspirin. There are no in vitro tests with which to identify patients with aspirin-induced urticaria. Therefore, oral aspirin challenges are the only way to identify aspirin-induced cutaneous reactions. Avoidance of aspirin or NSAIDs in these patients may eliminate acute flares of urticaria associated with aspirin/NSAID ingestion; however, the course of their chronic disease is unchanged.

NSAID-Induced Urticaria/Angioedema in Normal Individuals

Rarely, patients with no underlying risk factors develop urticaria/angioedema after ingestion of more than one of the NSAIDs. Interestingly, some of these patients develop chronic idiopathic urticaria at a later date. Again, as previously mentioned, the probable mechanism is caused by inhibition of COX-1 enzyme.

Single NSAID-Induced Urticaria/Angioedema in People Who Appear to Be Normal

In some patients who have no underlying risk factors, ingestion of aspirin or NSAIDs induces either acute urticaria or angioedema. These patients commonly react to only one NSAID or to aspirin; it is important to understand that crossreactivity between these drugs for as a cause of anaphylaxis is unusual. The probable mechanism involved is IgE-mediated. Prior sensitization to a specific drug occurs and after two or more exposures, an anaphylactic reaction may occur. 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. There are currently no clinical tests available to detect IgE to these agents.

Single NSAID-Induced Anaphylaxis

Similar to the previous classification individuals with this presentation appear to have an IgE-mediated, single-drug-induced reaction. These individuals often begin with an urticarial reaction to the individual agent, but do not make the association since they have (even often) taken the same medication in the past without a reaction. Therefore, they will take it again and suffer a more severe reaction, which can be anaphylactic at some point. Some patients appear to have anaphylaxis as the first sign of sensitivity.

These patients can be challenged with other structurally different NSAIDs with no harmful effect. In a retrospective study of 266 subjects brought to an ER with anaphylaxis, 52 patients (20%) were suspected of single-drug-induced anaphylaxis. About half of the episodes were caused by ASA or one of the NSAIDs (10). Interestingly, there is a report of celecoxib-induced anaphylaxis. (11). This specific COX-2 inhibitor does not crossreact with aspirin or other COX-1 NSAIDs.

Anaphylactoid Reactions to More Than One NSAID

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.

Blended Reactions: Combinations of Urticaria and Asthma Occurring in Otherwise Normal Individuals

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

Aspirin/NSAID-Induced Aseptic Meningitis and Hypersensitivity Pneumonitis

Other more rare presentations of ASA/NSAID sensitivity include aseptic meningitis and hypersensitivity pneumonitis. Both are presented briefly here. 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 (12). Activated lymphocyte-mediated response to ibuprofen has been documented in vitro, and may explain this reaction (13). It is a diagnosis of exclusion, since bacterial, viral, and autoimmune meningitis must be excluded. Patients typically present with fever, nausea, abdominal pain, arthralgias, and rash within hours of NSAID ingestion. All signs and symptoms typically resolve after discontinuation of the NSAID in question. To date, the four NSAIDs reported to cause aseptic meningitis are ibuprofen, sulindac, tolmetin, and naproxen, but not aspirin (12,13).

Rarely, patients present with NSAID-induced cough, fever, pulmonary infiltrates, and eosinophilia (14). The clinical course includes rapid resolution of infiltrates over a period of several wk with the use of systemic steroids. It appears to be an immune reaction; either delayed hypersensitivity or IgE-mediated. In 1983, Nader and Schillaci (15) induced typical pulmonary infiltrates and eosinophilia in patients within 24 h 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 (16–18). Hypersensitivity pneumonitis has been described for a number of different NSAIDs, but not for aspirin.

Detection of ASA/NSAID Sensitivity

Patients with aspirin/NSAID-induced asthma/rhinitis, urticaria, angioedema, or anaphylaxis cannot be identified with any known in vitro test. Because of this limitation, the only way to definitively establish the diagnosis is through provocative challenge testing. Aspirin challenges include oral, bronchial, or nasal routes.

In the United States, only oral aspirin challenges are available. Physicians who conduct 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 (GI), or vascular effects.

The more irritated the tracheobronchial tree, the more severe the bronchospastic reaction to aspirin 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, aspirin challenges cannot be safely and accurately performed. Despite the continuation of theophylline and intranasal and inhaled corticosteroids, aspirin- and NSAID-induced respiratory reactions still occur (19).

Leukotriene-modifier drugs (LTMDs) such as zileuton and montelukast have been shown to block reactions to low (provoking) doses of aspirin during oral aspirin challenges, but often do not inhibit the full dose (650 mg) aspirin-induced respiratory-tract reactions. Further, LTMDs block bronchospastic reactions more often than the upper respiratory tract (20,21). Although only 60% of patients with a history of asthmatic reactions to aspirin have positive challenges; performing aspirin challenges purely for diagnostic purposes is not recommended because of the severity of reactions during oral challenges. If the goal is aspirin desensitization and treatment, then

Table 2
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 h after each dose
Placebo day: FEV₁ baseline or first AM value > 70% predicted
First, AM FEV₁ value should be within 5% (up or down) from placebo
FEV₁ values should not change (i.e. < 15%) during 9-h placebo challenges

oral challenge with LTMD pretreatment makes sense. If no reaction occurs, this is not definitive proof that the patient has ASA (or if both the upper and lower respiratory-tract reactions were completely blocked), but the process will probably be easier for the patient to complete, and treatment with aspirin should commence even in the face of a negative challenge if the patient fits the diagnostic picture of AERD prior to the challenge.

Some medications should be discontinued 24 h prior to challenge, including anticholinergics, antihistamines, cromolyn, and short-acting inhaled beta agonists. Simultaneous use of anticholinergics and short-acting beta agonists may lead to false-positive reactions (22). After the effect of the medication disappears, the immediate decline in lung function may be misinterpreted as a true reaction. Antihistamines can block upper-respiratory-tract reactions to aspirin, which will interfere with the accuracy of clinical assessment (23). Cromolyn has minor inhibitory effects on the severity of the respiratory reaction induced by aspirin, but pretreatment with cromolyn delays the onset of AIA reactions (24).

At the Scripps Clinic, the following oral aspirin challenge protocol was developed and modified (Table 2). Aspirin oral challenges are conducted over a period of 3 d. All patients receive 30 mg of aspirin as their first dose. Very few patients react to 30 mg of aspirin. Depending on the patient’s history, they may be

advanced by 15 mg or 30 mg doses at 3–h intervals for a total of three doses. Therefore, individualization of doses is encouraged. 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 LTMD, the challenge test is determined to be negative.

The onset of reactions following aspirin ingestion occurs between 15 min and 1 h. Respiratory reactions will last from 1–24 h after the start of the reaction. Respiratory-tract signs and symptoms that commonly occur during positive oral aspirin and NSAID challenges include nasal congestion, anosmia, and headaches. After the reaction begins, it is reversed with appropriate treatment and subsequent aspirin challenges are suspended for that day.

Challenges for aspirin-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. Since those with active urticaria (at the time of the challenge) have a much higher prevalence of ASA, antihistamines should be tapered to the lowest effective dose (25). Most patients react to doses of aspirin between 325 and 650 mg and the reaction time from aspirin ingestion to onset of hives is generally longer than 1 h. Therefore, challenge protocol is usually adjusted to begin with doses of 150 mg of aspirin and increasing to 325 and 650 mg.

Drug challenge for anaphylaxis carries a certain risk. There are reports of oral challenges performed for aspirin/NSAID-induced anaphylactic reactions (26). However, indications for these are limited. In those patients who have not taken an NSAID since their initial reaction, challenge with a structurally different NSAID and noting no reaction to the second NSAID is the preferred strategy (27,28). If a crossreactive 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 aspirin for a specific medical condition, oral challenges may be performed. Small doses of 3–10 mg of aspirin are given initially, and should be conducted in an intensive care unit (ICU). If the challenge is positive, rapid desensitization with aspirin can be completed (28,29).

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 (30) first introduced inhalation challenge with aspirin-lysine in 1977. The onset of respiratory reaction after inhalation challenge is often less than 30 min, and bronchospasm is easily reversed with an inhaled beta agonist. Therefore, each increasing concentration can be delivered at 30-min intervals (31). This process seems convenient, and allows the test to be performed in an outpatient setting.

Why have we not adopted aspirin-lysine challenge in the United States? First, aspirin-lysine is unavailable in the United States. Second, Dahlen et al. (31) performed a study comparing oral aspirin and bronchial aspirin-lysine inhalation challenges in 22 patients. Both routes accurately detected bronchospastic reactions. Inhalation challenge produced limited and short bronchospastic reactions. Only 2/22 patients in the oral challenge group experienced solely naso-ocular reactions, and none in the bronchial-challenge group experienced naso-ocular reactions. This is not surprising because there is no direct naso-ocular contact in bronchial challenges. Oral aspirin challenges more closely approximate real-life challenges with aspirin/NSAIDs.

Another type of aspirin challenge is the nasal inhalation challenge with aspirin-lysine. Aspirin-lysine can induce local swelling of the nasal membranes in AERD-asthmatic patients. This challenge method has limited usefulness; however, because it has limited sensitivity when compared with oral or inhalation provo-

cation testing. Still, the test provides a rapid and safe means of confirming the diagnosis when positive.

Aspirin Desensitization and Cross-Desensitization

The first aspirin desensitization for an episode of anaphylaxis was reported in 1922 by Widal et al. (32) Desensitization is used here in its broadest sense, since IgE-mediated mechanisms have not been established for respiratory ASA. Historically, desensitization has been viewed as repeated exposure to injected antigens, leading to the reduction of IgE-mediated reactions.

In 1977, Bianco et al. (31) induced “tolerance” to inhaled aspirin-lysine after repeated inhalations in aspirin-sensitive asthmatic patients. In 1980, Stevenson et al. (33) reported two aspirin-sensitive asthmatic who became refractory to aspirin after single-blind oral challenges with aspirin, both patients, after desensitization, experienced improvement in respiratory disease while taking daily doses of aspirin.

A state of tolerance can be induced and maintained by aspirin desensitization. This process includes administration of small incremental doses of aspirin over a period of 2–3 d until 400–650 mg of aspirin is tolerated. Thereafter, aspirin can be administered daily to maintain desensitization, between doses of 80 and 325 mg. After desensitization, the desensitized state persists for 2–5 d. (34) During this refractory period, NSAIDs may be taken with relative safety. Stevenson et al. (35) compared clinical outcomes after 1–6 yr of daily aspirin treatment. They found that patients who remain on maintenance therapy at doses of 325–650 mg BID usually respond with improvement of respiratory symptoms.

In patients with respiratory ASA, those who also have a history of arthritis, rheumatic diseases, or those patients who require antiplatelet therapy may be desensitized to aspirin. A desensitized patient then must take daily

aspirin indefinitely, or the patient can be switched to any crossreacting NSAID as long as aspirin or the NSAID is continued daily.

Crossreacting Substances

In patients with AERD and the cross-reacting cutaneous syndromes; NSAIDs—which preferentially inhibit COX-1 *in vitro*—cross-react with aspirin upon first exposure to the new NSAID. Those NSAIDs that inhibit COX-1 least require the greatest doses in order to cause crossreacting reactions with aspirin (36). Furthermore, cross-desensitization between aspirin 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 crossreactivity. Acetaminophen partially crossreacts with aspirin in patients with AERD, but only when high doses are administered. Delaney challenged aspirin sensitive asthmatics with 1000 mg of acetaminophen and found that 28% of patients developed respiratory reactions (37). Similarly, in a large study by Setticone and Stevenson (38), they challenged 50 aspirin-sensitive asthmatics with 1000 mg and then 1500 mg of acetaminophen. They found that 34% of the subjects developed respiratory reactions. However, 650 mg of acetaminophen appears safe in aspirin-sensitive asthmatics, 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 crossreact with aspirin. 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 basically nonexistent among aspirin-sensitive asthmatic patients (37–39). Reports of severe bronchospasm within minutes of receiving intravenous (iv) hydrocortisone led to a study by Feigenbaum et al. (40) who found that only

1 of 44 aspirin-sensitive asthmatics reacted to both hydrocortisone succinate and methylprednisone succinate. Re-administration of hydrocortisone succinate after aspirin desensitization continued to induce a respiratory reaction in this patient. This suggests a coincidental IgE-mediated reaction rather than cross-reactivity with aspirin.

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 aspirin or those COX-1 NSAIDs. A recent double-blind, placebo controlled study from Stevenson and Simon (41) at the Scripps Clinic, in 60 patients with demonstrated ASA, none had reacted to rofecoxib at therapeutic doses. This number has now been increased to 100, and indicates a 99% confidence that no crossreactivity to COX-2 inhibitors exists in AERD patients. A recent study by the same group, now in submission, found similar results with celecoxib.

The issue of crossreactivity to COX-2 inhibitors in patients with urticaria/angioedema from COX-1 inhibitors is not as clear-cut. It would appear that some crossreactivity may exist, but this is at most 30%—far less than the 100% that exists with other COX-1 inhibitors—however, we currently find it to be less than 10 at most. It is important to note that (apparently IgE-mediated) reactions to individual COX-2 inhibitors have been described; thus, some of the COX-1/COX-2 inhibitor “crossreactive” urticaria patients may actually have reactions by two different mechanisms: COX-1-inhibitor crossreacting urticaria and COX-2 IgE-mediated urticaria.

Inflammatory Cells of AERD

In 1971, Vane discovered the shared pharmacological effects of aspirin and NSAIDs on the inhibition of COX enzymes in the metabolic cascade of arachidonic acid metabolism (42). The COX enzymes exist in at least two iso-

forms, COX-1 and COX-2. COX-1 is expressed in most mammalian cells, and 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 the nasal and bronchial mucosa. Along with eosinophils, these cells are important in inducing ongoing inflammation. Both types of cells have been observed in nasal cytograms and nasal tissue biopsy from aspirin-sensitive asthmatics (43). Sladek et al. (44) analyzed broncho alveolar lavage (BAL) fluid from aspirin-sensitive asthmatics, and found an elevation in the number of eosinophils and eosinophil cationic protein when compared to controls. Yamashita et al. (45) found numerous eosinophils and degranulated mast cells in immunohistochemically stained polyp tissue of aspirin-sensitive asthmatics. Neutrophils and macrophages, which also synthesize arachidonic acid products, are found in BAL fluid from both aspirin-sensitive and aspirin-tolerant asthmatics. The fact that they are not increased in aspirin-sensitive asthmatics does not exclude their participation in AERD.

In 1980, Samuelsson (46) reported that a second metabolic pathway for arachidonic acid metabolism was also involved in inflammation. This pathway involves 5-lipoxygenase (5-LO) enzyme induction of leukotriene synthesis. Leukotrienes (C, D, and 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-LO pathway.

There is evidence that aspirin-sensitive asthmatics produce higher amounts of arachidonate products. Sladek et al. (44) measured higher concentrations of LTC₄ and TXB₄ in BAL taken from aspirin-sensitive asthmatics prior to aspirin-lysine challenge. Christie et al. (47) and Smith et al. (48) reported higher urinary LTE₄ and TXB₂ in aspirin-sensitive asthmatics when compared with controls. This

suggests that even prior to aspirin-challenge, aspirin-sensitive asthmatics produce more leukotrienes and prostanoids.

What stimulates and propagates such an inflammatory response? Szczeklik has suggested that AERD is the result of a chronic or latent viral infection of the respiratory tract, with activation of T-lymphocytes and secretion of cytokines, followed by recruitment, activation, and stimulation of inflammatory cells (49).

Pathogenesis of Aspirin-Respiratory Reactions

The clinical presentation of reactions to aspirin and other NSAIDs are similar to immediate hypersensitivity reactions. However, an antigen-antibody mechanism has never been demonstrated in AERD.

Based on the crossreactivity of AERD patients to structurally distinct NSAIDs upon first exposure, it is believed that initiation of aspirin-induced reactions is not based on antigen-antibody reactions, but by the inhibition in respiratory cells of intracellular COX enzymes (50). In vitro studies have shown that there may be a difference in function of COX enzymes when comparing aspirin-sensitive asthmatic and aspirin-tolerant patients (51). This may explain why more reactions are not seen with aspirin exposure.

A crucial event in the pathogenesis of aspirin-induced respiratory reaction occurs as aspirin/NSAIDs rapidly bind COX-1. There is a subsequent decrease in the synthesis of COX products such as prostaglandin E₂ (PGE₂). Under normal circumstances, PGE₂ both bronchodilates and inhibits 5-LO. AERD patients produce lower levels of PGE₂ than do aspirin-tolerant asthmatics. Without the modulating effects of PGE₂, it is more likely for bronchospasm to occur and the 5-LO pathway is preferentially stimulated, with a resultant increase in the production of leukotrienes. AERD patients also have upregulated cysLT1

receptors that can augment the effects of leukotrienes.

It is thus not surprising that most patients with aspirin-sensitive asthma excrete two- to 10-fold higher amounts of LTE₄ in their urine than asthmatics who are tolerant to aspirin. Christie et al. (47) found after oral challenge in aspirin-sensitive asthmatics, there was a significant elevation in urinary LTE₄. Several studies have also shown elevated LTC₄ and histamine in nasal lavage fluid after oral aspirin challenge. Similar findings have been reported in studies of the lower respiratory tract. Sladek et al. (44) obtained BAL after aspirin inhalation challenges in aspirin-sensitive asthmatics. The fluid contained elevated levels of LTC₄ and histamine.

It remains unclear why there is a subset of patients who are aspirin-sensitive, and why there is an overproduction of leukotrienes in those with the disease. As mentioned earlier, the modulating effect of PGE₂ on 5-LO is an essential target in the development of aspirin-respiratory disease. Sestini et al. (53) pretreated aspirin-sensitive asthmatics with PGE₂ by inhalation before aspirin inhalation challenge. No reactions were reported, and urinary LTE₄ did not increase.

Lipoxins are another (non-leukotriene) product of the 5-LO pathway and have anti-inflammatory properties that are basically the opposite of the pro-inflammatory effects of leukotrienes. It turns out that aspirin-sensitive asthmatics also have lower levels of (at least) Lipoxin A than do aspirin-tolerant asthmatics.

During aspirin desensitization, there is continued inhibition of COX-1 as well as phospholipase A₂. This leads to a decrease in the synthesis of leukotrienes and prostanoids. In addition, cysLT₁ receptors are downregulated, further blunting the effects of available leukotrienes. Studies have shown that during acute desensitization, there is a slight decrease in TXB₂ and LTB₄. In contrast, during chronic desensitization, LTB₄ synthesis declines substantially (54,55).

Treatment

Education of the patient with aspirin-induced disease is very important. Avoidance of aspirin and all crossreacting NSAIDs prevents respiratory and urticarial crossreacting events in previously sensitized patients. For those patients who are crossreactive, the patient should receive a list of drugs that are contraindicated, which includes the reaction potential of these drugs. In patients with single NSAID-induced urticaria, some blended reactions, anaphylaxis, hypersensitivity pneumonitis, and aseptic meningitis, it is not necessary to avoid dissimilar NSAIDs.

What if the urticaria patient has not taken another NSAID (or aspirin) since their reaction? In this case, if the patient does not have chronic idiopathic urticaria and the reaction was to ibuprofen or naproxen, then the overwhelming likelihood is that the reaction was single-NSAID-specific. In addition, since COX-1 inhibitor crossreacting anaphylaxis has not been described, the worst reaction a patient could have to a different NSAID would be urticaria (and/or peripheral angioedema). Thus, a graded-dose challenge to aspirin (or another NSAID of choice) seems to be of low risk for severe reaction (and will most likely be completely negative). However, avoidance of only the specific inciting NSAID or aspirin is important in preventing a recurrence of acute urticarial reactions, anaphylaxis, aseptic meningitis, and hypersensitivity pneumonitis.

Patients with aspirin-sensitive asthma can take acetaminophen for its analgesic or antipyretic properties. However, a crossreaction was reported after ingestion of 1000–1500 mg of acetaminophen in patients with aspirin-sensitive asthma (56). Patients can also take drugs with no activity or weak activity, such as sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, aza-propazone, and dextropropoxyphene (50). Selective COX-2 inhibitors are safe for patients with aspirin-sensitive asthma because COX-1 will continue to produce PGE₂.

AERD is an ongoing inflammation of both the upper and lower respiratory tract. Therefore, a major goal in controlling ASA 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 leukotrienes are responsible for most of the respiratory reactions seen in aspirin-sensitive asthma, then theoretically preventing synthesis of leukotrienes or blocking the cysLT₁ receptor may particularly effective in treating AERD. Recently, the anti-leukotriene drugs have been introduced as treatment of aspirin-sensitive asthma. However, for the most part, treatment with a 5-LO inhibitor provides only partial control of symptoms. A recent study (57) of 40 patients with aspirin-sensitive asthma found that treatment with zileuton provided acute and chronic improvement of pulmonary-function measurements. However, the changes were the same as for non-aspirin-sensitive asthmatics. Similar results have been shown in patients treated with leukotriene-receptor antagonists, such as montelukast. In a study by Kuna et al. (58), montelukast was given to 80 patients with aspirin-sensitive asthma who were not controlled with inhaled or oral steroids. After 4 wk, patients had an 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 were generally moderate at best, and no different than seen in non-aspirin-sensitive asthmatics.

There is an alternative to treating patients with aspirin-sensitive asthma. Through desensitization, aspirin tolerance can be induced and maintained. Selection of patients for aspirin desensitization therapy should include all AERD patients, except those whose disease is controlled with topical corticosteroids and LTMDs (unless they require the use of aspirin or NSAIDs for other conditions).

Aspirin treatment significantly reduces need for sinus surgeries, systemic steroids, emergency room visits and hospitalizations in patients with AERD (59). Ideal candidates for aspirin-desensitization treatment include those patients with recurrent or chronic sinusitis and nasal polyps.

In some difficult-to-control cases, "triple therapy" including 5-LO inhibitor, cysLT receptor antagonist, and desensitization is required. This makes good theoretical sense because zileuton is only about a 35% 5-LO inhibitor, so leukotrienes will still be formed in significant amounts, and there are other pro-inflammatory products of this pathway that are not cysteinyl leukotrienes, including leukotriene B₄ and 5-HETE.

Although therapeutic doses of aspirin average 650 mg/d, tolerance can be maintained at 81 mg (the dose for cardiovascular disease prophylaxis). Patients taking 325 mg/d can tolerate full therapeutic doses of aspirin or NSAIDs on a *prn* basis (if regular full-dose NSAID therapy is required for another condition, this can be administered since with aspirin desensitization, cross-desensitization to other COX-1 inhibitors exists).

Conclusion

The last two decades have provided many advances into understanding the pathogenesis of AERD. The discovery of the many important mediating properties of the LTMDs has allowed further studies to reveal appropriate treatment opportunities. It is evident that much more research is needed and expected in this area. ASA remains a complex heterogeneous disease with many clinical manifestations. Proper classification of reactions to aspirin and NSAIDs will help to formulate a more accurate understanding of the literature. Without *in vitro* tests to determine which patients are at risk, making a definitive diagnosis becomes an even more tedious process. Fortunately, patients with AERD can tolerate

COX-2 inhibitors without the need for challenge and desensitization. Although aspirin/NSAID avoidance is paramount treatment; high-potency inhaled corticosteroids, aspirin desensitization and treatment; LTMDs are effective in treating many of these patients and in helping them to avoid nasal/sinus surgery and side effects from use of systemic steroids.

References

1. Stevenson, D., Simon, R. A., and Zuraw, B. (2002), in *Allergy: Principles and Practice*. Middleton, E., Jr., Ellis, E. F., Yuninger, J. W., Reed, C. E., Adkinson, F., Jr., Busse, W. W., eds.
2. Szczeklik, A. and Stevenson, D. (2001), *Ann. Allergy* **87**, 177–180.
3. Giraldo, B., Blumenthal, M. N., and Spink, W. W. (1969), *Ann. Intern. Med.* **71**, 479–496.
4. McDonald, J. R., Mathison, D. A., and Stevenson, D. D. (1972), *J. Allergy Clin. Immunol.* **50**, 198–207.
5. Szczeklik, A., Nizankowska, E., and Duplaga, M. (2000), *Eur. Respir. J.* **16**, 432–436.
6. Stevenson, D. (1998), *Immunol. Allergy Clin. North Am.* **18**, 773–798.
7. Bosso, J. V., Schwartz, L. B., and Stevenson, D. D. (1991), *J. Allergy Clin. Immunol.* **88**, 830.
8. Mathison, D. A., Lumry, W. R., Stevenson, D. D., and Curd, J. G. (1982), *J. Allergy Clin. Immunol.* **69**, 135.
9. Moore-Robinson, M. and Warren, R. P. (1967), *Br. Med. J.* **4**, 262.
10. Kemp, S. F., Lockey, R. F., Wolf, B. L., et al. (1995), *Arch. Intern. Med.* **155**, 1749–1754.
11. Levy, M. and Fink, J. (2001), *Ann. Allergy* **87**, 72–73.
12. Greenberg, G. N. (1998), *South Med. J.* **81**, 1463–1464.
13. Marinac, J. S. (1992), *Ann. Pharmacother.* **26**, 813–821.
14. Weber, J. C. P. and Eissigman, W. K. (1986), *Br. J. Rheumatol.* **25**, 5–6.
15. Nader, D. A. and Schillaci, R. F. (1983), *Chest* **83**, 280–282.
16. Buscaglia, A. J. and Cowden, F. E. (1984), *JAMA* **1**, 65–66.
17. Goodwin, S. D. and Glenney, R. W. (1992), *Arch. Intern. Med.* **152**, 1521–1524.
18. Londino, A. V., Wolf, G. L., and Calabro, J. J. (1984), *JAMA* **252**, 1853–1854.
19. Pleskow, W. W., Stevenson, D. D., Mathison, D. A., et al. (1983), *J. Allergy Clin. Immunol.* **71**, 574–579.
20. Pauls, J. D., Simon, R. A., Daffern, P. J., et al. (2000), *Ann. Allergy Asthma Immunol.* **85**, 40–45.
21. Stevenson, D., Simon, R. A., Mathison, D. A., et al. (2000), *Ann. Allergy Asthma Immunol.* **85**, 477–482.
22. Stevenson, D. D. (1988), *N. Engl. Reg. Allergy Proc.* **9**, 135–142.
23. Szczeklik, A. and Serwonska, M. (1979), *Thorax* **34**, 654.
24. Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1984), *J. Allergy Clin. Immunol.* **73**, 162.
25. Bosso, J. V. and Simon, R. A. (1991), in *Food Allergy: Adverse Reactions to Foods and Food Additives*. Metcalfe, D. D., Sampson, H. A., Simon, R. A., eds., Blackwell Scientific Publications, Boston, pp. 288–300.
26. Czerniawska-Mysik, G. and Szczeklik, A. (1981), *Allergy* **36**, 381–386.
27. Quiralte, J., Blanco, C., Castillo, R., et al. (197), *Ann. Allergy Asthma Immunol.* **78**, 293–296.
28. Stevenson, D. (2001), *North American Clinics Allergy and Immunology* **21**, 11–21.
29. Stevenson, D. (1998), *North American Clinics Allergy and Immunology* **18**, 4–773.
30. Bianco, S., Robuschi, M., and Petrigini, G. (1997), *IRCS J. Med. Sci.* **5**, 129.
31. Dahlen, B. and Zetterstrom, O. (1990), *Eur. Respir. J.* **3**, 527–534.
32. Widal, M. F., Abrami, P., and Lermeyez, J. (1922), *Presse Med.* **30**, 189.
33. Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1980), *J. Allergy Clin. Immunol.* **66**, 82–85.
34. Pleskow, W. W., Stevenson, D. D., Mathison, D. A., et al. (1982), *J. Allergy Clin. Immunol.* **69**, 11–19.
35. Stevenson, D. D., Hankammer, M. A., and Mathison, D. A. (1996), *J. Allergy Clin. Immunol.* **98**, 751.
36. Szczeklik, A., Gryglewski, R. J., and Czernigwska-Mysik, G. (1997), *J. Allergy Clin. Immunol.* **60**, 276–284.
37. Delaney, J. C. (1976), *Clin. Allergy* **6**, 177–184.
38. Settupane, R. A. and Stevenson, D. D. (1989), *J. Allergy Clin. Immunol.* **84**(1), 26–33.
39. Stevenson, D. D. (1989), in *Progress Allergy Clinical Immunology*. Pichler, W. J., Stadler, M. M., Dahinden, C. A., Pecoud, A. R., Frei, P., Schneider, C. H., and deWeck, A. L., eds. Hogrefe and Huber, Lewiston, NY, pp. 462–473.
40. Feigenbaum, B. A., Stevenson, D. D., and Simon, R. A. (1995), *J. Allergy Clin. Immunol.* **96**, 545–548.
41. Stevenson, D. D. and Simon, R. (2001), *J. Allergy Clin. Immunol.* **108**, 47–51.
42. Vane, J. R. (1971), *Nature* **231**, 232–235.
43. Moneret-Vautrin, D. A., Hsieh, V., Wayoff, M., et al. (1990), *Ann. Allergy* **64**, 513–518.
44. Sladek, K., Dworski, R., Soja, J., et al. (1994), *Am. J. Respir. Care Med.* **149**, 940–946.
45. Yamashita, T., Tsuyi, H., Maeda, N., et al. (1989), *Rhinology* **8**, 15–24.
46. Samuelsson, B., Hammarstroem, S., Murphy, R. C., et al. (1980), *Allergy* **35**, 375–381.
47. Christie, P. E., Tagari, P., Ford-Hutchinson, A. W., et al. (1991), *Am. Rev. Respir. Dis.* **143**, 1025–1029.
48. Smith, D. M., Hawksworth, R. J., Thien, F. C., et al. (1992), *Eur. Respir. J.* **5**, 693–699.

49. Szczeklik, A. (1990), *Eur. Respir. J.* **3**, 588–593.
50. Szczeklik, A. and Stevenson, D. D. (1999), *J. Allergy Clin. Immunol.* **104**, 5–13.
51. Juergens, U. R., Christiansen, S. C., Stevenson, D. D., et al. (1992), *J. Allergy Clin. Immunol.* **90**, 636–645.
52. Arm, J. P., O'Hickey, S. P., Spur, B. W., et al. (1989), *Am. Rev. Respir. Dis.* **140**, 148–153.
53. Sestini, P., Armetti, L., Gambaro, G., et al. (1996), *Am. J. Respir. Crit. Care Med.* **153**, 572–575.
54. Ferreri, N. R., Howland, W. C., Stevenson, D. D., et al. (1988), *Am. Rev. Respir. Dis.* **137**, 847–854.
55. Juergens, U. R., Christiansen, S. C., Stevenson, D. D., et al. (1995), *J. Allergy Clin. Immunol.* **96**, 148–156.
56. Settipane, R. A., Shrank, P. J., Simon, R. A., et al. (1995), *J. Allergy Clin. Immunol.* **96**, 480–485.
57. Dahlen, B., Nizankowska, E., and Szczeklik, A. (1998), *Am. J. Respir. Crit. Care Med.* **157**, 1187–1194.
58. Kuna, P., Malmstrom, K., Dahlen, S. E., et al. (1997), *Am. J. Respir. Care Med.* **155**, A975.
59. Stevenson, D. D., Hankammer, M. A., Mathison, D. A., et al. (1996), *J. Allergy Clin. Immunol.* **98**, 751–758.