
Blocking aspirin-induced bronchospasm

The initial report of aspirin intolerance appeared more than a century ago, only 3 years after aspirin was synthesized.¹ Fatal reactions from aspirin were described in the 1930s.^{2,3} However, it was not until 1968 that Samter and Beers⁴ described a clinical triad of nasal polyposis, bronchial asthma, and “life threatening reactions to acetylsalicylic acid” as a clinical syndrome.

We now recognize that patients with this syndrome exhibit an aggressive inflammation of the upper and lower airways,⁵ for which provocation of asthma with or without nasal or ocular symptoms after ingesting aspirin (and other nonsteroidal anti-inflammatory drugs) is a marker. Despite avoidance of aspirin and cross-reacting drugs, this subgroup of patients frequently experience refractory rhinosinusitis and asthma, which requires repeated sinus surgery procedures and regular administration of oral steroids. The syndrome of aspirin-exacerbated respiratory disease (AERD) affects an estimated 4% to 10% of adult asthmatic patients.⁶ In as many as 50% of AERD patients, asthma is severe and steroid dependent.⁷ Once AERD develops, it is present for the rest of the patient's life.

The term *desensitization* has traditionally been used to describe a procedure that entails modification of IgE-mediated (allergic or anaphylactic) potential to a substance, frequently an antibiotic such as penicillin, via its repetitive administration in a graded-dose fashion. Widal et al⁸ treated a patient in 1922 with gradually increasing doses of aspirin so that instead of reacting to aspirin when a previously established provoking dose was administered, aspirin reexposure was tolerated, in advancing doses, without adverse reaction. Zeiss and Lockey⁹ observed the same phenomenon of aspirin desensitization, and ultimately this procedure was used to allow individuals with AERD who require aspirin (or an aspirin-like drug) for treatment of arthritis or cardiovascular conditions to safely take aspirin without adverse reaction.

The aspirin desensitization procedure, in which a state of tolerance can be induced and maintained, entails administration of incremental oral doses of aspirin for several days until a dosage of 650 mg (2 tablets) of aspirin can be taken without adverse reaction. Because aspirin-provoked reaction may be delayed for up to 3 hours, the minimum interval between doses of aspirin must reflect this; for this reason, the desensitization may span 3 to 4 days. Aspirin desensitization entails provoking respiratory reaction to aspirin, then administering the same dose that provoked this reaction, such that an individual may have repeated reactions to the same dose. When an aspirin-sensitive individual no longer reacts to 650 mg of aspirin, desensitization has been achieved. Aspirin

desensitization can be maintained indefinitely if aspirin is taken on a daily basis. A number of studies have demonstrated that if aspirin is taken regularly to perpetuate the desensitized state, approximately two thirds of AERD patients experience improvement.^{5,10}

Bronchospastic reaction in AERD results from enhanced release of leukotrienes provoked by aspirin¹¹ in combination with greater target organ sensitivity to leukotrienes.¹² Cyclooxygenase inhibition results in a loss of the protective bronchodilator prostaglandin E₂ (PGE₂) and leads to amplified generation of bronchoconstrictor leukotrienes. More specifically, removal of PGE₂, a potent inhibitor of 5-lipoxygenase, leads to a loss of its braking effect, thereby promoting release (and overproduction) of leukotrienes.⁵ The rate-limiting enzyme leukotriene C₄ is overexpressed in AERD patients; a correlation between the degree of leukotriene C₄ synthase activity and the degree of aspirin sensitivity exists.¹³ It is the one-two punch of greater leukotriene release and exaggerated airway response to leukotrienes that explains the major manifestation of the AERD syndrome recognized by Samter and Beers⁴: aspirin-induced bronchospasm.

Aspirin-provoked reaction can be attenuated by administration of antileukotriene drugs¹⁴; however, the protection is not complete, and the response is heterogeneous.¹⁵ The antileukotriene drugs shift the dose-response curve to the right and transfer aspirin-provoked reaction to the upper airway.¹⁶ However, aspirin-provoked reaction has also been attenuated in AERD patients by pretreatment with cromolyn,^{17,18} nedocromil,¹⁸ salmeterol,¹⁹ clemastine,²⁰ inhaled PGE₂,²¹ acyclovir,²² and more recently tacrolimus.²³ One would expect that agents that directly modify leukotriene effects, either via 5-lipoxygenase inhibition or leukotriene receptor antagonism, would have a more substantial impact on aspirin-provoked bronchospasm than other asthma controller drugs, but how do the blocking effects of antileukotriene agents compare with the effect of other controllers, such as inhaled steroids, long-acting β -agonists, and theophylline? In this issue of the *Annals*, White et al²⁴ report a large study of 678 AERD patients undergoing aspirin desensitization from 1981 to 2004 in which the blocking effects of various controller agents were examined. Interestingly, their data clearly demonstrate that antileukotriene drugs exert the most substantial influence on aspirin-provoked reaction. Qualitatively similar effects were observed for inhaled steroids and long-acting β -agonists. Curiously, patients exposed to theophylline exhibited an opposite effect: these patients were more likely to experience lower airway reactions during aspirin desensitization. Ostensibly, this would imply that for AERD patients taking

theophylline who are scheduled to undergo aspirin desensitization tapering off this medication before proceeding with desensitization is in their best health care interest. However, the variation in combinations of medication exposures in AERD patients in this study in large part reflected the changing trends in asthma pharmacotherapy during the period of study, and the authors were unable to control for underlying disease severity in their analyses. Patients taking theophylline were more likely to be desensitized during the 1980s and would not have received asthma medications available more recently (eg, more potent inhaled steroids). For these reasons, additional evidence is required to establish a reverse effect of theophylline on aspirin-provoked reaction.

Despite exposure to medications that can attenuate aspirin-induced bronchospasm,^{16–23} this reaction can be volatile and potentially life-threatening. Patients with AERD should not undergo this procedure at a time when asthma is unstable. Because serious bronchospasm may occur at any time during aspirin desensitization, this procedure needs to be performed in a setting that will permit patients to be closely monitored throughout the procedure and in which emergency-resuscitative equipment and trained personnel are readily available. Based on the findings reported by White et al,²⁴ before taking an aspirin a day AERD patients should also be receiving combination controller therapy.

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