

Side effects from daily aspirin treatment in patients with AERD: Identification and management

Andrew A. White, M.D. and Donald D. Stevenson, M.D.

Since the 1980s, aspirin desensitization followed by long-term treatment with aspirin in Aspirin Exacerbated Respiratory Disease (AERD) has been recognized to be an effective add-on to standard anti-inflammatory treatment. Recent studies outlining safer and more streamlined protocols for aspirin desensitization have begun to move aspirin desensitization from the inpatient setting at highly specialized centers to the outpatient community of allergy specialists and pulmonologists. It is now more incumbent than ever for all physicians caring for these patients to be familiar, not only with treatment of AERD, but with the potential complications that may arise with continued use of higher-dose aspirin therapy.

In this issue of *Allergy and Asthma Proceedings*, Baker and Quinn present an excellent review of the gastrointestinal risks associated with aspirin therapy.¹ The AERD patient truly represents a unique clinical situation that, in recent decades, is not encountered in any other patient population taking daily aspirin therapy. First, aspirin desensitization leads to impermanent tolerance of aspirin. Thus after only 48 hours without an aspirin dose, respiratory sensitivity to aspirin and all nonsteroidal anti-inflammatory drugs (NSAIDs) returns.² Therefore, temporary discontinuation of aspirin is not a reasonable option for patients experiencing side effects. Second, the lowest dose of aspirin in the published literature that is shown to reduce polyp burden and improve asthma outcomes is 300 mg once per day. This small study by Rozsasi *et al.* showed that one 300-mg aspirin daily prevented polyp formation, whereas in a second group taking aspirin 100 mg daily it did not.³ In a long-term study at our institution, at least 325 mg twice daily was required to control AERD. In some patients, who failed to respond to 325 mg twice daily, increasing aspirin to 650 mg twice daily then controlled respiratory inflammation.⁴ Although doses as low as 81mg of aspirin a day will reliably maintain aspirin desensitization,² this dose is usually ineffective at controlling AERD. In our experience, the

majority of patients who present for aspirin desensitization do so for the benefits to their airway disease rather than for cardiac or rheumatologic conditions. Thus, decreasing the dose of aspirin is generally not a practical solution for patients experiencing gastrointestinal side effects or bleeding. Finally, AERD patients frequently have aggressive airway inflammation, which necessitates the use of high-dose nasal steroids, inhaled corticosteroids, and in many patients either frequent systemic corticosteroid bursts or low-dose continuous systemic steroids. The potential for corticosteroid effects compounded on the NSAID-induced gastritis and bleeding risk is certainly a concern in this patient group.^{5,6}

It should not be overlooked that aspirin has a variety of other side effects that also need to be considered when consenting a patient for aspirin desensitization. Baker and Quinn¹ nicely summarize the known reasons for discontinuation of aspirin therapy based on available data. Additionally, NSAIDs inhibit prostaglandin-mediated afferent vasodilation, and, in conjunction with angiotensin-converting enzyme-inhibitor drugs, angiotensin receptor blocker drugs, or dehydration, may contribute to a decline in renal function.

It would appear that an algorithmic approach to prophylaxis in the patients requiring long-term high-dose aspirin therapy might be beneficial. For all patients with established risk factors for gastrointestinal bleeding, the addition of a proton pump inhibitor at the conclusion of aspirin desensitization seems to us a reasonable strategy. For the remaining AERD patients, we are inclined to wait and see whether gastric pain or bleeding occurs. We respectfully disagree with the author's implication that all patients on high-dose aspirin therapy need prophylaxis for gastrointestinal side effects. There seems to be very significant difference in individual patients as to how well they tolerated daily aspirin. In the article by Lee *et al.*,⁴ gastritis was just as likely to occur in patients receiving 325 mg aspirin twice daily as in the population receiving 650 mg twice daily and occurred in less than 10% of AERD patients. We have followed the vast majority of patients who have taken aspirin 650 mg twice daily for years and are struck by the paucity of bleeding or gastric side effects.

Therefore, only if gastric pain or bleeding occurs would we add a proton pump inhibitor or a histamine-2 blocker. Recent evidence does raise concern about long-term consequences of potent acid suppression including the potential for increased pneumonia,⁷ decreased vitamin and calcium absorption with loss of bone mineral density,⁸ and potential for drug interactions, namely with clopidogrel.⁹ Although many of these issues require further study, the FDA has required modification of safety information on proton pump inhibitors. These issues should also be discussed with patients, and in certain situations, the potential risk of PPI therapy may outweigh the benefit, particularly when prophylactic lifelong therapy is being considered.

Our group has anecdotally found misoprostol, a substitute for PGE₂, at 200 µg 3–4 times daily to be a useful addition to AERD patients experiencing gastric pain from aspirin therapy. Unfortunately, misoprostol use leads to uterine contractions and is therefore absolutely contra-indicated in women of childbearing potential. It does have gastrointestinal side effects, particularly nausea, which may also limit its usefulness in some patients. However, when taken with food and gradually titrating up the dose, most patients can tolerate this medication over time.

The issue of bleeding, particularly cutaneous ecchymosis, with or without known preceding trauma, is the consequence of inhibition of platelet thromboxane B₂ by aspirin's destruction of cyclo-oxygenase 1. It is a nettlesome problem, particularly in older patients with fragile skin and capillaries. There is not an easy answer for these patients, except the conundrum of putting up with bruising or reducing and sometimes stopping aspirin therapy. Serious bleeding in the nose, lungs, and GI tract are unusual but discontinuation of aspirin is usually required if this complication occurs.

The only other problematic event is the appearance of ASA-induced urticaria. This is really a separate drug reaction to aspirin and, although fortunately rare, does require concomitant treatment with antihistamines, sometimes bursts of corticosteroids, and occasionally discontinuation of aspirin.

AERD is a unique inflammatory airway disease of the respiratory mucosa. It is vitally important that physicians treating AERD are aware not only of the role of aspirin desensitization in the long-term management of this condition, but are able to provide to our patients an evidence-based discussion on the risk–benefit ratio of long-term aspirin therapy. Our appraisal of the existing data and our own clinical experience concludes that, for almost all patients, the benefit of aspirin therapy outweighs the risk and that, although gastrointestinal side effects occur, they are infrequent and serious gastrointestinal bleeding remains an uncommon event.

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