Aspirin-exacerbated respiratory disease: An easy-to-overlook diagnosis

July 01, 2006
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Abstract: Patients who have aspirin-exacerbated respiratory disease (AERD) usually experience upper and lower respiratory tract symptoms about 1 to 2 hours after taking aspirin or another NSAID that inhibits the enzyme cyclooxygenase-1. In addition to symptoms such as nasal congestion, rhinorrhea, paroxysmal sneezing, periorbital edema, laryngospasm, and intense flushing, patients may have severe--often life-threatening--exacerbations of asthma. AERD occurs in about 10% to 20% of patients with asthma and in about 30% of asthmatic patients with nasal polyposis. However, AERD also occurs in patients who do not have any of these predisposing conditions. In patients with AERD, aspirin desensitization can improve asthma control, reduce the need for corticosteroids, and reduce the need for sinus surgery. (J Respir Dis. 2006;27(7):282-290)

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Aspirin: A brief history

Over the centuries, the use of aspirin has extended from the treatment of pain and fever to the prevention and management of a multitude of diseases and chronic conditions, including coronary artery disease, stroke, colon cancer, and mastocytosis. The first documented use of aspirin-related compounds was in 200 BCE when the Greek physician Hippocrates prescribed the bark and leaves of the willow tree (rich in salicin) as a treatment for pain and fever. The use of willow leaves is also mentioned in the works of Dioscorides in 100 CE and Galen in 200 CE. It was not until 1838 that the Italian chemist Raffaele Piria synthesized salicylic acid from salicin.

In 1897, Felix Hoffman, a chemist working at Bayer (a then little-known company in Germany), started experimenting with different techniques to decrease the irritating gastric effects of salicylic acid for his father who had rheumatism. He succeeded with the creation of acetylsalicylic acid, which has been the most frequently used medication worldwide since 1899. Aspirin has been available over the counter (OTC) in the United States since 1915. Although it has proved to be a miracle drug for millions, it is a source of considerable morbidity for others.

In 1922, Widal and associates described the first case of aspirin sensitivity, asthma, and nasal polyposis along with the first successful attempt at aspirin desensitization. The constellation of aspirin sensitivity, asthma, and nasal polyposis was described by Max Samter in the 1960s and is still often referred to as Samter's triad.

It is increasingly recognized that many patients with AERD do not have asthma and experience respiratory symptoms only after ingestion of aspirin. Since not all patients who react adversely to aspirin meet all criteria for Samter's triad, the term "aspirin-exacerbated respiratory disease" was adopted to more accurately describe this syndrome. The term "AERD" is used to describe a condition in patients who experience upper or lower respiratory tract symptoms after ingestion of aspirin or other NSAIDs that inhibit the enzyme cyclooxygenase (COX)-1. This term is preferable to "aspirin-intolerant asthma" because some of these patients do not have asthma, and ingestion of aspirin elicits only upper airway symptoms.

Epidemiology and presentation

More than 26 million Americans have asthma. Of these persons, it is estimated that 10% to 20% experience an idiosyncratic reaction after ingestion of aspirin or other NSAIDs that inhibit COX-1. It is estimated that 20% to 30% of patients with chronic hyperplastic eosinophilic sinusitis (CHES) have an exacerbation of upper and lower airway symptoms on exposure to aspirin and other
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NSAIDs. Interestingly, two thirds of patients with asthma, nasal polyps, and sinus disease experience no untoward effects of COX-1 inhibition.

Large clinical studies have determined that 57% to 66% of patients with a diagnosis of AERD are female and that the average age at onset of rhinitis/sinusitis, nasal polyps, or asthma is between 30 and 34 years. In one study, atopy was reported in only 33% of patients, a figure not significantly different from the prevalence of atopy in the population without AERD, suggesting that the mechanisms involved in allergic (IgE) sensitization are not relevant to the pathophysiology of AERD. Up to 6% of patients with AERD have an affected family member, which suggests a genetic predisposition.

Aspirin sensitivity is not considered an "allergic" disorder because the mechanism is not IgE-mediated, but rather it is a biochemical consequence of COX-1 inhibition in susceptible persons (see "The pathogenesis of AERD"). In contrast to IgE-mediated reactions, NSAIDs that inhibit COX-1 can cause symptoms on initial ingestion in patients with AERD and do not require previous sensitization.

Furthermore, since these reactions reflect the pharmacologic effects of COX-1 inhibition, patients react to structurally unrelated compounds (such as aspirin and NSAIDs), whereas compounds structurally related to aspirin (such as the yellow dye tartrazine or dietary salicylates) are generally well tolerated. A partial list of NSAIDs that inhibit COX-1, and thus may precipitate respiratory symptoms, is shown in Table 1.

Patients with AERD may experience nasal congestion, rhinorrhea, paroxysmal sneezing, injection of the conjunctivae, periorbital edema, laryngospasm, intense flushing, and severe--often life-threatening--exacerbations of asthma; these symptoms typically occur about 1Z|x to 2 hours after taking aspirin or other NSAIDs that inhibit COX-1. Patients can experience predominantly lower or upper respiratory tract symptoms; however, most have both simultaneously.

The provoking dose of aspirin varies among patients. Some patients tolerate small doses, while others react to the same dose with severe bronchospasm, resulting in intubation or death. In graded diagnostic challenges, reactions most commonly occur at aspirin doses of about 60 to 100 mg. The diagnosis is suspected in any patient with a compelling clinical history of upper or lower respiratory tract symptoms within 1 to 2 hours after aspirin or NSAID exposure. In addition, for patients who have avoided ingestion and cannot provide a history of safely ingest-ing these agents, it is prudent to assume the presence of aspirin/NSAID sensitivity if the patient has moderate to severe asthma, especially with evidence of extensive sinus disease and nasal polyps.

In patients in whom AERD is suspected, the definitive diagnosis can be made only by performing a challenge with oral aspirin in a controlled inpatient setting. Diagnostic challenges should be performed only by a trained physician in a location where advanced cardiopulmonary resuscitation services are available. It should be noted that about 25% of patients with a convincing clinical history of aspirin allergy have a negative aspirin challenge. Aspirin desensitization

Paradoxically, patients who react to aspirin and related compounds have better symptom control after undergoing aspirin desensitization and maintaining lifelong aspirin therapy. Aspirin desensitization is a proven therapy in patients with AERD. It decreases basal and aspirin-stimulated leukotriene synthesis. It also has been demonstrated to decrease sensitivity to cysteinyl leukotrienes (CysLTS) by dramatically down-regulating expression of CysLT receptors. Investigators have shown that 2 weeks of aspirin therapy decreases leukotriene B₄ synthesis to levels found in control patients.

Large clinical studies that examined the efficacy of aspirin desensitization have shown that about 67% of patients respond to aspirin desensitization with a significant improvement in smell scores, decreased nasal symptoms, and diminished need for antibiotics to treat sinusitis. It should be noted that in this series, about 15% of patients were unable to complete aspirin desensitization because of adverse effects or a medical contraindication to aspirin. Other investigators have also demonstrated that patients who have undergone aspirin desensitization require fewer courses of antibiotics and have a decreased need for sinus surgery, with a restored sense of smell.

In our studies, we observed that the incidence of acute sinus infection was reduced from a mean of 158 days per year in the year before aspirin desensitization to a mean of 61 days per year following desensitization.

Full benefit from aspirin desensitization requires that comorbid conditions contributing to concurrent rhinitis--especially allergic rhinitis--and sinusitis also be addressed. The benefits are tempered by the risks of desensitization and long-term aspirin administration.
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Aspirin desensitization may be indicated in patients with AERD who require aspirin treatment for an unrelated medical condition, such as coronary artery disease or rheumatoid arthritis. Selective COX-2 inhibitors are generally well tolerated by persons with AERD, but these agents do not attenuate respiratory symptoms.

Aspirin desensitization involves successive ingestion of increasing doses of aspirin until a therapeutic dose is achieved (normally 650 mg twice daily). Aspirin desensitization should be performed in an inpatient setting under direct medical supervision by a physician who is experienced in aspirin desensitization, because the procedure can precipitate life-threatening asthma exacerbations. The use of systemic corticosteroids and leukotriene modifiers reduces, but does not eliminate, the risk associated with aspirin desensitization.

During aspirin desensitization, continuous monitoring of patients' vital signs and lung function is required. Patients are pretreated with systemic corticosteroids—for example, 0.5 mg/kg of prednisone twice a day starting 24 hours before and continuing through the duration of the procedure—in addition to a leukotriene inhibitor twice a day starting 24 hours before aspirin desensitization.

Leukotriene inhibitors blunt lower respiratory tract reactions without significantly attenuating upper respiratory tract reactions and, as such, patients experience predominantly naso-ocular symptoms. Some specialists also recommend the addition of a long-acting β₂-agonist, such as formoterol, to help prevent bronchospasm.

Aspirin is administered orally at 2-hour intervals over 2 to 3 days in incremental doses until a final dose of 650 mg is tolerated (Table 2). Forced expiratory volume in 1 second (FEV₁) is measured before the administration of each dose, and the dose is held constant if FEV₁ is less than 80% of the baseline FEV₁. If the FEV₁ drops below 80%, patients are treated with inhaled or nebulized bronchodilators and, if necessary, anticholinergics, until the FEV₁ is restored. In these instances, patients are rechallenged with the same (or lower) dose of aspirin that was responsible for the asthma exacerbation, and subsequent doses are increased as tolerated.

At the conclusion of successful aspirin desensitization, patients are generally discharged from the hospital with instructions to take 650 mg of aspirin twice a day. In patients who can medically tolerate aspirin, it is considered safe to give other NSAIDs.

Studies show that patients can skip a daily dose of aspirin without becoming resensitized. However, an increasing percentage of patients react each day after missing 2 consecutive days until, at about 1 week, all patients have lost their tolerance. We recommend that patients receiving the above-mentioned dose of aspirin be given a proton pump inhibitor for gastric lining protection.

Summary of recommendations

AERD is a common clinical entity, with an estimated 10% to 20% of patients with asthma experiencing an exacerbation on ingestion of aspirin or other NSAIDs. The diagnosis of AERD should be suspected in any patient who has moderate to severe persistent asthma that is suboptimally controlled with maximal medical therapy and who has recurrent nasal polyp growth after surgery. These patients may be excellent candidates for aspirin desensitization.

Although cross-reactivity among all NSAIDs is not absolute, physicians should assume that an adverse reaction to one NSAID is tantamount to sensitivity to all NSAIDs. Most patients with AERD can tolerate acetaminophen, nonaspirin salicylates, and selective COX-2 inhibitors. However, since a small percentage of patients react to these compounds, these agents should be used cautiously, with the initial dose administered under medical supervision.

Patients with asthma who have never used an NSAID represent a common clinical problem. Any patient with moderate to severe persistent asthma and nasal polyposis who has an uncertain aspirin or NSAID exposure history should undergo aspirin challenge under medical supervision, since 20% to 30% of these patients will have adverse reactions to these drugs.

Persons with mild asthma who have never been exposed to aspirin or NSAIDs should be educated about the risk and offered the opportunity to undergo challenge testing under careful medical supervision to determine whether this class of medications is safe for them. Patients with AERD need to be educated to be extremely vigilant about reading the labels of OTC medications, since aspirin and NSAIDs are found in hundreds of OTC preparations for a variety of ailments.

Patients with AERD typically have moderate to severe persistent asthma with associated CHES and nasal polyposis. Therefore, management frequently requires the use of multiple medications—including leukotriene inhibitors, antihistamines, and inhaled or systemic corticosteroids—in addition to aspirin desensitization. Concomitant IgE-mediated inflammation of the respiratory tract by aeroallergens needs to be ruled out, because it can act as a confounder in patients with severe symptoms.
Aspirin desensitization can be an effective adjunct in the management of AERD, and it should be performed in a controlled inpatient setting where cardiopulmonary resuscitation is immediately available.

Further elucidation of the pathogenic mechanism of AERD holds promise for the development of effective treatments. Histologic specimens show sinus and nasal polyp tissue rich in eosinophils. Since eosinophils are a primary source of CysLTs and fibrogenic growth factors, drugs that directly inhibit their presence and activation could potentially provide benefit to patients who have AERD. Drugs targeting 5-lipoxygenase (5-LO) and 5-LO-activating protein also hold promise to ameliorate the burden of disease experienced by these patients.

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