

Adverse Respiratory Reactions to Aspirin and Nonsteroidal Anti-inflammatory Drugs

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Aspirin-exacerbated respiratory disease (AERD) is an adult-onset condition that manifests as asthma, rhinosinusitis/nasal polyps, and sensitivity to aspirin and other cyclooxygenase-1 (COX-1)–inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs). There is no cross-sensitivity to highly selective COX-2 inhibitors. AERD is chronic and does not improve with avoidance of COX-1 inhibitors. The diagnosis of AERD is made through provocative challenge testing. Following a positive aspirin challenge, patients can be desensitized to aspirin and NSAIDs. The desensitized state can be maintained indefinitely with continued daily administration. After desensitization, there is an approximately 48-hour refractory period to adverse effects from aspirin. The pathogenesis of AERD remains unknown, but these patients have been shown to have multiple abnormalities in arachidonic acid metabolism and in cysteinyl leukotriene 1 receptors. AERD patients can take up to 650 mg of acetaminophen for analgesic or antipyretic relief. Patients can also use weak COX-1 inhibitors, such as sodium salicylate or choline magnesium trisalicylate. Treatment of AERD patients with antileukotriene medications has been helpful but not preferential when compared with non-AERD patients. An alternative treatment for many AERD patients is aspirin desensitization. This is particularly effective in reducing upper-airway mucosal congestion, nasal polyp formation, and systemic steroids.

Introduction

Aspirin, or acetylsalicylic acid (ASA), the first nonsteroidal anti-inflammatory drug (NSAID), has been used for more than 100 years for its analgesic, anti-inflammatory, and platelet-inhibitory properties. Within the past 40 years, a variety of NSAIDs have been introduced. Both ASA and NSAIDs are generally well tolerated; however, there are various side effects 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, among others: hepatitis, erythema multiforme, anemia, hepatotoxicity, interstitial nephritis, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Several types of pseudoallergic and allergic reactions to ASA and NSAIDs have been described [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 ASA intolerance, ASA idiosyncrasy, pseudoallergic reactions, and ASA sensitivity. As the framework for discussing sensitivity to ASA/NSAIDs, in this article the new classification recently proposed by Stevenson and Szczeklik [2] is used. In addition, the issues of cross-reactivity with COX-2 inhibitors will also be discussed.

Aspirin-exacerbated Respiratory Disease

Samter and Beers [3] were the first to describe the classic triad of asthma, rhinitis/nasal polyps, and ASA sensitivity. This description has become more complicated over the years, and most recently has been expanded to include chronic sinusitis. It is important to remember that ASA respiratory disease, not ASA sensitivity, is the underlying problem. In those patients with ASA-exacerbated respiratory disease (AERD), avoiding ASA and NSAIDs does not change the course of respiratory inflammation, which, once it begins, progresses with time.

Aspirin-exacerbated respiratory disease, which is virtually only seen in adulthood, has a variable prevalence. Giraldo *et al.* [4] noted that 5% of hospitalized adult asthmatics reported a history of ASA-induced respiratory reactions. In 1972, the Scripps Clinic and Research Foundation found 9% of challenged adult asthmatics to be sensitive to ASA; however, this was in a referral population that tended to include more severe asthmatics, and, therefore, this figure is likely larger than that in the overall asthmatic population. It is clear that the prevalence of ASA sensitivity in asthmatics with associated chronic sinusitis and/or nasal polyps increases this number significantly to 30% to 40% [5].

The prevalence of ASA-sensitive asthma also appears to be higher in females. Of 300 ASA-sensitive asthmatics referred to Scripps Clinic from 1995 to 2001, 174 (58%) were female, and 126 (42%) were male [6•].

Typically, ASA respiratory disease affects adults who are between 20 and 40 years of age. In the Scripps Clinic study [6•], nasal polyps or asthma first developed in these patients at approximately age 34. In the European Network study of ASA-induced asthma, persistent rhinitis appeared at a mean age of 29.7 years, followed by the development of asthma symptoms [7]. The natural history of AERD indicates that the respiratory tract inflammation frequently precedes the development of ASA- and NSAID-induced reactions. These patients, previously in good health, typically relate a story of developing an ordinary upper respiratory illness (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. At Scripps [6•], at least 200 patients with AERD have been followed, some for more than 30 years, and have not seen spontaneous remissions.

Radiographic abnormalities range from mucoperiosteal thickening to complete opacification of the sinuses. At Scripps Clinic, between 1991 and 1997, 234 patients with AERD were referred for ASA desensitization. Two hundred patients were proven by challenge to be sensitive to ASA. Previous sinus CT scans were not available for six patients; however, in the remaining 194 patients, 96% (187 patients) had abnormal sinus radiographs or CT scans [8]. Inflammation might be limited to the upper respiratory tract, but, more likely, lower respiratory tract inflammation develops as well.

There are no *in vitro* tests to measure ASA sensitivity. The physician should be suspicious of an asthmatic patient with nasal polyps and chronic pansinusitis. It is important to remember, however, that most of the patients with this clinical presentation will never have reactions to ASA 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, because they might develop AERD in the future [9].

Aspirin/Nonsteroidal Anti-inflammatory Drug-induced Hypersensitivity Pneumonitis

Another presentation of ASA/NSAID sensitivity is hypersensitivity pneumonitis. Rarely, patients present with NSAID-induced cough, fever, pulmonary infiltrates, and eosinophilia [10]. The clinical course includes rapid resolution of infiltrates over several weeks with the use of systemic steroids. It appears to be an immune reaction that either delays hypersensitivity or is IgE-mediated. Nader and Schillaci [11] induced typical pulmonary infiltrates and eosinophilia in patients within 24 hours of challenge with naproxen. Lung biopsies of infiltrates revealed interstitial lymphocytes and eosinophils. Subsequently, there have been three other controlled oral challenges with naproxen in sensitive patients,

with similar responses [12–14]. Hypersensitivity pneumonitis has been described for many different NSAIDs, but not for aspirin.

Detection of Aspirin/Nonsteroidal Anti-inflammatory Drug Sensitivity

Patients with ASA/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 make the diagnosis is through provocative challenge testing. ASA challenges include oral, bronchial, or nasal routes.

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

The more irritable the tracheobronchial tree, the more severe the bronchospastic reaction to ASA challenge. Therefore, oral and inhaled corticosteroids, intranasal corticosteroids, theophylline, and long-acting bronchodilators should be continued at the time of oral challenges. Discontinuing these medications can lead to worsening of asthma and subsequent decline in lung function. In these situations, ASA challenges cannot be safely and accurately performed. Despite continuing theophylline, respiratory reactions to intranasal and inhaled corticosteroids, ASA, and NSAIDs still occur [15].

Leukotriene modifier drugs (LTMDs), such as zileuton and montelukast, have been shown to block reactions to low (provoking) doses of ASA during oral ASA challenges, but often do not inhibit full-dose (650 mg), ASA-induced, respiratory tract reactions. Furthermore, LTMDs block bronchospastic reactions more often than the upper respiratory tract [15,16]. Although only 60% of patients with a history of asthmatic reactions to ASA have positive challenges, performing ASA challenges purely for diagnostic purposes is not recommended owing to the severity of reactions during oral challenges. If the goal is ASA desensitization and treatment, oral challenge with LTMD pretreatment makes sense; however, if no reaction occurs, it is not certain that the patient is ASA sensitive (or if both the upper and lower respiratory tract reactions were completely blocked), but the process will likely be easier for the patient to complete, and treatment with ASA should commence, even in the face of a negative challenge, if the patient fits the diagnostic picture of AERD prior to the challenge.

There are some medications, however, that should be discontinued 24 hours before challenge. These include anticholinergics, antihistamines, cromolyn, and short-acting inhaled beta agonists. Simultaneous use of anticholinergics and short-acting beta agonists might lead to false-positive reactions. After the effect of these medications disappears, the

Table 1. Oral challenge protocol to detect respiratory reactions induced by ASA

Time	ASA doses, mg*		
	Day 1	Day 2	Day 3
7:00 AM	Placebo	30	100–150
10:00 AM	Placebo	45–60	150–325
1:00 PM	Placebo	60–100	650

*Start challenges, if baseline forced expiratory volume in 1 second (FEV₁) is 70% or more than predicted, without bronchodilator. Alternatively, if the absolute FEV₁ value is >1.5L and represents the best previous FEV₁ value, proceed with oral challenge. On the placebo day, FEV₁ values should vary by <10% from baseline, and starting FEV₁ value on day 2 should be within 10% of the starting value on day 1. ASA—acetylsalicylic acid.

following decline in lung function might be misinterpreted as a true reaction. Glucocorticoids have been shown to attenuate the severity of reactions [17]. Antihistamines can block upper respiratory tract reactions to ASA, which will interfere with the accuracy of clinical assessment [18]. Cromolyn has minor inhibitory effects on the severity of the respiratory reaction induced by ASA, but pretreatment with cromolyn delays the onset of ASA-induced asthmatic reactions [19].

At Scripps Clinic, the following oral ASA challenge protocol was developed and modified (Table 1). ASA oral challenges are conducted over 3 days [20]. All patients received 30 mg of ASA as their first dose. Very few patients react to 30 mg of ASA. Depending on the patient's history, dosages may be advanced by 15 mg or 30 mg at 3-hour 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 more than 10 mg of prednisone or a leukotriene modifier drug, the challenge test is determined to be negative.

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

Inhalation Challenge with Aspirin-lysine

Although it is not available in the United States, inhalation challenge is routinely performed in other parts of the world and deserves mention. Bianco *et al.* [21] first introduced inhalation challenge with ASA-lysine in 1977. The onset of respiratory reaction with inhalation challenge is commonly less than 30 minutes, and bronchospasm is easily reversed with an inhaled beta agonist. Therefore, each increasing concentration can be delivered at 30-minute intervals [22]. This seems

to be more convenient and allows the test to be performed in an outpatient setting.

Why have we not adopted this type of ASA challenge in the United States? First, the test is not available in the United States. In addition, Dahlen and Zetterstrom [23] performed a study comparing oral and bronchial inhalation ASA challenges in 22 patients. Both routes accurately detected bronchospastic reactions. Inhalation challenge produced limited and short bronchospastic reactions. Only 2/22 patients experienced only naso-ocular reactions in the oral challenge group and none in the bronchial challenge group. This is not surprising, because there is no direct naso-ocular contact in bronchial challenges. Oral ASA challenges more closely approximate real-life challenges with ASA/NSAIDs.

Another type of ASA challenge is the nasal inhalation challenge with ASA-lysine [24]. ASA-lysine can induce local swelling of the nasal membranes in AERD asthmatic patients. The study is restricted, however, by limited sensitivity when compared with oral or inhalation provocation testing. Nevertheless, the test provides a rapid and safe means of confirming the diagnosis when it is positive.

Aspirin Desensitization and Cross-desensitization

The first ASA desensitization for an episode of anaphylaxis was reported in 1922 by Widal *et al.* [25]. Desensitization is used in its broadest sense, because IgE-mediated mechanisms have not been established for ASA respiratory sensitivity. Historically, desensitization has been viewed as repeated exposure to injected antigens, leading to the reduction of IgE-mediated reactions.

In 1977, Bianco *et al.* [21] induced "tolerance" to inhaled ASA-lysine after repeated inhalations in ASA-sensitive asthmatic patients. In 1980, Stevenson *et al.* [26] reported two ASA-sensitive asthmatic patients who became refractory to ASA after single, blind, oral challenges with ASA. Both patients, after desensitization, experienced improvement in respiratory disease while taking daily doses of ASA.

A state of tolerance can be induced and maintained by aspirin desensitization. This process includes administration of small incremental doses of ASA over 2 to 3 days until 400 to 650 mg of ASA are tolerated. Thereafter, ASA can be administered daily to maintain desensitization, in doses of 80 and 325 mg. After desensitization, the desensitized state persists for 2 to 5 days [27]. During this refractory period, NSAIDs may be taken with relative safety. Stevenson *et al.* [28] compared clinical outcomes after 1 to 6 years of daily ASA treatment. They found that patients who remain on maintenance therapy at doses of 325 to 650 mg BID usually respond with improvement of respiratory symptoms.

From a practical standpoint, those patients with a history of arthritis or rheumatic diseases, or those patients who require antiplatelet therapy can be desensitized to ASA and then take daily ASA indefinitely, or patients can be switched

to any cross-reacting NSAID, as long as ASA or the NSAID is continued daily.

Cross-reacting Substances

In patients with AERD and the cross-reacting cutaneous syndromes; NSAIDs, which preferentially inhibit COX-1 in vitro, cross-react with ASA upon first exposure to the new NSAID. Those NSAIDs that inhibit COX-1 the least require the smallest doses of NSAIDs in cross-reacting with ASA [29]. Furthermore, cross-desensitization between ASA and any of the NSAIDs that inhibit COX-1 occurs routinely.

Acetaminophen is a weak inhibitor of COX-1 and, therefore, poses a challenge in determining the element of cross-reactivity. Acetaminophen partially cross-reacts with ASA in patients with AERD, but only when administered in high doses. Delaney [30] challenged ASA-sensitive asthmatics with 1000 mg of acetaminophen and found that 28% of patients developed respiratory reactions [30]. Similarly, in a large study by Settiple and Stevenson [31], 50 ASA-sensitive asthmatics were challenged 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 ASA-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 cross-react with ASA. However, their compounds have not been shown to inhibit COX-1. Azo dyes, frequently found in coloring for food, drinks, drugs, and cosmetics, have been reported to induce bronchospasm. However, more recent studies have shown that azo intolerance is basically nonexistent among ASA-sensitive asthmatic patients [32]. Reports of severe bronchospasm within minutes of receiving hydrocortisone intravenously led to a study by Feigenbaum *et al.* [33], who found only one of 44 ASA-sensitive asthmatic patients reacted to both hydrocortisone succinate and methylprednisone succinate. Re-administration of hydrocortisone succinate after ASA desensitization continued to induce a respiratory reaction in this patient. This suggests a coincidental IgE-mediated reaction rather than cross-reactivity with ASA.

The recent development of highly selective COX-2 inhibitors, such as rofecoxib and celecoxib, has reduced many of the adverse side effects commonly seen with COX-1 inhibitors. Theoretically, these drugs should not cross-react with ASA or COX-1 NSAIDs. A recent double-blind, placebo-controlled study from Stevenson and Simon [34•] at the Scripps Clinic found that in 60 patients with demonstrated aspirin sensitivity, none reacted to rofecoxib at therapeutic doses. This number has now been increased to more than 100 and indicates a 99% confidence that no cross-reactivity to COX-2 inhibitors exists in AERD patients. A recent study by the same group [35], now in submission, found similar results with 75-mg doses of rofecoxib. The same results have been found with celecoxib.

Inflammatory Cells of Aspirin-exacerbated Respiratory Disease

In 1971, Vane [36] discovered the shared pharmacologic effects of ASA and NSAIDs on inhibition of COX enzymes in the metabolic cascade of arachidonic acid metabolism. The COX enzymes exist in at least two isoforms, COX-1 and COX-2. COX-1 is expressed in most mammalian cells. COX-2 is induced during inflammation.

Both mast cells and eosinophils synthesize arachidonic acid products. All biochemical events related to AERD appear to occur in mast cells of nasal and bronchial mucosa. Along with eosinophils, they are important cells in inducing ongoing inflammation. Both types of cells have been observed in nasal cytograms and nasal tissue biopsy from ASA-sensitive asthmatics [37]. Sladek *et al.* [38] analyzed bronchoalveolar lavage (BAL) fluid from ASA-sensitive asthmatics and found elevation in the number of eosinophils and eosinophil cationic protein compared with controls. Yamashita *et al.* [39] found numerous eosinophils and degranulated mast cells in immunohistochemically stained polyp tissue of ASA-sensitive asthmatics. Neutrophils and macrophages, which also synthesize arachidonic acid products, are found in lavage fluid from both ASA-sensitive and ASA-tolerant asthmatics. The fact that they are not increased in ASA-sensitive asthmatics does not exclude their participation in AERD.

In 1980, Samuelsson *et al.* [40] reported that a second metabolic pathway for arachidonic acid metabolism was also involved in inflammation. This pathway involves 5-lipoxygenase enzyme induction of leukotriene synthesis. Leukotrienes (C, D, and E₄ [LTC, LTD, LTE₄]) are potent mediators of chemotaxis of eosinophils, increased vascular permeability, mucous gland secretion, and bronchoconstriction. Interestingly, as the COX pathway is blocked, there is preferential diversion to the 5-lipoxygenase pathway.

There is evidence that ASA-sensitive asthmatics produce higher amounts of arachidonate products. Sladek *et al.* [38] measured higher concentrations of LTC₄ and thromboxane (TX)B₄ in BAL fluid taken from ASA-sensitive asthmatics prior to ASA-lysine challenge. Christie *et al.* [41] and Smith *et al.* [42] reported higher urinary LTE₄ and TXB₂ in ASA-sensitive asthmatics when compared with controls. This suggests that even before ASA challenge, ASA-sensitive asthmatics produce more leukotrienes and prostanoids.

What stimulates and propagates such an inflammatory response? Szczeklik [43] 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.

Pathogenesis of Aspirin-induced Respiratory Reactions

Clinical presentation of reactions to ASA and other NSAIDs are reminiscent of immediate hypersensitivity reactions.

However, an antigen-antibody mechanism has never been demonstrated in AERD.

Based on the cross-reactivity of AERD patients to structurally distinct NSAIDs on first exposure, it is thought that initiation of ASA-induced reactions is not based on antigen-antibody reactions but on intracellular COX enzyme inhibition in respiratory cells [44]. In vitro studies have shown that there might be a difference in function of COX enzymes when comparing ASA-sensitive asthmatic and ASA-tolerant patients [45]. This might be an explanation of why more reactions are not seen with ASA exposure.

A crucial event in the pathogenesis of ASA-induced respiratory reaction occurs as ASA/NSAIDs rapidly bind COX-1. There is a subsequent decrease in the synthesis of COX products, such as PGE₂. PGE₂, under normal circumstances, both bronchodilates and inhibits 5-lipoxygenase. Two studies have now shown that fibroblasts (from the upper and lower airways) of AERD patients produce lower levels of PGE₂ than do ASA-tolerant asthmatics [46,47]. Without the modulating effects of PGE₂, it is more likely for bronchoconstriction to occur, and the 5-lipoxygenase pathway is preferentially stimulated, with resultant increase in the production of leukotrienes. Compared with ASA-tolerant asthmatics, AERD patients have been shown to have increased numbers of inflammatory cells with CysLT₁ receptors [48]. AERD patients also have upregulated CysLT₁ receptors, which can augment the effects of leukotrienes.

It is, therefore, not surprising that most patients with ASA-sensitive asthma excrete two- to 10-fold higher amounts of LTE₄ in their urine than asthmatics who are tolerant to ASA. Christie *et al.* [49] found, after oral challenge in ASA-sensitive asthmatics, that there was a significant elevation in urinary LTE₄. Several studies have also shown elevated LTC₄ and histamine in nasal lavage fluid after oral ASA challenge. Similar findings have been reported in studies of the lower respiratory tract. Sladek *et al.* [50] obtained BAL fluid after ASA inhalation challenges in ASA-sensitive asthmatics. The fluid contained elevated levels of LTC₄ and histamine. Recently, further evidence for the role of mast cells in the pathogenesis of AERD has been elucidated. Bochenek *et al.* [51] have demonstrated elevated levels of a PGD₂ metabolite and tryptase in the blood of AERD patients (at baseline and with further increase following aspirin challenge).

It remains unclear why there is a subset of patients who are ASA-sensitive and why there is an overproduction of leukotrienes in those with the disease. As mentioned earlier, the modulating effect of PGE₂ on 5-lipoxygenase is an essential target in the development of ASA respiratory disease. Sestini *et al.* [52] pretreated ASA-sensitive asthmatics with PGE₂ by inhalation before ASA-inhalation challenge. No reactions were reported. In addition, urinary LTE₄ did not increase.

Lipoxins are another (nonleukotriene) product of the 5-lipoxygenase pathway and have anti-inflammatory properties that are basically the opposite of the pro-inflammatory effects of leukotrienes. ASA-sensitive asthmatics also have lower levels of (at least) lipoxin A than do ASA-tolerant asthmatics.

During ASA desensitization, there is continued inhibition of COX-1 as well as phospholipase A₂. This leads to a decrease in 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 [53].

Treatment

Educating the patient with ASA-induced disease is very important. Avoidance of ASA and all cross-reacting NSAIDs prevents acute respiratory events in sensitive patients. The patient should receive a list of drugs that are contraindicated. In patients with hypersensitivity pneumonitis, it is only necessary to avoid the implicated NSAID.

Patients with ASA-sensitive asthma may take 650 mg of acetaminophen for analgesic or antipyretic properties. However, a cross-reaction was reported after ingestion of 1000 to 1500 mg of acetaminophen in patients with ASA-sensitive asthma [31]. Patients can also take drugs with no activity or weak activity, such as: sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextropropoxyphene [1••]. Selective COX-2 inhibitors are safe for patients with ASA-sensitive asthma because COX-1 will continue to produce PGE₂ [34,35].

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

If leukotrienes are responsible for most of the respiratory reactions seen in ASA-sensitive asthma, theoretically, preventing synthesis of leukotrienes or blocking the CysLT₁ receptor might be particularly effective in treating AERD. Recently, the antileukotriene drugs have been introduced as treatment of ASA-sensitive asthma. However, for the most part, treating with a 5-lipoxygenase inhibitor provides only partial control of symptoms. A study by Dahlen *et al.* [54] of 40 patients with ASA-sensitive asthma found that treatment with zileuton provided acute and chronic improvement of pulmonary function measurements. However, the changes were the same as those for non-ASA-sensitive asthmatics. Similar results have been shown in patients treated with LT receptor antagonists, such as montelukast. In a study by Kuna *et al.* [55], montelukast was given to 80 patients with ASA-sensitive asthma who were not controlled with inhaled or oral steroids. After 4 weeks, patients had improvement in pulmonary function as measured by forced expiratory volume at 1 second (FEV₁), fewer nocturnal asthma symptoms, more asthma-free days, and improvement in quality of life. However, overall, the effects were moderate, at best, and no different than those seen in non-ASA-sensitive asthmatics.

There is an alternative to treating patients with AERD: aspirin desensitization/treatment [26]. Through desensitization, ASA tolerance can be induced and maintained. Selection of patients for ASA desensitization/treatment therapy should include all AERD patients, except those whose disease is controlled with topical corticosteroids and leukotriene modifier drugs (unless they require the use of ASA or NSAIDs for other conditions). ASA-desensitization treatment is particularly effective in reducing upper-airway mucosal congestion and nasal polyp formation.

Using doses of ASA (650 mg BID on average) over a number of years, several additional studies [26,56,57,58••] have shown significant reduction in respiratory disease activity (including sinusitis), need for further sinus surgery, reduction in hospitalizations, and requirement for systemic corticosteroids ($P = 0.004$ to <0.0001). Side effects from daily ASA therapy were usually limited to gastric irritation, but in 13% of treated patients, ASA had to be discontinued because of this complication [32]. In data from our most recent series of 172 AERD patients, who were followed from 1995 to 2000, after ASA desensitization and daily ASA treatment, the following results were observed: 24 (14%) discontinued ASA because of side effects (usually gastritis) and 31 (18%) failed to respond to questionnaires, discontinued ASA for reasons other than side effects, or discontinued ASA because they believed it was not effective treatment for their respiratory disease. The remaining 117/172 (68%) responded to ASA treatment. The effects are seen as early as 6 months after initiation of aspirin therapy [59•]. We have also shown that the benefit of ASA treatment is independent of anti leukotriene treatment [60].

In some difficult-to-control cases, "triple therapy," including 5-lipoxygenase inhibitor, CysLT receptor antagonist, and desensitization is required. This makes good theoretic sense because zileuton is only approximately a 35% 5-lipoxygenase inhibitor, and, therefore, leukotrienes will still be formed in significant amounts, and there are other proinflammatory products of this pathway that are not CysLTs, including LTB₄ and 5-hydroxyeicosatetraenoic [acid] (HETE).

Although therapeutic doses of ASA 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 ASA or NSAIDs on an as needed basis. If regular, full-dose NSAID therapy is required for another condition, this can be administered, because with ASA desensitization, cross-desensitization to other COX-1 inhibitors can exist.

Conclusions

The past two decades have provided many advances into understanding the pathogenesis of AERD. The discovery of the many important mediating properties of the leukotriene modifiers has allowed further work into finding appropriate treatment opportunities. It is evident that much more research is needed and expected in this area. ASA sensitivity

remains a complex, heterogeneous disease with many clinical manifestations. Proper classification of reactions to ASA and NSAIDs will enable more accurate understanding of the literature. Without in vitro tests to determine patients at risk, making a definitive diagnosis becomes an even more tedious process. Fortunately patients with AERD can tolerate COX-2 inhibitors without the need for challenge and desensitization. Although ASA/NSAID avoidance is paramount treatment, the use of intranasal and inhaled, high-potency, topical corticosteroids; ASA desensitization; and treatment with the addition of LTMDs are effective in treating many of these patients and can help them avoid nasal/sinus surgery and side effects from using systemic steroids.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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