

Rapid Aspirin Challenge in Patients with Aspirin Allergy and Acute Coronary Syndromes

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Abstract Aspirin allergy in a patient with acute coronary syndrome represents one of the more urgent challenges an allergist may face. Adverse reactions to aspirin are reported in 1.5 % of patients with coronary artery disease. A history of adverse reaction to aspirin often leads to unnecessary withholding of this medication or use of alternative antiplatelet therapy which may be inferior or more costly. Aspirin therapy has been shown to reduce morbidity and mortality in patients with coronary artery disease. Rapid aspirin challenge/desensitization in the aspirin allergic patient has been consistently shown to be both safe and successful in patients with acute coronary syndromes.

Keywords Aspirin allergy · Aspirin reaction · Acute coronary syndrome · Coronary artery disease · Aspirin therapy · Aspirin challenge · Aspirin desensitization · Aspirin benefit

Introduction

Aspirin has been consistently shown to reduce morbidity and mortality associated with coronary artery disease. There is a general consensus for its net benefit in secondary prevention of coronary artery disease (CAD) and for acute ischemic syndromes. The most recent American College of Cardiology/American Heart Association (ACA/AHA) guidelines

recommend daily doses of 75 to 162 mg for secondary prevention of coronary artery disease. Similarly, the ACA/AHA guidelines recommend an immediate loading dose of non-enteric coated aspirin in patients presenting with probable or definitive non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI), with daily dosing indefinitely thereafter. Use of aspirin for these indications has resulted in a reduction in recurrent myocardial infarctions and death [1]. Unfortunately, a reported history of an adverse reaction to aspirin often results in the avoidance of this potentially lifesaving medication. This is despite numerous studies which have shown that patients may safely undergo rapid aspirin challenge/desensitization, including in the setting of acute coronary syndromes [2–11].

Aspirin reactions in the general population have been estimated to range from 0.3 to 0.9 % [12]. Reported aspirin reactions in patients with CAD appear to be even more common. A recent review of 9565 patients with CAD revealed that 1.5 % of patients reported a prior reaction to aspirin. In this same review, aspirin was withheld in 76.1 % of patients, while clopidogrel was substituted for aspirin in 17.6 % of patients. Only four patients were referred to an allergist. All four patients underwent successful aspirin challenge/desensitization and subsequently tolerated daily aspirin therapy [13•].

Evaluation and management of patients with a reported history of reaction to aspirin require further characterization of the nature of their reaction. Adverse drug reactions (ADRs) are classified broadly into two groupings, type A and type B [14]. Type A events are fairly common in healthy patients at sufficiently high doses and include overdose, various side effects, drug-drug interactions, and indirect effects such as alteration of the gut microbiome by antibiotics. The most common type A reactions resulting from aspirin include several side effects such as dyspepsia, gastric ulcers, and gastrointestinal bleeding. These

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reactions are less common at low doses such as 81 mg daily. Even with higher dosing, concurrent treatment with a proton pump inhibitor may prevent these side effects and allow the patient to tolerate daily aspirin. Patients with type A ADRs do not require and will not benefit from aspirin challenge/desensitization. These patients can usually be treated with daily aspirin without further evaluation by an allergist.

Type B ADRs due to aspirin and/or non-steroidal anti-inflammatory drugs (NSAIDs) include several distinct hypersensitivity syndromes, both non-immune and immune/IgE mediated. Thus, these syndromes may be divided by their pathophysiologic mechanism, either COX-1 inhibition (a non-immune mediated “class effect” likely to occur with aspirin or any NSAID) or a probable IgE-mediated reaction to a single NSAID. Key components of the history must then include a discussion of prior reactions not only to aspirin but to NSAIDs as well. The various syndromes have been previously described and are discussed below [15, 16•]:

COX 1 Inhibition—Class Effect Reactions

- *Aspirin exacerbated respiratory disease (AERD)*—AERD is characterized by asthma, recurrent sinus disease with nasal polyps, and sensitivity to aspirin and NSAIDs. Asthma and sinus disease with nasal polyps are chronic components of AERD and occur in the absence of exposure to aspirin. Patients experience acute worsening in their nasal and respiratory symptoms within 1–2 h of ingestion of aspirin or NSAIDs. These reactions are evoked by COX-1 inhibition rather than an IgE-specific signaling mechanism. Prostaglandin E2 (PGE2) is an important mast cell stabilizer and inhibitor of the 5-lipoxygenase pathway, acting to prevent histamine release and the accumulation of leukotrienes. COX-1 inhibition by NSAIDs diminishes PGE2, releasing the constitutive restraint on 5-lipoxygenase, culminating in a rapid rise in cysteinyl leukotrienes. Reactions can be quite severe, particularly if bronchospasm occurs in a patient with poorly controlled asthma. The severity of these reactions warrants premedication before aspirin challenge/desensitization. This will be discussed in more detail in relation to our suggested challenge protocol. AERD should be considered in patients with a history of asthma, as the prevalence of AERD among asthmatics is estimated to be 7 %. When combined with finds of pansinusitis, up to one third of asthmatic will have underlying AERD [17].
- *NSAID exacerbated cutaneous disease*—Between 20 and 40 % of patients with chronic urticaria report worsening of their urticaria and/or angioedema with ingestion of aspirin or NSAIDs [18]. A history obtained from these patients is notable for preceding urticaria in the

absence of NSAIDs. Patients generally report previous tolerance to NSAIDs but now experience worsening of their urticaria with these medications. Reactions are dose dependent, and low dose aspirin may be below the threshold to cause a response. Alternatively, some may react to even a low dose aspirin. These patients represent some of the most difficult to desensitize as they may continue to experience worsening of cutaneous symptoms. In fact, of the 11 failed rapid aspirin desensitizations reported in the literature, five of the patients had underlying chronic urticaria with worsening of their cutaneous disease [19].

- *NSAID induced cutaneous reaction*—Patients without AERD or preexisting chronic urticaria may also experience class effect reactions from COX 1 inhibition. In these patients, de novo urticaria and angioedema is precipitated by aspirin or other NSAIDs. The mechanism is felt to be similar to the above reactions with COX-1 inhibition leading to depletion of PGE2 and subsequent histamine release from mast cells. Cutaneous manifestations may vary from urticaria to isolated periorbital angioedema [20, 21]. Patients without preexisting chronic urticaria tend to be more easily desensitized than those with chronic urticaria.

Probable IgE-Mediated Reactions

- *Single NSAID induced cutaneous or systemic reactions*—Reaction to a single NSAID is suggestive of a probable IgE-mediated reaction and has even been proven by skin prick and ELISA in the case of propyphenazone [22]. In contrast, reaction through COX-1 inhibition would be expected to occur with any NSAID at a sufficient dosage. Further evidence for the existence of specific IgE to NSAIDs includes the observation that some patients will also react to structurally similar NSAIDs but will not react to structurally dissimilar NSAIDs. Ibuprofen is the most commonly reported medication causing single NSAID reactions in the USA. Aspirin is structurally dissimilar to NSAIDs and accordingly should not cause a reaction in a patient with single NSAID induced reactions. IgE-mediated reactions to aspirin are rarely suggested in the literature. There are two reports of patients who experienced urticaria only to aspirin. One such patient tested positive by skin prick to lysyl-aspirin and the other tested positive by radioallergosorbent inhibition testing to lysyl-aspirin [23, 24]. Certainly, this suggests that IgE-mediated reactions to aspirin including anaphylaxis could occur, though there are no convincing cases in the literature. A recent review of drug induced anaphylaxis did find frequent reports of severe reactions due to NSAIDs, though all observed reactions to aspirin were noted to be a class effect rather than an IgE-mediated process [25•].

Other Reactions

- Other reactions to NSAIDs have been reported include severe and life-threatening skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These reactions to NSAIDs are extremely rare, however, and aspirin is almost never implicated as a possible etiology [26]. In the case that aspirin is implicated in SJS/TEN, aspirin challenge should not be attempted. Similarly, aspirin challenge should not be attempted if aspirin is implicated as a cause of drug rash with eosinophilia and systemic symptoms (DRESS), serum sickness, or allergic interstitial nephritis. These are reactions in which aspirin challenge/desensitization could be life threatening and/or entirely ineffective due to the underlying mechanisms involved.

Aspirin Challenge Protocols—a Review of the Literature

As with most drug challenge/desensitizations, there are numerous published protocols available in the literature. These protocols vary based on starting dose, dosing interval, dose escalation, and dose at completion. A lack of consensus may in some part be due to inherent heterogeneity in the study population. Desensitization protocols are performed on a series of patients with self-reported adverse reactions to aspirin. The study population may include a mix of patients with various hypersensitivity syndromes, as well as some with prior side effects of aspirin. Other included patients may have previously experienced a reaction to another medication while also taking aspirin, where aspirin may have been a so-called “innocent bystander.” Patients who experienced a side effect of aspirin, or reacted to another medication completely, should be able to complete the challenge/desensitization without reaction. The inclusion of these patients makes it difficult to directly compare protocol success rates.

Rapid aspirin challenge/desensitization in patients with acute coronary syndromes, however, may be viewed separately from other challenge/desensitizations in non-urgent situations. The immediate need for aspirin in patients with acute coronary syndromes trumps the competing desire to accurately diagnose these patients as aspirin allergic or not. The short-term goal becomes the safe and expedient administration of aspirin for antiplatelet effect. In these circumstances, the prevention of severe reactions and the ability to take daily aspirin become the most important end points. In this respect, the variety of aspirin challenge/desensitization protocols has all been successful. A 2015 review by Woessner found 255 cases of reported aspirin desensitizations in patients with coronary artery disease. Two hundred forty-four of these desensitizations were noted as “successful” with the subsequent tolerance of daily aspirin therapy [19]. No significant morbidity or

mortality has been reported in either successful or failed attempts [2–11].

The safety and success of aspirin challenge/desensitization using various protocols demonstrate that there is no single correct approach. The majority of protocols begin with very low doses of aspirin ≤ 1 mg. The protocol described by Wong et al. begins at a dose of 0.1 mg [2]. Although there is no direct harm in beginning at these very low doses, they do add additional time to the protocol and may delay challenge/desensitization to prepare these doses which are not commercially available. A 2011 study of AERD patients by Lee and Stevenson found that most reactions occurred at doses between 45 and 100 mg of aspirin [26]. A 2005 study by Asero evaluated 117 patients self-reporting a history of urticaria or angioedema with a single NSAID. Asero used an initial challenge dose of 125 mg of aspirin in an effort to differentiate single NSAID reactions from NSAID induced cutaneous reactions due to COX-1 inhibition. Though 28 of the 117 patients did develop urticaria, not a single patient experienced a severe reaction [27]. These findings suggest that a starting dose need not be exceptionally low, particularly in patient reporting a reaction limited to urticaria. A lack of compelling evidence to support IgE-mediated reactions to aspirin also negates the need for very low initial doses.

As previously mentioned, the end dose of aspirin varies between protocols, up to a maximum of 325 mg. Higher doses are more likely to elicit a reaction due to COX-1 inhibition in patients with AERD, a history of chronic urticaria or urticaria/angioedema induced by COX-1 inhibitors. The need for higher doses of aspirin in the acute management of coronary syndromes has been addressed by the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial. CURRENT–OASIS 7 investigators found no difference between high dose and low dose aspirin combined with clopidogrel with respect to cardiovascular death, myocardial infarction, or stroke following acute coronary syndromes [28]. Protocol dosing to 325 mg in the acute setting may induce unnecessary reactions when a goal maintenance dose of only 81 mg is required.

Timing of Challenge/Desensitization

Ideally, aspirin challenge/desensitization would be performed before there is an urgent indication for aspirin, while the patient is in good health. This highlights the utility of referring all patients with reported aspirin or NSAID reactions to an allergist due to the inherent risk of coronary artery disease as patients age. Aspirin challenge/desensitization may be challenging in the patient experiencing an acute coronary syndrome. These patients are sometimes hemodynamically unstable or critically ill at the time aspirin is needed. Though there are no reports of serious adverse events due to rapid aspirin challenge/desensitization,

there is an inherent risk in challenging an unstable patient. Therefore, it would seem prudent to stabilize the patient including coronary stent placement, if indicated, prior to evaluation for aspirin challenge/desensitization. Once the patient is stabilized, challenge/desensitization may be performed as an inpatient or after discharge in the outpatient setting.

In addition to delaying challenge/desensitization of unstable patients, there is one other group in which delay may be reasonably considered. That is, patients with active urticaria are less likely to be successfully desensitized. As previously mentioned, 5 of the 11 unsuccessful desensitizations reported in the literature occurred in patients with active urticaria [19]. Though the risk of a life-threatening reaction is highly unlikely in these patients, challenge/desensitization tends to be unsuccessful due to worsening of urticarial symptoms. If a reasonable alternative antiplatelet regimen is available, this may be considered with plan for aspirin challenge/desensitization at a later date after the patient's urticaria has remitted.

Alternative Antiplatelet Regimens

If aspirin challenge/desensitization must be delayed, which antiplatelet regimen should be used in the interim? In patients presenting with unstable angina or NSTEMI, ACA/AHA guidelines recommend that all patients treated conservatively without stent placement receive dual antiplatelet therapy with aspirin and clopidogrel for up to 1 year. In the aspirin allergic patient, they recommend monotherapy with clopidogrel [29]. Thus, if a stent is not placed, clopidogrel monotherapy may be utilized until the patient is stable enough for aspirin challenge/desensitization. Patients requiring percutaneous intervention with placement of a bare metal or drug-eluting stent also require dual antiplatelet therapy for at least 1 month and at least 1 year, respectively. Alternative antiplatelet regimens in the aspirin allergic patient are not described in the ACA/AHA guidelines in patients undergoing stent placement. This is both a reflection of a lack of evidence to recommend alternative antiplatelet regimens as well as the importance of aspirin therapy. Alternative antiplatelet regimens in the aspirin allergic patient are an active area of debate. A recent journal article posed the question to a panel of cardiologists as to what antiplatelet regimen should be used in an aspirin allergic patient who has undergone stent placement. Though a number of cardiologists appropriately suggested aspirin desensitization if possible, there were a variety of antiplatelet regimens suggested including various monotherapies or combinations of clopidogrel, ticagrelor, prasugrel, cilostazol, rivaroxaban, and warfarin [30]. Ultimately, the choice of antiplatelet therapy will be decided by the preference of the cardiologist. Though certainly not ideal, this debate suggests that there are alternative antiplatelet agents which may be utilized in the short term to manage an unstable patient until aspirin challenge/desensitization may be performed.

Suggested Approach to the Aspirin Sensitive Patient

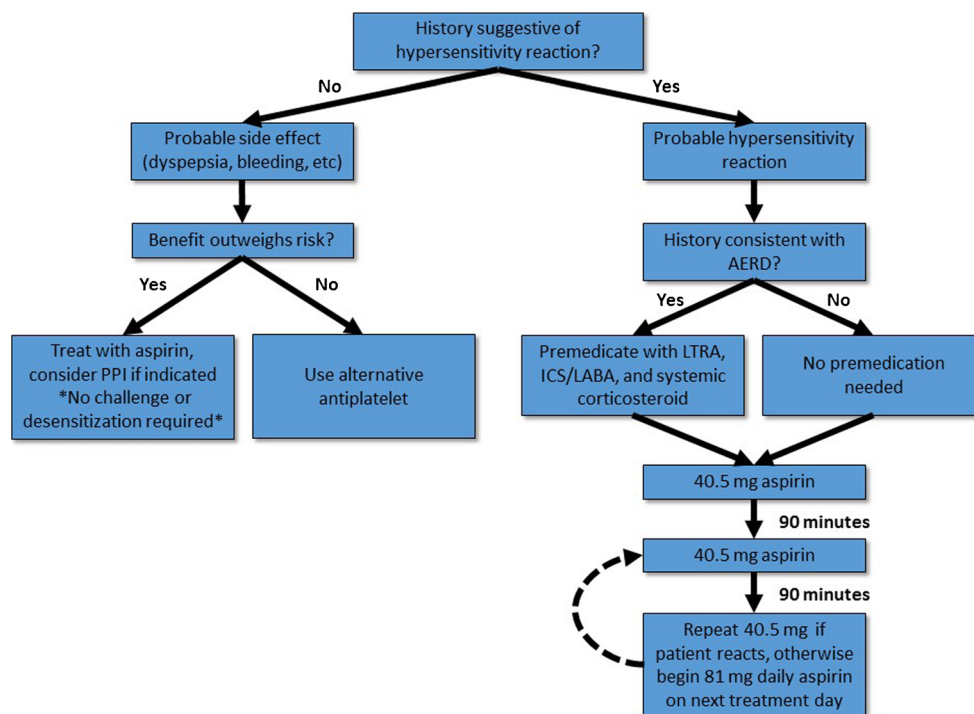
With the above observations and evidence in mind, we offer our experience at Scripps Clinic in the management of patients with acute coronary syndromes requiring rapid aspirin challenge/desensitization. Our algorithm and protocol are summarized in Fig. 1. A thorough history should be obtained from each patient when possible to determine the nature of prior reactions. Type A ADRs, including side effects such as dyspepsia and bleeding, should first be differentiated from a history suggestive of type B ADRs including the various hypersensitivity syndromes. In those patients reporting a history of a common side of aspirin, risks and benefits of aspirin therapy must be weighed by the treating physician. It should be noted that gastrointestinal side effects can often be prevented by concurrent treatment with a proton pump inhibitor.

Patients with a history of aspirin reaction concerning for SJS/TEN, DRESS, serum sickness, or allergic interstitial nephritis, however, should be excluded from undergoing aspirin challenge. All others reporting a history suggestive of aspirin or NSAID hypersensitivity or those with an unclear history of reactions are candidates for rapid aspirin challenge/desensitization. Care should be made to assess each patient for underlying AERD, as severe reactions can occur particularly in patients with uncontrolled asthma. In those with a history suggestive of AERD, baseline spirometry, if available, should be assessed prior to administration of aspirin. Patients with presumed AERD should be premedicated with montelukast, a combination inhaled corticosteroid/long acting bronchodilator (ICS/LABA) and systemic corticosteroids. Rescue medications including injectable epinephrine should be readily available for all patients undergoing aspirin challenge/desensitization.

We suggest an initial dose of aspirin of 40.5 mg (1/2 of an 81 mg tablet). The patient should then be observed for a full 90 min before an additional dose is administered. If symptoms occur, the patient should be treated with appropriate medication such as antihistamines, intranasal oxymetazoline, or nebulized bronchodilators, prior to continuing the protocol. A second dose of 40.5 mg aspirin may then be administered (cumulative dose of 81 mg). If the patient reacts to the second dose of aspirin, an additional 40.5 mg dose may be administered after treatment of symptoms. If the patient does not react after 90 min of observation, the protocol is complete, and daily aspirin therapy with 81 mg may continue the next day.

Protocol to Increase Aspirin Dosing Above 81 mg Daily

There are two main reasons to further increase the dose of daily aspirin therapy above 81 mg. The first is that a cardiologist may request a dose increase for further antiplatelet effect. The second is that patients with AERD may not be fully desensitized and/or may not experience the protective effect of aspirin desensitization at such low doses. AERD patients

Fig. 1 Oral aspirin challenge/desensitization algorithm

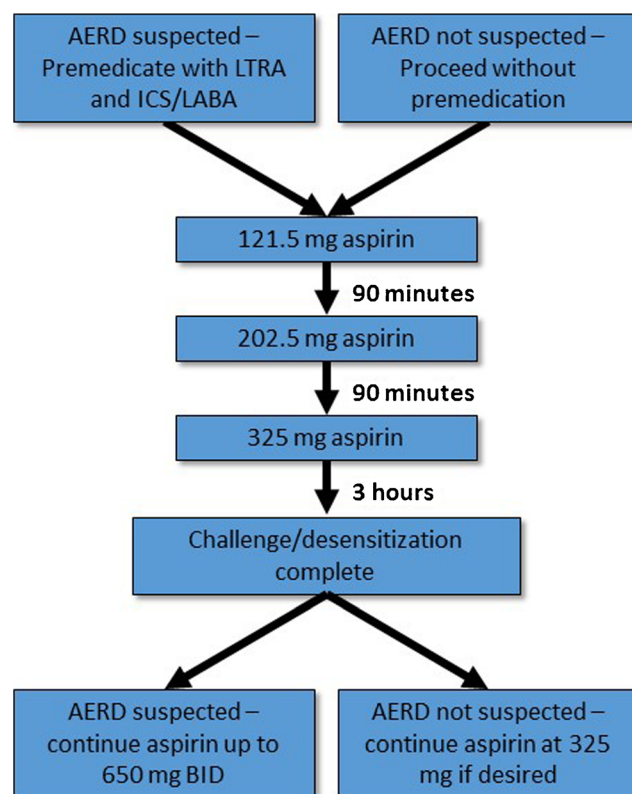
who are not fully desensitized would also not be able to take additional doses of aspirin or NSAID for “as-needed” pain relief. For these reasons, an increase in aspirin dosing may be desired. Our recommended protocol to increase aspirin dosing from 81 to 325 mg is described below and summarized in Fig. 2. This challenge/desensitization protocol may be performed while the patient is still in the acute care setting or after discharge in the outpatient setting.

Similar to our initial oral aspirin challenge/desensitization algorithm, patients with a history suggestive of AERD should be premedicated with montelukast and an ICS/LABA. Aspirin dosing begins at 121.5 mg (1½ of 81 mg tablets), followed by 202.5 mg (2½ of 81 mg tablets) and 325 mg doses in 90 min intervals. The patient is observed for 3 h after the final dose to monitor for delayed reactions. Patients who complete the protocol may be safely dosed with 325 mg daily. They should also tolerate additional doses of aspirin or NSAIDs for relief of pain. AERD patients are started on higher doses of aspirin for therapeutic effects including reduction in aggressive polyp formation and improvement in nasal and respiratory symptoms. Standard dosing for AERD patients after desensitization is generally 325 or 650 mg twice daily. No further desensitization steps are required for doses higher than 325 mg [31].

Conclusion

With rare exceptions, patients reporting a history of adverse reactions to aspirin may be safely treated with aspirin after challenge/desensitization. The importance of aspirin for

secondary prophylaxis of coronary artery disease and management of acute coronary syndromes is well established, with guidelines noting unequivocal benefits including reduced morbidity and mortality. A practical, easy-to-apply algorithm

**Fig. 2** Protocol to increase aspirin dosing from 81 mg daily

for aspirin challenge/desensitization in the acute setting is vital for timely evaluation and management. Here, we have provided a simple two-step protocol. Regardless of which protocol the consulting allergist chooses, it is important to continue to share with our cardiology colleagues that aspirin challenge/desensitization may safely be performed on their patients in the acute setting.

Compliance with Ethics Standards

Conflict of Interest Drs. Cook and White declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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