

Aspirin Desensitization/Challenge in 3 Patients With Unstable Angina

Alex G. Ortega-Loayza, MD, Syed Raza, MD, Anthony J. Minisi, MD, On Topaz, MD, Andrew Heller, MD and Ion S. Jovin, MD

Abstract: Aspirin sensitivity is relatively frequent and can be a major problem in patients who need percutaneous coronary intervention and stenting with subsequent dual antiplatelet therapy. Desensitization is often the therapy in these patients, but this can prolong the time to revascularization significantly. Rapid oral aspirin desensitization protocols have been described since 2000. However, data are lacking on the optimal strategy for aspirin desensitization and determining which patients are mostly benefited from this desensitization. The authors describe the use of a Wong-modified protocol in 3 patients who had known aspirin sensitivity and who had unstable angina and an indication for percutaneous coronary intervention.

Key Indexing Terms: Aspirin allergy; Desensitization; Stent; Acute coronary syndrome. [Am J Med Sci 2010;340(5):418–420.]

Acetylsalicylic acid [aspirin (ASA)] is a salicylate that irreversibly inhibits cyclooxygenase-1 and 2 enzymes, which results in decreased formation of prostaglandin precursors. It is a key agent in cardiovascular therapy.¹ Moreover, dual platelet therapy with aspirin and clopidogrel significantly reduces secondary cardiovascular events in the patients with acute coronary syndrome with and without ST elevation.² In addition, dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI) is a class I recommendation by the American College of Cardiology. However, in patients with hypersensitivity to aspirin, antiplatelet therapy can become a problem. Aspirin desensitization is an important strategy in these patients.³

There is a classification based on the mechanism of hypersensitivity, risk factors and cross-sensitivity to nonsteroidal antiinflammatory drugs (NSAIDs). Types I, II and III are classified as pseudoallergic reaction to aspirin because it is mediated by a pathway different from antigen-directed antibodies: excessive production of leukotrienes by 5-lipoxygenase, which results in mast-cell degranulation and release of histamines and cytokines. Type I hypersensitivity manifests as respiratory symptoms such as rhinitis and asthma. Type II is observed in patients with chronic idiopathic urticaria, and it manifests as angioedema and increase in urticaria. Type III hypersensitivity shows the same symptoms as type II reactions in patients without chronic idiopathic urticaria. These patients manifest symptoms after the first dose of aspirin or NSAID. On the other hand, the type IV and V hypersensitivities are mediated by aspirin-directed immunoglobulin E antibodies that rarely cross-react with other NSAIDs. The type IV reaction

presents as angioedema and urticaria, and the type V is a classical anaphylaxis reaction. These reactions require repeated exposure to promote antibody formation.^{4,5}

The most common protocols for aspirin desensitization are the rapid protocols. They can provide practitioners with a useful option to desensitize patients with aspirin hypersensitivity at the time when they are acutely managed for cardiovascular events,⁵ especially when the patients require early invasive strategies with stent implantation.⁶ We report the use of a safe and rapid oral ASA desensitization/challenge protocol in 3 patients with unstable angina who underwent a PCI with stent implantation.

The protocol used in our hospital is based on the protocol of Wong with some modifications: 0.5 mg of ASA was given as initial dose, and it was doubled every 30 minutes (0.5, 1, 2, 4, 8, 16, 32, 64 and 100 mg) while monitoring vital signs. The time to complete the protocol was approximately 240 minutes. Patients were premedicated with antihistamines (diphenhydramine, 50 mg). Beta-blockers were held the day before the desensitization to prevent any potential increase in the severity of a possible anaphylactic reaction or interference with the action of epinephrine during treatment of such a reaction. The different available protocols are shown in Table 1.

CASE REPORTS

Patient 1

A 57-year-old man with known 70% stenosis of the ramus intermedius, hypertension, hypercholesterolemia and obesity was admitted for percutaneous coronary angioplasty because of worsening anginal symptoms and dyspnea. His previous reaction to salicylic acid was throat swelling. No allergy to NSAIDs. No history of asthma or chronic urticaria. The patient completed the desensitization protocol after 4 hours without any complications. He was premedicated with diphenhydramine. He underwent successful PCI of the ramus with placement of a bare metal stent. One year after the procedure, the patient continued with 81 mg of ASA daily without complications.

Patient 2

A 57-year-old man with postcoronary artery bypass grafting a year before admission and a history of diabetes, hypertension, atrial fibrillation and transient ischemic attacks and cerebral vascular accidents was admitted with a diagnosis of unstable angina. The previous reaction of the patient to aspirin was lips and eyes swelling and generalized itchiness approximately 20 years earlier when he took 2 tablets of aspirin. No allergy to NSAIDs. No history of asthma or chronic urticaria. Diphenhydramine (every 6 hours) was started before the desensitization (and prednisone because of an allergy to iodine). He underwent successful PCI of the left main trunk and of the ostial circumflex with placement of drug-eluting stents.

From the Department of Internal Medicine (AGO-L, SR, AJM, OT, ISJ), Virginia Commonwealth University, Richmond, Virginia; and Departments of Surgery (AH) and Medicine (AJM, OT, ISJ), McGuire VA Medical Center, Richmond, Virginia.

Submitted January 31, 2010; accepted in revised form May 4, 2010.

Correspondence: Alex G. Ortega-Loayza, MD, Department of Internal Medicine, Virginia Commonwealth University, 1200 East Broad St, East Wing 602, Richmond, VA 23298 (E-mail: aortegaloayza2@mcvh-vcu.edu).

TABLE 1. Rapid aspirin desensitization protocols

Protocol	Premedication	Initial aspirin dose (mg)	Final aspirin dose (mg)	Dosing interval (min)	Time to complete protocol (min)	Reported rate of success
Wong et al ¹²	Antihistamines and prednisone	0.1	325	10–30	90–180	9/11
Silberman et al ⁹ protocol A	None	1	100	30	210	6/7
Silberman et al ⁹ protocol B	None	5	75	30	150	8/9
Rossini et al ⁶	None	1	100	30–120	330	23/26
Hobbs et al ¹⁰	Prednisone, montelukast and cetirizine	1	325	15, then 20, 30 and 40 (for the last 3 doses)	210	12/13
Dalmau et al ¹¹	None	0.1	100	15–20	132	5/5

One year after the procedure, the patient continued with 81 mg of ASA daily without complications.

Patient 3

A 62-year-old man with hypertension, diabetes, hypercholesterolemia and gastric reflux was admitted because of anginal chest pain at rest. His previous reaction to ASA was hives approximately 10 years previously. No allergy to NSAIDs. No history of asthma or chronic urticaria. ASA desensitization was done before PCI. The patient was premedicated with diphenhydramine and completed a total of 3 doses. The patient did not develop any complication for 18 hours after desensitization. However, 2 hours after the morning dose of 81 mg of ASA, patient started to complain of rash and itchiness on his face that then spread to his body. The patient improved with diphenhydramine. He was not rechallenged with ASA. The desensitization was considered as a failure, and no other attempts were made. Patient underwent a successful PCI with placement 3 of drug-eluting stents and was discharged on clopidogrel and cilostazol.

DISCUSSION

We describe 3 patients with a history of ASA hypersensitivity and unstable angina who were seen at our hospital. They underwent desensitization/challenge and coronary stenting, and no major cardiac events during follow-up have occurred. The first 2 patients had successful desensitizations. However, patient 3 failed the desensitization. It might be that this reaction was pharmacologically mediated or an anaphylactoid reaction. One possible theory was that the patient needed to be desensitized for his symptoms (urticaria), not a specific aspirin dose, and 100 mg was not enough to do this. When patients are desensitized for sinonasal or respiratory symptoms, they are typically taken to large doses and often maintained on 650 mg of ASA twice a day. Perhaps, this would have been effective in this case too.

ASA sensitivity can be manifested by aspirin-exacerbated respiratory tract disease, urticaria/angioedema or anaphylaxis.⁷ The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10%, and for aspirin-induced urticaria, the prevalence varies from 0.07% to 0.2% in the general population.⁸ A classification system for aspirin hypersensitivity has been developed by Gollapudi et al.⁴ ASA desensitization therapy refers to slowly increasing the exposure to oral ASA to reduce and/or eliminate pharmacological and presumed immunologic reactions while monitoring for

symptoms of hypersensitivity.^{4,9} The effects of desensitization are temporary because it is not an immunotherapy; if the drug is interrupted, the patient recovers his previous sensitivity within a few days.⁹

Current protocols have described multiple failures for desensitization especially in patients with chronic idiopathic urticaria^{6,10} and patients with severe asthma.⁶ The reason why patients fail desensitization is unclear, but the pathway might be mediated through leukotriene production and seems to be dose dependent.⁵ When patients fail desensitization, alternate antiplatelet medication such as cilostazol or dipyridamole can be used. This is of key importance in some patients with coexistent resistance to clopidogrel.⁴

Ideally, all these patients should be hemodynamically stable before desensitization. However, given the nature of cardiac disease, there can occasionally be a significant risk of clinical deterioration if intervention is not completed within a short time frame. In these cases, desensitization can be safely performed but should be done in an intensive care unit with proper monitoring and tools for resuscitation immediately available. Patients who undergo desensitization therapy successfully should receive ASA indefinitely because sensitivity will recur if there is a lapse >48 hours after discontinuation. If the patients miss more than 2 days of therapy, they should contact their cardiologist before resuming therapy in view of concerns about resensitization.¹⁰

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