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Sensitivity to Antiplatelet Agents in Patients with Acute Coronary Syndromes: Role of Desensitization Therapy

By ANTONIO ROCCA MD, PhD, and GORDON MOE, MD

The importance of aspirin and other antiplatelet agents is well-established for several indications, ranging from acute coronary syndromes (ACS) to percutaneous coronary intervention (PCI). However, there is a significant proportion of patients with coronary artery disease (CAD) who are unable to tolerate acetylsalicylic acid (ASA) and other antiplatelet agents due to drug sensitivity. This poses a therapeutic dilemma for practitioners. One potential approach to circumvent this problem is the use of desensitization therapy. By examining several case scenarios, this issue of *Cardiology Rounds* reviews the approaches to the patient with CAD and a preexisting sensitivity to antiplatelet agents, including the use of desensitization therapy for ASA and clopidogrel sensitivity.

The activation and aggregation of platelets during ACS and PCI have emerged as very important therapeutic targets aimed at decreasing morbidity and mortality. ASA[1-3] and antagonists of the adenosine diphosphate (ADP) receptor – ticlopidine and clopidogrel[4] – are the cornerstones of therapy for CAD. Furthermore, the glycoprotein (GP) IIb/IIIa receptor antagonists also exert antiplatelet effects by inhibiting the final common pathway of platelet activation; they are also important agents for use in high-risk ACS and prior to PCI.[5-7] However, several therapy registries have shown that the rate of antiplatelet utilization in ACS is suboptimal.[8,9] This finding may be explained, in part, by significant adverse reactions to antiplatelet agents, in particular, ASA, ticlopidine, and clopidogrel.

One approach to circumvent these adverse reactions is through desensitization therapy. Modification of the immune response against the antigen has been utilized in the arena of antibiotic sensitivity,[10] as well as insulin allergy.[11] Several series have examined the role of desensitization therapy to non-steroidal anti-inflammatory drugs (NSAIDs);[12,13] however, there are only a few reports examining desensitization therapy for ASA,[14-17] and only one for clopidogrel,[18] in patients with CAD. By examining several cases involving patients with CAD and sensitivities to various antiplatelet agents, one can become familiar with alternative strategies, including desensitization therapy and novel antiplatelet agents.

Case 1: An 82-year-old woman presents with a non-ST elevation myocardial infarction (NSTEMI), including dynamic electrocardiograph (ECG) changes. She is taken to the catheterization laboratory where a circumflex lesion is identified over a long span and she is treated with a drug-eluting stent. ASA and clopidogrel are used in the standard fashion. She has a history of multiple drug reactions, but none to ASA or clopidogrel. On the second day, a diffuse, erythematous, macular, papular rash is noted. From this description, what is the most likely cause of the rash? How should she be managed?

Case 2: A 75-year-old woman with a past history of unstable angina is found to have a subtotal occlusion of the right coronary artery. She undergoes PCI with a drug-eluting stent placed over a long lesion. She is then treated with ASA and clopidogrel. Unfortunately, she develops an urticarial rash that is attributed to clopidogrel. Clopidogrel is stopped and ticlopidine is used in its place. She returns, complaining of a 2-week history of watery diarrhea characterized by up to 8-10 loose bowel movements each day. Is an antiplatelet sensitivity reaction at fault? How should she be managed?

Beneficial actions of antiplatelet agents

The prothrombotic features of platelets are normally kept in check by factors synthesized by an intact endothelium (eg, nitric oxide and prostaglandin I_2 (PGI_2). However, when there is disruption of the intact endothelium, platelets are exposed to prothrombotic moieties and become activated,

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

resulting in the release of pro-adhesion and aggregation factors such as ADP, fibrinogen, and von Willebrand factor. The activation of platelets then proceeds in an exponential fashion which, in the case of unstable angina and ST elevation myocardial infarction (STEMI), is pathological.[1] As a result, several antiplatelet agents have been demonstrated to exert clinical benefits in a variety of indications, including acute myocardial infarction (MI) and in patients at high-risk for MI and acute stroke.[2]

ASA

ASA inhibits both platelet activation and aggregation, mainly via the inhibition of cyclooxygenase-1 (COX-1). This irreversible inhibition of enzymatic activity results in the decreased conversion of arachidonic acid to the downstream metabolite, thromboxane A2, which is a potent stimulator of platelet aggregation.[1,19] The clinical benefits of ASA were first witnessed in the ISIS-2 trial, which demonstrated that ASA therapy in STEMI resulted in a reduction in mortality of 23%.[20] Furthermore, ASA use was associated with a significant reduction in mortality or recurrent MI in patients with unstable angina or NSTEMI.[21]

Ticlopidine

Ticlopidine was the forerunner of clopidogrel and was used initially in patients undergoing PCI. In this paradigm, ticlopidine was used in addition to ASA and, in the Intracoronary Stenting and Antithrombotic Regimen (ISAR),[22] led to a significant reduction in the combined endpoint of death, MI, angiographic thrombosis, or revascularization.

However, the use of ticlopidine is associated with uncommon, but important adverse reactions that limit its use. The most common include diarrhea, nausea, and vomiting that occur in up to 50% of patients.[4] Skin rash is also common. Approximately 2% of patients develop the serious side effect of neutropenia, which results in severe neutropenia (<450 neutrophils per mm^3) in 0.9% of treated patients.[4] As a result, complete blood counts should be performed every 2 weeks during the first 3 months of therapy. Other rare adverse reactions include thrombotic thrombocytopenic purpura and bone marrow aplasia.

Clopidogrel

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial demonstrated that the addition of clopidogrel to ASA reduced cardiovascular death, MI, or stroke in patients presenting with unstable angina.[23] The PCI-CURE [24] and the Clopidogrel for the Reduction of Events During Observation (CREDO)[25] trials demonstrated that the addition of clopidogrel to ASA therapy in patients awaiting PCI was associated with a significant 33% reduction in major cardiac events. Recently, in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)[26] and ClOpidogrel and Metroprolol in Myocardial Infarction Trial (COMMIT) studies, patients presenting with STEMI who received thrombolytic therapy[27] experienced important reductions in the combined event rates of death and reinfarction with the use of clopidogrel, in addition to ASA and heparin. Clopidogrel is increasing in popularity as an antiplatelet agent, in part, due to its favourable side effect profile when compared to ticlopidine. Like ticlopidine, the most common reactions involve the gastrointestinal system; however, the risk of severe rash was 0.26% in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study,[28] while the incidence of neutropenia was rare.

Prevention of stent thrombosis/ instent restenosis

In the early series of stent use in PCI, the risk of subacute stent thrombosis was substantial with the use of ASA alone, occurring in up to 3% to 5 % of patients.[29] The addition of anticoagulation therapy did not improve the rates of thrombosis in subsequent studies. However, with the addition of ticlopidine, this statistic dramatically improved to approximately 0.5%.[3] The CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS) trial compared ticlopidine to clopidogrel after successful coronary angioplasty and found the rate of adverse cardiovascular endpoints was not significantly different.[30]

Major adverse reactions of ASA

It is becoming evident that the prevalence of ASA sensitivity is not insignificant, it occurs in up to 10% of the general population when ASA-exacerbated respiratory disease is considered.[19] The adverse effects of ASA are best classified as pharmacologic and immunological reactions. Pharmacological reactions are those that occur as a direct result of inhibition of enzymatic activity by a drug. In the case of ASA, this would be inhibition of the COX-1 enzyme, which results in less arachidonic acid being converted to thromboxane A2 (which produces the beneficial effects of decreased platelet activation and aggregation). However, COX-1 inhibition also leads to decreased production of prostaglandin (PG) E_2 the predominant inhibitor of histamine release and the enzyme 5-lipoxygenase activating protein. This, in turn, leads to increased production of leukotrienes, the mediators of bronchoconstriction and increased vascular permeability.

On the other hand, some reactions to ASA are clearly not related to the mechanistic action of the drug, but to an immunologic reaction to the drug itself. It is important to make this distinction, since it dictates which patients can undergo desensitization therapy.

ASA-exacerbated respiratory disease

ASA can cause an exacerbation of respiratory disease, usually in patients with a pre-existing history of asthma, ASA-sensitivity, and nasal polyps. ASA-exacerbated respiratory disease is the cause of asthma in 10%-15% of cases.[14] The reaction induced by ASA involves rhinorrhea, mucosal irritation, and bronchospasm due to depletion of PGE_2 via COX-1 inhibition. The relative lack of PGE_2 promotes histamine release from mast cells and the formation of several leukotrienes that induce airway hyperresponsiveness. This reaction to ASA is also termed a "Type I" reaction and is grouped in the pharmacological classification of ASA reactions.[19] Since it is the result of enzymatic inhibition, there is cross-reactivity with other NSAIDs that also inhibit COX-1. However, the selective COX-2 inhibitors rarely cause this form of respiratory disease.[19]

Table 1: Types of reactions to acetylsalicylic acid and other NSAIDs and clinical risk factors

Type	Reaction	Underlying risk factor	Cross-reactions to other NSAIDs	First exposure reaction	Mechanism of sensitivity	Able to undergo desensitization
I	NSAID-induced rhinitis and asthma	Asthma, nasal polyps, sinusitus	Yes	Yes	COX-1 inhibition	Yes
II	NSAID-induced urticaria/ angioedema	Chronic idiopathic urticaria	Yes	Yes	COX-1 inhibition	No
III	NSAID-induced urticaria/angioedema	None	Yes	Yes	COX-1 inhibition	Yes
IV	NSAID-induced urticaria/angioedema	None	No	No	Immunologic*	Yes
V	NSAID-induced anaphylaxis	None	No	No	Immunologic*	Yes

NSAID-induced cutaneous disease

NSAID-induced reactions involve the development of urticaria and/or angioedema. Urticaria is defined as the production of a wheal within the dermal layer due to the release of inflammatory mediators. Angioedema is best defined as an increase in vascular permeability from inflammatory mediators that causes fluid to leak into the space below the dermal layer.[31] These two reactions can coexist with exposure to ASA. There are 3 groups in the overall classification of ASA reactions that involve cutaneous disease.

- Type II: The first is the development of urticaria/ angioedema in the context of preexisting chronic idiopathic urticaria. ASA can cause exacerbation of the urticaria in up to 30% of patients. This is classified as a "Type II" reaction and, while the pathogenesis is not clearly understood, it appears to be similar to ASA-exacerbated respiratory disease, in that, excessive leukotriene production due to COX-1 inhibition leads to significant vascular permeability.[19] Since COX-1 inhibition is implicated in the pathogenesis, there is significant cross-reaction with NSAIDs.
- Type III reactions to ASA involve urticaria/angioedema as a result of COX-1 inhibition.
- Type IV reactions are immunological and mediated by immunoglobulin (Ig) E production upon exposure to a single prior agent. Since this is a hapten-mediated event, cross-reactivity with other NSAIDs is not possible (Table 1).

Overview of desensitization therapy

A significant proportion of patients do not receive appropriate antiplatelet therapy. For example, a large registry of therapy delivered for MI in the mid-1990s indicated that up to 20% of patients are discharged from hospital without a prescription for ASA.[9] The prevalence of ASA sensitivity in patients with CAD is difficult to establish, in part due to the confusion that arises when patients state that they are "allergic" to ASA or NSAIDs. This allergy "perception" may run a spectrum, ranging from a true anaphylactic reaction, to one that is benign and not life-threatening. Consideration of desensitization therapy may benefit patients who have a true sensitivity to antiplatelet agents.

Desensitization therapy is a technique that was first implemented in the treatment of antibiotic allergy. Its aim is to modify an allergic response by the host to one that is less-noxious. Type I hypersensitivity reactions are mediated by IgE antibodies located on mast cells that cause histamine release once the IgE molecules bind the antigen. This form of reaction represents the major mechanism behind the allergic phenomenon and the target for modification by desensitization.[31] This is achieved by administering very small amounts of the drug in question in a graded fashion until the target dose is reached. The approach is capable of diverting the host response away from an IgE-mediated response toward an IgG-mediated response, thus producing an antibody response that is not associated with acute allergic hypersensitivity reaction.

Desensitization to ASA

ASA desensitization therapy refers to the elimination of pharmacological and immunological reactions by gradually increasing exposure to ASA.[19] The mechanisms of desensitization therapy differ according to the type of adverse reaction induced by ASA. In the COX-1-mediated reaction, desensitization results in decreased leukotriene production and decreased histamine release after mast cell stimulation.[13] In patients with IgE-mediated reactions, the exact mechanisms involved in achieving desensitization are unclear. It appears to be similar to penicillin desensitization, in that, repeated and sustained exposure to ASA leads to saturation of IgE antibody sites on basophils and mast cells, thus causing a gradual depletion of intracellular mediators in the adverse reaction.[32]

It is important to differentiate between pharmacological and immunological reactions in order to determine which patients can safely proceed with desensitization. However, this may be difficult to ascertain since blended reactions can occur. Some clues to a pharmacological reaction include an adverse reaction that occurs on first exposure to the drug. In addition, cross-reactivity with other NSAIDs strongly indicates that a pharmacological reaction is present. In contrast, the lack of cross-reactivity with other NSAIDs and reactions that occur after prior exposures imply the presence of an immunological reaction. It is important to make these determinations. For example, if the reaction to ASA is deemed to be secondary to COX-1 inhibition, then desensitization should be considered. Likewise, if the reaction is the result of another NSAID, the involvement of COX-1 would make cross-reactivity a strong possibility if ASA was added to the therapeutic regimen. If the reaction is deemed immunologic toward another NSAID, without anaphylaxis, then the likelihood of a cross-reaction to ASA would be very unlikely and ASA could be safely added to the strategy of therapy in ACS without the need for desensitization therapy.[19]

For the majority of patients with ASA and NSAID sensitivity, the procedure is well tolerated, except for those with chronic idiopathic urticaria. About 30% of these patients can

Table 2: Desensitization protocols

Time (min)	Protocol A (mg)	Protocol B (short version, mg)
0	1	5
30	2	10
60	4	20
90	8	40
120	16	75
150	32	
180	64	
210	100	

have an exacerbation of underlying respiratory and cutaneous reactions. However, in patients with CAD, the data regarding the safety of this therapy are less clear. In several small case series of patients with stable CAD and ASA sensitivity, all had successful desensitization without exacerbating their underlying CAD.[17] However, there are no published reports of ASA desensitization in patients with CAD who have anaphylactoid reactions to ASA; therefore, it is recommended that these patients not undergo desensitization.[14]

Unstable patients presenting with ACS and an ASA allergy should first have their ACS managed, then desensitization therapy can be considered. In those undergoing PCI, the optimal strategy for antiplatelet therapy is yet to be determined. However, bare metal stents are recommended in this population, given the need for dual antiplatelet agents in the context of drug-eluting stents.[33] After undergoing desensitization, it is imperative for the patient to take the drug continuously, since sensitivity may recur if drug exposure is eliminated within 7 days.[34] The dose needed to maintain the desensitized state is usually ASA 325 mg.[35]

There are several published protocols for ASA desensitization. All involve the gradual introduction of increasing doses of ASA to the target dose.[14,15,19] An allergist should be involved and sensitization should take place in a well-monitored setting with the capability of dealing with the airway and circulatory complications associated with a failed desensitization.[19] Silberman et al devised a protocol that was specifically tested in 16 patients presenting with ACS; 2 versions are shown in Table 2. The adverse reaction to ASA was primarily angioedema/urticaria. Most patients presented with NSTEMI, but 4 of the 16 had a recent STEMI. Immediate tolerance was achieved in 88% of the patients on the first attempt, with no major adverse cardiac events occurring during a median follow-up period of 13.7 months. Two patients were treated for ASA-induced angioedema and ASA-exacerbated respiratory disease during the desensitization, which underscores the need for appropriate monitoring for up to 3-4 hours after the last dose in the protocol because of the potential for delayed hypersensitivity reactions.[14]

It is recommended that ß-blockers be withheld for at least 24-48 hours prior to desensitization, since they can cause increased mast cell synthesis and release of histamine in the presence of mast cell-stimulating compounds.[36] In addition, ß-blocker use is a risk factor associated with anaphylaxis from allergen immunotherapy.[37] Furthermore, ß-blockers may limit the effectiveness of epinephrine use in the treatment of anaphylaxis and cause unopposed α-adrenergic effects on the cardiovascular system.[36]

Desensitization to clopidogrel

One case series in the literature examined 3 patients with clopidogrel-induced urticaria who underwent successful desensitization. These patients also had a reaction to ticlopidine when it was used in place of clopidogrel. It is impossible to confirm if there is an allergy to clopidogrel, since no test is available for detecting IgE antibody production to clopidogrel. The patients who underwent successful desensitization had Type I (IgE-mediated) hypersensitivity. The protocol began with an oral dose of 0.005 mg; the doses were doubled every 30 minutes until a final dose of 75 mg was reached. The patients were then observed for 1-3 hours after the protocol ended.[18]

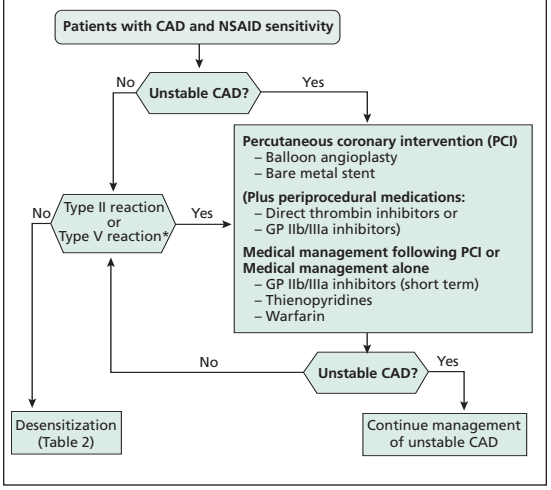
Case 3: A 41-year-old female with a history of hypertension presents with a 2-month history of exertional angina. An exercise stress test is strongly positive and she is referred for an angiogram to document CAD. She has a history of an ASA allergy that results in throat and facial swelling. The angiogram shows a 90% lesion in the proximal left anterior descending artery at the bifurcation of the first diagonal branch. She is referred for angioplasty. How will her ASA sensitivity affect her management around the time of her angioplasty? How should you proceed?

Case 4: A 75-year-old female presents with an NSTEMI complicated by congestive heart failure and is admitted to the coronary care unit. She is initially treated with clopidogrel and low-molecular weight heparin. ASA is not included in the therapeutic regimen because she states that she is intolerant of ASA because it has caused "shortness of breath and body swelling." Her list of current medications includes Alka-Seltzer. She is referred for coronary catheterization. Should she undergo ASA desensitization in order to include this important therapeutic agent?

Alternative strategies

Cilostazol: Cilostazol is a novel antiplatelet agent derived from the quinolone group of drugs that is used primarily in the Far East and the United States (US). Due to its phosphodiesterase-inhibiting functions, it can inhibit platelet activation. In the US, it is approved as therapy for intermittent claudication. When compared with ticlopidine in a post-PCI model, there were no differences in the rate of death or MI, and it led to lower rates of target vessel revascularization over a 9-month follow-up period.[38] Furthermore, in a trial comparing cilostazol and clopidogrel, there were no differences in the rates of subacute stent thrombosis or major adverse cardiac events, including death, MI, and target vessel revascularization within 30 days (2.6% in group 1 vs 2.0% in group 2, $p = 0.61$). Additionally, side effects requiring cessation of the study drug (0.6% each) did not differ statistically between groups.[39]

Figure 1: Proposed algorithm for ASA/NSAID sensitivity in CAD[19]



EPC stents: As an alternative to ticlopidine and clopidogrel, the benefits of stents that capture circulating endothelial progenitor cells (EPC) via antibodies fixed to the luminal face of the stent were recently demonstrated. These cells are capable of rapidly forming a neointima so that the risk of thrombosis and restenosis against the foreign material quickly abates. Recently, the first study using these stents in humans was reported. The rate of stent thrombosis was 0% at the 9-month follow-up mark for the 16 patients enrolled in the study. Furthermore, the rate of major adverse cardiac and cerebrovascular events was 6.3%.[40] Thus, these stents are an attractive alternative in patients who fail antiplatelet desensitization.

Cases revisited

Case 1: This case demonstrates the classic maculopapular rash that can develop in patients who are treated with clopidogrel. This corresponds to a type I IgE-mediated allergic response. The patient's urticaria responded well to corticosteroid and dimenhydrinate therapy following the discontinuation of the drug. In this case, subacute stent thrombosis was prevented by substitution of ticlopidine.

Case 2: In this scenario, the patient previously had a urticarial reaction to clopidogrel. Ticlopidine was substituted for clopidogrel; however, unfortunately, she developed diarrhea that can occur in up to 50% of patients on ticlopidine. She underwent successful clopidogrel desensitization therapy with no recurrence of her urticaria. The diarrhea was a concern because it might have compromised her ability to absorb the clopidogrel necessary for maintaining her desensitization.

Case 3: This is an example of ASA-induced angioedema that occurred on the first exposure to ASA without a significant history of cross reactivity to other NSAIDs. Therefore, this is in keeping with an immunologic reaction to ASA and is classified as a type IV ASA reaction that should then be amenable to ASA desensitization. Therefore, with the guidance of a clinical immunologist, she underwent ASA-desensitization therapy. Unfortunately, she had a recurrence of her angioedema that prompted the termination of her desensitization protocol. A repeat desensitization was not attempted. Her CAD was stable and, therefore, a special request was made to implement the first EPC stent in North America, since she could not have ASA therapy. The EPC stent was successfully delivered and there was no requirement for antiplatelet use.

Case 4: In this case, it is unclear whether the patient has a true ASA allergy by her history alone. However, a careful review of her medications revealed that she was also consuming a fair amount of Alka-Seltzer that happens to contain ASA. Therefore, this patient could not have a true allergy to ASA and she did not undergo ASA desensitization. However, this case underscores the necessity for taking a careful history of allergies and any other medications that the patient may be consuming since many common remedies contain ASA. The patient tolerated the addition of ASA without difficulty.

Summary and recommendations

Patients with antiplatelet sensitivity comprise an important subset of those presenting with CAD. Unstable patients with ACS should be treated directly, without the agent in question. For those proceeding with PCI, bare metal stents should be used with appropriate antiplatelet therapy, including GP IIb/IIIa inhibitors. Desensitization therapy can play an important role in stable CAD, opening the avenue for maximal benefit from antiplatelet therapy. A proposed algorithm for ASA/NSAID allergy has been proposed by Gollapudi (Figure 1).[19] In the case of clopidogrel allergy, ticlopidine may be substituted with appropriate monitoring; however, if it causes significant reactions, clopidogrel desensitization may be considered with the aid of an allergist. Desensitization therapy can be utilized as an effective alternative when antiplatelet utilization is limited by sensitivity reactions, thus enabling optimization of an important therapy in patients with CAD.

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