Pathogenesis of Aspirin-Induced Reactions in Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

• Aspirin-exacerbated respiratory disease • Pathogenesis • Cysteinyl leukotrienes
• Prostaglandins • Mast cell • Platelet-leukocyte aggregates

KEY POINTS

- Aspirin-induced reactions in aspirin-exacerbated respiratory disease (AERD) result from the inhibition of COX-1 and cause a spectrum of reaction symptoms that range from localized respiratory symptoms to systemic symptoms involving the gastrointestinal tract and skin.
- The route of aspirin exposure and premedication with leukotriene modifying drugs (LTMDs) (ie, montelukast, zafirlukast or zileuton) influence the severity of aspirin-induced reactions. Intranasal desensitization protocols and the use of LTMDs allow for decreased bronchospasm and lowered rates of extrarespiratory symptoms.
- The release of tryptase, cysteinyl leukotrienes, histamine, and prostaglandin D_2 supports a central role for the mast cell in aspirin-induced reactions.
- Platelet-leukocyte aggregates are increased in AERD and are hypothesized to contribute to the overproduction of cysteinyl leukotrienes.
- Future studies of therapeutics that target mast cells, eosinophils, platelets, and inflammatory lipid and innate type 2 immune mediators in carefully phenotyped subjects are the key to improving our understanding of the classic aspirin-induced reactions in AERD.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) encompasses 2 distinct disease phases: the chronic baseline inflammation of the upper and lower respiratory tract characterized by nasal polyposis and asthma and the acute hypersensitivity reactions triggered by inhibitors of cyclooxygenase (COX)-1. As Drs Stevenson and Szczeklik[1]

Disclosures: The authors have no relevant disclosures to report.
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Immunol Allergy Clin N Am 36 (2016) 681–691
http://dx.doi.org/10.1016/j.iac.2016.06.005 **immunology.theclinics.com**
0889-8561/16/$ – see front matter

nicely observed, "exposure to aspirin [or other COX-1 inhibitors] does not initiate or even perpetuate the underlying respiratory inflammatory disease"[1]; yet the acutely exaggerated pathophysiology observed in the setting of an aspirin-induced respiratory reaction not only serves as the diagnostic gold standard but also offers insight into the cellular and biochemical derangements that underlie AERD. Our current understanding of the pathogenesis of aspirin reactions in AERD comes from studies of aspirin challenges performed in carefully phenotyped subjects. Our future progress in this disease lies in interventional trials of targeted therapeutics in the same carefully phenotyped populations.

CLINICAL FEATURES OF REACTIONS

The consistent clinical features of aspirin-induced reactions have greatly informed our current understanding of the pathophysiology of AERD. Classically, exposure to aspirin elicits upper and/or lower respiratory symptoms within 30 to 180 minutes in patients with AERD. In addition to aspirin, these respiratory reactions are triggered by any inhibitor of COX-1 (eg, ibuprofen, naproxen, ketorolac) and can even be triggered by high doses of acetaminophen ($\geq$650 mg), which has mild COX-1 inhibitor properties,[2] but not by selective COX-2 inhibitors.[3,4] These reactions represent hypersensitivity reactions, which are not immunoglobulin (Ig) E–dependent and, therefore, are not formally classified as allergic.

In North America there are 2 well-validated and most often clinically applied aspirin challenge protocols,[5,6] involving oral aspirin and/or intranasal instillation of ketorolac, with a third protocol in Europe[7] that uses intranasal lysine aspirin. In addition to respiratory symptoms, a subset of patients with AERD also develops extrarespiratory or systemic symptoms involving the skin and gastrointestinal tract following exposure to a COX-1 inhibitor.[6,8] The route of aspirin challenge and the premedication regimen selected are the key predictors of both respiratory symptom severity and rates of extrarespiratory symptoms. In a study of 677 patients undergoing an oral aspirin challenge protocol, 38.6% of patients who were not on a leukotriene-modifying drug (LTMD) (n = 417) had a decrease in forced expiratory volume in the first second of expiration (FEV_1) of greater than 20%.[9] Whereas, of the 260 patients on an LTMD (ie, montelukast, zafirlukast, or zileuton), only 17.7% of patients had a decrease in FEV_1 of greater than 20%.[9] No benefit was seen with systemic steroids in this population; no comment was made on the change in rates of extrarespiratory symptoms, which were observed in less than 20% of the total study population. Further work has shown that on occasion LTMDs can completely prevent reaction symptoms during an oral aspirin challenge.[10] These effects of LTMDs support our current understanding of the cysteinyl leukotriene (cysLT) derangements in AERD and are covered in greater detail later.

Changing the route of aspirin exposure from oral to intranasal decreases the severity of the respiratory and extrarespiratory symptoms observed during the aspirin challenge. Because the soluble form of aspirin, lysine aspirin, is not available in the United States, the standard intranasal protocol uses intranasal ketorolac over 4 doses before completing the protocol with oral aspirin at 60 mg, 100 mg, 160 mg, and 325 mg.[11] A study of 100 patients desensitized using this intranasal ketorolac protocol demonstrated that it can be a safer way of inducing desensitization when compared with 100 patients desensitized using only oral aspirin. Intranasal ketorolac decreased the mean decrease in FEV_1 (average decrease of 13.4% in oral challenge vs 8.5% in intranasal) and decreased the percentage of patients who developed extrapulmonary reactions (23% with intranasal ketorolac vs 45% with oral challenge), particularly