

Medications as asthma triggers

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Of all the identifiable asthma triggers, drugs or medications probably comprise a minority, yet they can occur with grave consequences [1]. Aspirin (acetylsalicylic acid, ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for a vast majority, and other agents, such as β -blockers, angiotensin-converting enzyme (ACE) inhibitors, cholinergic agonists, cholinomimetic alkaloids, chemotherapeutic agents, diuretics, corticosteroids, antibiotics, radio-contrast, neuromuscular, and anesthetic agents have been reported to cause bronchospasm or mimic asthma [1]. Most of the agents inducing respiratory reactions also cause multisystemic manifestations. There are a number of pharmacologic stimuli directly or indirectly causing bronchial responsiveness, such as acetylcholine, methacholine, carbachol, histamine, prostaglandin (PG) D_2 , leukotriene (LT) $C_4/D_4/E_4$, adenosine, tachykinins, bradykinin, metabisulfite/ SO_2 , and propranolol [2]. This article focuses on the common medications intended to provide “beneficial pharmacologic and medical effect” that have the potential to cause a distinct respiratory reaction in mostly susceptible individuals due to various mechanisms versus drugs that cause multisystemic adverse reactions. The three main groups are ASA/NSAIDs, β -blockers, and ACE inhibitors.

Aspirin and nonsteroidal anti-inflammatory drugs

Although willow bark had been used for centuries for its curative properties such as antipyresis, salicin as its active ingredient was first isolated in its pure form in the eighteenth century. Chemical manipulations to prepare acetylsalicylic

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acid (ASA) followed for many years before it was formally introduced as “aspirin” in the medical literature in 1899 [3]. Although there had been anecdotal reports of angioedema, urticaria, and bronchospastic reactions associated with ASA almost a hundred years after salicin was first isolated and only 3 years after the drug was first synthesized, the first description of a clinically distinct syndrome of ASA sensitivity, asthma, and nasal polyposis was published in 1922 [4,5]. It had taken many more years before the triad became a popular clinical entity recognized by Samter and Beers in 1968 [5]. Cellular, molecular, and genetic mechanisms have been elucidated in the last two decades.

NSAIDs, including ASA, are commonly used for relief of inflammation, fever, and pain. The chronic use of ASA has gained popularity because of evidence of its protective effect for cardiovascular disease and colorectal adenomas and carcinomas. Most individuals are able to use NSAIDs/ASA without developing adverse reactions, but a substantial minority develop a specific clinical syndrome characterized by a persistent inflammatory disease of the airways preceding manifestations of ASA sensitivity, labeled as ASA-exacerbated respiratory disease (AERD), more popularly recognized as ASA-induced or ASA-intolerant asthma (AIA) or ASA triad. Complete avoidance of this class of medications does not necessarily alter the progression of the underlying disease process, suggesting that the relationship is not directly causal.

The relationship between ASA sensitivity and airway disease seems to be complex. Although there is a direct temporal development of upper and lower airway symptomatology within minutes to hours of drug exposure, there has been evidence of its association with a chronic asthma course or severity, for reasons still unclear. In a study of 1000 adult patients with asthma seen at a university hospital in Poland, ASA intolerance confirmed by inhalation challenge was found in 9%. Almost a third of cases with severe asthma had ASA intolerance, and this was found to be a significant factor for the development of severe asthma (odds ratio [OR] 5.44, 95% confidence interval [CI] 2.47–8.41; $P < 0.001$), confirmed further by multiple logistic regression analysis [6]. In a cross-sectional study of asthmatics from Western Australia, using a detailed questionnaire that addressed food, chemical, and drug sensitivities, ASA intolerance was associated with more severe asthma (OR 2.96, 95% CI 1.18–4.86; $P = 0.023$) [7]. Patients with AIA seemed to have a more severe and unstable disease course based on number of asthma attacks, doctor's visits, and self-rated asthma severity. In some European studies, 14% to 24% of asthmatics requiring mechanical ventilation were found to have a history of NSAID/ASA sensitivity [8,9]. These studies support the association between asthma severity and ASA sensitivity.

Prevalence

A comprehensive review [10] published recently of the prevalence of AIA substantiates the discrepancy in prevalence rates reported in many studies, likely reflecting differences in diagnostic methods used in the evaluation of ASA

intolerance (eg, questionnaire versus provocation challenges) or differences in populations studied. In this meta-analysis in which the primary outcome was to determine whether ASA ingestion triggered an asthmatic response, participants were grouped according to the following to account for selection bias: (1) All patients with asthma with or without a history of AIA, (2) subjects preselected based on a reliable history of AIA or markers of an increased risk of the syndrome, or (3) patients with no evidence of AIA. The pooled prevalence rates of AIA based on oral provocation testing for the unselected asthma population, preselected population with history of AIA, and preselected population with no history of sensitivity were 21.1% (95% CI 13.6–28.6), 29.5% (95% CI 18.2–40.8), and 9% (95% CI 3.7–14.3), respectively. Much lower rates for ASA sensitivity for the unselected asthma population and preselected population with history of AIA (2.7% [95% CI 1.6–3.8] and 12.2% [95% CI 8.0–16.4], respectively) were found from verbal report alone. Lower prevalence found from questionnaire-based studies or verbal history may be attributed to intentional precautionary avoidance of NSAIDs by asthmatics due to general awareness of potential risk of adverse reactions or to a lack of perception of mild drug-induced reactions because of their relatively delayed onset of reaction.

Mechanisms

Precipitation of an asthmatic attack by ASA/NSAIDs is not based on an antigen–antibody reaction; cross-reactivity to structurally different NSAIDs is well established. In a similar manner, after ASA desensitization, tolerance to other NSAIDs that inhibit cyclooxygenase (COX) is observed [11]. The primary mechanism of the pharmacologic action of and intolerance to ASA/NSAIDs is thought to involve the inhibition of the COX enzyme and PG synthesis and activation of the LT pathways in the respiratory tract (Fig. 1). COX enzymes exist in at least two isoforms, COX1 (constitutive) and COX2 (inducible), which are encoded by distinct genes [12]. COX1 is found in most mammalian cells, including respiratory epithelial and endothelial cells, airway smooth muscle, fibroblasts, mast cells, and alveolar macrophages. COX2 is induced during inflammation and synthesizes inflammatory prostanoids, which participate in some inflammatory diseases, such as arthritis.

The cysteinyl-LT pathway has been well characterized. Its three primary enzymes are 5-lipoxygenase, 5-lipoxygenase activating protein (FLAP or ALOX5), and LTC₄ synthase. Cysteinyl-LTs are potent proinflammatory mediators known to cause bronchospasm, mucus hypersecretion, vascular permeability, airway edema, and eosinophil recruitment to the airways. Although speculative, ASA/NSAIDs, as COX inhibitors, preferentially shunt arachidonic acid metabolism into the 5-lipoxygenase pathway by depleting PGE₂ [13], a known inhibitor of LT synthesis that has anti-inflammatory and smooth muscle relaxant properties [14].

That enhanced production of cysteinyl-LTs is present in patients with clinically stable AIA compared with ATA subjects has been found in many

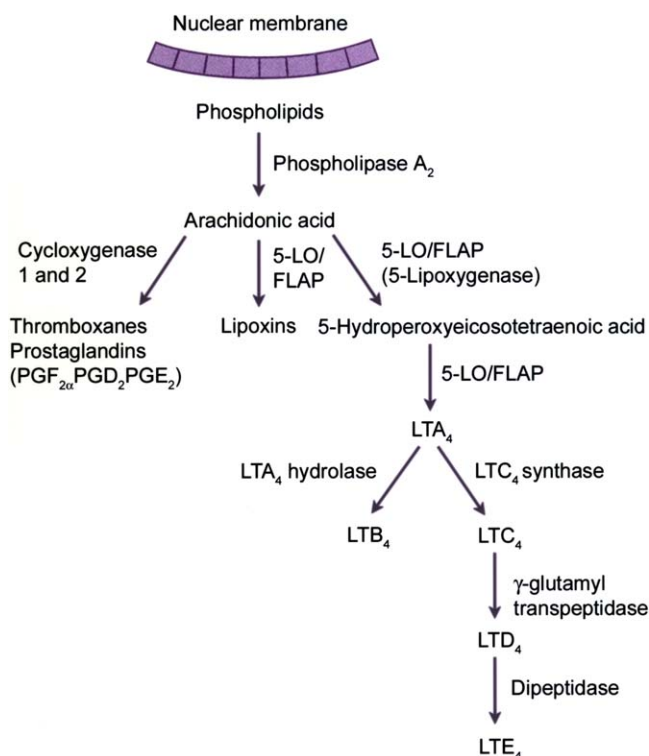


Fig. 1. Arachidonic acid cascade through the cyclooxygenase and the 5-lipoxygenase (5-LO) pathways. FLAP, 5-lipoxygenase activating protein (or ALOX5); LT, leukotriene; PG, prostaglandin. (From Stevenson DD, Simon RA, Zuraw BL. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. In: Middleton E, Reed C, Ellis E, et al. Allergy principles & practice. St. Louis (MO): Mosby, Inc.; 2001. p. 1701; with permission.)

studies showing elevated LTE₄ levels in the urine [15–17]. Furthermore, urinary LTE₄ levels increased after oral or inhaled ASA provocation challenges. Whether COX inhibition (measured by a fall in urinary thromboxane [TX]A₂ metabolite, 11-dehydro-TXB₂) is associated with enhanced cysteinyl-LT production in AIA who underwent an inhaled ASA and methacholine challenges was explored by Sladek and Szczeklik [18]. In this study, although both provocation challenges elicited a significant drop in lung function, only after the ASA challenge was there an evidence of eicosanoid alteration, demonstrated by a fall in urinary 11-dehydro-TXB₂ and a sevenfold increase in urinary LTE₄ excretion. An extension of these findings focusing on changes in arachidonic acid metabolites in the airway has been evaluated [19]. After provocation challenge with inhaled L-lysine-ASA, patients with AIA had decreases in PGE₂, PGF_{2α}, TXB₂, and PGD₂ and an increase in LTE₄ levels. These findings suggest that small amounts of inhaled ASA can incite bronchospasm accompanied by diminished PG formation and enhanced 5-lipoxygenase activity leading to an elevation in LTE₄ in

the airway of patients with AIA. No alterations in 12- and 15-hydroxyeicosate-traenoic production in bronchoalveolar lavage fluid (BALF) were found. Although it was possible that not enough L-lysine ASA was used to provoke this specific change, it could also be surmised that ASA-induced COX inhibition does not activate the 15-lipoxygenase pathway.

A study by Szczeklik et al [20] demonstrated that the ASA-precipitated increase in cysteinyl-LT in the respiratory tract is specific for the clinical syndrome of AIA. Bronchoscopy performed 15 minutes after a bronchial instillation of L-lysine ASA revealed an elevation in LTC₄, LTD₄, and LTE₄ levels and IL-5 only in AIA, with a concomitant reduction in PGE₂ and TXB₂ in AIA and ATA subjects. In ATA, ASA caused a reduction in PGD₂, PGF₂α, 9α, 11β-PGF₂ levels, whereas no such change in these COX metabolites in AIA subjects was found, which further predisposes for airway obstruction, given that PGE₂ is already reduced. In addition, the AIA group had a significant increase in eosinophil count in the BALF. There was also evidence of mast cell activation based on the elevation in histamine levels after the bronchial challenge with highly significant correlations between levels of histamine and LTs, although no increase in tryptase levels in the airway was detected.

Another arachidonic acid metabolite that is upregulated with ASA-induced COX inhibition and may offer another mechanism in AIA is mast cell activation causing increased PGD₂ synthesis or release. PGD₂ is a major COX metabolite in mast cells (which can infiltrate an airway smooth muscle cell) and alveolar macrophages. Unlike PGE₂, it is known to cause bronchospasm. AIA subjects were found to have elevated baseline plasma PGD₂ metabolite (9α,11β-PGF₂), serum tryptase, and urinary LTE₄ levels compared with ATA and healthy nonatopic control subjects. These findings indicate that there could be an ongoing process of mast cell or macrophage activation even in clinically stable AIA. However, the findings of elevated products of mast cell activation have not been consistently found in other studies [20,21].

The genetic mechanisms involved in why this condition exists only in a subgroup of asthmatics have been of significant interest given numerous reports published recently. Only differences in LTC₄ synthase expression distinguish patients with AIA from ATA. LTC₄ synthase is a membrane-bound glutathione transferase expressed in eosinophils, basophils, and monocyte-macrophages and is a key enzyme in the synthesis of cysteinyl-LTs, converting LTA₄ to LTC₄. In a study by Cowburn et al [22], there was a fivefold over-representation of cells expressing LTC₄ synthase in bronchial biopsies from AIA subjects compared with ATA. In addition, no difference in immunostaining of bronchial biopsy specimens for COX1, COX2, 5-lipoxygenase, ALOX5, and LTA₄ hydrolase between ASA and ATA patients was found. Only the LTC₄ synthase cell counts in the submucosa, and none of the other eicosanoid pathway enzymes, correlated with basal cysteinyl-LT levels in the BALF and bronchial responsiveness to L-lysine-ASA. Furthermore, the expression of LTC₄ synthase mRNA in AIA biopsies was found mostly in EG2+ eosinophils, with only a small proportion from activated mast cells and macrophages. The gene coding LTC₄ synthase is located

on the long arm of chromosome 5 (5q35) in a region implicated in asthma by linkage analysis and adjacent to a region (5q31–33) that includes a number of candidate asthma genes [23,24].

Sanak et al [23] described an adenine (A) to cytosine (C) transversion 444 base pairs (bp) upstream (–444) of the translation start site of the LTC₄ synthase gene during screening of the 5' region of the gene and reported that the polymorphic C_{–444} allele occurred more commonly in patients with AIA (relative risk 2.62–3.89). In a population of asthmatic patients in Poland, the allele C frequency was 39% in patients with AIA and 26% and 25% in ATA subjects and healthy controls, respectively. Although LTC₄ synthase has been identified as a likely candidate gene for the AIA phenotype, the polymorphic C_{–444} allele has been found to be associated with AIA in a Polish population but not in American, Japanese, and Australian populations [25–27].

In conclusion, increased production of cysteinyl-LT at baseline and after ASA provocation suggests that these mediators contribute significantly to the pathogenesis of AIA. AIA subjects have an over-expression of the LTC₄ synthase in their airways. Although the LTC₄ synthase genotype is the likely component that could characterize AIA because the association of the C_{–444} allele in the promoter region of the LTC₄ synthase gene and AIA has been established, it has not been shown in several populations.

Approach to diagnosis and treatment

Clinical features and natural history

ASA/NSAID sensitivity is strongly suggested by a history of distinct clinical reactions (such as bronchospasm or rhinitis or urticaria/angioedema or anaphylaxis) that occur in proximity of ingestion of the medication, much like an allergic reaction, although the mechanisms are entirely different and are thought to be primarily mediated by COX inhibition. Some manifestations may be drug specific and are likely immune mediated and may have a delayed onset (eg, aseptic meningitis, hypersensitivity pneumonitis, hepatitis, erythema multiforme, anemia, interstitial nephritis, toxic epidermal necrolysis, and Steven Johnson syndrome) [28].

From a large survey ($n = 500$) in 10 countries participating in the European Network on Aspirin-Induced Asthma, the natural history and clinical characteristics of AIA were studied [29]. The diagnosis of AIA was based on a typical history, with 91% of the patients being able to perform ASA inhalation challenges. The inhaled provocation challenges were not done in the 9% of patients with an unequivocal history due to clinical instability or lack of consent. AIA developed according to a characteristic pattern: Perennial rhinitis first appeared at a mean age of 29.7 ± 12.5 years (in half it was thought to be related to a flu-like/viral illness) followed by asthma and ASA intolerance occurring about 4 years later; eventually nasal polyp formation develops. Females outnumbered males by

2.3:1, having rhinitis and ASA intolerance manifestations occurring earlier and with more progressive and severe courses than males. Although a third of patients could not identify any precipitating factors that led to the first attack of asthma, upper respiratory infection, NSAID/ASA ingestion, and allergen or industrial exposure were identified in 45%, 14%, and 11% of subjects. Symptoms of ASA reaction included dyspnea, nasal discharge and obstruction, skin reactions, conjunctival irritation, angioedema, and shock (hypotension and loss of consciousness in 6%). Inhaled corticosteroids were used by 80% of patients, and 51% of patients were oral corticosteroid dependent (mean dose of 8 mg prednisone per day). Fifteen percent of subjects with nasal polyps or sinus disease did not report a known ASA reaction but had a positive bronchial challenge. In 2 of the 16 centers, skin prick tests and measurements of serum IgE were performed. At least a third of patients were atopic and had an earlier onset of rhinitis and asthma, although they did not seem to have a different age at which ASA intolerance or nasal polyposis was detected.

A study of the natural history of AERD in patients admitted to the Scripps Clinic in California was published recently [30]. Three hundred fifty-two consecutive patients with a presumptive diagnosis of AERD were evaluated, and 85% experienced a respiratory reaction during single-blind, oral ASA challenges. The types of respiratory responses were more encompassing in the United States study, in which they included upper and lower respiratory reactions. In those with a confirmed AERD, similar to the European study, the average age at onset of AERD was 34 years, and the majority (57%) were female. In contrast to the European study in which female patients seemed to acquire a more severe disease, there were no significant gender differences in regard to the clinical characteristics in the United States study. The patients had averaged 2.3 hospitalizations and five emergency room visits for asthma. Thirty percent were on a chronic oral corticosteroid medication. There was no ethnic or familial distribution of AERD. The patients had experienced five sinus infections per year and had undergone an average of three sinus surgeries. Only 6% had not had any sinus operation. Over two thirds of patients had at least two prior reactions to NSAIDs including ASA. Although two thirds of patients were atopic, only 1% reported a family history of AERD.

Although the two studies may have used subjects who may have different features in terms of disease severity, they demonstrate that AERD is a distinct clinical syndrome in which a characteristic pattern emerges (eg, respiratory tract manifestations frequently preceding ASA/NSAID-induced reactions), which seems to be influenced by gender and atopic status, and in whom a majority develop a severe protracted course.

Diagnosis

There are no clinically available in vitro or cutaneous tests to diagnose AERD or ASA/NSAID sensitivity. The history is not always accurate because many subjects are unaware of their intolerance to ASA. The gold standard is a provo-

cation challenge testing by oral, inhaled L-lysine ASA, nasal, or intravenous (only done in Japan) ASA [31]. The primary indication for the challenge is an ill-defined history of ASA tolerance or a suspected intolerance for desensitization or research purposes. Provocation tests should be performed by specialists in settings with adequate facilities for resuscitation.

Oral challenges are most commonly performed because this route resembles real-life exposure; hence, multisystemic symptoms, such as bronchial, upper airway, ocular, cutaneous, gastrointestinal, etc., can be elicited. In some centers, measurement of urinary LTE₄ is obtained for research purposes. The test is conclusive if a 20% drop in FEV₁ is documented, if significant symptoms arise, or if the maximum dose is attained (500–650 mg). The oral challenge protocol to detect respiratory reactions induced by ASA that was developed at the Scripps Clinic is depicted in Table 1 [11].

Inhaled ASA challenges are less risky (the reaction is easily reversed with an inhaled beta-agonist) and shorter (the elapsed time to bronchospasm is less than 30 minutes, and the entire test can be completed in less than 5 hours) to perform than the oral test, and, although both are reported to have similar specificity, an oral challenge can be more sensitive especially in drawing out extrabronchial symptoms [32]. The nasal challenge is performed by instillation of L-lysine ASA into the inferior nasal conchae. Anterior rhinomanometry is used to evaluate for changes in nasal patency and flow. However, the challenge cannot be performed in patients with severe nasal obstruction or who have large fluctuations in nasal flow at baseline. It is an option for patients in whom bronchial or provocation tests cannot be performed due to significant bronchial reactivity [31,33].

Treatment of aspirin-exacerbated respiratory disease

Available clinical practice guidelines for asthma treatment are applicable for the treatment of AIA. Corticosteroid therapy remains a mainstay in the treatment

Table 1

Oral challenge protocol to detect respiratory reactions by acetylsalicylic acid

Time	ASA doses (mg) ^a		
	Day 1	Day 2	Day 3
7 AM	Placebo	30	100–150
10 AM	Placebo	45–60	150–325
1 PM	Placebo	60–100	650

Start challenges, if baseline FEV₁ is 70% or greater than predicted, without bronchodilator. Alternatively, if the absolute FEV₁ is greater than 1.5 liters and represents the best prior 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.

^a ASA doses should be individualized: Start with 30 mg of ASA in everyone but increase to 45 mg for the second dose if the historic reaction was severe or to 60 mg if the historic reaction was milder. From Stevenson DD, Simon R, Zuraw B. Sensitivity to aspirin and NSAID drugs. In: Adkinson NF, John Yunginger J, Busse W, Bochner B, Holgate S, Middleton E, editors. Middleton's allergy: principles and practice. 6th edition, vol 2. St Louis: Mosby; 2003. p. 1698; with permission.

of persistent asthma, even for AIA individuals, who often require aggressive anti-inflammatory coverage such as oral corticosteroids. Given the convincing evidence that cysteinyl-LT production is upregulated presumed to be secondary to a diversion of the arachidonate metabolism from COX inhibition, it would seem reasonable that LT-modifying agents would play a prominent role in alleviating ASA/NSAID-induced reactions. LT modifiers (5-lipoxygenase inhibitors and LT antagonists) have been found to be effective in the chronic therapy of patients with AIA and rhinitis in addition to those provided by inhaled corticosteroid therapy [34,35].

Rhinosinusitis and nasal polyposis greatly affect the morbidity and quality of life of AIA patients. Due to a high recurrence rate of at least 30%, polypectomy alone is not recommended, and other medications or desensitization are almost always necessary [36]. Topical corticosteroids are the treatment of choice. LT receptor antagonists are also reported effective in alleviating symptoms of nasal polyposis in these patients.

Education for the patient that includes discussion of adverse effects and cross-reactivity between ASA and other COX1-inhibiting drugs is crucial. For the physician, flagging medical records and appropriate communication with the patient and other members of the medical or surgical team is important.

Cross-reactivity and therapeutic implications

Individuals with AIA should be provided with a list of contraindicated drugs that are nonselective COX inhibitors and safe alternative medications (Box 1). The potency of these agents in causing bronchospasm seems to be in proportion to their relative potency or specificity in inhibiting COX, so that weak COX1 inhibitors tend to be tolerated at usual doses [37]. Common anti-inflammatory agents thought to be safe for use in asthmatic patients in usual doses include sodium salicylate, choline salicylate, salicylamide, dextropropoxyphene, benzydamine, and chloroquine [33,38]. Salsalate (Disalcid), nimesulide, and meloxicam (preferential inhibitors of COX2 but also inhibit COX1) induce bronchospasm at higher doses [39–41].

Acetaminophen, which preferentially blocks COX3 and is a known weak COX1 inhibitor, has been shown at doses of 150 to 600 mg to induce bronchospasm in only 6% of AIA patients [38]. From the Scripps Clinic, in AIA patients who underwent a single-blind acetaminophen challenge procedure, 24% and 32% developed bronchospasm at 1000- and 1500-mg doses, respectively [43]. There were no positive acetaminophen challenge results in patients with negative ASA challenge. Hence, the general recommendation on the use of acetaminophen in AIA stable patients include avoidance of acetaminophen at doses of 1000 mg or greater, especially in exquisitely ASA-sensitive patients.

The safety of recently developed highly selective COX2 inhibitors (eg, celecoxib and rofecoxib) has been demonstrated in numerous studies, and these can be recommended as alternative medications in AIA due to their analgesic,

Box 1. Drugs or chemicals that inhibit COX1 and cross-react or only partially inhibit COX1 and drugs that are selective COX2 inhibitors**NSAIDs that inhibit COX1**

- Ibuprofen (Motrin, Rufen, Advil)
- Indomethacin (Indocin)
- Sulindac (Clinoril)
- Tolmetin (Tolectin)
- Naproxen sodium (Anaprox)
- Fenoprofen (Nalfon)
- Naproxen (Naprosyn)
- Meclofenamine (Meclomen)
- Ketorolac tromethamine (Toradol)
- Etodolac (Lodine)
- Oxaprozin (Daypro)
- Diclofenac (Voltaren)
- Ketoprofen (Orudis, Oruvail)
- Flurbiprofen (Ansaid)
- Piroxicam (Feldene)
- Nabumatone (Relafen)
- Mefenamic acid (Ponstel)

Low incidence of cross-reactivity: analgesics that are poor inhibitors of COX1 enzymes and only with high concentrations of the drug

- Acetaminophen (Paracetamol)
- Disalicylic acid (Disalcid)
- Meloxicam [40]

Selective COX2 inhibitors

- Nimesulide [41]
- Rofecoxib [45,46]
- Celecoxib [42,44]

Data from Stevenson DD. Approach to the patient with a history of adverse reactions to aspirin or NSAIDs: diagnosis and treatment. Allergy Asthma Proc 2000;21:25–31.

antipyretic, and anti-inflammatory properties [29,44–46]. None of the AIA patients developed bronchospasm to celecoxib or rofecoxib. Even with almost complete tolerance to COX2 inhibitors by AIA patients, the use of these medications in NSAID-intolerant subjects may not be generalizable, especially for patients who manifest with NSAID-induced urticaria/angioedema or anaphylaxis in whom cutaneous or anaphylactoid reactions can still develop [47,48]. Hence, careful use of COX2 inhibitors or performing a supervised provocation challenge may be recommended for these patients.

Acetylsalicylic acid desensitization

ASA desensitization refers to the process of inducing refractoriness to ASA or NSAIDs by administration of incremental doses of oral or inhaled ASA until all reactions disappear. A protocol that was developed and refined at the Scripps Clinic by Stevenson et al uses increasing doses of ASA in 5 days until the maximum dose of 650 mg is tolerated [11,49]. Daily doses of ASA (325 to 650 mg twice daily) are administered, and improvement in the underlying chronic respiratory symptoms can be achieved during maintenance of the desensitized state. The refractory state lasts 2 to 5 days, with gradual return to sensitivity between 2 and 4 days when ASA is withheld [50]. Cross-desensitization is also attained for other NSAIDs; hence, these can be used as substitutes for ongoing ASA treatment. ASA desensitization should be considered for AIA patients with recalcitrant respiratory symptoms and polyp formation, despite optimal pharmacotherapy including high doses of systemic corticosteroids and repeated sinus surgery, and in patients with concomitant medical conditions requiring the use of ASA/NSAIDs, such as arthritis and other rheumatologic or cardiac disease.

Several reports from the Scripps Clinic of their experience with ASA desensitization have consistently shown significant improvement in nasal/sinus and asthma symptoms [51–53]. In their latest publication, of 172 patients with AIA who underwent desensitization between 1995 and 2000, 67% responded favorably to ASA treatment in terms of significant improvement in nasal (including sense of smell) and asthma symptoms and reduction in sinus infections, hospitalizations/ER visits for asthma, and requirement for systemic corticosteroids, most of which were apparent by the first 6 months of treatment and persisted for 1 to 5 years [51]. Fourteen percent discontinued treatment because of adverse effects (of which gastritis is the most common), and in 19% ASA treatment was discontinued for different reasons such as those unrelated to side effects, lack of adherence, or lack of effects.

Although ASA desensitization can be successful for improvement of asthma and rhinosinusitis, the mechanisms are not clear. A possible conjecture is that continued inhibition of COX1 and phospholipase A₂ could lead to a decrease in LT synthesis and other proinflammatory prostanoids by downregulation of cysteinyl-LT receptors [54]. Chronic desensitization has been associated with a decline in LTB₄ synthesis [55] and reduction in urinary LTE₄ levels [54].

Although considerable strides have been made in the past two decades in understanding the pathogenesis of this syndrome, there are many unanswered questions that relate to what stimulates the initial inflammatory response in the upper and lower airway, why COX inhibition does not produce significant reactions in most asthmatics, and what the mechanism is behind the chronic severe asthma and rhinosinusitis in AIA despite avoidance of ASA/NSAIDs. In addition, it is not certain why distinct clinical reactions (respiratory versus cutaneous versus cardiovascular) are triggered and how the intolerance is acquired.

Beta-blockers

β -adrenergic blocking agents are indicated for common medical conditions such as stable angina, myocardial infarctions (MIs), hypertension, heart failure, coronary artery disease, and arrhythmias. In addition, these medications are used in the management of hyperthyroid disease, acute stress reactions, generalized anxiety, essential tremor, glaucoma, and prophylaxis for migraines. Due to the extensive medical conditions for which β -blockers are proven effective and for which they can have a major impact on survival and quality of life, there is a large population, including asthmatics, who could benefit from their use. For instance, in over 100,000 adult survivors of MI, 21% were found to have asthma or chronic obstructive pulmonary disease [56]. Historically, β -blockers have been contraindicated in asthma due to concern for exacerbating asthma symptoms. However, the availability of newer formulations and more information on the benefits of β -blockers are causing a re-examination of their role in the asthmatic population.

In almost all asthmatics, nonselective β -blockade causes bronchoconstriction and increases bronchial hyper-responsiveness to methacholine and histamine [57,58]. It is likely that multiple mechanisms underlie this effect. The involvement of parasympathetic nerves seems rational because they are the dominant bronchoconstrictor neural pathway in the airways [59]. In support of parasympathetic involvement, cholinergic receptor blockade by oxitropium bromide was shown to inhibit propranolol-induced bronchospasm (PIB) [60]. Atropine [57] and pilocarpine also inhibited PIB in asthmatics [61]. The degree of the protective effect of atropine on PIB varied between individual asthmatics, suggesting heterogeneity in the cause of PIB in asthma [57].

There is evidence of other mechanisms contributing to the bronchoconstriction caused by β -blockers in asthmatics. One such pathway may include the non-adrenergic noncholinergic (NANC) nerves. Vasoactive intestinal peptide is a neurotransmitter of NANC nerves in the airways, and it has been shown to attenuate PIB independent of cholinergic blockage [62]. Another pathway may involve endogenous epinephrine tonically inhibiting cholinergic neurotransmission. A β -blocker may remove this effect, causing an increase in acetylcholine release to airway smooth muscle cells, promoting bronchoconstriction. This would affect asthmatics who are hyper-responsive to acetylcholine but would not affect healthy individuals [59].

Cellular mechanisms may play a role because cromones attenuate PIB to varying degrees [63,64]. It was proposed that PIB may be due to blockade of β -receptors on the mast cell surface, causing the release of chemical mediators such as histamine, cysteinyl-LT, and TXA₂. However, neither a LT-receptor nor a TXA₂ receptor antagonist was effective at alleviating PIB in asthmatics [65], and histamine levels were not found to be elevated with PIB [66].

Description of relevant pharmacologic and pharmacokinetic properties

β -adrenergic receptors (β_1 and β_2) are part of a large family of hormone and neurotransmitter receptors that initiate their function by coupling to a guanine nucleotide-binding protein [67]. When β -blockers occupy the receptor site, they act as a competitive antagonist that binds to the β -adrenergic receptor without activation [68]. Although β_1 and β_2 -adrenoreceptors are widely distributed in the cardiovascular [67] and the respiratory systems [69], β_2 -receptors are found four times more frequently in the airways [70], whereas β_1 -adrenoceptors predominate in the heart. The stimulation of β_2 -adrenoceptors causes muscular relaxation [67], blood pressure reduction [71], and bronchoconstriction [72]; β_1 cardiac stimulation causes an increase in the rate and force of contraction [67]. Nonselective β -adrenoceptor blockers block β_1 and β_2 receptors. Lower doses of β_1 antagonists preferentially bind to β_1 receptors, but as the plasma concentration of the β_1 blocker increases, its binding becomes less selective and increasingly inhibits β_2 receptors [73,74].

Different β -blockers have inherent properties (Table 2) [75] that help determine which β -blocker is indicated for the patient, and some features might have a more prominent impact on an asthmatic patient. β -blockers can be divided into those with or without intrinsic sympathomimetic activity (ISA). For those with ISA, in the presence of high-background sympathomimetic activity the

Table 2
Pharmacologic characteristics of β -adrenergic antagonists

Medication	Receptors	Lipophilicity	ISA
Acebutolol	β_1	Moderate	Yes
Atenolol	β_1	Low	No
Metoprolol	β_1	Moderate	No
Pindolol	β_1, β_2	Moderate	Yes
Timolol	β_1, β_2	Moderate	No
Nadolol	β_1, β_2	Low	No
Propranolol	β_1, β_2	High	No

Abbreviation: ISA, intrinsic sympathomimetic activity.

Data from Hoffman BB. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Gillman AG. Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; 2001. p. 215–53.

medication acts as an antagonist, and with low or absent background sympathetic activity it acts as an agonist [67].

Therapeutic implications

Nonselective β -blockers are contraindicated in asthma because they have been shown to significantly decrease pulmonary function and place the patient at risk for acute bronchospasm. Regular use of noncardioselective β -blockers was demonstrated to cause a 13.5% decrease in FEV₁ [76]. This reduction is significant for asthmatics with severe airflow obstruction. In addition, severe bronchoconstriction and fatal attacks have been reported even with a topical ophthalmic application of a β -blocker [77,78]. This is important in conditions for which nonselective β -blockers are indicated; hence, alternative medications should be used.

Although a few studies have demonstrated significant effects of cardioselective β -blockers on lung function [79], their use may be tolerated in some asthmatics [80]. A meta-analysis of randomized, blinded, placebo-controlled trials that studied the effects of cardioselective β -blockers on FEV₁, symptoms, and inhaled β_2 -agonist use in patients with mild to moderate reactive airway disease was recently reported [76]. Administration of a single dose of a cardioselective β -blocker was associated with a 7.46% (95% CI 5.59–9.32) reduction in FEV₁ and a 4.63% (95% CI 2.47–6.78) bronchodilator reversibility in FEV₁ compared with placebo, with no concomitant increase in symptoms. Analysis of several trials lasting from 3 days to 4 weeks demonstrated no significant change in FEV₁ (–0.42%; 95% CI –3.74–2.91), symptoms, or inhaler use compared with placebo but maintained an 8.74% (95% CI 1.96–15.52) increase in β -agonist bronchodilator response. Hence, it seems that cardioselective β -blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease and can therefore be used for these patients. However, this meta-analysis has significant limitations, which include variable and generally short medication courses, exclusion of severe asthmatics, and lack of information on the effects of cardioselective β -blockers on asthma exacerbations. Long-term studies are needed to fully define the safety profile of cardioselective β -blocker use in asthmatics [81].

There is evolving evidence that in specific circumstances the benefits of cardioselective β -blockers outweigh the risks for asthmatics. A study of 3800 asthmatics showed a protective effect of a β -blocker on mortality within 2 years after MI (12% versus 20% mortality rate in β -blocker-treated and untreated asthmatics, respectively, with a relative risk of 0.6) [82]. The guidelines established by the American College of Cardiology and the American Heart Association suggest that β -blocker therapy after MI is appropriate for many elderly patients with asthma as long as they are closely monitored for adverse events [83]. Ipratropium bromide is the treatment of choice for β -blocker-induced bronchospasm [80]. Other drugs, including β_2 agonists, atropine, aminophylline,

isoproterenol, steroids, halothane, and glucagon, have also reversed the bronchospastic effects of β -blocking agents [84].

Angiotensin-converting enzyme inhibitors

ACE inhibitors are considered to be an effective and, in some cases preferred, intervention for the treatment or prevention of hypertension, cardiovascular diseases and their complications, and diabetic nephropathy. ACE inhibitors are usually well tolerated, and in the general population the more common side effects include cough, hypotension, and hyperkalemia [85]. Angioedema has been reported in rare cases [86], and there is a risk of teratogenicity during the second and third semester of pregnancy [87].

The reported incidence of ACE inhibitor-associated cough is 10% to 20% [88–90]. Prior asthma or bronchospasm is not a risk factor for developing cough as an ACE inhibitor adverse effect [91]. The cough has been described as dry, nonproductive, persistent, or hacking; often starting as a tickling sensation in the back of the throat; sometimes worse at night or on lying down; and as being episodic [90]. It can occur 1 day to several months after starting the medication and normally persists while taking the medication. It usually disappears within several days but may persist for up to 4 weeks after discontinuing the medication [86]. In asthmatics, the cough does not cause a decrease in lung function [92] and should not be responsive to treatment with albuterol. In patients with congestive heart failure, it is important to consider cough as a possible ACE inhibitor side effect before attributing it to pulmonary congestion [86].

ACE inhibitors are generally safe in most asthmatics [93]. Studies in patients with chronic airflow obstruction showed no significant change in their FEV₁ over the treatment period [92,94,95]. In addition, bronchial reactivity has been shown to remain unchanged with ACE inhibitors [92,95,96].

There have been few reports of bronchoconstriction and bronchial reactivity associated with this class of medication [91,97,98]. In one case report, a 51-year-old man developed intermittent shortness of breath and wheezing within a month of starting captopril that resolved upon discontinuation of the medication [97]. In another case report, a known asthmatic developed immediate worsening of dyspnea and wheezing upon starting enalapril [98]. The New Zealand Adverse Reactions Center registered 596 adverse respiratory events to enalapril, captopril, and lisinopril, including cough in 86% and bronchospasm and dyspnea in 8%. Unspecified reactions in 6% were noted [91]. Based on these reports, significant respiratory compromise seems rare but is a possible adverse effect of an ACE inhibitor.

ACE inhibitors have varying pharmacologic and pharmacokinetic profiles in regard to their lipophilic properties and requirement for hepatic biotransformation [85,99]. Although these properties may affect the potency and duration of activity of ACE inhibitors and consequently create practical prescription preferences to allow for once-daily dosing, there may be other factors, such as race and gender, that can affect the efficacy and side-effect profile of these medications. Studies

have shown that the adverse effect of cough occurs nearly three times more often in women [86,100,101], and African Americans and Asians have a three- to fourfold higher risk of angioedema [71].

Mechanisms of angiotensin-converting enzyme inhibitor-induced respiratory reactions

The mechanisms of ACE inhibitor-induced cough are not completely defined but may be mediated by bradykinin and substance P [102]. ACE is present in membrane-bound form in endothelial cells, epithelial cells, and in the brain; and in a soluble form in the blood and other body fluids [99]. It catalyzes the conversion of angiotensin I into angiotensin II [85], which acts directly on vascular smooth muscle, increasing the peripheral and central vascular tone. It also stimulates aldosterone secretion, leading to sodium and water retention [99].

ACE acts as a kininase enzyme that degrades inflammatory compounds such as bradykinin, substance P, and neurokinin A [2,103]. Bradykinin increases vascular permeability and promotes vasodilation through stimulating arachidonic acid metabolite production and nitric oxide production [99]. Substance P is a tachykinin present in neurons arising from the vagus nerve beneath the epithelium of the trachea and major bronchi. It may mediate the afferent vagal impulses to the medullary cough center, resulting in cough [90]. Therefore, ACE inhibitors have the potential to create an abundance of kinins (eg, bradykinin, substance P, and neurokinin A) by inhibition of the ACE kininase enzyme action.

A mechanism that invokes substance P involvement in the causation of cough as an adverse reaction to an ACE inhibitor in some patients may be an increased cough reflex sensitivity. This theory is supported by the fact that patients with ACE inhibitor cough, compared with those without, have an increased cough response to capsaicin [104]. Capsaicin acts by depolarizing sensory neurons, causing release of substance P [105], and has been used to quantify the sensitivity of the cough reflex [106]. The involvement of PGs in the mechanism causing cough is also evidenced by the fact that the COX inhibitor sulindac has been shown to relieve the ACE inhibitor-induced cough in some patients [107,108].

As in ACE inhibitor-induced cough, the mechanism involved in ACE inhibitor-induced bronchoconstriction is elusive. There are reports implicating a specific sensitivity to bradykinin. Inhalation of bradykinin has been shown to decrease FEV₁ and cause bronchoconstriction in asthmatics but not significantly in healthy control subjects [109,110]. How bradykinin induces bronchoconstriction is not clear but may be due to cholinergic vagal reflex mechanisms and selective stimulation of C-fiber afferent nerves [109]. Histamine and prostanoids may contribute a small component to the response [108,111].

Approach to management and therapeutic implications

When an ACE inhibitor-induced respiratory reaction is suspected, the most practical approach seems to be a trial off the ACE inhibitor before pursuing

multiple tests because this may save the patient from undergoing an extensive work-up [86]. If a person experiences cough with one ACE inhibitor, they will likely have cough with another ACE inhibitor and therefore should try a different type of medication [86,90]. One possible alternative is an angiotensin II receptor blocker, which produces hemodynamic effects similar to those of ACE inhibitors but does not have the adverse side effect of cough [103]. The alternative medication chosen is dictated by each individual's clinical situation. In patients who have a cough side effect where it is deemed important that they remain on an ACE inhibitor, oral theophylline [112] or cromolyn sodium can help to treat the cough, causing it to remit in some patients [113]. Treatment with the COX inhibitor sulindac has been shown to help reduce ACE inhibitor cough, but more information is needed on the long-term effects of sulindac used in combination with an ACE inhibitor before it can be recommended [107].

Summary

The means by which certain medications can trigger asthma vary in terms of acuity of onset, severity, and mechanisms involved. Certain medications, such as nonselective β -blockers, are expected to cause bronchoconstriction in almost all asthmatics and therefore should be avoided. Although ASA/NSAIDs or β -blockers can induce immediate bronchoconstriction, ACE inhibitors can manifest with adverse respiratory reactions within a day to weeks of use. ASA-induced reactions tend to occur several years after the onset of rhinitis/asthma phenotype, suggesting that an underlying inflammatory process triggers the development of ASA sensitivity. The severity of reactions in AERD can range from mere nasocular to profound anaphylactoid presentation, attributed most likely to COX inhibition. The mechanisms involved in bronchospasm or increased responsiveness to β -blockers or ACE inhibitors also need further investigation.

The general and most practical approach is avoidance and cautious use of the drugs, especially if susceptibility is known for an asthmatic. However, these medications can exert a major role in the management of common diseases, some of which have serious and debilitating complications. Fortunately, controller therapy for asthma and equally efficacious alternatives (eg, angiotensin II receptor blockers) or more selective medications (eg, selective COX2 inhibitors and cardioselective β -blockers) for the treatment of these conditions are now available. In the case of ASA sensitivity, desensitization is another worthy option.

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