

Aspirin Treatment of Patients with Aspirin Intolerance, Asthma, and Nasal Polyps

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ABSTRACT

Patients with the triad of aspirin (ASA) intolerance, asthma, and nasal polyps present a clinical challenge for the allergist because their polyps generally are refractory to traditional treatments and their asthmatic symptoms may become more difficult to control with time. These patients can be desensitized and treated with ASA with subsequent improvement in their nasal and respiratory symptoms. This article describes one such individual and briefly reviews the literature regarding this triad. The diagnosis of ASA intolerance, mechanistic studies, a desensitization protocol, and new therapies are reviewed. (Allergy and Asthma Proc 22: 377–382, 2001)

CASE PRESENTATION

A 38-year-old female elementary school teacher with asthma was referred for management of recurrent nasal polyps and sinusitis. She had a history of perennial and seasonal allergic rhinitis attributed to dust mite and ragweed.

Initially, nasal polyps had been diagnosed approximately 10 years earlier, and she had suffered from persistent nasal obstruction and anosmia for several years. She generally had one episode of sinusitis requiring antibiotics annually and had undergone three nasal polypectomies. Past treatments included several topical nasal steroid preparations and, recently, she had been started on montelukast. Dust

mite or ragweed exposure was associated with flares of sneezing and rhinorrhea.

The patient had moderate persistent asthma (forced expiratory volume in 1 second [FEV₁] 60–80%), which was triggered by exercise, cold-air exposure, and upper respiratory tract infections (URIs). She had been hospitalized three to four times for asthma but had never been in an intensive care unit (ICU) setting or intubated. Her asthma had become more difficult to control during the year before her visit.

The patient's medications on presentation were fluticasone metered dose inhaler (MDI), 440 µg twice daily (b.i.d.); albuterol MDI as needed; montelukast, 10 mg daily (q.d.); cetirizine, 10 mg q.d.; and multivitamins.

She was unaware of any sensitivity to aspirin (ASA) or other nonsteroidal anti-inflammatory drugs (NSAID). She had been advised years ago to avoid these and generally did so, although she recalled taking ibuprofen approximately 5 years earlier without problems and she tolerated acetaminophen.

She had never smoked, was without other health problems, and had a family history of mild ragweed allergy in one sibling.

On physical exam, she appeared well and had normal vital signs. Head and neck exam was remarkable for bilateral nasal polyps that could be readily visualized with a nasal speculum and were protruding slightly from one nostril. Her lung exam was normal, and skin was clear and nondermatographic. Baseline spirometry showed an FEV₁ of 85% of predicted and a mean forced expiratory flow 25–75% (FEF_{25–75}) of 34% of predicted.

The clinical impression was that of a patient with moderate persistent asthma and severe recurrent nasal polyposis

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and sinusitis. There was no specific history to suggest ASA or NSAID intolerance.

BRIEF HISTORY OF ASA INTOLERANCE

ASA was first used clinically at the turn of the century.¹ By 1919, the first report of an asthmatic reaction to ASA appeared,² and several deaths from asthma after ASA ingestion were reported in the 1930s. The triad of ASA intolerance, asthma, and nasal polyposis or rhinosinusitis, was described formally by Samter and Beers in 1969.³

ASA INTOLERANCE HAS VARYING PRESENTATIONS

Four general types of adverse reactions to ASA have been recognized:

1. Urticaria/angioedema
2. Rhinosinusitis/conjunctivitis/asthma
3. Anaphylaxis
4. Hypersensitivity pneumonitis

This review will focus on the management of the type of adverse reaction characterized by some combination of rhinosinusitis with or without nasal polyposis, conjunctivitis, and asthma. A given patient may present with the combination of severe rhinosinusitis and asthma or with recurrent nasal polyposis and rhinitis but only mild or absent asthma.⁴ NSAID ingestion typically precipitates flares in nasal congestion and rhinorrhea and/or in asthmatic symptoms. The causal relationship between NSAIDs and such flares may go unrecognized by the patient.

PREVALENCE AND CLINICAL CHARACTERISTICS OF NONSTEROIDAL ANTI-INFLAMMATORY INTOLERANCE

ASA intolerance is an acquired disease with a prevalence of 3–20% in adult patients with asthma.^{5,6} ASA intolerance is found in up to 30% of patients with the combination of nasal polyps, rhinosinusitis, and asthma.⁴ It is less common in children, although prevalence has not been well studied in the pediatric population. Atopy is present in ~50% of patients with the triad, and family histories of ASA sensitivity are rare.^{3,4} The classic presentation is typified by the onset of rhinosinusitis followed by nasal polyps and worsening asthma when patients reach 30 or 40 years of age, although some patients' asthma may improve with time.³ Those patients with nasal polyposis report congestion, anosmia, and impaired gustatory sense as prominent symptoms. Patients may describe exacerbations in asthma symptoms or worsening nasal symptoms after administration of NSAIDS, with reactions typically occurring within 20 minutes to 3 hours after ingestion.³

APPROACH TO PATIENTS WITH THE TRIAD OF ASA INTOLERANCE, ASTHMA, AND NASAL POLYPOSIS: ASA CHALLENGE, DESENSITIZATION, AND SUBSEQUENT TREATMENT

Over the past 10 or 20 years, physicians and patients have noticed that some patients with ASA intolerance and the triad, who had, nonetheless, received regular ASA therapy, paradoxically experienced an improvement in their nasal symptoms. This situation generally arose either in patients whose ASA intolerance was unrecognized or in patients with known sensitivity who needed ASA therapy for other medical conditions (*i.e.*, cardiovascular or rheumatologic disease) and therefore had been desensitized before treatment.

Several early studies attempted to verify the beneficial effects of ASA treatment on ASA-intolerant patients, but these were limited by small sample sizes and were inconclusive. In 1990, a clinical study of 107 patients accomplished this objective.⁷ This study examined the long-term effects of ASA desensitization and subsequent treatment on ASA-intolerant rhinosinusitis and asthma. All patients had challenge-proven ASA intolerance and moderate/severe rhinosinusitis asthma. They were divided into three groups: 35 patients were desensitized and took ASA continuously, 42 patients avoided ASA after initial challenge, and 30 patients were desensitized and took ASA for a time but stopped for various reasons (*e.g.*, many developed gastrointestinal [GI] side effects). During the 2–9 years of follow-up (average, 4 years), the following were assessed: nasal and chest symptoms, medication use, outpatient and emergency room visits, hospital stays, upper respiratory tract infections requiring antibiotics, steroid use, and sinus surgeries. Doses of ASA taken ranged from 325 mg q.d. to 650 mg four times a day (q.i.d.), with an average of 650 mg b.i.d.

Patients continuously taking ASA showed statistically significant reductions in all of the foregoing parameters, except nasal steroid use, which was decreased but not to a level of statistical significance. The group that took ASA for a time but then stopped the medication also improved by most measurements but trended back toward baseline after discontinuation. The authors concluded that long-term ASA use prevents or retards ongoing inflammation in the nose, sinuses, and bronchial tree.

PROTOCOL FOR ASA CHALLENGE AND DESENSITIZATION

Stevenson has published a review of the challenge and desensitization of 106 patients, which provides guidelines for patient selection, a protocol, and observations about the phenomenon.⁸ Appropriate patients for challenge and possible ASA treatment include those for whom ASA or NSAIDs would have an important impact on other co-existent diseases (especially cardiovascular disease), those with refractory sinus disease necessitating repeated surgery-

ies, those with asthma requiring high maintenance doses of systemic steroids,^{4,6} and those not at high risk for GI sequelae. It has been advised that patients undergo challenge only after their asthma is as well controlled as possible; baseline FEV₁ should be $\geq 70\%$ of prior recorded best value and at least 1.5 L. Also, reversibility of airway obstruction should be documented to confirm the diagnosis.⁸ Antihistamines and inhaled sympathomimetics should be discontinued 24 hours before initiating the procedure. Corticosteroids and methylxanthines should be continued at the usual doses. Peripheral intravenous (i.v.) access should be established. Positive reactions are variably defined as those causing a decline in the FEV₁ of $\geq 15\text{--}25\%$ from baseline. Spirometry should be performed before administering each step.

It is imperative to allow a minimum of 2 hours between doses, to accommodate the delayed onset reactions seen in many patients. Rarely, patients may report reactions even later, after ASA ingestion, and for such patients, dosing intervals should be adjusted further, *e.g.*, at 6-hour intervals. This is in contrast to protocols used for patients without asthma or the triad, which may involve shorter dosing intervals. In the inpatient setting, more than three doses can be administered per day, shortening the overall length of the procedure.

The protocols for challenge and desensitization differ in their end points. A challenge is designed only to document a threshold dose and confirm ASA sensitivity. Desensitization is intended to continue through the patient's threshold dose and achieve tolerance to a goal dose. A reaction is expected if the patient is ASA intolerant. Once induced, it is treated, and the patient is given no further doses until pulmonary function has returned to baseline (usually 2–24 hours). For desensitization, the inciting dose then is readministered. The patient may or may not react again. The same dose is given repeatedly until there is no reaction, and then the protocol proceeds as before. This is continued until the patient tolerates 650 mg ASA without reaction, at which point, desensitization is complete. The following outline is an example protocol for desensitization:

Day	Time	Dose
1	8:00 A.M.	Placebo
	11:00 A.M.	Placebo
	2:00 P.M.	Placebo
2	8:00 A.M.	3 mg of ASA
	11:00 A.M.	15 mg of ASA
	2:00 P.M.	30 mg of ASA
3	8:00 A.M.	30 mg of ASA
	11:00 A.M.	60 mg of ASA
	2:00 P.M.	100 mg of ASA
4	8:00 A.M.	100 mg of ASA
	11:00 A.M.	150 mg of ASA
	2:00 P.M.	325 mg of ASA
5	8:00 A.M.	325 mg of ASA
	11:00 A.M.	650 mg of ASA

Stevenson made several observations. All ASA-intolerant patients could be desensitized. The dose of ASA that elic-

ited the first reaction roughly predicted the rapidity with which desensitization occurred, *i.e.*, if a patient reacted to a dose below 100 mg, desensitization took repeated exposures and more reactions occurred before the patient became desensitized. After desensitization to ASA, all patients tested also were cross-desensitized to other NSAIDs. ASA desensitization is thought to be sustainable indefinitely, provided the patient continues ASA on a q.d. or q.o.d. basis. Last, airway responsiveness to methacholine and antigen inhalation remained unaltered after ASA desensitization. In a later article, the authors recommended an optimal dose of 650 mg b.i.d., with a range of 325 mg q.d. to 650 mg q.i.d.⁴ Notably, a recent study showed that of 60 ASA-intolerant patients with asthma challenged with the new cyclooxygenase 2 (COX-2) inhibitor rofecoxib, none reacted with respiratory or nasal symptoms, indicating a lack of cross-reactivity with this class of medication.⁹

MECHANISTIC STUDIES OF ASA INTOLERANCE

Although the approach to ASA desensitization is similar to that used to desensitize to drugs that elicit immunoglobulin E (IgE)-mediated allergy, there is little evidence to suggest that ASA sensitivity involves IgE. ASA-intolerant patients react to multiple NSAIDs with widely divergent structures, arguing against a common shared antigenic determinant. Conversely, structurally related salicylates that are not potent because COX inhibitors do not induce reactions.^{10,11} Furthermore, the potency with which an NSAID provokes bronchospasm correlates to its strength as a COX inhibitor.¹²

Many investigators have made contributions toward understanding the mechanisms of ASA intolerance. Only the briefest overview is within the scope of this article. The cellular pathway by which leukotrienes, thromboxanes, and prostaglandins are generated is shown in Fig. 1. ASA and other NSAIDs are COX inhibitors.

Several studies point to increased leukotriene generation in ASA-intolerant asthma. Leukotriene C₄ (LTC₄), LTD₄, and LTE₄ are potent spasmogens for nonvascular smooth muscle,¹³ induce mucus secretion, increase vascular permeability, and trigger chemotaxis of various inflammatory cells. Ferreri *et al.*¹⁴ were among early investigators to show differences in leukotriene regulation between ASA-intolerant and -tolerant patients. This group showed that ingestion of ASA, in sensitive subjects, elicited the release of LTC₄ into nasal secretions. This was not seen in patients without ASA intolerance or in sensitive patients after desensitization. This finding could be explained by the inhibition of COX causing increased generation of the spasmogenic leukotrienes LTC₄, LTD₄, and LTE₄ (Fig. 1).

A similar finding was reported by Christie *et al.*¹⁵ in a study examining urinary leukotrienes following ASA challenge in ASA-intolerant patients with asthma. Urinary LTE₄ increased fourfold in these patients but was unchanged after ASA challenge in control patients with asthma. In addition,

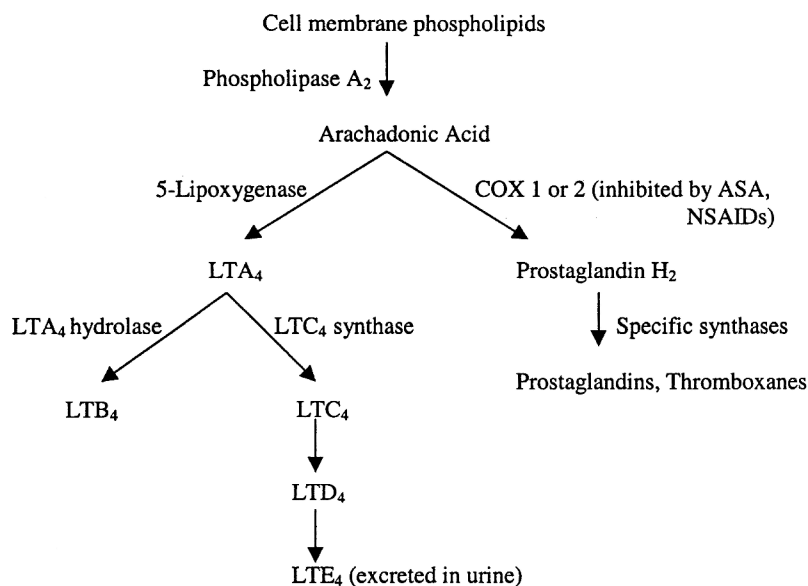


Figure 1. The cellular pathways for generation of inflammatory mediators. COX 1 and 2 convert arachidonic acid to prostaglandin H_2 .

the baseline levels of urinary LTE_4 were sixfold higher in sensitive patients than in asthmatic controls.

These studies suggest that the cells of ASA-sensitive individuals have an up-regulated 5-lipoxygenase (5-LO) pathway, rendering them intolerant to drugs that inhibit the alternative COX pathway. Jurgens *et al.* showed that peripheral monocytes of ASA-sensitive patients produced greater baseline levels of arachidonic acid products than those of nonsensitive patients with asthma or patients who do not have asthma and did so on a continuous basis.¹⁶ This could be postulated to set up an ongoing chemotaxis of inflammatory cells into target tissues such as the nasal and respiratory mucosa, which then would be acutely exacerbated by the addition of a COX inhibitor.⁴ Cowburn *et al.*¹⁷ obtained bronchial biopsy specimens from ASA-tolerant and -intolerant patients with asthma and from subjects who did not have asthma and compared immunohistochemical staining for various enzymes in the leukotriene and prostaglandin pathways. The numbers of cells staining positive for LTC_4 synthase were 5-fold higher in the tissues of ASA-intolerant patients than those of ASA-tolerant patients, and 18-fold higher than normals. These data raise the possibility that a continuum exists in LTC_4 expression and that the ASA-intolerant patient with asthma represents one extreme of that spectrum.

There are also interesting data regarding the role of prostaglandin E_2 (PGE_2), which when inhaled, has been shown to protect against ASA-induced bronchospasm.^{18,19} PGE_2 also inhibits synthesis of leukotrienes,^{20,21} mast cell degranulation,²² T-cell activation,²³ and several other components of the inflammatory process. Through these actions, PGE_2 may provide a constitutive break on the generation of proinflammatory mediators. ASA, by blocking the generation of the prostaglandins, would disrupt this counter-regulatory system.

O'Hickey *et al.*²⁴ studied another hypothesis, *i.e.*, that there is increased end-organ sensitivity to leukotrienes in ASA-sensitive patients. This was tested by experimentally determining the dose of LTE_4 that caused a 35% drop in specific airway conductance, which was found to be 16 times lower in patients with asthma with ASA sensitivity as compared with asthma patients without ASA sensitivity and which normalized after ASA desensitization. These data suggested that there was, indeed, an enhanced sensitivity to leukotrienes in the airways of ASA-sensitive patients with asthma.

Because the condition of ASA intolerance appears to be mediated by an aberration(s) in leukotriene regulation, leukotriene inhibitors (in the form of receptor blockers or 5-LO inhibitors) have been evaluated as candidates for the treatment of ASA sensitivity. Isreal *et al.*²⁵ tested the role of 5-LO products in mediating the ASA response in ASA-sensitive patients by treating with zileuton, a 5-LO inhibitor, for 1 week before ASA challenge. Zileuton prevented the fall in FEV_1 and the development of naso-ocular symptoms. Interestingly, however, a later study of similar design by Pauls *et al.*²⁶ showed that a subset of such patients still had responses to ASA challenge but at higher doses than those given in the original challenges, suggesting that zileuton had shifted the dose-response curve in some patients, rather than truly blocking the phenomenon.

Although the impact of antileukotriene agents on the phenomenon of ASA intolerance remains an area of active work, the clinical usefulness of these medications was established in a double-blind, placebo-controlled, crossover study in which patients received 6 weeks of zileuton (600 mg q.i.d.) or placebo.²⁷ With zileuton treatment, improvements in both pulmonary and nasal function resulted, with an increase in average FEV_1 , higher morning and evening peak expiratory flows, improved sense of smell, decreased

rhinorrhea, and less nasal congestion compared with placebo. Similar studies with montelukast or zafirlukast have not been reported in ASA-intolerant patients with asthma.

The relative roles of various inflammatory cells, particularly mast cells and eosinophils, also have been studied. Mast cells and increased numbers of eosinophils can be identified in nasal polyp tissue.²⁸ Both cell types are capable of leukotriene production. Fischer *et al.*²⁹ assayed the nasal lavage fluid of ASA-sensitive patients after ASA challenge, for leukotrienes and nasal tryptase. Nasal tryptase increased significantly after challenge, showing the involvement of mast cell degranulation in this process. In Cowburn's study, mentioned previously, the majority of LTC₄ synthase-positive cells were eosinophils. The roles of monocytes, macrophages, and neutrophils remain to be characterized.

REVISITING THE CASE

Because the patient described previously recalled taking NSAIDs in the past without difficulty, she was initially challenged with ASA in the outpatient setting. Doses up to 81 mg were tolerated without clinical reaction. However, 20 minutes after receiving 160 mg (the protocol used for challenge differed from the foregoing), she became dyspneic and her FEV₁ dropped to 42% of predicted (a >50% reduction). She received two nebulized treatments of albuterol/ipratropium (a combination she was known to respond well to) with gradual return of pulmonary function to near baseline and she had no other sequelae. The diagnosis of ASA intolerance was made. She was discharged on a 1-week course of prednisone. Later, she was admitted to the hospital for desensitization, using the foregoing protocol. During the procedure, she experienced an asymptomatic drop in FEV₁ of <10% from baseline after 60 mg of ASA, and, subsequently, a drop of 25% after the 100-mg dose, accompanied by wheezing and dyspnea. The latter was treated with nebulized albuterol. She completed the protocol to a final dose of 325 mg without further reactions and was discharged on 325 mg ASA q.d.. Her dose subsequently was increased to 650 mg q.d. as an outpatient. Long-term follow-up is not yet available.

This patient's reported history of having tolerated NSAIDs in the past did not accurately predict her clear sensitivity on challenge. Many patients tolerate ASA for some years before the sensitivity develops, and the initial reactions may not be recognized by the patient as related to the ingestion of the drug.¹ Most authors propose an inpatient setting for patients with suggestive histories or for those whose asthma is moderate to severe. However, for patients in whom suspicion for ASA intolerance is quite low, appropriately staffed outpatient settings may be suitable. In the outpatient setting, i.v. access is recommended and inpatient transfer must be readily available.

In summary, although the mechanism of ASA intolerance has not yet been characterized fully, it involves aberrant regulation of leukotrienes. Among the new therapies avail-

able, leukotriene inhibitors show particular promise. For carefully selected patients with ASA intolerance, asthma, and nasal polyposis and who have not responded adequately to conventional therapy and a trial of an antileukotriene agent, ASA desensitization and treatment offers the possibility of a simple and effective treatment.

REFERENCES

1. Asad SI. Clinical and biochemical aspects of "aspirin sensitivity." *N Engl J Allergy Proc* 7:105-108, 1986.
2. Ott L. Discussion remark. *JAMA* 73:760, 1919.
3. Samter M, and Beers RF, Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 68:975-983, 1968.
4. Stevenson DD. Commentary: the American experience with aspirin desensitization for aspirin-sensitive rhinosinusitis and asthma. *Allergy Proc* 13:185-192, 1992.
5. Chafee FH, and Settipane GA. Aspirin intolerance. I. Frequency in an allergic population. *J Allergy Clin Immunol* 53:193-199, 1973.
6. Spector SL, Wangaard CH, and Farr RS. Aspirin and concomitant idiosyncracies in adult asthmatic patients. *J Allergy Clin Immunol* 64:500-506, 1979.
7. Sweet JM, Stevenson DD, Simon RA, and Mathison DA. Long-term effects of aspirin desensitization—treatment for aspirin-sensitive rhinosinusitis asthma. *J Allergy Clin Immunol* 85:59-65, 1990.
8. Stevenson D. Aspirin desensitization. *N Engl J Allergy Proc* 7:101-4, 1986.
9. Stevenson DD, and Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 108:47-51, 2001.
10. Szczeklik A, Gryglewski RJ, and Czerniawska-Mysik G. Clinical patterns of hypersensitivity to non-steroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol* 60:276-284, 1977.
11. Szczeklik A, Nizankowska E, and Dworski R. Choline magnesium trisilicylate in patients with aspirin-induced asthma. *Eur Respir J* 3:535-539, 1990.
12. Szczeklik A, Gryglewski RJ, and Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *BMJ* 1:67-69, 1975.
13. Drazen JM, Austen KF, Lewis RA, et al. Comparative airway and vascular activities of leukotrienes C-1 and D in vivo and in vitro. *Proc Natl Acad Sci USA* 77:4354-4358, 1980.
14. Ferreri NR, Howland WC, Stevenson DD, and Spiegelberg HL. Release of leukotrienes, prostaglandins and histamine into nasal secretions of aspirin-sensitive asthmatics during reaction to aspirin. *Am Rev Respir Dis* 137:847-854, 1988.
15. Christie P, Tagari P, Ford-Hutchinson AW, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in ASA-sensitive asthmatic subjects. *Am Rev Respir Dis* 143:1025-1029, 1991.
16. Juergens UR, Christiansen SC, Stevenson DD, and Zuraw BL. Inhibition of monocyte leukotriene B₄ production after aspirin desensitization. *J Allergy Clin Immunol* 96:148-156, 1995.
17. Cowburn AS, Sladek K, Soja J, et al. Overexpression of leukotriene C₄ synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 101:834-846, 1998.
18. Pasargiklian M, Bianco S, Allegra L, et al. Aspects of bronchial reactivity to prostaglandins and aspirin in asthmatic patients. *Respiration* 34:79-91, 1977.
19. Mastalerz L, et al. Protective effects of prostaglandin E₂ (PGE₂) on airway obstruction induced by aspirin (ASA) in aspirin-intolerant asthmatics. *Eur Respir J* 7(suppl 18):434, 1994.
20. Kuehl FA, Jr., Dougherty HW, and Ham EA. Interaction between prostaglandins and leukotrienes. *Biochem Pharmacol* 33:1-5, 1984.
21. Christman BW, Christman JW, Dworski R, et al. Prostaglandin E₂ limits arachidonic acid availability and inhibits leukotriene B₄ syn-

- thesis in rat alveolar macrophages by a nonphospholipase A2 mechanism. *J Immunol* 151:2096–2104, 1993.
22. Peters SP, Schulman ES, Schleimer RP, et al. Dispersed human lung mast cells. Pharmacologic aspects and comparison with human lung tissue fragments. *Am Rev Respir Dis* 126:1034–1039, 1982.
 23. Minakuchi R, Wacholtz MC, Davis LS, and Lipsky PE. Delineation of the mechanism of inhibition of human T cell activation by PGE₂. *J Immunol* 145:2616–2625, 1990.
 24. O'Hickey SP, Arm JP, Rees PJ, and Lee TH. Airway responsiveness to methacholine after inhalation of nebulized hypertonic saline in bronchial asthma. *J Allergy Clin Immunol* 83:472–476, 1989.
 25. Isreal E, Fischer AR, Rosenberg MA, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis* 148:1447–1451, 1993.
 26. Pauls JD, Simon RA, Daffern PJ, and Stevenson DD. Lack of effect of the 5-lipoxygenase inhibitor zileuton in blocking the oral aspirin challenges in aspirin-sensitive asthmatics. *Ann Allergy Asthma Immunol* 85:40–45, 2000.
 27. Dahlen B, Nizankowska E, Szczeklik A, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 157:1187–1194, 1998.
 28. Park HS, Hwang SC, Nahm DH, and Yim HE. Immunohistochemical characterization of the cellular infiltrate in airway mucosa of toluene diisocyanate (TDI)-induced asthma: comparison with allergic asthma. *J Korean Med Sci* 13:21–26, 1998.
 29. Fischer AR, Rosenberg MA, Lilly CM, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol* 94:1046–56, 1994. □

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