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Aspirin allergy in patients with myocardial infarction: the allergist's role

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Introduction

Drug hypersensitivity can preclude patients from receiving the drug of choice to treat a specific illness. In some cases, such as penicillin allergy in a pregnant woman with syphilis,[1] the drug is clearly indicated, and allergists may be called on to induce temporary drug tolerance (desensitize). In other cases, the medication benefit is not as clear, and allergists must weigh desensitization (DS) risks against the risks and benefits of alternative medications. For aspirin (ASA) hypersensitivity, a significant amount of literature has been published addressing scenarios in which patients with aspirin-exacerbated respiratory disease (AERD) are desensitized to ASA, but little has been published to address the issue of ASA hypersensitivity in patients with other types of ASA hypersensitivity and myocardial infarction (MI). Of the protocols for these patients that have been published, none have been prospectively randomized, validated, or clearly documented to alter the immune system, making the diagnosis and treatment pathway unclear at times. ASA is clearly of benefit in patients with ST-segment elevation MI (STEMI) or non-STEMI.[2] In patients who tolerate ASA, ASA therapy is expected; other antiplatelet agents are additions, not substitutions.[3] In the era of dual antiplatelet therapy, allergists can offer cardiology colleagues a valuable service if called on to evaluate patients reporting ASA hypersensitivity.

ASA Hypersensitivity Epidemiology and Categories

The prevalence of patients with MI reporting ASA hypersensitivity is not clearly defined. A recent study has reported 1.5% of the cardiac population giving a history of ASA adverse events, with only 21% of these patients having a history compatible with ASA hypersensitivity.[4] Another study has noted 2.6% of patients admitted for cardiac catheterization with ASA hypersensitivity.[5] This percentage of the cardiac population is manageable for allergists desiring to incorporate ASA evaluations, graded challenges, and DSs into their consultative service repertoire if not already provided.

Aspirin hypersensitivity can generally be grouped into 4 categories: (1) rhinitis and asthma induced by nonsteroidal anti-inflammatory drugs (NSAIDs), (2) chronic urticaria or angioedema induced by NSAIDs, (3) urticaria or angioedema induced by multiple NSAIDs, and (4) single NSAID-induced reactions[6] Type 1 generally refers to AERD. Patients are sensitive to all NSAIDs, and it is mediated by the cyclooxygenase (COX)-1 mechanism. Other categories typically displaying cross-reactivity to COX-1–inhibiting NSAIDS include types 2 and 3.[7] Type 4 is thought to be possibly mediated by IgE. Some patients have a mixed presentation and do not fit neatly into a specific category.[6,8] Many patients who cannot take COX-1 inhibitors can take COX-2 inhibitors, but these are not a substitute for ASA in patients who have had MI.

Graded Challenge vs DS

The difference between a diagnostic, multistep graded challenge and DS can be a bit hazy, particularly when it comes to ASA. In general, graded challenges are meant to diagnose or rule out drug allergy, whereas DS is undertaken to alter the immune system and render effector cells less reactive by administering increasing doses of the medication.[1,9] Tolerance is temporary but should last as long as there is continued administration of the drug.[9] DSs for patients with AERD are somewhat different and combine the principles of a graded challenge and DS: a critical portion of the DS procedure is the demonstration of a mild respiratory reaction, thus proving the hypersensitivity and placing the patient in a refractory state so that DS can be completed.[9] For patients with type 2 to 4 ASA hypersensitivity, whether DS should elicit hypersensitivity symptoms is not clear.[9] For other medication classes, such as antibiotics, DS is possible to complete without any manifestations of hypersensitivity.[1,9] According to the 2010 drug allergy practice parameters, it is thought that graded drug challenges of more than 4 or 5 steps may induce drug tolerance (desensitize)[9]; thus, there is a gray area determining crossover from a graded challenge to DS. It would seem reasonable that this gray area could be avoided by designing diagnostic graded challenges with no more than 3 steps and DSs with at least 6 steps, although this approach could be debated. These controversies do not apply to patients with AERD.

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Table 1
Outpatient multiday protocol[a] for patients with asthma-exacerbated respiratory disease[10]

Step	Day	Time (h)	Dose (mg)	Cumulative dose (mg)
1	1	0	20.25[b]	20.25
2	1	3	60.75	81
3	1	6	81	162
4	2	0	101.25	263.25
5	2	3	162.5	425.75
6	2	6	325	750.75

[a]Vital signs and forced expiratory volume in 1 second are measured each hour. Reactions typically occur with doses of 20 to 101 mg. After stabilization, the dose should be repeated and the patient monitored for 3 additional hours. This may occur on day 1 or 2. If, on day 1, nasal, gastrointestinal, or cutaneous reactions occur, the patient should be pretreated with H_1 and H_2 receptor blockers for the remainder of the procedure. See text for further details.
[b]Alternatively, the initial dose may be 40.25 mg. The cumulative dose would be 770.75 mg if the procedure began at this point.

The combination of a diagnostic graded challenge and DS has been well established, and specific protocols have been well studied.[9,10]

In patients with MI and good histories for true ASA hypersensitivity, the rationale behind going straight to DS is the concern that positive graded challenges might exacerbate the underlying coronary artery disease.[1,5,7] This approach is controversial. Some cite ASA as a cause of anaphylaxis,[11,12] whereas others maintain that anaphylaxis to ASA does not exist in patients without AERD.[13] Perhaps in a patient without AERD, the greatest risk of a positive reaction would be that of cutaneous symptoms, but some allergists may desire to take a more cautious approach and proceed with DS instead of a graded challenge. Time and resources are spent on this approach, and then the patient is required to take daily ASA, undergoing repeat DS if a break in ASA therapy occurs. Fortunately, this is a patient population in which daily ASA is desirable.

If the evaluating allergist judges a diagnostic graded challenge to be safe in a particular patient and the potential for histamine-mediated exacerbation of the underlying cardiac disease to be low, then this would be the preferred procedure. However, if a more cautious approach of going straight to DS seems warranted, rapid DS protocols provide options to get ASA on board quickly and safely in patients without AERD. The problem with rapid protocols is that they are not validated, and their immunomodulating potential has not been appropriately documented. Conversely, their lengths preclude them from clearly being negative diagnostic graded challenges if completed without reaction. Despite these issues, they have been reported to be safe and successful in patients with good histories for ASA allergy and cardiac disease; patients continue to do well on ASA after these procedures. Patients with MI and type 2 to 4 ASA hypersensitivity provide a unique challenge; until such time as these issues are better elucidated, practicing allergists should be aware of the options that exist, although imperfect.

Should the allergist decide to proceed with DS, there are several protocols to choose from. Patients with histories indicative of AERD should be desensitized using a slow, multiday protocol. A small series of patients with AERD and coronary disease has been reported to be safely desensitized.[7] The Scripps Clinic protocol may be used in inpatients or outpatients with AERD; it takes 2 to 4 days to complete[10] (Table 1). Patients with MI reporting other types of ASA hypersensitivity may undergo rapid oral DS procedures, completing them in the course of a few hours.[5,7,14–16] Only 1 of these rapid protocols has been used in the outpatient setting[15] (Table 2). Table 3 presents an example of a rapid protocol used in the inpatient setting. Randomized trials have not been performed on rapid protocols. Rapid protocols begin with small doses of ASA, such as 0.1 or 1 mg. Although not common, objective hypersensitivity symptoms have been documented to small doses of ASA.[14,15,17] Typically, however, patients do well during rapid

Table 2
Rapid outpatient protocol[a,15]

Step	Dose (mg)	Volume (mL)[b]	Cumulative dose (mg)
1	1	0.1	1
2	10	1	11
3	20	2	31
4	40	4	71
5	80	8	151
6	160	16	311
7	325	entire tablet	636

[a]Doses are administered 15 minutes apart. The protocol can be performed in inpatients and outpatients.
[b]Volume was obtained by dissolving 1 Alka-Seltzer tablet (contains 325 mg of aspirin; Bayer Healthcare, Bayer Consumer Care, Morristown, New Jersey) in 32.5 mL of water for a 10-mg/mL solution. See text for further details.

procedures. Success rates for DS on the first attempt are high: 88.5%,[5] 87.5%,[16] 81.8%,[14] and 91.3%,[15] although not all in the last group had MI. Not only were the initial success rates good, patients continued to tolerate ASA in these series. In the first 3 series, follow-up ranged from 1 to 24 months, with only 2 patients discontinuing ASA owing to mild symptoms. In the last series, follow-up was not completed for all patients, but only 2 patients were noted to discontinue ASA owing to hypersensitivity symptoms, also mild. Other reasons patients discontinued ASA included peptic ulcer[5] and noncardiac surgery.[16] Hypersensitivity symptoms necessitating discontinuation of DS were usually mild. Because the immunomodulating potential of these protocols is unknown, these patients may not have been hypersensitive to ASA. McMullan and Wedner[15] reported patients who safely completed a rapid protocol despite hypersensitivity symptoms during DS.

ASA Benefit in Patients with MI

Because allergists may be asked to assist in the evaluation and possible DS of patients with MI reporting ASA hypersensitivity, awareness of current cardiology recommendations is beneficial. Table 4 lists recommendations for ASA therapy in patients with unstable angina or non-STEMI.[3] Attempting DS in ASA-hypersensitive patients treated medically without stenting is briefly mentioned, but no further recommendations on this point are given. Dosing tables indicate that all patients are to receive ASA; other medications are considered additional.[3]

Table 4 also lists current recommendations for ASA therapy in patients with STEMI. Neither ASA hypersensitivity nor alternative therapy is mentioned.[18] In the most current percutaneous coronary intervention (PCI) guidelines, ASA DS is no longer mentioned. In 2005 it was mentioned that ASA DS could be performed in select patients, but no other information was given.[19,20] The STEMI guidelines and guidelines for those undergoing PCI give a class III

Table 3
Rapid inpatient protocol[a,14]

Step	Dose (mg)	Cumulative dose (mg)
1	0.1	0.1
2	0.3	0.4
3	1	1.4
4	3	4.4
5	10	14.4
6	20	34.4
7	40	74.4
8	81	155.4
9	162[b]	317.4
10	325[b]	642.4

[a]Doses are administered at 10- to 20-minute intervals.
[b]Doses noted to be optional depending on the desired final dose of aspirin. See text for further details.