

Aspirin-Induced Asthma

Laszlo T. Vaszar¹* and Donald D. Stevenson²

¹Stanford University School of Medicine, Division of Pulmonary & Critical Care Medicine, 300 Pasteur Drive, Stanford, CA 94305; and ²Division of Allergy, Asthma and Immunology, Scripps Clinic Medical Group, Inc., 10666 North Torrey Pines Rd., La Jolla, CA 92037

Introduction

Aspirin-induced asthma (AIA) is an inflammatory disease of the respiratory tract in which bronchospasm and naso-ocular reactions (*see* Table 1) occur after ingestion of aspirin (1–3). Naso-ocular reactions and bronchospasm occur within 30–180 min after ingestion of aspirin and are dose-dependent. Small doses of ASA produce small reactions but full therapeutic dose of ASA (650 mg) usually induces severe and difficult to reverse asthma, leading to anaphylaxis in few cases (1).

Epidemiology

An estimated 15–20% of adult asthmatics, and up to 40% of asthma patient with nasal polyps and sinusitis are affected by AIA (2,4). In a study of 35 consecutive cases of life-threatening asthma requiring mechanical ventilation nine patients (26%) experienced a sudden unexpected deterioration and five of the nine (14% of total, 55% of the sudden decline group) had ingested aspirin prior to their the asthma attack and admission to the hospital (5). In a retrospective study of 147 patients that required emergent mechanical ventilation for near-fatal asthma, 25% turned out to have AIA (6).

The typical patient is female, in 57–70% of cases (1,2,7–10), in her third or fourth decade of life (11). AIA is rare in children and is rarely found in other family members (2,12).

*Author to whom all correspondence and reprint requests should be addressed.

Table 1
Frequency of Symptoms Following Aspirin Ingestion

Symptoms	Frequency (%)
Dyspnea	84
Rhinorrhea and nasal congestion	96
Urticaria	21
Rash	19
Tearing	92
Angioedema	9
Anaphylactic shock ^a	4

^a Diagnostic criteria unclear; includes self-reported episodes of loss of conscience.
Adapted from ref. (10).

Table 2
NSAIDS that Cross-React with Aspirin in Causing Respiratory Reactions

Generic name	Brand name
Piroxicam	Feldene
Indomethacin	Indocin
Sulindac	Clinoril
Tolmetin	Tolectin
Ibuprophen	Motrin, Advil, Rufen
Naproxen (Naproxen sodium)	Naprosyn (Aleve, Anaprox)
Fenoprofen	Nalfon
Meclofenamate	Meclomen
Mefenamic acid	Ponstel
Flurbiprofen	Ansaid
Diflunisal	Dolobid
Ketoprophen	Orudis, Oruval
Diclofenac	Voltaren
Ketorolac	Toradol
Etodolac	Lodine
Nabumetone	Relafen
Oxaprozine	Daypro

Adapted from ref. (2).

Pathogenesis

Attempts to identify an antigen antibody-reaction as a mechanistic explanation for AIA respiratory disease or the reaction to ASA have failed. Skin testing with lysine-aspirin has consistently yielded negative results in these asthmatics (13).

The common denominator of different drugs (*see* Table 2) that cross-react with ASA in AIA patients appears to be related to the inhibition of cyclooxygenase (COX), which also explains how aspirin and

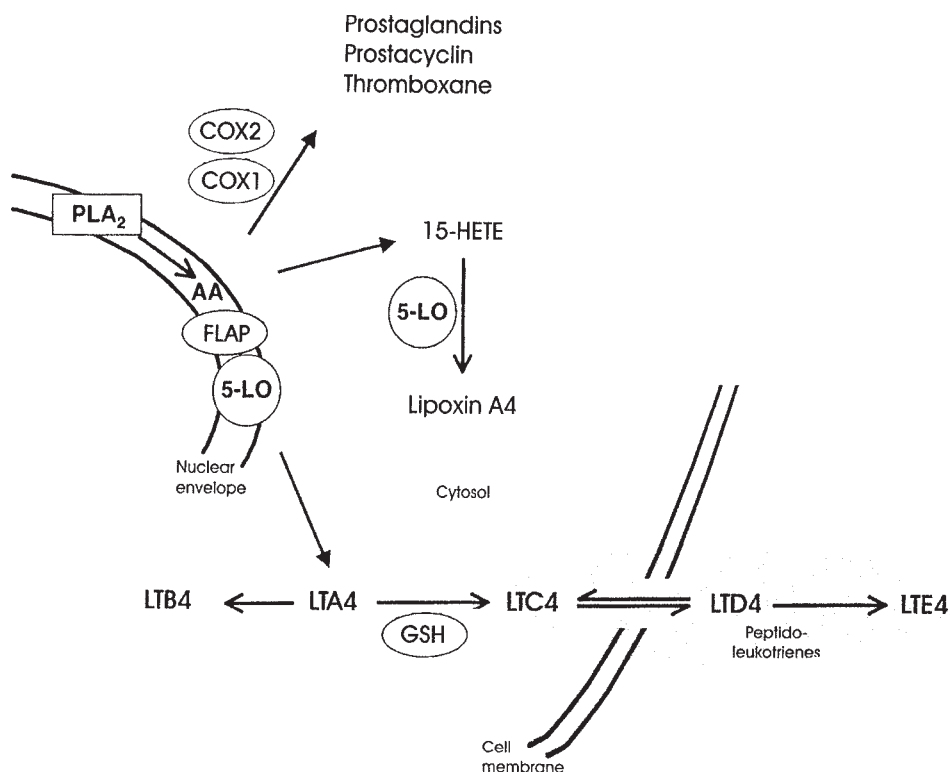


Fig. 1. The arachidonic acid cascade (GSH, reduced glutathione; PLA₂, phospholipase A₂).

the other nonsteroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory and analgesic effects (14). AIA disease appears to be an intense eosinophilic inflammatory disorder of the nasal, sinus, and bronchial tissues. Infiltration of the respiratory mucosa with eosinophils and mast cells is intense and mediators of these cells are likely to be responsible for both the ongoing inflammation and the respiratory reactions that are activated by ASA and NSAIDs. Leukotrienes (LTs) are found in the urine in high concentrations at baseline, before ingestion of ASA. After ingestion of ASA, large amounts of LTs are formed and can be measured in the urine (14).

Leukotrienes in AIA

Arachidonic acid (AA) is one of the essential fatty acids and is released from membrane phospholipids by the activation of membrane Phospholipase-A₂. The products of AA metabolism (TX, LT, and PG) are known collectively as eicosanoids. (Fig. 1). Different functional pools of AA exist within a cell type and the subset of AA released from nuclear envelope phospholipids is bound by FLAP, an integral nuclear

envelope protein and is subsequently processed by 5-LO. The compartmentalization of 5-LO and the co-localization of cytosolic 5-LO and FLAP on the nuclear envelope are dynamically regulated processes that are key determinants of LT synthesis (18).

The increased LT production in stable and exacerbated AIA is demonstrated by increased elimination into urine, bronchoalveolar lavage (BAL), and nasal lavage fluids. Measuring LT levels in human biological fluids *in vivo* is important both in terms of elucidating the pathophysiology of AIA and to assess the effectiveness of therapeutic interventions (24).

Although BAL (25,26), and nasal secretions (27,28) levels were also studied, most data involve measurement of LT levels in the urine, a fluid that is the final pathway of elimination for much of the total body LT pool, does not require invasive methodologies for collection, is essentially free of cells (and hence of interference from *ex vivo* production) and has a stable metabolite (LTE4) that can be quantified by well-described, sensitive immunological techniques (24).

Several studies have documented that resting urinary LTE4 is significantly higher in AIA patients compared with aspirin tolerant asthma patients (29,30), and ingestion of aspirin led to a further 3.6–4-fold increase in urinary LTE4 levels after aspirin, but not placebo, challenge in aspirin-sensitive asthma patient subjects that was not seen in the control asthmatics (29,31). Inhalation of lysine-aspirin also leads to increases in urinary LTE4 (32,33). The elevated urinary LTE4 level returned to the prechallenge levels in 4–6 h (33).

It appears that the urinary excretion (as a marker of production) of LT does not correlate with clinical response to aspirin, and cannot therefore be used to titrate or anticipate the severity of the clinical presentation. Thus the measurement of LTE4 did not predict the extent of bronchial hyperresponsiveness or degree of airflow obstruction in a study of AIA patients compared to normal subjects and aspirin-tolerant asthma patients (30). In the AIA group there was no relationship between urinary LTE4 and PD20 (the provocative dose producing a 20% fall in the FEV1), or between urinary LTE4 and baseline forced expiratory volume in one second (FEV1), expressed as percent of the predicted (30). In another study, the degree of increase for individual patients did not correlate with the degree of bronchospasm or inhibition of platelet thromboxane B2 formation (31).

Studies of nasal lavage fluids (27,28) added credence to the concept of LT and histamine contributing to the naso-ocular and bronchospastic symptoms characteristic of reactions to aspirin with their findings of increased levels of LTC4 and histamine in nasal lavage fluids of symptomatic AIA patients who also demonstrated a significant decreases in the FEV1 in response to challenge with aspirin.

Despite evidence implicating LTs in the pathogenesis of AIA, the exact mechanism of dysregulation remains unknown, and is the subject of several hypotheses.

The shunting hypothesis, proposes that AA metabolites are shunted from the COX pathway onto the 5-LO pathway resulting in preferential synthesis of LTs. However intuitive, this proposition is refuted by several lines of evidence. First, no decrease in PGE₂ was noted at the small doses of aspirin required to induce symptoms (60–150 mg) (11). Second, the absence of a correlation between the measured levels of LTs in the urine and the degree of bronchospasm, or inhibition of platelet thromboxane B₂ formation, makes it unlikely that a direct “shunting” of arachidonate into LT synthesis represents the mechanism of aspirin-induced asthma (31,39).

The target-organ sensitivity hypothesis states that in affected individuals end organs demonstrate an exaggerated response to products of the 5-LO pathway. A prototypical experimental proof for this hypothesis is the finding of significantly higher airway reactivity to LTE₄ in patients with AIA compared with aspirin tolerant asthma patients, despite comparable airway histamine responses (40).

According to the COX-2 hypothesis (41), in AIA patients COX-2 predominates and is modified by aspirin to produce 15-HETE, normally a 15-LO product. The airway epithelium appears to be the major source of 15-HETE in the human lung and significantly higher levels of 15-HETE are present in specimens of asthma patients compared with normal controls, raising the possibility that 15-HETE is involved in airway inflammation (42). The production of PGs and TX is blocked by aspirin. Further, experimental evidence suggests that 15-HETE is metabolized by leukocyte 5-LO to 15-epilipoxins (43), a novel class of metabolites with a role that still awaits clarification (41). Recent evidence (44) does indeed implicate inadequate COX-2 regulation in the pathogenesis of AIA/rhinitis even though COX-2 levels were lower in AIA subjects in that study compared with aspirin-induced asthma/rhinitis patients. Further investigations are needed to decide the merit of the COX-2 hypothesis.

Genetics

The genetic mechanisms of AIA have so far eluded understanding, with only a few families having been described as presenting with this non-Mendelian, low-inheritance syndrome (12). Previous studies have suggested associations of human lymphocyte antigens (HLA), A, B, and C loci antigens with specific subgroups of asthma. DR antigen typing applied to AIA patients showed no statistically significant increase in any known DR antigen nor any correlation with A or B locus typing (45).

Site-directed mutagenic studies of LTC₄-synthase have identified two critical residues necessary for the specific conjugation of LTA₄ to reduced glutathione. This observation, as well as the limited cellular distribution, and chromosomal localization are consistent with LTC₄-synthase as a candidate gene for asthma, having diverged from its other gene family members. More specifically, profound overexpression of LTC₄-synthase in aspirin-induced asthma seems to be a principal determinant of the respiratory reactions to aspirin, and a single-nucleotide polymorphism in the 5' regulatory region associates significantly with the aspirin-intolerant phenotype in Polish patients. On the surface, these data support a gene for LTC₄-synthase as a candidate to explain why AIA asthmatics synthesize more LTs than other asthmatics or normals. Unfortunately, the single nucleotide polymorphism in the 5' region is found in normals and non-ASA sensitive asthmatics. Furthermore, when a more heterogeneous American population of ASA induced asthmatics was investigated (Penrose, J. F., study in submission), there was no difference in the appearance of the single nucleotide polymorphism in ASA sensitive, nonsensitive and normals controls. Interpretation of these data are difficult to resolve but open the intriguing possibility that ASA respiratory disease is the phenotypic expression of many gene abnormalities. Because there are multiple enzymatic steps leading to the synthesis of LTs, there are multiple opportunities for abnormal gene expression either in the enzyme gene itself or the proximate promoter genes. Further studies of gene regulation will likely contribute to our understanding of the LTC₄-synthase gene, as well as other candidate genes as potentially responsible for the allergic inflammation underlying AIA (46).

Further evidence could emerge from the recent finding in AIA patients of a family of mutations in the G + C-rich transcription factor binding regions of the 5-LO gene consisting of the deletion of one, deletion of two, or addition of one zinc finger (Sp1/Egr-1) binding sites in the region 176 to 147 bp upstream from the ATG translation start site where there are normally 5 Sp1 binding motifs in tandem (47).

Clinical Presentation and Course

In the 365 patients enrolled in the Aspirin-induced Asthma Network in Europe (AIANE) symptoms of rhinosinusitis appeared at the mean age of 30 yr, followed about two yr later by bronchial asthma, and three more years later aspirin-intolerance was noted (10). A significant proportion of their patients suffered from severe asthma, although recent evidence points to subtle individual variability along a spectrum of severity in response to equivalent provoking doses of aspirin (39).

Nineteen to twenty-two percent of patients were also atopic (10,11,48) and there is no reason to believe atopy is required or co-linked to AIA. A family history of NSAIDs intolerance was present in 5% of patients, and consisted mostly of rhinitis symptoms after ASA ingestion (10).

Identified or reported nasal polyps were present in 58% of the AIANE patients (10), with other authors reporting incidences of 36–77% (4,9,50). However, the diagnostic rigor with which polyp identification is pursued is a critical variable from one study to another. Also, the point in time of the investigation will also determine the presence of polyps. Most experts think that it is unlikely that AIA patients will go through their entire course of illness without forming nasal polyps. Multiple polypectomies are common in AIA (9,50), and 41% of the AIANE patients had 1–5 such operations (10).

In the 12 mo preceding their registration into the AIANE database 10% of the patients were hospitalized, mostly once or twice because of exacerbations of bronchial asthma (10), but the prognosis in AIA appeared to be no different from aspirin-tolerant asthma patients in a 17-yr prospective study (51).

Diagnosis

Aspirin provocation tests are necessary to establish the diagnosis of AIA even in patients exhibiting the appropriate clinical presentation (asthma with relapsing nasal polyps and chronic sinusitis), given that two-thirds of patients with a typical clinical profile are not sensitive to aspirin or NSAIDs during challenge (2). Currently in the United States only the oral aspirin challenges (53) are clinically available, and their detailed protocols are described elsewhere (2). Given the possibility of severe bronchospasm and nasal, cutaneous, and GI side effects with the challenge, physicians performing these tests should be experienced with them and be prepared to aggressively treat the accompanying complications (2).

Inhalation challenge with L-lysine acetylsalicylic acid is routinely performed in Europe and other parts of the world and is discussed here briefly (54–56). It was found to be easy to interpret and to control, even in severely asthmatic patients, with symptoms restricted to the bronchial system. (57,58). It is not clear whether L-lysine aspirin inhalation induces late asthmatic reactions (59).

Management

Once the diagnosis is established avoidance of triggering NSAIDs should naturally be emphasized. Given the rarity of true AIA and the

genuine utility of NSAIDs in the treatment of common conditions, the diagnosis of AIA should be rigorously established, lest the burden of NSAID avoidance be inappropriately placed on a patient with AIA. More specific management choices include the novel LT blockers, in addition to classic asthma medications (glucocorticoids, beta agonists) and cromolyn.

Blockade of 5-LO: Zileuton

The enzyme 5-LO contains a nonheme iron in the ferrous (2+) state, which is converted to ferric (3+) form upon activation of the enzyme and its translocation to the nuclear membrane. Zileuton is a "redox inhibitor" that blocks this conversion of the iron atom (60). Several studies have investigated the ability of zileuton to block ASA-induced respiratory reactions. Thus, zileuton provides partial inhibition of the airway response to oral aspirin (61), and in a double-blind, crossover trial zileuton prevented the fall in FEV1, but it did not improve the baseline, pre-aspirin FEV1 (34). Treatment with zileuton also prevented the development of nasal, gastrointestinal, and dermal symptoms in response to the same provoking dose of ASA, but doses that were higher than the provoking doses were not used (34,86). Doses of ASA above threshold dose (usually 30–60 mg of ASA) are not blocked by zileuton. In other words, it is not safe to take ASA in usual therapeutic doses if one is taking the "blocker" zileuton.

The potential for zileuton to treat aspirin respiratory disease was the subject of a large double-blind, placebo-controlled, crossover study (62) of six wk of treatment with zileuton (600 mg, four times daily). There was an increased baseline FEV1 in the treatment group as well as higher morning and evening peak expiratory flow rate (PEFR) values on zileuton compared with placebo. Zileuton also diminished nasal dysfunction, one of the cardinal signs of AIA, causing the return of smell, less rhinorrhea, and a trend for less stuffiness and higher nasal inspiratory flow during treatment. Zileuton also caused a small but distinct reduction of bronchial hyper-responsiveness to histamine. Treatment inhibited urinary excretion of LTE4 but did not change airway reactivity to inhaled LTD4, supporting the contention that zileuton specifically inhibited LT biosynthesis. That study suggested that the addition of a LT pathway inhibitor such as zileuton may yield a better control of AIA than what is achieved by treatment with medium to high doses of glucocorticosteroids alone (62).

LT Receptor Blockade: Montelukast, Pranlukast, Zafirlukast

AIA is the most LT-dependent model of asthma and as such is the most suitable to evaluate the effect of antileukotriene treatment in

asthma (60). A double-blind, randomized, crossover study of 16 adults with mild or moderate AIA subjected to inhalation of methacholine and sulpyrine demonstrated that pranlukast protected against NSAID-induced bronchoconstriction through mechanisms that were related to the improvement both of bronchial hyperresponsiveness and hypersensitivity to NSAID, without effecting the urinary excretion of LTE₄ (63).

In a double-blind, randomized, crossover study of basal airway function in eight asthmatic patients with documented aspirin intolerance, the leukotriene receptor antagonist verlukast (MK-0679) caused bronchodilation, which lasted for at least nine h, with an average peak improvement in FEV₁ of 18% above the predrug baseline. This effect was found to correlate strongly with the severity of asthma and aspirin sensitivity (64). The evaluation of verlukast was however halted after phase II clinical trials noted the presence of liver dysfunction in some patients (60).

A study of the effect of inhalation of the LTD₄ antagonist SK&F 104353 on the response to aspirin ingestion found a partial response, ranging from 43–74% in five of six subjects. In the remaining subject, there was no effect of the drug on the asthmatic response. The variability in protection may suggest additional mechanisms eliciting AIA (11,65).

Churg-Strauss syndrome (CSS) was described in association with both zafirlukast but also montelukast, a new LT receptor antagonist with a different molecular structure than zafirlukast, suggesting that the occurrence of CSS in asthmatic patients receiving LT modifiers appears to be related to unmasking of a previously existing vasculitic syndrome due to corticosteroid withdrawal and not from a direct drug effect (66).

Despite preliminary evidence to suggest that antileukotriene drugs provide additional anti-inflammatory effects in patients taking inhaled steroids (37,67), it is not yet clear if their major role is as bronchodilators or steroid-sparing anti-inflammatory medications (60).

Glucocorticoids

Glucocorticosteroids are widely used in the treatment of asthma, including AIA, as evidenced by the fact that in the 12 mo preceding their registration into the AIANE database 79% of patients were treated with inhaled steroids, 51% required oral steroids, and 20% were treated with intravenous steroids (10). Despite this widespread use, their mechanism of action is unknown. Recently, inhibition of AA metabolism has been suggested as one possible mechanism of action. High doses of systemic steroids have little effect on arachidonic acid metabo-

lism in normal nonasthmatic humans, although inhaled budesonide does reduce AA metabolism in circulating monocytes, presumably by affecting these cells during their passage through the lung (36).

Intranasal fluticasone is an effective therapy for chronic eosinophilic rhinitis in patients with AIA, leading to decreased symptom scores, increased peak nasal inspiratory flows, and blunted response to aspirin nasal challenge (68).

A rational basis for chronic steroid use in AIA is provided by a double-blind, crossover study of 13 aspirin-sensitive asthmatics in whom a two-d pre-treatment with prednisone did not affect the response to aspirin challenges, whereas a 10-d pre-treatment with oral, inhaled, and intranasal steroids offered total clinical protection against bronchospasm produced by threshold doses of aspirin in five of eight patients, partial protection in other two patients and no protection in one (69).

Other Management Approaches

Inhaled salmeterol significantly attenuated the bronchoconstriction and the increase in urinary LTE₄ in response to inhaled lysine-aspirin, suggesting that it may be effective in the management of AIA (70). Acyclovir, an inhibitor of the DNA polymerase of the herpes virus, was found to protect against aspirin-induced attacks of asthma through mechanisms unrelated to its bronchodilator property but related to the improvement of bronchial hypersensitivity to sulphydryl. Maximum levels of urinary LTE₄ in the treatment group of this double-blind, randomized, crossover study was significantly lower than that in controls, leading the authors to speculate that it probably acts by inhibiting the release of cysteinyl LTs (71). Similar results and conclusions are reported by the same group with inhaled cromolyn sodium (72). Sodium cromoglycate and nedocromil sodium are equally effective in attenuating aspirin-induced bronchoconstriction (73). These studies nuance the results of earlier trials in which slight but significant improvements in FEV₁ and FEF of 25–75% were noted without changes in the peak expiratory flow rate, the symptoms of asthma, the doses of additional medication, or the index of disability (74). The PGE₁ analog misoprostol did not significantly improve asthma control in a double-blind, crossover, randomized, placebo-controlled study of 17 AIA patients over six wk, although it did reduce the rhinorrhea score (75).

Desensitization

All patients with aspirin sensitive respiratory disease can be desensitized to aspirin by oral administration of increasing doses of

aspirin. Once desensitized and treated with daily high-dose ASA (650 mg BID), improvement in both asthma and nasal disease occurs in the majority of these patients (76,77). The results proved lasting in a prospective study of 65 patients desensitized, then treated daily with aspirin for one to six yr (mean, 3.1 yr) (78). Furthermore, a reduction of systemic corticosteroids became possible with ASA desensitization followed by long-term daily ASA treatment (79).

A retrospective study of desensitization analyses of baselines revealed that both continuous and discontinued groups during ASA treatment demonstrated statistically significant reduction in number of hospitalizations per year, emergency room visits per year, outpatient visits per year, upper respiratory infections-sinusitis-antibiotics per year, need for nasal polypectomies and additional sinus operations, and improvement in the sense of smell compared to the control group. Simultaneously, the ASA-treatment groups were able to significantly reduce systemic corticosteroid dosage, the number of corticosteroid bursts per year, and, in the continuous group only, significantly reduce inhaled corticosteroids (79).

The mechanisms of desensitization remain to be elucidated but appear to be distinct from a direct effect on LT synthesis (39). For example, a study of aspirin-induced leukotriene release following aspirin desensitization found that although there was significantly less aspirin-induced LTE₄ excretion after desensitization, substantial amounts of LTE₄ were still produced without any significant change in lung function (80).

A study of target-organ responsiveness to LTE₄ found a marked decrease of responsiveness after desensitization to aspirin, prompting the authors to speculate that the efficacy of desensitization may relate in part to a selective downregulation of LTE₄ receptors within the airways (40).

Selective Inhibition of COX-2

When the need for pain control or antiinflammatory medications arises in an AIA patient, acetaminophen, a weak inhibitor of COX can be used safely, provided that the dose does not exceed 1000 mg, a level beyond which cross reactivity with aspirin has been documented to occur frequently (34%), albeit consisting of mild reactions only (81).

Nimesulide, a selective COX-2 inhibitor is generally well-tolerated by NSAID-intolerant patients and patients with AIA (82). In a single-blind, placebo-controlled, oral challenge of 60 AIA adults, 55 (91.7%) tolerated nimesulide with no adverse reaction. Five (8.3%) patients responded to the oral challenge with urticaria/angioedema in three patients, mild rhinitis in one patient, and mild dyspnea in one patient

(83). In another study of 150 AIA patients nimesulide and high doses of acetaminophen (2 g) provoked reactions in 9/101 patients (8.9%) (84). Similar levels of tolerance are reported with other selective COX-2 inhibitors: meloxicam, etodolac, and celecoxib. (85). We have now challenged 37 consecutive aspirin-sensitive asthmatics with celecoxib and 60 with rofecoxib and none reacted (unreported studies). From the preliminary data, it appears that inhibition of COX-1 is an important step in initiating the reactions of AIA and that COX-2 inhibition does not lead to respiratory reactions.

Conclusions

The typical clinical presentation of AIA is that of a middle-aged asthmatic with recurrent nasal polyps and secondary chronic sinusitis. Nevertheless, only one-third of patients with this presentation have a positive aspirin-challenge test (2). Their prognosis is no different than that in aspirin-tolerant asthma. Mechanistically, the COX response to ASA is altered in AIA through an unknown mechanism, leading to an etiologic role for PepLTs and opportunities for therapeutic interventions with LT blockade and aspirin desensitization. These therapeutic interventions provide varying but incomplete degrees of protection in this interesting syndrome.

Reference

1. Samter, M., and Beers, Jr., R. F. (1968) Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann. of Int. Med.* **68**(5); 975–983.
2. Stevenson, D. D. and Simon, R. A. (1998) Sensitivity to aspirin and nonsteroidal antiinflammatory drugs, in *Allergy. Principles and Practice*, 5th ed. Middleton, J., Ellis, E. F., Yunginger, J. W., Reed, C. E., and Adkinson, Jr., N. F. eds. Mosby, St. Louis, MO, pp. 1225–1234.
3. Szczeklik, A., Gryglewski, R. J., and Vane, J. R. (1998) *Eicosanoids, Aspirin and Asthma*. Marcel Dekker, New York.
4. Chafee, F. H., Settipane, G. A., and Klein, D. E. (1974) Aspirin intolerance. I. Frequency in an allergic population. *J. Allergy Clin. Immunol.* **53**(4); 193–199.
5. Bellomo, R., McLaughlin, P., Tai, E., and Parkin, G. (1994) Asthma requiring mechanical ventilation. A low morbidity approach. *Chest* **105**(3); 891–896.
6. Marquette, C. H., Saulnier, F., Leroy, O., Wallaert, B., Chopin, C., Demarcq, J. M., et al. (1992) Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near- fatal attack of asthma. *Am. Rev. Respir. Dis.* **146**(1); 76–81.
7. Settipane, G. A., Chafee, F. H., and Klein, D. E. (1974) Aspirin intolerance. II. A prospective study in an atopic and normal population. *J. Allergy Clin. Immunol.* **53**(4); 200–204.
8. Pina, J., Barbado, A., Marques, D., Leitao, M. C., Duarte, C., Gomes, M. J., and Amaral-Marques, R. (1984) Our experience with acetylsalicylic acid hypersensitivity. *Allergol. et Immunopathol.* **12**(3); 217–223.
9. Ogino, S., Harada, T., Okawachi, I., Irifune, M., Matsunaga, T., and Nagano, T. (1986) Aspirin-induced asthma and nasal polyps. *Acta Oto-Laryngo*. (Suppl.)**430**; 21–27.

10. Nizankowska, E., Duplaga, M., Bochenek, G., and Szczeklik, A. (1998) Clinical course of aspirin-induced asthma. results of AIANE, in *Eicosanoids, Aspirin and Asthma, Lung Biology in Health and Disease*. Szczeklik, A., Gryglewski, R. J., and Vane, J. R., eds. Marcel Dekker, New York, pp. 451–472.
11. Lee, T. H., Smith, C. M., Arm, J. P., and Christie, P. E. (1991) Mediator release in aspirin-induced reactions. *J. Allergy Clin. Immunol.* **88**(6); 827–829.
12. Szczeklik, A., and Sanak, M. (2000) Genetic mechanisms in aspirin-induced asthma. *Am. J. Respir. Crit. Care Med.* **161**(2); S142–S146.
13. Szczeklik, A. and Stevenson, D. D. (1999) Aspirin-induced asthma: advances in pathogenesis and management. *J. Allergy Clin. Immunol.* **104**(1); 5–13.
14. Szczeklik, A. (1998) Mechanism of aspirin-induced asthma, in *Eicosanoids, Aspirin and Asthma, Lung Biology in Health and Disease*. Szczeklik, A., Gryglewski, R. J., and Vane, J. R., eds. Marcel Dekker, New York, pp. 299–315.
15. Lee, T. H. (1993) Mechanism of bronchospasm in aspirin-sensitive asthma. *Am. Rev. Respir. Dis.* **148**(6 Pt 1); 1442–1443.
16. Haeggstrom, J. Z. and Samuelsson, B. (1998) Overview of the 5-lipoxygenase pathway, in *Five-Lipoxygenase Products in Asthma, Lung Biology in Health and Disease*. Drazen, J. M., Dahlen, S.-E., and Lee, T. H., eds. Marcel Dekker, New York, pp. 1–10.
17. Murphy, R. C., Hammarstrom, S., and Samuelsson, B. (1979) Leukotriene C: a slow-reacting substance from murine mastocytoma cells. *Proc. Natl. Aca. USA* **76**(9); 4275–4279.
18. Peters-Golden, M. and Brock, T. G. (2000) Intracellular compartmentalization of leukotriene biosynthesis. *Am. J. Respir. Crit. Care Med.* **161**(2); S36–S40.
19. Mitchell, J. A., Akarasereenont, P., Thiemermann, C., Flower, R. J., and Vane, J. R. (1993) Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc. Natl. Acad. Sci. USA* **90**(24); 11,693–11,697.
20. Pavord, I. D. and Tattersfield, A. E. (1995) Bronchoprotective role for endogenous prostaglandin E₂. *Lancet* **345**(8947); 436–438.
21. Sousa, A., Pfister, R., Christie, P. E., Lane, S. J., Nasser, S. M., Schmitz-Schumann, M., and Lee, T. H. (1997) Enhanced expression of cyclo-oxygenase isoenzyme 2 (COX-2) in asthmatic airways and its cellular distribution in aspirin-sensitive asthma [see comments]. *Thorax* **52**(11); 940–945.
22. Vane, J. and Botting, R. (1987) Inflammation and the mechanism of action of anti-inflammatory drugs. *FASEB J.* **1**(2); 89–96.
23. Szczeklik, A., Gryglewski, R. J., and Czerniawska-Mysik, G. (1975) Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *BMJ* **1**(5949); 67–69.
24. Westcott, J. Y. and Taylor, I. K. (1998) Measurement of leukotrienes from human biological fluids, in *Five-Lipoxygenase Products in Asthma, Lung Biology in Health and Disease*. Drazen, J. M., Dahlen, S.-E., and Lee, T. H., eds. Marcel Dekker, New York, pp. 245–81.
25. Sladek, K., Dworski, R., Soja, J., Sheller, J. R., Nizankowska, E., Oates, J. A., and Szczeklik, A. (1994) Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. *Am. J. Respir. Crit. Care Med.* **149**(4 Pt 1); 940–946.
26. Szczeklik, A., Sladek, K., Dworski, R., Nizankowska, E., Soja, J., Sheller, J., and Oates, J. (1996) Bronchial aspirin challenge causes specific eicosanoid response in aspirin-sensitive asthmatics. *Am. J. Respir. Crit. Care Med.* **154**(6 Pt 1); 1608–1614.
27. Ferreri, N. R., Howland, W. C., Stevenson, D. D., and Spiegelberg, H. L. (1988) Release of leukotrienes, prostaglandins, and histamine into nasal secretions of

- aspirin-sensitive asthmatics during reaction to aspirin. *Am. Rev. Respir. Dis.* **137(4)**; 847–854.
28. Picado, C., Ramis, I., Rosello, J., Prat, J., Bulbena, O., Plaza, V., Montserrat, J. M., and Gelpi, E. (1992) Release of peptide leukotriene into nasal secretions after local instillation of aspirin in aspirin-sensitive asthmatic patients. *Am. Rev. Respir. Dis.* **145(1)**; 65–69.
 29. Christie, P. E., Tagari, P., Ford-Hutchinson, A. W., Charlessen, S., Chee, P., Arm, J. P., and Lee, T. H. (1991) Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am. Rev. Respir. Dis.* **143(5 Pt 1)**; 1025–1029.
 30. Smith, C. M., Hawksworth, R. J., Thien, F. C., Christie, P. E., and Lee, T. H. (1992) Urinary leukotriene E4 in bronchial asthma. *Eur. Respir. J.* **5(6)**; 693–699.
 31. Knapp, H. R., K. Sladek, and G. A. Fitzgerald. 1992. Increased excretion of leukotriene E4 during aspirin-induced asthma. *Journal of Laboratory & Clinical Medicine* **119(1)**; 48–51.
 32. Kumlin, M., Dahlen, B., Bjorck, T., Zetterstrom, O., Granstrom, E., and Dahlen, S. E. (1992) Urinary excretion of leukotriene E4 and 11-dehydro-thromboxane B2 in response to bronchial provocations with allergen, aspirin, leukotriene D4, and histamine in asthmatics. *Am. Rev. Respir. Dis.* **146(1)**; 96–103.
 33. Christie, P. E., Tagari, P., Ford-Hutchinson, A. W., Black, C., Markendorf, A., Schmitz-Schumann, M., and Lee, T. H. (1992) Urinary leukotriene E4 after lysine-aspirin inhalation in asthmatic subjects. *Am. Rev. Respir. Dis.* **146(6)**; 1531–1534.
 34. Israel, E., Fischer, A. R., Rosenberg, M. A., Lilly, C. M., Callery, J. C., Shapiro, J., Cohn, J., Rubin, P., and Drazen, J. M. (1993) The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am. Rev. Respir. Dis.* **148(6 Pt 1)**; 1447–1451.
 35. Sebaldt, R. J., Sheller, J. R., Oates, J. A., Roberts, L. J. D., and FitzGerald, G. A. (1990) Inhibition of eicosanoid biosynthesis by glucocorticoids in humans. *Proc. Natl. Acad. Sci. USA* **87(18)**; 6974–6978.
 36. Manso, G., Baker, A. J., Taylor, I. K., and Fuller, R. W. (1992) In vivo and in vitro effects of glucocorticosteroids on arachidonic acid metabolism and monocyte function in nonasthmatic humans. *Eur. Respir. J.* **5(6)**; 712–716.
 37. O'Shaughnessy, K. M., Wellings, R., Gillies, B., and Fuller, R. W. (1993) Differential effects of fluticasone propionate on allergen-evoked bronchoconstriction and increased urinary leukotriene E4 excretion [see comments]. *Am. Rev. Respir. Dis.* **147(6 Pt 1)**; 1472–1476.
 38. Dahlen, B. (2000) Treatment of aspirin-intolerant asthma with antileukotrienes. *Am. J. Respir. Crit. Care Med.* **161(2)**; S137–S141.
 39. Daffern, P. J., Muilenburg, D., Hugli, T. E., and Stevenson, D. D. (1999) Association of urinary leukotriene E4 excretion during aspirin challenges with severity of respiratory responses. *J. Allergy Clin. Immunol.* **104(3 Pt 1)**; 559–564.
 40. Arm, J. P., O'Hickey, S. P., Spur, B. W., and Lee, T. H. (1989) Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. *Am. Rev. Respir. Dis.* **140(1)**; 148–153.
 41. Mitchell, J. A. and Belvisi, M. G. (1997) Too many COX (cyclo-oxygenase) spoil the broth: aspirin-sensitive asthma and 5-lipoxygenase. *Thorax* **52(11)**; 933–935.
 42. Kumlin, M., Hamberg, M., Granstrom, E., Bjorck, T., Dahlen, B., Matsuda, H., Zetterstrom, O., and Dahlen, S. E. (1990) 15(S)-hydroxyeicosatetraenoic acid is the major arachidonic acid metabolite in human bronchi: association with airway epithelium. *Arch. Biochem. Biophys.* **282(2)**; 254–262.
 43. Claria, J. and Serhan, C. N. (1995) Aspirin triggers previously undescribed bioactive eicosanoids by human endothelial cell-leukocyte interactions. *Proc. Natl. Acad. Sci. USA* **92(21)**; 9475–9479.

44. Picado, C., Fernandez-Morata, J. C., Juan, M., Roca-Ferrer, J., Fuentes, M., Xaubet, A., and Mullol, J. (1999) Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. *Am. J. Respir. Crit. Care Med.* **160**(1); 291–296.
45. Jones, D. H., May, A. G., and Condemi, J. J. (1984) HLA DR typing of aspirin sensitive asthmatics. *Ann. Allergy* **52**(2); 87–89.
46. Penrose, J. F. and Baldasaro, M. H. (1999) Leukotriene C4 synthase: a candidate gene for the aspirin-intolerant asthmatic phenotype. *Allergy Asthma Proc.* **20**(6); 353–360.
47. In, K. H., Asano, K., Beier, D., Grobholz, J., Finn, P. W., Silverman, E. K., et al. (1997) Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. *J. Clin. Invest.* **99**(5); 1130–1137.
48. Bochenek, G., Nizankowska, E., and Szczeklik, A. (1996) The atopy trait in hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* **51**(1); 16–23.
49. Giraldo, B., Blumenthal, M. N., and Spink, W. W. (1969) Aspirin intolerance and asthma. A clinical and immunological study. *Ann. Int. Med.* **71**(3); 479–496.
50. Grzelewska-Rzymowska, I., Rozniecki, J., Szmidt, M., and Kowalski, M. L. (1981) Asthma with aspirin intolerance. Clinical entity or coincidence of non-specific bronchial hyperreactivity and aspirin intolerance. *Allerg. Immunopathol.* **9**(6); 533–538.
51. Speer, F., Denison, T. R., and Baptist, J. E. (1981) Aspirin allergy. *Ann. Allergy* **46**(3); 123–126.
52. Picado, C., Castillo, J. A., Montserrat, J. M., and Agusti-Vidal, A. (1989) Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eu. Respir. J.* **2**(2); 127–129.
53. McDonald, J. R., Mathison, D. A., and Stevenson, D. D. (1972) Aspirin intolerance in asthma. Detection by oral challenge. *J. Allergy Clin. Immunol.* **50**(4); 198–207.
54. Bianco, S., Robuschi, M., and Petrigni, G. (1977) Aspirin induced tolerance in aspirin-asthma detected by a new challenge test. *IRCS J. Med. Sci.* **5**; 129–136.
55. Phillips, G. D., Foord, R., and Holgate, S. T. (1989) Inhaled lysine-aspirin as a bronchoprovocation procedure in aspirin-sensitive asthma: its repeatability, absence of a late-phase reaction, and the role of histamine. *J. Allergy Clin. Immunol.* **84**(2); 232–241.
56. Melillo, G., Padovano, A., Cocco, G., and Masi, C. (1993) Dosimeter inhalation test with lysine acetylsalicylate for the detection of aspirin-induced asthma. *Ann. Allergy* **71**(1); 61–65.
57. Dahlen, B. and Zetterstrom, O. (1990) Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. *Eur. Respir. J.* **3**(5); 527–534.
58. Dahlen, B. (2000) Treatment of Aspirin-intolerant Asthma with Antileukotrienes. *Am. J. Respir. Crit. Care Med.* **161**(2); S137–S141.
59. Park, H. S. (1995) Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients. *Clin. Exp. Allergy* **25**(1); 38–40.
60. Shuaib Nasser, S. M. and Lee, T. H. (1998) Cysteinyl-leukotriene receptor antagonism and -lipoxygenase inhibition in asthma, in *Five-Lipoxygenase Products in Asthma, Lung Biology in Health and Disease*. Drazen, J. M., Dahlen, S.-E., and Lee, T. H., eds. Marcel Dekker, New York, pp. 283–306.
61. Dahlen, B. and Dahlen, S. E. (1995) Leukotrienes as mediators of airway obstruction and inflammation in asthma. *Clin. Exp. Allergy* **25**(Suppl)2; 50–54.

62. Dahlen, B., Nizankowska, E., Szczeklik, A., Zetterstrom, O., Bochenek, G., Kumlin, M., et al. (1998) Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am. J. Respir. Crit. Care Med.* **157**(4 Pt 1); 1187–1194.
63. Yoshida, S., Sakamoto, H., Ishizaki, Y., Onuma, K., Shoji, T., Nakagawa, H., et al. (2000) Efficacy of leukotriene receptor antagonist in bronchial hyper-responsiveness and hypersensitivity to analgesic in aspirin-intolerant asthma [In Process Citation]. *Clin. Exp. Allergy* **30**(1); 64–70.
64. Dahlen, B., Margolskee, D. J., Zetterstrom, O., and Dahlen, S. E. (1993) Effect of the leukotriene receptor antagonist MK-0679 on baseline pulmonary function in aspirin sensitive asthmatic subjects [see comments]. *Thorax* **48**(12); 1205–1210.
65. Christie, P. E., Smith, C. M., and Lee, T. H. (1991) The potent and selective sulfidopeptide leukotriene antagonist, SK&F 104353, inhibits aspirin-induced asthma. *Am. Rev. Respir. Dis.* **144**(4); 957–958.
66. Wechsler, M. E., Finn, D., Gunawardena, D., Westlake, R., Barker, A., Haranath, S. P., et al. (2000) Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* **117**(3); 708–713.
67. Dworski, R., Fitzgerald, G. A., Oates, J. A., and Sheller, J. R. (1994) Effect of oral prednisone on airway inflammatory mediators in atopic asthma. *Am. J. Respir. Crit. Care Med.* **149**(4 Pt 1); 953–959.
68. Mastalerz, L., Milewski, M., Duplaga, M., Nizankowska, E., and Szczeklik, A. (1997) Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* **52**(9); 895–900.
69. Nizankowska, E. and Szczeklik, A. (1989) Glucocorticosteroids attenuate aspirin-precipitated adverse reactions in aspirin-intolerant patients with asthma. *Ann. Allergy* **63**(2); 159–162.
70. Szczeklik, A., Dworski, R., Mastalerz, L., Prokop, A., Sheller, J. R., Nizankowska, E., et al. (1998) Salmeterol prevents aspirin-induced attacks of asthma and interferes with eicosanoid metabolism. *Am. J. Respir. Crit. Care Med.* **158**(4); 1168–1172.
71. Yoshida, S., Sakamoto, H., Yamawaki, Y., Shoji, T., Akahori, K., Onuma, K., et al. (1998) Effect of acyclovir on bronchoconstriction and urinary leukotriene E4 excretion in aspirin-induced asthma. *J. Allergy Clin. Immunol.* **102**(6 Pt 1); 909–914.
72. Yoshida, S., Amayasu, H., Sakamoto, H., Onuma, K., Shoji, T., Nakagawa, H., and Tajima, T. (1998) Cromolyn sodium prevents bronchoconstriction and urinary LTE4 excretion in aspirin-induced asthma. *Ann. Allergy Asthma Immunol.* **80**(2); 171–176.
73. Robuschi, M., Gambaro, G., Sestini, P., Pieroni, M. G., Refini, R. M., Vaghi, A., and Bianco, S. (1997) Attenuation of aspirin-induced bronchoconstriction by sodium cromoglycate and nedocromil sodium. *Am. J. Respir. Crit. Care Med.* **155**(4); 1461–1464.
74. Gwin, E., Kerby, G. R., and Ruth, W. E. (1977) Cromolyn sodium in the treatment of asthma associated with aspirin hypersensitivity and nasal polyps. *Chest* **72**(2); 148–153.
75. Wasiak, W. and Szmidt, M. (1999) A six week double blind, placebo controlled, crossover study of the effect of misoprostol in the treatment of aspirin sensitive asthma. *Thorax* **54**(10); 900–904.
76. Stevenson, D. D. (1986) Aspirin desensitization. *N. Engl. Regional Allergy Pro.* **7**(2); 101–104.
77. Stevenson, D. D. (1992) Commentary: the American experience with aspirin desensitization for aspirin-sensitive rhinosinusitis and asthma. *Allergy Proc.* **13**(4); 185–192.

78. Stevenson, D. D., Hankammer, M. A., Mathison, D. A., Christiansen, S. C., and Simon, R. A. (1996) Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J. Allergy Clin. Immunol.* **98(4)**; 751–758.
79. Sweet, J. M., Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1990) Long-term effects of aspirin desensitization—treatment for aspirin-sensitive rhinosinusitis-asthma. *J. Allergy Clin. Immunol.* **85(1 Pt 1)**; 59–65.
80. Nasser, S. M., Patel, M., Bell, G. S., and Lee, T. H. (1995) The effect of aspirin desensitization on urinary leukotriene E4 concentrations in aspirin-sensitive asthma. *Am. J. Respir. Crit. Care Med.* **151(5)**; 1326–1330.
81. Settipane, R. A., Schrank, P. J., Simon, R. A., Mathison, D. A., Christiansen, S. C., and Stevenson, D. D. (1995) Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J. Allergy Clin. Immunol.* **96(4)**; 480–485.
82. Senna, G. E., Passalacqua, G., Andri, G., Dama, A. R., Albano, M., Fregonese, L., and Andri, L. (1996) Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* **14(2)**; 94–103.
83. Bavbek, S., Celik, G., Ediger, D., Mungan, D., Demirel, Y. S., and Misirligil, Z. (1999) The use of nimesulide in patients with acetylsalicylic acid and nonsteroidal anti-inflammatory drug intolerance. *J. Asthma* **36(8)**; 657–663.
84. Giuseppe, P., Antonino, R., Alessandro, D. B., Donato, Q., Marina, D. F., Donatella, P., Francesca, G., and Alberto, V. (1997) Floctafenine: a valid alternative in patients with adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann. Allergy Asthma Immunol.* **78(1)**; 74–78.
85. van Ryn, J. and Pairet M. (1999) Clinical experience with cyclooxygenase-2 inhibitors. *Inflammation Res.* **48(5)**; 247–254.
86. Pauls, J. D., Simon, R. A., Daffer, P. J., and Stevenson, D.D. (2000) Lack of effect of the 5-LO inhibitor zileuton in blocking oral aspirin challenges in aspirin sensitive asthmatics. *Ann. Allergy Asthma Immunol.*, **85(1)**; 40–45.