

Welcome, New House Staff

On behalf of the Department of Pharmacy Services at the University of Washington Medical Center, Harborview Medical Center, Seattle Cancer Care Alliance, and UW Medicine Neighborhood clinics, I would like to welcome you. We look forward to working with you during your residency.

You will be receiving copies of the *Drug Therapy Topics* newsletter on a monthly basis. This newsletter is a source of current pharmacotherapy-related information as well as a major communication between the Department of Pharmacy Services, the Pharmacy and Therapeutics Committee, and the medical staff. It is intended, in part, to keep you updated on additions and deletions to the medical centers' formulary, along with changes in policies and procedures as approved by the Pharmacy and Therapeutics Committee. Your input into its content is welcome.

The medical centers' *Drug Formulary* provides key information regarding drug availability, along with procedures pertaining to medication use. You will be provided with a personal copy of the formulary. For expanded and updated clinical details on all drugs and for "alerts" regarding formulary drugs, you may also access the formulary and the UW Drug Information Center website electronically at <http://uw.pnrx.org>.

If you have any questions regarding pharmacy services, please ask the clinical pharmacist on the unit or in the clinic or call one of the following pharmacy phone numbers. Again, a sincere welcome from all of us.



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Aspirin-Induced Asthma

Colleen Ann Catalano, Pharm.D.

I. INTRODUCTION

Documented adverse reactions to aspirin date back to the early 1900s, when violent episodes of bronchospasm were reported after aspirin ingestion. In the 1960s, indomethacin was introduced and adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs) were similarly recognized. In 1999, NSAIDs that selectively inhibit cyclooxygenase-2 (COX-2) enzymes were introduced, and these too have been associated with allergic reactions in susceptible patients.

Aspirin-induced asthma (AIA) consists of a clinical triad of asthma, aspirin sensitivity, and nasal polyposis in response to aspirin and other NSAIDs.¹ This condition has alternately been referred to as the aspirin triad, aspirin sensitivity, aspirin-exacerbated respiratory disease (AERD), Samter's syndrome, as well as aspirin-intolerant and aspirin-induced asthma. The term aspirin-induced asthma (AIA) is widely used and currently accepted in clinical medicine and we will refer to it as such throughout this article.

In this state of continuous inflammation, ingestion of aspirin in a subset of asthma patients appears to temporarily intensify the inflammatory process, leading to exacerbation of asthma symptoms. It was originally thought that this immediate hypersensitivity reaction was the result of an antigen-antibody reaction; however, an antibody response following a skin test with ASA lysine has not been observed.² Moreover, IgE antibodies against either aspirin or NSAIDs have not been isolated.³ Since there is no immunologic component in AIA reactions, they are most appropriately referred to as hypersensitivity reactions. Three types of immediate hypersensitivity reactions can be induced following the ingestion of aspirin in those with AIA: (i) bronchospasm and rhinoconjunctivitis, (ii) urticaria/angioedema, and (iii) anaphylaxis. Aspirin hypersensitivity is most often manifested as respiratory reactions, including bronchospasm, profuse rhinorrhea, and conjunctival injection. The present review will focus on the respiratory, non-immunologic types of hypersensitivity to aspirin and other NSAIDs.

II. CLINICAL PRESENTATION OF AIA

Reports regarding the prevalence of AIA among adults are conflicting. AIA has been estimated to occur in as low as 0.07% and as high as 2% of the general population.³⁻⁵ Up to 20% of asthmatics are sensitive to aspirin and other NSAIDs.⁶ Moreover, aspirin sensitivity has been reported in 35-52% of patients with nasal polyps and up to 65% of patients with bronchial asthma and nasal polyps.⁴ AIA is usually acquired in the third or fourth decade of life, with rhinorrhea and nasal congestion being the typical presenting symptoms. Often, the patient reports a viral upper respiratory tract infection prior to the onset of rhinitis. Rhinorrhea and nasal congestion persist and become perennial, difficult to treat, and are associated with chronic sinusitis complicated by nasal polyposis. Approximately 1-5 years following the onset of rhinitis there is a progression to asthma and aspirin sensitivity.⁴ AIA symptoms develop within 1-3 hours following ingestion of aspirin or nonselective NSAIDs and are usually accompanied by profuse rhinorrhea, bronchospasm, conjunctival injection, generalized flushing, and periorbital edema. Once established, aspirin sensitivity is usually present for life.

III. AIA

Asthma is a continuous inflammatory condition of the airways and is characterized by hypertrophy of airway smooth muscle, shedding of airway epithelium, sub-basement membrane fibrosis, excessive secretion of mucus, and multicellular inflammation involving mast cells, neutrophils, eosinophils, macrophage, basophils, and lymphocytes.³ Different from asthma, however, the pathogenetic mechanism of AIA is complex and not completely understood. It has been hypothesized that AIA is linked to abnormalities in arachidonic acid (AA) metabolism and specifically, the inhibition of synthesis of protective prostaglandins (PGs) by cyclooxygenase (COX). This results in an imbalance of anti-inflammatory PGs and proinflammatory leukotrienes (LTs) (Figure 1). A second hypothesis argues that aspirin causes modifications in the structure of COX-2 resulting in the generation of products in the lipoxygenase (LO) pathway. Recently, however, research has focused on the identification of a genetic variant of the LTC₄ synthase responsible for the conversion of LTA₄ to LTC₄, the first of the LTs. In order to understand the pathophysiology of AIA, a brief overview of the arachidonic acid cascade is warranted and described here.

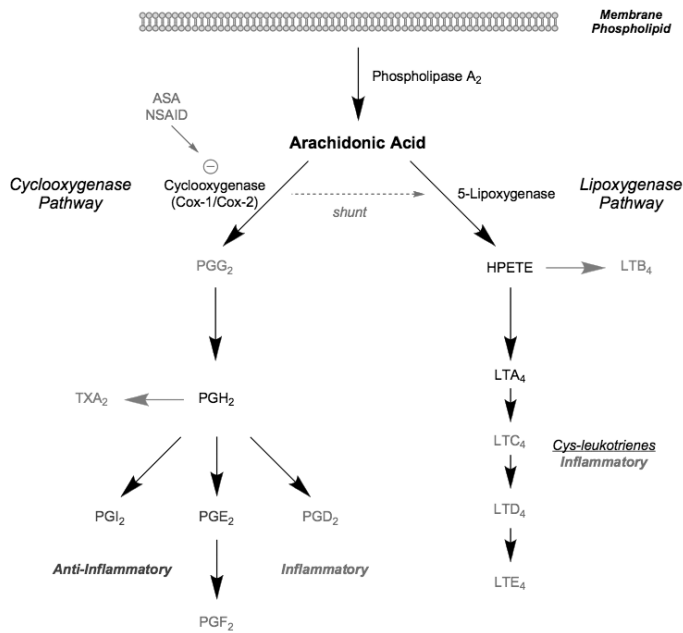


FIGURE 1: Arachidonic Acid Cascade.^{1,3} AA generates both PGs and LTs. Aspirin and nonselective NSAIDs inhibit COX-1 and COX-2 resulting in a block in the synthesis of protective prostanoids, mainly PGE₂. Consequently, this diverts AA metabolites to the LO pathway and the synthesis of inflammatory LTs. Selective NSAIDs inhibit COX-2, which is the enzyme responsible for inflammation and pain. The biosynthesis of thromboxanes is omitted for simplicity.

IV. AA CASCADE

AA is a polyunsaturated fatty acid that is present in the phospholipids of cell membranes. COX is the rate-limiting enzyme responsible for the conversion of AA to PGs. The AA cascade generates both prostanoids via the COX pathway, and LTs via the lipoxygenase pathway. At the outset, AA is cleaved from a phospholipid molecule by the enzyme phospholipase A₂. AA is a precursor of the eicosanoids, which consist of prostaglandins (PG), prostacyclins (PGI), leukotrienes (LT), and thromboxanes (TX). All three types of prostanoids (PG, PGI, TX) originate from PGH₂. The COX enzyme exists in two isoforms, COX-1 and COX-2. COX-1, the constitutive form, produces protective PGs that regulate normal physiological processes such as GI mucosal integrity, vascular homeostasis, and renal function. COX-2, on the other hand, is induced by inflammatory stimuli such as cytokines, and produces PGs involved with inflammation and pain (Figure 1).

The second eicosanoid biosynthetic pathway involves the enzyme 5-lipoxygenase (5-LO), which converts AA into HPETE and is the precursor for LTA₄. LTA₄ is ultimately cleaved to form LTC₄, which is transported out of the cell, and a glutamic acid is removed to form LTD₄. LTD₄ is then cleaved to make LTE₄. Often referred to as cysteinyl leukotrienes (Cys-LTs) because they have an amino acid in their structure, LTs play an important role in the inflammatory process.

V. EFFECT OF ASPIRIN ON AA METABOLISM

The COX enzyme is inhibited by aspirin and NSAIDs. COX-1 inhibitors accelerate the depletion of protective PGE₂ that normally protects against the effects of bronchoconstriction and mast cell mediator release.⁷ Aspirin is an irreversible inhibitor of COX-1 that causes a reduction in the biosynthesis of PGs, which is likely the principal mechanism by which aspirin relieves pain and inflammation. Inhibition of the COX pathway further diverts AA metabolism to the lipoxygenase pathway, causing a shunt from production of protective prostanoids toward the production of inflammatory LTs. Non-selective NSAIDs also block COX-1 and COX-2 enzymes, but do so reversibly and to varying degrees. A number of NSAIDs are available to selectively inhibit either COX-1 or COX-2, though they vary in their degree of selectivity. Most adverse effects of aspirin and NSAIDs are associated with inhibition of COX-1, whereas anti-inflammatory actions result from inhibition of COX-2.

VI. PATHOPHYSIOLOGY OF AIA

AIA is a distinct clinical syndrome in which aspirin and several other analgesics precipitate an asthma attack. Several hypotheses exist to explain the underlying pathogenic mechanism of AIA (Figure 1). The first was proposed in 1975 and suggested that inhibition of the COX-1 enzyme by aspirin-like agents triggered asthma attacks in the airways of sensitive patients.⁹ Since that time, several studies have supported this hypothesis and this has led to the formulation of the COX theory.^{10,11} Inhibition of the COX-1 enzyme is the common feature of medications that trigger this reaction. As described above, COX-1 inhibition results in accelerated depletion of PGE₂, a protective PG, while COX-2, induced under inflammatory conditions, is responsible for synthesis of pathological PGs that produce pain and fever. Evidence suggests that reduction of PGE₂ by agents that inhibit the COX-1 enzyme, such as aspirin and NSAIDs, results in depletion of protective PGE₂ and unrestrained synthesis of new LTs, provoking an inflammatory response in patients with AIA.⁷

A second hypothesis suggests that LTs are the principal mediators of AIA. In this model, aspirin-induced bronchoconstriction is caused by the shunting of AA metabolism away from prostaglandin production toward leukotriene (LT) production. This is due to a proposed modification in the structure of COX-2 resulting in the generation of products in the LO pathway. LTs can mediate bronchial smooth muscle constriction and can increase mucous secretion, vascular permeability, and cellular infiltration. It remains uncertain, however, which step in the pathway is responsible for the overproduction of LTs in patients with AIA.¹³

Avoidance of aspirin, aspirin-containing products, and all other NSAIDs with similar activity in patients with AIA is crucial to prevent life-threatening reactions.

AIA is usually acquired in the third or fourth decade of life, with rhinorrhea and nasal congestion the typical presenting symptoms.

Up to 20% of asthmatic patients exhibit hypersensitivity to aspirin and NSAIDs.⁶

The Global Strategy for Asthma Management and Prevention (GINA) guidelines are updated yearly and accessible at www.ginasthma.com.¹²

Aspirin-induced asthma is a complex inflammatory process consisting of the following triad of clinical symptoms in response to aspirin and other NSAIDs:¹

- asthma
- aspirin sensitivity
- chronic rhinosinusitis with nasal polyps

There is no immunologic component in AIA reactions.²

A third hypothesis suggests that the phenotype of AIA is associated with an allelic variant, 2444C, of LTC₄ synthase (LTC₄S)¹³. This polymorphism, consisting of an A to C transversion in the promoter region of the LTC₄S gene, results in an increased expression pattern of the enzyme; this polymorphism appears to be a risk factor for adverse reactions to aspirin and NSAIDs in asthma. An understanding of genetic polymorphisms of this disorder may assist in creating new diagnostic and treatment alternatives. A number of other mechanisms, including an association with a viral infection, have been proposed to explain the pathogenesis of AIA.¹⁴ Overall, the etiology of AIA is complex and, while a great deal of knowledge of the pathophysiology of AIA has been gained, a number of questions remain unanswered. Further investigation of the role of COX isoforms, lipoxygenase pathway enzymes, the mediators produced in regulating airway function, as well as identification of genetic polymorphisms in the candidate genes associated with asthma, will be necessary to confirm the significance of each in AIA.

VII. DIAGNOSIS

The diagnosis of AIA is generally based on clinical history. There are no *in vitro* tests to detect or measure aspirin sensitivity. AIA describes those patients who, after ingestion of aspirin or NSAIDs, develop upper and lower respiratory tract symptoms including rhinorrhea, nasal congestion, and bronchospasm. These are dose-dependent reactions in which the severity of reactions increases with increasing doses of aspirin. When AIA is suspected but there is no history of possible aspirin hypersensitivity, diagnosis can be established with certainty only by provocation tests using increasing doses of aspirin; however, since oral provocation testing can cause serious reactions, it is recommended that only clinicians experienced in medical emergency procedures perform this test.⁴ Provocation tests include oral, bronchial (inhaled), and nasal aspirin administration. The oral route is the most commonly used challenge method as it best represents natural exposure. The bronchial and nasal provocation tests are less sensitive and can be used as alternatives to the oral provocation test in patients with high suspicion of aspirin sensitivity.

TABLE 1: Management Strategy for Patients with Aspirin/NSAID Sensitivity⁴

MANAGEMENT STRATEGY	RECOMMENDATIONS
Avoid aspirin and all cross-reacting non-selective NSAIDs	All patients, unless aspirin or other nonselective NSAIDs are required for treatment of comorbid conditions
Desensitization	Patients with aspirin-induced asthma who: can only be controlled with unacceptably high doses of oral corticosteroids, require repeated polypectomy or sinus surgery, – or – need aspirin for the treatment of other diseases such as arthritis or thromboembolism
COX-2 selective NSAIDs	These agents are well tolerated in patients with aspirin-induced asthma
Leukotriene modifiers	As add-on therapy
Weak inhibitors of COX-1 enzyme (acetaminophen)	Weak anti-inflammatory agents, however, can be used as alternatives to aspirin/nonselective NSAIDs, acetaminophen should be used in single doses of <1000 mg

COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal anti-inflammatory agents

VIII. TREATMENT

The goals concerning the treatment of AIA are identical to those in published guidelines for asthma, namely those of the National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA). Inhaled corticosteroids (ICS) are considered first-line therapy in all asthma treatment guidelines. If asthma is not adequately controlled with ICS alone, a B₂-adrenoceptor agonist can be added to ICS therapy. Consequently, ICS and B₂-adrenoceptor antagonists remain the preferred asthma therapy, including that of AIA.¹²

Management of AIA includes educating the patient regarding avoidance of aspirin and all cross-reacting NSAIDs to prevent devastating respiratory events (Table 1). Avoidance of aspirin, however, may not always be possible in patients with aspirin sensitivity, particularly in patients requiring cardiovascular prophylaxis, patients with significant corticosteroid-induced adverse effects and those with rheumatoid or osteoarthritis. Desensitization may be necessary for those patients with AIA to allow for the clinical use of aspirin. By slowly increasing oral doses of aspirin, immunologic and pharmacologic reactions are eliminated. Desensitization results in reduction in LT production, down-regulating LT receptors, and decreased extracellular histamine levels after mast cell stimulation. If desensitization is successful, patients should remain on aspirin indefinitely, otherwise they will return to sensitivity in 2 to 4 days; desensitization is not recommended in patients who require intermittent use of aspirin or NSAIDs.⁶

Several successful desensitization protocols have been developed for patients with aspirin-induced asthma. Small incremental doses of aspirin are administered every 2-24 hours until 400-650 mg is tolerated.³ Aspirin desensitization is maintained indefinitely with a daily dose of as little as 81 mg. Rapid desensitization over 2.5-3.5 hours is possible for those patients with coronary artery disease urgently requiring aspirin therapy. "Cross-desensitization" to other nonselective NSAIDs occurs once the patient is desensitized to aspirin.⁴

LT-modifying agents have also been used in patients with aspirin to control their sinusitis and asthma. The use of LT modifiers has gained popularity, as some believe that LTs are responsible for most of the respiratory reactions seen in AIA. LT modifiers either inhibit the synthesis of LTs by blocking 5-lipoxygenase or by blocking the LT receptors.¹⁵ Early studies demonstrated that pretreatment with LT modifiers attenuated the nasal and bronchial reactions in aspirin-sensitive asthmatic patients.¹⁴ More recently, however, studies indicate that LT modifiers do not completely block this enzyme or receptors and alternative mediators may be involved in aspirin-induced respiratory reactions.¹⁶⁻¹⁹ Whatever the case, the evidence to support the use of LT modifiers in the management of patients with AIA is weak and their use may be limited to add-on therapy; patients with AIA who are using LT modifiers should remain cautious when taking concomitant aspirin or NSAIDs.

Inhibition of COX-1 enzyme by aspirin and nonselective NSAIDs is central in the development of reactions observed in patients with hypersensitivity to these agents. Conversely, selective COX-2 inhibitors have not been shown to cross-react in most patients and can usually be recommended as anti-inflammatory alternatives to the nonselective NSAIDs for those patients with AIA. Celecoxib, for example, is well tolerated by a majority of AIA patients, as constitutive COX-1 will continue to synthesize the protective prostanoid, PGE₂.^{6,20} In theory, selective COX-2 inhibitors may be an alternative in aspirin- or NSAID-sensitive patients due to minimal effects on COX-1 and PGE₂.²¹

There are no *in vitro* tests to detect or measure aspirin sensitivity. Diagnosis of AIA is based on clinical history.

Most adverse effects of aspirin and NSAIDs are associated with inhibition of COX-1, whereas anti-inflammatory actions result from inhibition of COX-2.

In a subset of patients with asthma, aspirin induces clinical symptoms associated with increased levels of lipoxygenase products, which play an important role in the inflammatory process.⁷

Several hypotheses exist to explain AIA; however, none have been fully proven or disproven.

The common consensus of opinion proposes that a biochemical process is involved in AIA and is mediated by blocking the cyclooxygenase (COX) pathways.¹³

COX-1 produces protective PGs that regulate normal physiological processes, whereas, COX-2 is induced by inflammatory stimuli such as cytokines, and produces PGs involved with inflammation and pain.⁷

Inhibition of COX can provide relief from the symptoms of inflammation and pain; this is the method of action of NSAIDs, aspirin, and ibuprofen.

Arachidonic acid metabolism gets shunted away from prostanoid production and into leukotriene synthesis, resulting in an increase in leukotriene production.⁷

Leukotrienes induce bronchoconstriction, edema formation, and mucus production in airways and are the mediators of asthma.

The classical COX inhibitors are not selective (i.e., they inhibit all types of COX), and inhibit prostaglandin (PG) synthesis by COX-1, and this inhibition results in depletion of protective PGE₂ and unrestrained synthesis of new LTs, provoking an inflammatory response in patients with AIA.⁷

The use of LT modifiers in the management of patients with AIA may be limited to add-on therapy.

TABLE 2: NSAIDs That Have a High Cross-Sensitivity with Aspirin³

Diclofenac	Ketoprofen	Meclofenamate	Piroxicam
Etodolac	Ketorolac	Mefanamic acid	Sulindac
Fenoprofen	Ibuprofen	Naproxen	
Flurbiprofen	Indomethacin	Nabumetone	

Acetaminophen is a weak inhibitor of the COX-1 enzyme and may cross-react with aspirin when high doses are used. While low or moderate doses of acetaminophen (<1000 mg single dose) may be considered as an alternative analgesic or antipyretic agent in patients with AIA, even these may evoke an allergic response. An oral tolerance test should be performed with acetaminophen 500 mg before the drug is recommended for regular use.⁶ Table 2, above, contains a list of NSAIDs that have a high cross-sensitivity with aspirin.

IX. CONCLUSION

Despite the recent expansion of knowledge regarding its pathophysiology, AIA remains widely under-recognized and under-diagnosed in the asthmatic population and can lead to unfortunate and life-threatening asthma attacks after ingestion of aspirin and the older NSAIDs. The lack of awareness by health care professionals, as well as deliberate avoidance of aspirin and NSAIDs by asthmatic patients, can perhaps explain these irregularities.

Investigations into the pathogenesis of AIA are only recently starting to provide insight into the management of patients with AIA. Avoidance of aspirin and non-selective NSAIDs, use of selective COX-2 inhibitors, as well as the use of acetaminophen in doses <1000 mg are options for management of AIA. LT modifiers prevent AIA only in some patients while others are left unprotected. The role of LT modifiers requires further study before they can be recommended for patients with AIA. Equally important, aspirin desensitization may be an alternative therapeutic option in a subgroup of AIA patients.

Clearly, there is controversy surrounding the underlying pathogenic mechanism of AIA; however, most hypotheses focus on abnormal AA metabolism, which probably accounts for the adverse respiratory reactions to aspirin. Indeed, the use of aspirin and non-selective NSAIDs are contraindicated in patients with AIA.

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Selective COX-2 inhibitors can be considered alternatives in patients with AIA; however, close monitoring after the first dose is recommended until more data are available.⁶

Aspirin sensitivity is often associated with intolerance to other NSAIDs.¹

In AIA patients requiring aspirin or NSAIDs *aspirin desensitization* may be an option.

Most important, the use of aspirin and nonselective NSAIDs is contraindicated in patients with AIA.

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P&T COMMITTEE BRIEF SUMMARY June 15, 2008

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S)	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE
Leflunomide (Arava®)	10 mg, 20 mg, 100 mg	Rheumatoid arthritis agent	Treatment of BK virus nephropathy in kidney transplant patients	Loading dose of 60 mg orally daily for three days followed by 20-60 mg or greater targeting a serum concentration of 40-100 µg/mL
Etravirine (Intelence®)	100 mg tablets	Non-nucleoside reverse transcriptase inhibitor	Treatment of HIV-1 in patients with resistance to NNRTs and PIs	200 mg orally BID

FORMULARY DELETIONS

Delavirdine (Rescriptor®)	Removed due to lack of usage
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OTHER ACTION

Dexmedetomidine (Precedex®)	MAINTAIN current restrictions to HMC Neurosurgery for awake craniotomies, post-operative Parkinson's implant patients, and operating room (OR) and anesthesia services at both HMC and UWMC, and expand usage to pediatric ICU patients who are followed by the Neurosurgery, Neuro-Critical Care Intensivists, and/or Pediatric Intensivists.
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