

ADVERSE REACTIONS TO NONSTEROIDAL ANTI- INFLAMMATORY DRUGS

Donald D. Stevenson, MD

Aspirin or acetylsalicylic acid (ASA) was first synthesized in 1897 by Felix Hoffmann, an employee of the Bayer Company in Germany. For the past 100 years, aspirin, the first nonsteroidal anti-inflammatory drug (NSAID), has been used by billions of individuals as an anti-inflammatory, analgesic, and antipyretic agent. For the past 40 years, ASA's platelet-inhibitory activity has been used to prevent arterial thrombosis. Since the 1960s, a growing list of additional NSAIDs have been synthesized and marketed worldwide, mainly for their anti-inflammatory effects in the treatment of arthritis. Some NSAIDs, such as ibuprofen and naproxen, are currently sold over the counter for alleviation of headaches, menstrual cramps, musculoskeletal pain syndromes, and inflammatory arthritis. Other NSAIDs are dispensed by prescription and are mostly used to treat musculoskeletal disorders and arthritis (Table 1). Exposure of humans to ASA and NSAIDs is enormous, and, for the most part, these drugs are well tolerated.

ASA and the other NSAIDs induce a number of adverse side effects. Some adverse reactions are caused by the shared pharmacologic effects of all NSAIDs in inhibiting a ubiquitous enzyme, cyclo-oxygenase (e.g., in gastritis, peptic ulcerations, and nephritis). Other reactions are idiosyncratic, drug-specific, and include hepatitis, erythema multiforme, and multiple blood dyscrasias.⁸³ In addition, several pseudo-allergic and allergic adverse reactions to ASA and other NSAIDs have been recognized. This article reviews these diverse reactions to ASA and other NSAIDs in detail (Table 2). In addition, current investigations of

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From the Division of Allergy, Asthma, and Immunology, Department of Medicine, Scripps Clinic, The Scripps Research Institute, La Jolla, California

Table 1. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) THAT CROSS-REACT WITH ASPIRIN (ASA) IN RESPIRATORY AND CUTANEOUS PSEUDOALLERGIC REACTIONS

Generic	Brand Names
Piroxicam	Feldene
Indomethacin	Indocin
Sulindac	Clinoril
Tolmetin	Tolectin
Ibuprofen	Motrin, Rufen, Advil
Naproxen	Naprosyn
Naproxen sodium	Anaprox, Aleve
Fenoprofen	Nalfon
Meclofenamate	Meclomen
Mefenamic acid	Ponstel
Flurbiprofen	Ansaid
Diffunisal	Dolobid
Ketoprofen	Orudis, Oruvail
Diclofenac	Voltaren, Cataflam
Ketorolac	Toradol
Etodolac	Lodine
Nabumetone	Relafen
Oxaprozin	Daypro

alleged adverse effects and cross-reactivity of food additives and dyes also are reviewed.

RESPIRATORY CROSS-REACTIONS

ASA and NSAIDs can induce rhinorrhea, laryngospasm, and bronchospasm in some patients with underlying rhinosinusitis and asthma.⁸⁰ Various terms have been used to describe the respiratory reactions to NSAIDs, including *ASA intolerance*,⁶⁵ *ASA idiosyncrasy*,⁷⁸ *pseudo-allergic reactions*, or *ASA sensitivity*.⁹¹ ASA and all other NSAIDs, which inhibit cyclo-oxygenase (COX), cross-react with each other in respiratory reactions. Furthermore, respiratory reactions are dose-dependent, such that small doses of ASA or other NSAIDs do not induce any reactions, but larger doses of COX-inhibiting drugs induce progressively more severe reactions.⁹⁹

Concept of ASA Respiratory Disease

Sensitivity to ASA and other NSAIDs occurs in patients with chronic rhinitis, sinusitis, nasal polyps, and asthma. ASA disease is the underlying respiratory inflammation that starts and continues in the absence of exposure to ASA and NSAIDs; however, such patients can only be identified as ASA-sensitive after experiencing a respiratory reaction to ASA or any other NSAID. Except for their sensitivity to ASA and NSAIDs, ASA-sensitive asthmatics cannot be distinguished from patients with similar clinical presentations. Respiratory inflamma-

Table 2. TYPES OF REACTIONS TO ASA AND OTHER NSAIDs

Reaction Type	Underlying Disease	Cross-Reactions	Arachidonic Acid Dysfunction	Other Immunologic Mechanisms
Cross-reacting respiratory	Rhinitis, polyps, sinusitis, asthma	ASA/NSAID	Yes	None
Cross-reacting urticaria	Chronic urticaria	ASA/NSAID	Yes	None
Urticaria/anaphylaxis	None	None	No	IgE-mediated
NSAID-induced aseptic meningitis	None	None	No	Delayed hypersensitivity
NSAID-induced hypersensitivity pneumonitis	None	None	No	Delayed hypersensitivity

tion frequently precedes the development of ASA- and NSAID-induced reactions by a number of years but may appear simultaneously.^{43, 80} Because ASA- and NSAID-induced reactions can only be observed clinically, and there are no *in vitro* tests to measure ASA sensitivity, it is likely that subclinical reactions to ASA and NSAIDs occur in some patients who have ASA disease but in whom external manifestations of a respiratory reaction, after ingestion of an NSAID, are too subtle to verify the presence of a clinical reaction.⁹¹

Clinical Features of Acetylsalicylic Acid Disease

The typical patient with ASA respiratory disease is an adult between 20 and 40 years of age, of either sex, suffering from asthma and rhinosinusitis with nasal polyps. After having been in good health and having uncomplicated upper respiratory tract infections (URIs) in the past, the patient characteristically develops a URI that clinically appears to be induced by a respiratory virus. Unlike past episodes of URIs, however, inflammation in the nasal and sinus membranes persists, worsens, and eventually evolves into a chronic eosinophilic rhinosinusitis, usually with nasal polyps and secondary purulent pansinusitis.⁹¹ The inflammatory disease may be limited to the upper airway,⁴⁴ but more commonly, lower respiratory tract inflammation with bronchospasm joins the upper airway disease. This intrinsic type of asthma progresses, frequently requires corticosteroids to maintain bronchial or nasal function, and usually becomes complicated by intractable pansinusitis. Samter⁶⁵ was the first to describe the classic ASA triad, consisting of rhinitis with nasal polyps, asthma, and ASA sensitivity. This description has been expanded by us to a quadrad, which includes rhinitis with or without polyps, sinusitis, asthma, and ASA sensitivity.^{87, 91}

As knowledge about ASA disease is more widely disseminated, many physicians are cognizant of the potential dangers of ASA-induced reactions. Therefore, some physicians advise all of their asthmatics, regardless of prior history, to avoid both ASA and NSAIDs. As the number of asthmatics avoiding ASA and NSAIDs grows, a larger pool of potential ASA-sensitive asthmatics becomes available.

Table 3 summarizes the clinical characteristics of patients with ASA disease. Because of the frequent use of topical corticosteroids, most nasal cytograms are devoid of eosinophils. Peripheral blood eosinophilia is also significantly suppressed if systemic corticosteroids are used. Anosmia is highly characteristic of ASA respiratory disease.⁸⁴ Another important clinical characteristic is the high prevalence of opacification of one or more paranasal sinuses in ASA-sensitive asthmatic patients. Roentgenographic abnormalities, detected by either plain roentgenograms or CT scans, range from complete opacification of one or more sinuses to air-fluid levels and mucoperiosteal thickening.^{48, 78, 88} As the disease progresses, the sinuses become more opacified and usually evolve into pansinusitis. Two hundred thirty-four ASA-sensitive asthmatics referred to Scripps Clinic for aspirin desensitization were observed between the years 1991 and 1997. All 234 patients underwent oral ASA challenges, and 200 were proven to be ASA-sensitive during challenges. Documentation could not be obtained of prior sinus radiographs or computed tomographic (CT) scans in six patients. In the remaining 194 patients, 187 (96%) had abnormal sinus opacifications by radiograph or CT scan, usually pansinusitis. Of this group of selected ASA-sensitive asthmatics, 172 of 194 (89%) had undergone prior sinus surgery. The diagnostic point

Table 3. CLINICAL FEATURES OF ASTHMATIC PATIENTS WITH ASPIRIN DISEASE

Category	Feature
Age of onset	After age 10 to age 40
Rhinitis	Chronic congestion (> 90%) Associated IgE-mediated (20%)
Nasal symptoms	Congestion, rhinorrhea, anosmia,* paranasal headaches, sleep deprivation
Nasal examination	Pale, congested membranes polypoid tissue to polyps
Nasal smear	Eosinophils: variable† Mast cells: variable† PMNs: many Bacteria: variable
Sinus radiographs	Abnormal with any pattern Pansinusitis most common
Sinusitis	Intermittent evolving to chronic
Prior sinus surgery	Very common; usually multiple operations (Average: 1 sinus operation every 3 years)*
Asthma	Intermittent and usually in remission when sinuses inactive Chronic, severe, particularly when associated with chronic sinusitis

*Bursts of systemic corticosteroids or sinus operations temporarily restore sense of smell.

†Topical and systemic corticosteroids substantially decrease numbers of eosinophils and mast cells.

is that an asthmatic patient who cannot smell, has nasal polyps, and abnormal sinus radiographs may be susceptible to ASA respiratory sensitivity.

Oral Acetylsalicylic Acid Challenges for Respiratory Reactions

The only definitive diagnostic tests for ASA sensitivity are ASA challenges (i.e., oral, bronchial, or nasal). ASA-lysine delivered to either the bronchial tree or nasal membranes is used to detect ASA sensitivity in Europe and the Far East. In the United States, oral ASA challenges are available. It should be emphasized that oral challenges with increasing doses of ASA or NSAIDs can stimulate severe asthmatic reactions. Therefore, physicians conducting these challenges should be experienced in this procedure, and challenges should be performed in close proximity to an intensive care unit in which emergency resuscitative equipment and trained personnel are readily available in case intubation and ventilation are required.

There are several important rules regarding oral ASA challenges. Unstable or irritable tracheobronchial trees will respond to ASA with more severe bronchospastic reactions.⁶² Therefore, oral and inhaled corticosteroids, intranasal corticosteroids, theophylline, and long-acting oral bronchodilators should be continued at the time of challenges, if they were part of that patient's prior treatment regimen. Discontinuing the patient's asthma maintenance medications usually leads to worsening asthma and spontaneous decline in lung function values. Respiratory reactions to ASA and other NSAIDs routinely occur while patients are taking theophylline or oral and inhaled corticosteroids.⁶¹ Some medications, however, should be discontinued 24 hours prior to challenge: anticholinergics,

antihistamines, cromolyn, and short-acting inhaled beta-agonists.⁸² Cromolyn has minor effects on the severity of ASA-induced respiratory reactions,¹² but it delays the onset of an ASA-induced respiratory reaction,⁹⁵ potentially allowing the patient to inadvertently receive the next higher dose of ASA before the onset of reaction induced by the first ASA dose. The simultaneous use of inhaled anticholinergics and short-acting beta-agonists in patients undergoing these challenges sometimes leads to false-positive reactions.⁸² Inhaled bronchodilators improve lung function for 2 to 6 hours, at which point the drug's therapeutic effect disappears, leading to spontaneous decline in lung function values. Such a decline might be misinterpreted to be a respiratory reaction. In some unstable asthmatics, we have successfully added salmeterol inhalation every 12 hours to the regimen, without experiencing false-positive declines in forced expiratory volume (FEV₁) values during placebo challenges. Antihistamines can block upper respiratory tract reactions to ASA,¹⁰¹ which in turn interferes with accurate assessment of respiratory reactions.

The onset of asthmatic reactions or elapse time following ASA ingestion occurs between 15 minutes and 3 hours. Respiratory reactions last 1 to 24 hours after the start of the respiratory reactions. There is a refractory period of 2 to 5 days after an ASA-induced respiratory reaction, during which time the patient tolerates ASA or the NSAID.⁶⁰

At Scripps Clinic, ASA oral challenges are conducted over a 3-day period while the subject is an inpatient in the General Clinical Research Center. Table 4 contains the protocol that is used. On the first day, the patient receives two placebo capsules at 3-hour intervals with measurement of FEV₁ values every hour. FEV₁ values should vary by less than 15% from baseline. The next morning, the baseline FEV₁ value should be within 5% of the previous day's value. These measures ensure stability of the bronchial tree at the time of challenges. ASA administration begins on the second day, starting with 15 to 30 mg of ASA, depending on the patient's history. It should be noted that few patients react to 30 mg of ASA. Therefore, starting with 15 mg of ASA is almost always not associated with a respiratory reaction, even in patients with a history of severe life-threatening asthma after ingesting 650 mg of ASA previously. ASA is ingested every 3 hours in a stepwise manner (Table 4). Individualization of doses is encouraged, however. This schedule usually takes the form of deciding to advance from 30 to 45 mg, rather than to 60 mg of ASA in patients with marginal bronchial stability. A maximum of three doses of ASA are given per day. The signs and symptoms of a respiratory reaction are listed in Table 5. During ASA challenges, when the previous reactions are identified, further ASA challenges are suspended, and the reaction is reversed with five puffs of inhaled bronchodilators (e.g., metaproterenol, albuterol, or terbutaline) delivered by a

Table 4. 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 5% (up or down) from placebo.

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

Table 5. TYPES OF RESPIRATORY TRACT SIGNS AND SYMPTOMS THAT OCCUR DURING POSITIVE ORAL ASA AND NSAID CHALLENGES

Reaction Classification	Observed Findings
No reaction	No symptoms and changes in $FEV_1 < 15\%$
Classic	Greater than 20% decrease in FEV_1 associated with naso-ocular reactions
Pure asthma	Greater than 20% decrease in FEV_1 values
Pure rhinitis	Naso-ocular reaction alone
Partial asthma	Decline of 15%–20% in FEV_1 values combined with naso-ocular reaction
Laryngospasm	Crowing sounds in neck or upper chest Flow/volume curve: Inspiratory loop flat and notched

nebulizer aerosol device every 10 minutes until the reaction subsides (Fig. 1). If 650 mg of ASA is administered without any reaction, the oral challenge test is determined to be negative.

Prevalence of Acetylsalicylic Acid Respiratory Disease

Prevalence of ASA-sensitive asthma varies, depending on the study population and the methods used to detect and report such individuals. Some reports

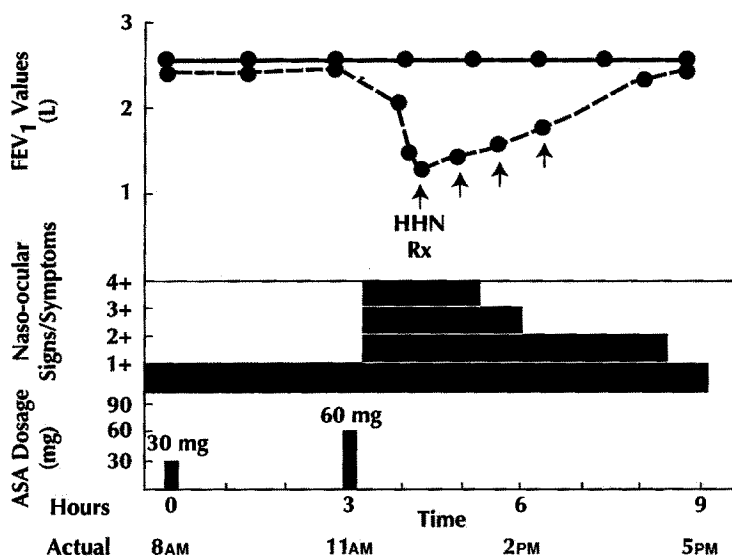


Figure 1. Typical classic reaction to aspirin. There was no reaction to 30 mg of ASA, but 60 mg of ASA induced both upper and lower respiratory tract reactions. Multiple treatments with albuterol in a hand held nebulizer (HHN) were required to counter bronchospasm, which did not completely reverse until 5 hours later. Solid line = placebo challenge; dashed line = ASA challenge.

present prevalence data based only on the patient's history of reactions to ASA.^{7, 18, 27} These studies underestimate ASA sensitivity because many patients cannot correlate an asthma attack with ASA or NSAID ingestion or have avoided ASA and NSAIDs entirely, eliminating any chance of reacting to one of these drugs.

Based on history alone, Falliers reported that less than 2% of approximately 1300 asthmatic children were ASA-sensitive.¹⁸ This observation, however, is also consistent with the observation that most ASA sensitivity occurs after age 10 and is uncommon in young children. In reviewing five other studies of ASA sensitivity in children in which prospective single-blind oral challenge studies were conducted,^{22, 63, 68, 104, 107} prevalence ranged from 0% to 28%. The study by Rachelefsky et al,⁶³ which reported a 28% prevalence of positive oral ASA challenges in their study population, included older children afflicted with more severe asthma and a high prevalence of chronic sinusitis.

Prevalence of ASA sensitivity in adult asthmatics also presents a large range. Giraldo et al²⁷ noted that 5% of hospitalized adult asthmatics reported a past history of ASA-induced respiratory reactions. By contrast, reports from tertiary referral centers in which prospective oral ASA challenges were performed detected significantly larger percentages of ASA-sensitive asthmatics in their study populations. In 1972, at Scripps Clinic and Research Foundation, 9% of consecutively challenged adult asthmatics were found to be ASA sensitive.⁴⁸ At the National Jewish Hospital, approximately 20% of their adult asthmatic population was reported to have ASA respiratory sensitivity based on oral ASA challenges.⁷⁸ The previous prevalence data are for all asthmatics without any screening for specific clinical characteristics.

Prevalence of ASA sensitivity in asthmatics with associated rhinosinusitis or nasal polyps, even without a history of ASA-induced respiratory reactions, increased significantly to 30% to 40%.^{15, 109} Those studies of adult asthmatics who reported a prior history of ASA-induced respiratory reaction identified a prevalence of ASA sensitivity by oral ASA challenges to range between 66% and 97%.^{15, 61, 78}

Desensitization with Acetylsalicylic Acid

Allergists think of desensitization as an alteration in immune responses, engineered by repeated exposure to injected antigens, thus reducing IgE-mediated reactions. Because IgE-mediated mechanisms have not been established for ASA respiratory sensitivity and are considered to be unlikely perpetrators of this reaction,⁸⁶ the term *desensitization* is used in this article in its broadest sense.⁶⁰ The initial report of successful ASA desensitization was published in 1922 by Widal et al.¹¹⁰ In 1976, Zeiss and Lockey¹¹³ independently reported a 72-hour refractory period to ASA after an indomethacin-induced reaction in one ASA-sensitive asthmatic. In 1980, Stevenson et al⁹⁴ reported two ASA-sensitive asthmatics who became refractory to ASA after single-blind oral challenges with ASA. After first achieving ASA desensitization, both patients experienced improvement in respiratory disease activity when they were then treated with daily ASA. All ASA-sensitive asthmatics are capable of undergoing desensitization to ASA. Since 1980, in the General Clinical Research Center, 480 consecutive ASA-sensitive patients have been successfully desensitized. After ASA desensitization, in the absence of further exposure to ASA, the desensitized state persists for 2 to 5 days with full sensitivity returning after 7 days.⁶⁰ Also, cross-desensitization between ASA and any of the NSAIDs that inhibit COX occurs routinely.⁶⁰ Desensitization is accomplished by reintroducing the dose of ASA that initiated

the ASA reaction on the previous day. If there is no reaction to the same dose, the next highest dose is given (see Table 4) and repeated until further reactions cease. This process of escalating doses of ASA continues until the patient can tolerate 650 mg of ASA without any reactions.

There are eight published studies that report efficacy of ASA desensitization followed by daily ASA treatment.^{9, 42, 44, 58, 84, 89, 94, 96} In the most recent study of 65 ASA-sensitive asthmatic patients treated with ASA, 650 mg twice daily, after ASA desensitization, Stevenson et al⁸⁴ compared clinical courses before and after 1 to 6 years of daily ASA treatment. Objective clinical criteria showed significant improvement in the patients' clinical courses, particularly a reduction in sinusitis while under treatment with ASA. At the same time, requirements for systemic corticosteroids significantly declined.

Cross-Reactions and Cross-Desensitization: Strong Inhibitors of Cyclo-oxygenase

All NSAIDs, which inhibit COX in vitro, cross-react with ASA, upon first exposure, in the respiratory reactions described previously (see Table 1).^{47, 61, 99} Furthermore, NSAIDs that inhibited COX in vitro, with the least concentration of drug, required the smallest doses of NSAIDs in cross-reacting with ASA.⁹⁹ All NSAIDs that cross-react with ASA also participate in cross-desensitization.⁶⁰

Cross-Reactions and Cross-Desensitization: Weak Inhibitors of Cyclo-oxygenase

Cross-reactivity between ASA and compounds that are weak inhibitors of COX, such as acetaminophen and salsalate, are of interest because of the marker of COX inhibition in predicting cross-reactivity. One would assume that weak inhibitors of COX would cross-react poorly if at all with ASA, based upon Szczeklik's⁹⁹ original in vitro studies.

Acetaminophen

Initial studies reported a low-to-absent rate of cross-reactivity between acetaminophen and ASA.^{17, 32, 78, 98} In these studies, however, oral challenges were performed with doses of acetaminophen equal to or less than 650 mg. Delaney¹⁵ challenged ASA-sensitive asthmatics with 500 mg of acetaminophen without inducing any reactions. He then doubled the dose of acetaminophen to 1000 mg and repeated the acetaminophen challenges. This time, 28% of known ASA-sensitive patients experienced respiratory reactions to acetaminophen. Hencowicz also reported greater and greater positive respiratory reactions to acetaminophen as the challenge doses of acetaminophen were increased.³²

Settipane and Stevenson⁷³ reported a study of three ASA-sensitive asthmatics who gave a history of respiratory reactions occurring 2 hours after ingesting acetaminophen. Double-blind, placebo-controlled oral challenges with acetaminophen and ASA were conducted. All three patients were shown to have ASA respiratory sensitivity at provoking doses of 60 mg of ASA. After challenge with 1000 mg of acetaminophen, all three experienced asthmatic reactions, but none reacted to 500 mg of acetaminophen. Two patients were temporarily desensitized to 1000 and 1500 mg of acetaminophen, but tolerance to 2000 mg was not attained. Two patients were then desensitized to ASA and were able to ingest

1000 mg of acetaminophen without adverse effect, demonstrating cross-desensitization. We suggested that acetaminophen, at high doses and in a small subset of ASA-sensitive asthmatics, behaves like ASA and NSAIDs with respect to cross-sensitivity reactions in the respiratory tract.

In a large study of 50 known ASA-sensitive asthmatics, using challenge doses of 1000 mg of acetaminophen and then 1500 mg, Settiple and Stevenson⁷² induced respiratory reactions in 34% of the study subjects. The respiratory reactions were generally mild, easily treated, and only occurred in a minority of ASA-sensitive asthmatics. Although it is likely that higher doses of acetaminophen (2000 mg or more) may have induced reactions in some patients not reacting to lower doses of acetaminophen, our concern about hepatotoxicity from acetaminophen prevented us from further testing this hypothesis.

Salsalate

Salsalate is an effective anti-inflammatory agent that is used in the treatment of arthritis. Salsalate is a weak inhibitor of COX. Stevenson et al⁸⁵ studied ten ASA-sensitive asthmatics to evaluate cross-sensitivity to salsalate. Two of the ten experienced bronchospastic reactions to salsalate, but only when 2 g of the drug were ingested. Repeat challenges with 2 g of salsalate reproduced the same reactions. The patients then underwent ASA challenge and desensitization. Once desensitized to ASA, the patients were able to ingest 2 g of salsalate without adverse reactions, demonstrating cross-desensitization. Similarly to acetaminophen, the same principle seems to apply. Salsalate, a weak inhibitor of COX, behaves like ASA and NSAIDs in producing respiratory reactions, but only when large doses are ingested and in a minority of ASA-sensitive asthmatics.

Cross-Reactions and Cross-Desensitization: Noninhibitors of Cyclo-oxygenase

Other chemicals, dyes, and additives have been reported to cross-react with ASA, although their compounds have not been proven to inhibit COX.^{1, 23, 65, 78} Such chemicals include azo and non-azo dyes, sulfites, monosodium glutamate, benzoates, and hydrocortisone succinate. Some have felt that ongoing ingestion of these substances causes ASA-sensitive subjects to have ongoing asthma and rhinitis, although they are avoiding aspirin.⁶⁵ Others, however, express serious doubts that there is any cross-reactivity between ASA and non-COX inhibiting chemicals.⁷⁴

Azo and Non-Azo Dyes

There are currently ten coal tar derivatives approved by the Food Dye and Coloring Act (FD & C) that are used as coloring agents in food, drink, and color coding of pills and tablets.⁷⁴ Azo dyes include tartrazine (FD & C Yellow #5), sunset yellow (FD & C Yellow #6), ponceau (FD & C Red #4), carmoisine (FD & C Red #2), and yellow #3. Non-azo dyes include erythrosine (FD & C Red #3), brilliant blue (FD & C Blue #1), and indigotin (FD & C Blue #2).

Tartrazine and Asthma

The best known azo dye is yellow #5 (tartrazine) because it has been promoted by many authors to be responsible for cross-sensitivity reactions with ASA.^{23, 36, 65, 78} When reviewing these publications, in which an apparent cross-

sensitivity was reported, one is struck by the fact that studies were conducted when the patients' airways were unstable, and antiasthmatic therapy had been simultaneously withdrawn. Therefore, spontaneous decreases in FEV₁ values occurred, perhaps suggesting to the uninitiated that tartrazine was responsible for the changes in FEV₁ values.^{81, 82} Weber et al¹⁰⁹ identified 13 ASA-sensitive asthmatics, via oral ASA challenges, out of a study population of 44 patients with rhinosinusitis and asthma. After withholding morning bronchodilators, they challenged all 44 patients with 2.5 to 25 mg of oral tartrazine. Seven patients (16%) experienced a decrease in FEV₁ values of at least 20%. The same seven patients were rechallenged 1 week later, but this time, bronchodilators were continued on the morning of tartrazine challenge. All seven patients ingested tartrazine, and follow-up FEV₁ values did not decline, suggesting that they were never sensitive to tartrazine in the first place. As is true with many severe asthmatics, withholding essential antiasthmatic medications leads to uncontrolled asthma and a decline in lung function values. These same seven patients were also challenged with six other azo and non-azo dyes without any asthmatic reactions.

In the largest study of tartrazine and ASA sensitivity, Stevenson et al⁹² challenged 150 known ASA-sensitive asthmatics with 25 and 50 mg of tartrazine. Six (4%) experienced a 20% or more decrease in FEV₁ values during open screening challenges with tartrazine. Five of six patients were available for follow-up and were rechallenged using a double-blind, placebo-controlled protocol. All repeat challenges with tartrazine, using the same dose associated with declining FEV₁ values in the screening challenges, then became negative. A second study of an additional 44 known ASA-sensitive asthmatics with tartrazine challenges also did not reveal any instances of cross-sensitivity between tartrazine and known ASA-sensitive asthmatics.⁹³ Tartrazine has not been shown to inhibit COX *in vitro* and, therefore, would not be expected to cross-react with ASA and NSAIDs.²⁴

It is still being debated whether or not tartrazine-induced respiratory reactions have ever occurred in asthmatics or if investigators have only reported spontaneous declines in pulmonary function studies in association with ingestion of tartrazine. In view of the current literature, however, it is difficult to recommend that ASA-sensitive asthmatics avoid any azo or non-azo dyes, unless a properly controlled oral challenge test documents a reaction to a specific dye.

Sulfites and Asthma

In 1981, Stevenson and Simon⁹⁰ reported on six patients with potassium metabisulfite sensitivity who gave histories of severe, life-threatening asthma attacks after eating restaurant meals contaminated with sulfites. With single-blind oral challenges, the authors reproduced the patients' asthmatic responses in the laboratory, using capsules containing 5 to 50 mg of potassium metabisulfite. Since 1986, the FDA has banned the use of sulfiting agents on raw fruits, vegetables, and, most recently, on fresh, peeled potatoes. Packaged foods and beverages containing more than 10 ppm of sulfur dioxide equivalents must carry sulfite-specific labeling. Because of these public health interventions in the United States, the risk of sulfite reactions in sulfite-sensitive asthmatics appears to be reduced. There is no evidence that ASA-sensitive asthmatics are at risk for sulfite reactions. In fact, Scripps Clinic investigators have challenged 125 consecutive ASA-sensitive asthmatics with up to 200 mg of potassium metabisulfite, and have never identified sulfite sensitivity in any ASA-sensitive asthmatic patients.

Monosodium Glutamate and Asthma

Allen et al¹ reported that 14 of 32 (41%) asthmatic subjects experienced bronchospasm 2 to 12 hours after ingesting capsules of 2.5 g of monosodium glutamate (MSG). Furthermore, Allen claimed that ASA sensitivity was a risk factor for MSG-induced reactions because of a high prevalence of ASA-sensitivity in patients reacting to MSG. The Allen et al¹ study has been criticized for the following reasons: withholding antiasthmatic medications followed by always challenging with placebo first and MSG last, pretreating selected patients with inhaled beta-agonists before morning challenges to maximize prechallenge lung function, use of peak flow meter rather than flow/volume spirometry, and inconsistent timing of challenges with placebo and MSG. Other investigators have not been able to reproduce Allen et al's results.^{25, 50, 69, 79} At Scripps Clinic, confirmed asthmatic reactions to MSG have not been identified during oral challenges with capsules of 2.5 g of MSG, despite challenging 26 patients, who by history, experienced asthma attacks in Asian restaurants and believed that they were sensitive to MSG. Furthermore, 60 known ASA-sensitive asthmatics were challenged in the Scripps Clinic General Clinical Research Center with 2.5 g of MSG, and none experienced bronchospastic reactions.

Hydrocortisone Succinate and Asthma

Despite prior reports of an association between aspirin sensitivity and allergic reactions to intravenous hydrocortisone,^{14, 100} current belief is that true cross-reactivity does not occur. Feigenbaum et al¹⁹ identified 1 of 45 known ASA-sensitive asthmatics who experienced an angioedema and respiratory reaction to intravenous hydrocortisone succinate. Unlike cross-reactions between the NSAIDs, however, cross-desensitization could not be achieved between hydrocortisone succinate and ASA in this patient. It seems likely that succinate functions as a drug hapten in inducing occasional IgE-mediated reactions. The only association with ASA-sensitive asthmatics is their excessive exposure to intravenous hydrocortisone succinate during severe bouts of asthma.

Mechanisms

Aspirin Respiratory Disease

Mechanisms that account for underlying ASA respiratory disease or respiratory reactions to ASA have been partly clarified.^{39, 40, 86} Vanselow and Smith¹⁰⁶ were the first to report a cross-reaction between ASA and indomethacin. This observation has been confirmed by subsequent investigators and is now recognized to be an irrefutable rule governing these reactions.^{5, 47, 98, 99} Immune recognition of ASA and the widely different NSAIDs seems unlikely, and first exposure reactions to NSAIDs occur routinely, eliminating any possibility of prior immune sensitization. Furthermore, IgE antibodies to ASA or NSAIDs have not been discovered in ASA-sensitive asthmatic patients.

In 1971, Vane¹⁰⁵ discovered the shared pharmacologic effect of ASA and NSAIDs, namely inhibition of COX in the metabolic cascade of arachidonic acid metabolism. Since Vane's discovery, many investigators have focused research on the cells participating in arachidonic acid metabolism.⁸⁶ With the discovery by Samuelsson^{66, 67} in the early 1980s of a second metabolic pathway (5-lipoxygenase), which synthesizes leukotrienes, it became apparent that arachidonate could be diverted preferentially down the 5-lipoxygenase pathway when the

primary COX pathway was blocked. The 5-lipoxygenase products, or leukotrienes, mediate chemotaxis (LTB_4), and are also potent mediators of bronchoconstriction, vasodilation, attraction of eosinophils, and mucous secretion (LTC_4 , LTD_4 , and LTE_4).^{2, 31, 41, 54, 103}

Figure 2 summarizes our current understanding of the pathogenesis of aspirin respiratory disease, ASA- and NSAID-induced reactions, and ASA desensitization.

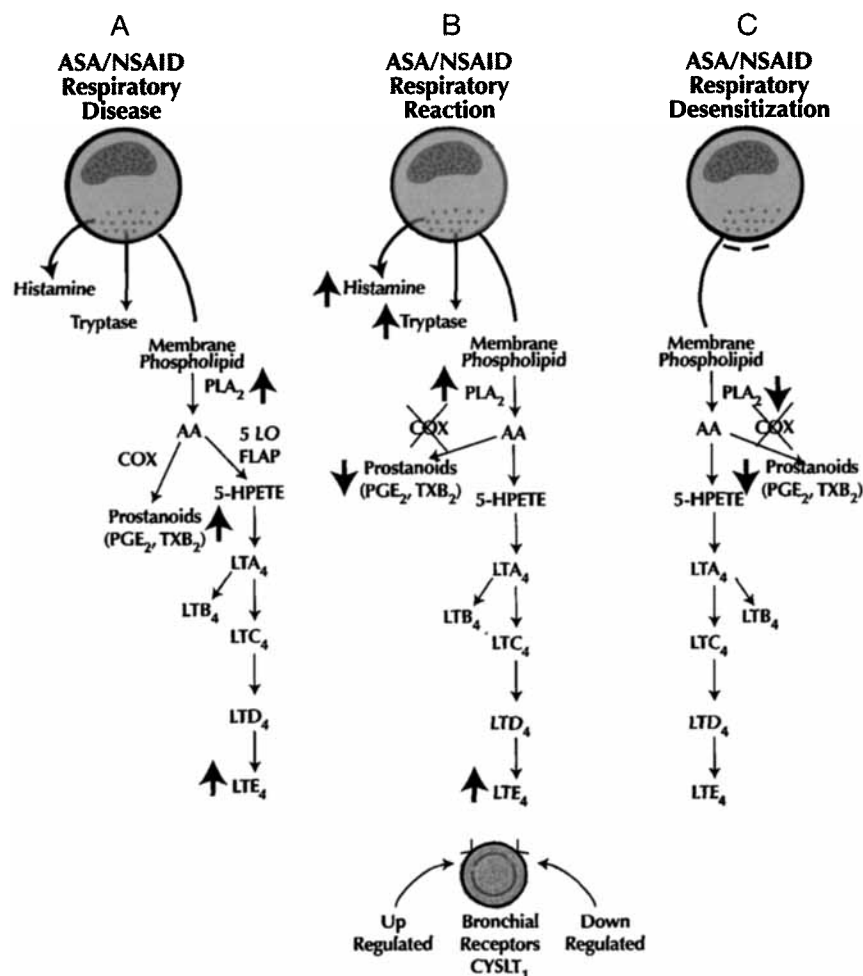


Figure 2. Pathogenesis of ASA respiratory disease, reaction, and desensitization. **A**, A mast cell secretes granular mediators and synthesizes excess prostanooids and leukotrienes (LTs). PGE_2 partially inhibits 5-LO. **B**, During an ASA-induced reaction, inhibition of COX reduces synthesis of PGE_2 , which enhances the effect of 5-LO and FLAP on increased synthesis of LTs. Up-regulated CysLT_1 receptors augment the effects of LTs. Furthermore, histamine and tryptase are released from mast cells in high concentrations. **C**, ASA desensitization occurs with blockage of histamine. Reduction, but not elimination, of LTs occurs. Down-regulated CysLT_1 receptors diminish the effect of LTs on target organs.

zation. All biochemical events shown in Figure 2 actually occur in mast cells with only terminal LTs and prostanoids leaving the cells to effect target receptors. Of particular note are cysLT_1 receptors, shown in the bottom of the figure. All three LTs stimulate the same receptors that are present on target cells: bronchial smooth muscle (bronchoconstriction), mucous glands (secretion of mucous), peribronchial venules (leakage of plasma with edema), and eosinophils (chemo-attractants). Most, but probably not all, ASA-sensitive respiratory disease and reactions can be explained by the process of stimulating cysLT_1 receptors.

Currently available data support the hypothesis that mast cells and eosinophils infiltrating nasal and bronchial mucosa are important cells in inducing ongoing inflammation of ASA respiratory disease. Both cells synthesize arachidonic products. Eosinophils release major basic protein. Mast cells release preformed granule-associated mediators (e.g., histamine and tryptase). Mast cells and eosinophils have been observed in the nasal cytograms, nasal tissue biopsies, bronchial biopsies, and bronchial alveolar lavage fluid from ASA-sensitive asthmatics.^{56, 75, 112} Sladek et al⁷⁵ analyzed bronchial alveolar lavage fluid from ASA-sensitive asthmatics and found an increased number of eosinophils and eosinophil cationic protein, when compared with the bronchial alveolar lavage fluid from control asthmatics. PMNs, mast cells, and macrophages were found in the lavage fluid from both aspirin-sensitive and insensitive patients. The fact that PMNs and macrophages are not preferentially increased in ASA-sensitive nasal and bronchial tissues does not exclude their potential participation in ASA disease because both are capable of forming arachidonic acid products. Furthermore, bronchial lavage fluid contained increased LTs before introduction of ASA-lysine.¹⁰³ Urine sampling in ASA-sensitive asthmatics, when compared with control asthmatics and normal subjects, reported higher levels of baseline LTE_4 and thromboxane B_2 in the urine of ASA-sensitive asthmatics.^{11, 76, 77} It appears that even before addition of aspirin, ASA-sensitive asthmatic patients were synthesizing substantially higher quantities of both COX and 5-Lipoxygenase (5-LO) products. Why such inflammation begins in the first place is the elusive question. Presumably, there is one or several selective biochemical anomalies in cellular inflammatory enzymes that segregate in ASA-sensitive asthmatics. Szczeklik⁹⁷ has suggested that ASA disease is a chronic or latent viral infection of the respiratory mucosa. The onset of ASA disease, following a viral URI, is compatible with this hypothesis. Szczeklik has proposed a hypothesis that activated T lymphocytes or other cells, in the absence of negative feedback, secrete excessive quantities of cytokines and chemokines. In turn, these upregulate enzymes in the inflammatory cells discussed earlier in this section.

ASA- and NSAID-Induced Respiratory Reactions

In the middle panel of Figure 2, pathogenesis of ASA-induced respiratory reactions is presented. Although a mast cell is depicted, there is no reason why similar arachidonate metabolism is not occurring in other inflammatory cells. Investigators have identified two COX molecules³⁰; COX-1 is constantly synthesized in many mammalian cells (i.e., constitutive form) with its products and prostanoids involved in many physiologic functions (e.g., prostaglandin E_2 [PGE_2] is protective of gut mucosa). A second isoform is COX-2, which is induced during inflammation. ASA and most NSAIDs inhibit both COX-1 and COX-2. A few newer NSAIDs, as well as dexamethasone, selectively inhibit only COX-2 and, therefore, do not cause gastric ulcerations at the same time that gut PGE_2 is preserved. The bulk of the evidence indicates that inhibition of COX-1 is the inciting event in ASA-induced respiratory reactions.

A hypothesis that might explain ASA- and NSAID-induced respiratory reactions has been proposed by Lee.⁴⁰ As shown in the center panel of Figure 2, ASA and NSAIDs rapidly bind to COX-1, immediately preventing synthesis of COX products, including PGE₂. This binding releases the inhibitory effects of PGE₂ on 5-LO. At the same time, arachidonic acid synthesis continues, preferentially driving arachidonate molecules down the 5-LO pathway. Whether or not ASA induces further synthesis of arachidonic acid via phospholipase-A₂ is not known; however, sufficient arachidonic acid substrate for presentation to 5-LO enzymes, stabilized by 5-lipoxygenase activating proteins (FLAP), probably is already available. Withdrawal of the potent inhibitory effect of PGE₂ on 5-LO is likely to be the pivotal event, allowing accelerated synthesis of arachidonate molecules into the leukotriene pathway.

To address this hypothesis, the first question is whether or not COX enzymes are peculiarly susceptible to ASA and NSAIDs. In vitro studies using peripheral blood monocytes from ASA-sensitive asthmatics, taken during respiratory reactions induced by oral challenges with 60 mg of aspirin demonstrated extraordinary rapid and complete inhibition of COX.³⁴ Such unique susceptibility of COX to the effects of ASA could represent the distinguishing molecular difference in ASA-sensitive asthmatics. This susceptibility is also consistent with the clinical observation that aspirin respiratory reactions are dose-dependent and tend to occur after ingesting 60 mg of aspirin. Ferreri et al²⁰ measured increased LTC₄, histamine, and decreased PGE₂ in nasal lavage fluid taken during oral aspirin challenges, which had induced rhinitic reactions in aspirin-sensitive asthmatics. Histamine and LTC₄ appeared in the nasal secretions slightly before the onset of nasal ocular reactions. Similar findings have been reported by other investigators.^{21, 37, 59} In a study by Sladik et al,⁷⁵ bronchial-alveolar lavage (BAL) fluid was obtained 30 minutes after ASA-lysine inhalation in 10 aspirin-sensitive asthmatics. Major basic protein, LTC₄, and histamine were increased in the BAL fluid, and thromboxane B₂ was decreased, when compared with baseline values. Szczeklik et al¹⁰² studied 11 aspirin-sensitive asthmatics and 14 aspirin-tolerant asthmatics. After challenge of the right middle lobe with known provoking doses of ASA-lysine, BAL was performed 15 minutes later. In the ASA-sensitive patients, after ASA challenge, BAL fluid contained significantly increased numbers of eosinophils, peptido-leukotrienes, and interleukin-5 (IL-5). Histamine and tryptase concentrations increased but did not reach statistical significance. PGE₂ concentrations declined in the BAL fluid, consistent with inhibition of COX.

In 1991, Christie et al¹¹ found significant increases in urinary LTE₄ concentrations, peaking at 6 hours after ASA-induced bronchospastic reactions. This important observation has been confirmed by other investigators who have also demonstrated a rapid decline in thromboxane B₂, a COX product, in the urine of ASA-sensitive asthmatics undergoing ASA-induced reactions.^{76, 77} Sestini et al⁷⁰ pretreated patients with PGE₂ by inhalation preceding ASA-lysine inhalation challenges. Despite challenges with ASA-lysine at previously established provoking doses, no reactions occurred. Simultaneously, urinary LTE₄ concentrations did not increase from baseline levels after ASA challenge, when PGE₂ pretreatment was in effect. The presence of inhaled PGE₂ in the bronchial tissues protected patients from ASA-induced reactions. Thus the elimination of PGE₂ and its artificial restoration appeared to cause or protect patients from ASA-induced respiratory reactions.

If leukotrienes cause nasal and bronchial reactions, drugs that antagonize or inhibit LTs should prevent ASA-induced reactions. A number of inhibitors or antagonists to the LTs have prevented ASA-induced reactions when threshold doses of aspirin were used for challenges.^{10, 13, 33, 55, 111}

Histamine is also playing some role in aspirin-induced reactions. Bosso et al⁶ measured serum tryptase and plasma histamine levels in 17 aspirin-sensitive rhinosinusitis asthmatic patients during oral aspirin challenges. Three of the 17 patients experiencing both nasal ocular bronchospastic reactions were found to have significant elevations of histamine and tryptase in the serum after the reaction. All three patients had similar reductions in their lung function values when compared with the remaining 14 patients but also experienced systemic symptoms and signs consisting of flushing, nausea, abdominal cramping, or diarrhea. Sladik et al⁷⁶ also noted increase serum tryptase during aspirin-provoked bronchospastic reactions. Pretreatment with antihistamines significantly diminished or prevented nasal and ocular symptoms of rhinorrhea and conjunctival injection but did not prevent bronchospastic reactions.¹⁰¹ During ASA-induced respiratory reactions, intravenous diphenhydramine and ranitidine also significantly prevented or treated flushing and gastrointestinal cramping or diarrhea.

Arm et al³ evaluated bronchial airway responsiveness to histamine and LTE₄ in aspirin-sensitive asthmatics and found a 13-fold increase in airway responsiveness to inhaled LTE₄ when compared with aspirin-sensitive asthmatics. There were no differences between the two groups with respect to their response to inhalation of histamine. Therefore, not only are LTs formed during ASA-induced reactions but also ASA-sensitive asthmatic airways are preferentially sensitive to the effects of the terminal LTs, further magnifying the intensity of bronchospasm that occurs during ASA-induced reactions.

Aspirin Desensitization

Mechanisms responsible for aspirin desensitization are shown on the right side of Figure 2. During acute desensitization, defined as 3 hours after the first ingestion of ASA, 650 mg without reaction, histamine, and LTC₄ disappeared in the nasal secretions.²⁰ Serum histamine and tryptase levels disappeared,⁶ and immediately following ASA desensitization a 20-fold decrease in bronchial airway responsiveness to inhaled LTE₄ occurred.³ In long term, after-aspirin desensitization treatment with 650 mg of aspirin, twice a day for at least 2 weeks, LTB₄ synthesis in monocytes declined substantially to the same levels as found in normal controls.³⁵ During chronic aspirin desensitization, in ASA-sensitive asthmatic subjects, Nasser et al³⁷ reported urine LTE₄ levels declined to lower values but not to values found in normal controls. Such experiments do suggest that aspirin desensitization, particularly long-term treatment with higher doses of aspirin, continues to inhibit COX-1 and may directly or indirectly inhibit phospholipase A₂, leading to diminished synthesis of prostanoids and LTs. Simultaneously, cysLT₁ bronchial receptors are downregulated, further blunting the effects of any available LTE₄.

Acetylsalicylic Acid Respiratory Disease and Leukotriene Modifiers

Theoretically, drugs that either inhibit or antagonize LTs should be effective in protecting ASA-sensitive asthmatics from inadvertent exposure to ASA or NSAIDs and in treating ASA disease. With respect to protection, the literature demonstrates that LT modifiers protect patients from bronchospasm during oral and inhalation ASA challenges when small provoking doses of ASA are used (usually 60 mg of ASA orally or 5 mg/mL of ASA-lysine by inhalation).^{10, 13, 33, 55, 111} Unfortunately, newer preliminary information suggests that protection is

inconsistent in preventing respiratory reactions after exposure to larger (therapeutic) doses of ASA or the other NSAIDs. Spontaneous reports of ASA-sensitive asthmatics, experiencing asthma attacks after inadvertent exposure to full therapeutic doses of ASA or one of the NSAIDs, while taking either zafirlukast or zileuton continuously, have been made available to the author by allergy colleagues in the United States.

The ASA desensitization procedure, described earlier, involves the induction of respiratory reactions on the way toward desensitization. In the presence of the protective effect of a leukotriene inhibitor, the idea that silent desensitization to ASA might occur makes theoretical sense. At the date of submission of this article, we have attempted to desensitize six known ASA-sensitive asthmatics during pre- and peritreatment with 600 mg of zileuton four times a day. All six patients had undergone prior oral ASA challenges followed by ASA desensitization. All six discontinued ASA for at least a month before returning for rechallenge with ASA while taking zileuton for a minimum of 1 week before challenge. One patient was not protected at all by zileuton, and reacted with a 53% drop in FEV₁ after 45 mg of ASA. Two patients had the same degree of respiratory reaction while taking zileuton, but the provoking dose was increased by one increment (30 to 60 mg and 60 to 100 mg). The fourth patient had a classic nasooocular reaction to 60 mg of ASA before and with zileuton protection. Only in the fifth and sixth patients was there any evidence that zileuton was protective. Both patients experienced mild bronchospastic or laryngeal reactions to ASA during prior oral ASA challenges and only after unusually high provoking doses of ASA (150 and 325 mg of ASA). Therefore, silent desensitization did not reliably occur in all patients, at least those using 600 mg of zileuton four times a day as the leukotriene modifier. Whether or not LT antagonists might be more efficacious in blunting reactions in the desensitization process remains to be determined. Reported respiratory reactions to ASA and NSAIDs have occurred, however, during ongoing treatment with zafirlukast. The author is not encouraged by the prospect that zafirlukast will provide protection in all patients during ASA desensitization.

Two products have been studied in the ongoing treatment of ASA respiratory disease: zileuton and montelukast, which in relatively short studies, significantly enhanced asthma control, using standard methods of assessment. After the short-term montelukast study, long-term open treatment with 10 mg of montelukast for over 2 years has been conducted. Significant long-term improvement has been observed in half of our Scripps Clinic ASA-sensitive asthmatics treated with daily montelukast; however, other patients discontinued the study because of lack of efficacy of montelukast. Because LT overproduction is characteristic of ASA disease, fine tuning of the proper therapeutic dosing with these products is likely to be more important than in other types of asthma.

CUTANEOUS CROSS-REACTIONS

Concept of Acetylsalicylic Acid Cutaneous Disease

The characteristics of ASA-sensitive urticarial patients are much less complex. A minority of patients afflicted with chronic idiopathic urticaria report an exacerbation of hives, with or without concomitant angioedema, after ingesting either ASA or any of the NSAIDs.^{29, 80} Avoidance of ASA in such patients

eliminates acute flares of hives associated with ingestion of ASA or NSAIDs but does not change the course of the patients' chronic idiopathic urticaria.

Oral Acetylsalicylic Acid Challenge: Urticaria

A simple clinical or in vitro test to determine ASA-sensitive urticaria does not exist. Again, oral ASA challenge can prove the existence of ASA sensitivity. Such challenges can be performed in an outpatient office. Patients with chronic active urticaria who receive antihistamines should continue antihistamines because stopping them a day or two before the challenge may result in therapeutic escape and a spontaneous flare of hives unrelated to the challenge drug. Discontinuing antihistamines may produce false-positive results.⁴ Patients with intermittent urticaria may be challenged during a remission while avoiding antihistamines. We use a skin scoring technique described in detail in other publications.^{46, 91} This technique discriminates quantitatively between more or fewer hives.

Prevalence of Acetylsalicylic Acid Cutaneous Disease

Using proper challenge techniques and objective scoring criteria, true ASA-induced urticarial reactors have been identified, with prevalence data of ASA-flaring urticaria in patients with chronic idiopathic urticaria between 21% and 30%.^{8, 46, 51} Furthermore, it appears that disease activity at the time of challenge plays an important role in whether or not ASA or NSAIDs can exceed a threshold of responsiveness and generate urticaria. For example, Mathison et al⁴⁶ noted that 70% of patients whose urticaria was active at the time of challenge reacted to ASA. By contrast, only 6% of patients whose urticaria was quiescent at time of challenge reacted to ASA challenge.

Acetylsalicylic Acid Desensitization: Urticaria

Unlike ASA-sensitive asthma rhinosinusitis, ASA-sensitive urticaria does not appear to be amenable to desensitization. Mathison et al⁴⁶ found that after an ASA- or NSAID-provoked urticarial reaction there followed a brief refractory period (24 to 72 hours) in which a significant decline in urticaria occurred. If ASA was continued, however, a virulent flare of urticaria reappeared and continued until ASA was discontinued. Since then we have attempted desensitization with ASA in 30 patients with chronic urticaria, and the results have been the same as those described by Mathison in the original five patients.

Tartrazine and Urticaria

The theory that azo and non-azo dyes induce urticaria is difficult to prove or disprove. Like asthma, studies that attempted to prove that tartrazine induces urticaria must be reviewed critically. Many oral challenge studies with tartrazine during active urticaria, particularly if antihistamines were also withheld, resulted in therapeutic escape of hives, which were inappropriately attributed to tartrazine.

In the 1970s a number of reports of tartrazine-induced urticaria claimed positive reactions to tartrazine, ranging from 10% to 100%.^{16, 36, 49, 64} Apparent cross-reactivity with ASA has also been claimed.^{26, 36, 71} Unfortunately these studies were not double blinded, and antihistamines were also withheld during the challenges.

In a study by Stevenson et al,⁹² 19 patients with histories suspicious for tartrazine-exacerbated urticaria underwent single-blind challenges with 25 and 50 mg of tartrazine. One of nineteen patients developed urticaria after a dose of 25 mg of tartrazine. Five days later, a double-blind, placebo-controlled challenge with 25 mg of tartrazine was conducted and urticaria occurred again. The same patient was challenged with up to 650 mg of ASA without a flare of hives, demonstrating that tartrazine-induced urticaria was unrelated to the state of ASA sensitivity in this patient. Indeed, in the same study, five known ASA-sensitive urticaria patients were challenged with tartrazine and did not react. By using double-blind, placebo-controlled challenges Murdoch et al⁵² demonstrated that at least 2 of 24 patients developed hives after ingesting a panel of four azo dyes, which included tartrazine. In summary, it does appear that tartrazine and other azo dyes can rarely induce urticaria, but there is no evidence that tartrazine cross-reacts with ASA in ASA-sensitive urticaria patients.

ACUTE URTICARIA AND ANGIOEDEMA AND ANAPHYLACTIC REACTIONS TO ASA OR NSAIDS IN OTHERWISE NORMAL INDIVIDUALS

In individuals who do not have underlying risk factors, ingestion of ASA or one of the NSAIDs induces either acute urticaria or angioedema or anaphylaxis. Cross-reactivity does not occur, a fact that distinguishes these reactions from the two cross-reacting syndromes described previously. It is likely that immune recognition, probably by IgE, mediates acute urticaria or anaphylaxis, with ASA or an NSAID acting as the drug hapten. The reasons for this position are as follows: (1) such patients characteristically react to only one NSAID or to ASA and almost never cross-react in the whole class of COX inhibitor drugs; (2) ASA or NSAID anaphylactic reactions occur after two or more exposures to the same NSAID, suggesting prior sensitization to the specific drug haptens; (3) patients who develop anaphylaxis to ASA or to a single NSAID appear to be otherwise normal or have an underlying disease, such as arthritis, which predisposes them to excess exposure to NSAID haptens; and (4) skin-sensitizing antibodies to ASA have been identified by skin testing in patients with acute urticaria after ASA challenge.³⁸ In addition, using reversed cutaneous anaphylaxis, Evans blue dye extravasation occurred only at the skin sites where sera from patients experiencing anaphylaxis after zomepirac had been placed (unpublished data, McNeil Laboratories).

Identification of Patients with Anaphylactic Sensitivity to ASA or NSAIDs

Neither *in vitro* testing or immediate cutaneous testing have been developed sufficiently to be reliable in detecting such sensitivity to ASA or the NSAIDs. This is probably a technical problem related to the metabolic clearance of

NSAIDs and formation of antigenically distinct molecules. This failure to detect IgE antibodies *in vitro*, however, places the patient and clinician in a relatively untenable position, requiring the practitioner to rely on a history of prior reactions. Such a state produces two significant problems: inaccurate patient memory and what alternative medications the patient might take to solve his or her problem, assuming that the patient's original history was accurate.

Oral challenges for anaphylactic reactions have been conducted, but the indications are limited and the danger is higher than those described for ASA-sensitive asthma and urticaria. Such oral challenges with the suspect drug should be conducted in an intensive care unit with the patient already prepared for the worst consequences of anaphylaxis. Except for ASA itself, however, challenges with the suspect drug are rarely appropriate because the only indicated challenges are to other NSAIDs, to which the patient has not reacted historically or, even safer, has never undergone prior exposure. Therefore, challenges with a different NSAID are performed for reassurance and with no expectation of a reaction. The patient can then take the new NSAID for the indicated medical condition. The latter has been the practice at Scripps Clinic, and we have been gratified to not record any reactions to alternative NSAIDs to which the patient had never been previously exposed. In a study by Quiralte et al,⁶² 15 patients were challenged who gave a history of a prior urticarial or anaphylactic reaction to a specific NSAID. They were given a number of NSAIDs at different times, including paracetamol (acetaminophen), salsalate, diflunisal, mefenamic acid, diclofenac, piroxicam, ketoprofen, dipyrrone, and aspirin. None of the patients reacted to the alternative NSAIDs. This discussion does not, unfortunately, apply to patients giving a history of anaphylaxis after ingesting aspirin, which is clearly the best platelet inhibitor available and is generally agreed on to be essential treatment during and after angioplasty. Therefore, ICU challenges with ASA by increasing doses after starting with 3 mg of ASA and doubling the dose every 30 minutes up to 80 mg as the top challenge dose are sometimes indicated. Because 80 mg of ASA is an effective inhibitor of platelets, this dose is acceptable, and the time and additional danger required to reach a dose of 325 or 650 mg of ASA are generally not necessary. Table 6 contains a protocol to consider when conducting ASA challenges in patients who give a history of acute urticaria or anaphylaxis after ASA in the past.

NSAID-INDUCED HYPERSENSITIVITY MENINGITIS

There are rare cases in which a specific NSAID, usually used to treat arthritis over a long time frame, induced aseptic meningitis.⁴⁵ The mechanism is probably immune reactions to specific NSAIDs, and the reaction has not been associated with ASA. Activated lymphocyte-mediated response to ibuprofen has been documented *in vitro* and may explain this reaction.⁴⁵ Alternatively, specific IgG and immune complexes, which have been measured in intrathecal fluid during such reactions, may play a role in the pathogenesis of drug-induced meningitis.²⁸

NSAID-INDUCED HYPERSENSITIVITY PNEUMONITIS

Rarely, in patients without underlying risk factors, exposure to specific NSAIDs have induced cough, fever, pulmonary infiltrates, and eosinophilia.¹⁰⁸ Thus allergic alveolitis or hypersensitivity pneumonitis has been described for a number of different NSAIDs but not for aspirin. Cross-reactivity does not occur.

Table 6. ORAL CHALLENGES TO DETECT PROBABLE IgE-MEDIATED CUTANEOUS AND SYSTEMIC REACTIONS TO INDIVIDUAL NSAIDs OR ASA

Reaction Types	Responses	Initial Dose ASA (mg)	Advance Dose Schedule	Interval Between Challenges (min)	Range Reaction Dose (mg)
Acute urticaria* (normal individual)	Urticaria	15	Doubling	30	30–60
Anaphylaxis*† (normal individual)	Urticaria and anaphylaxis	3	Doubling	30	30–60

*Most patients can be managed by avoiding the suspected NSAID and undergoing challenge with another NSAID or ASA to prove new NSAID drug acceptance.

†Performed in ICU with IVs in place and all available modalities of treatment available.

NSAID-induced hypersensitivity is also probably an immune reaction. Oral challenges with the suspect NSAID by Nader and Schillaci⁵³ induced typical pulmonary infiltrates. Lung biopsies of infiltrates revealed interstitial lymphocytes and eosinophils. Either delayed hypersensitivity reactions to specific NSAIDs or IgE-mediated reactions with late-phase responses, or both, could explain hypersensitivity pneumonitis reactions.

CONCLUSION

ASA and NSAIDs can induce asthmatic attacks or flares of urticaria in distinct populations of asthmatic patients or patients with urticaria. They can also produce anaphylactic reactions in otherwise normal individuals. Specific NSAIDs rarely induce aseptic meningitis or hypersensitivity pneumonitis.

Dyes, preservatives, and additives have received a distorted reputation for inducing more respiratory and cutaneous reactions than actually occur. Although carefully conducted challenge studies have documented that some of these compounds induce either urticaria or asthma, most patients who report such associations experience negative responses during properly controlled oral challenges with the suspected substance.

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Address reprint requests to

Donald D. Stevenson, MD
 Scripps Clinic
 The Scripps Research Institute
 10666 North Torrey Pines Road
 La Jolla, CA 92037