

Rapid Oral Aspirin Desensitization for Patients with Aspirin Allergy Requiring Dual Antiplatelet Therapy

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Introduction

ASPIRIN is a cornerstone pharmacological therapy for patients with coronary artery disease (CAD). Specifically, dual antiplatelet therapy, aspirin along with clopidogrel, has proven of benefit for prevention of adverse cardiovascular events. However, 0.07% to 0.2% of the general population have aspirin-induced urticaria, and 10% of patients with asthma have aspirin allergy that precludes their use of aspirin.¹

Procedures that provide for rapid, oral aspirin desensitization have been reported in the literature. This article describes the need for using aspirin, patients who might benefit from oral aspirin desensitization, mechanism of action, several published protocols, and the protocol being used at Hartford Hospital.

Patient Benefit from Rapid, Oral Aspirin Desensitization

In the three studies delineated below, dual antiplatelet therapy significantly reduced the risk of adverse cardiovascular events below the rate seen with aspirin alone.

Investigations in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial published evidence that combining clopidogrel plus aspirin reduced the rate of cardiovascular deaths, nonfatal acute myocardial infarction (AMI), and stroke from 11.4% to 9.3% in patients with acute coronary syndrome (ACS) without ST-segment elevation. Benefit of dual antiplatelet therapy with regard to reduction in the rate of cardiovascular deaths, nonfatal AMI, and stroke was

found at 24 hours and was sustained for the duration of the 12-month study.²

The Clopidogrel for the Reduction of Events During Observation (CREDO) study demonstrated a 26.9% risk reduction of adverse cardiovascular events when patients undergoing percutaneous coronary intervention (PCI) used both daily aspirin and clopidogrel for 12 months as compared to daily aspirin alone. This was the first study to show an advantage for using dual antiplatelet therapy post-PCI for 12 months.³

Adding clopidogrel to aspirin and fibrinolytic therapy for patients who had an ST-segment elevation AMI decreased the rate of death, occlusion of infarct-related artery, or recurrent AMI from 21.7% to 15.0% at 30 days. The use of dual antiplatelet therapy in this study reduced the percentage of patients with occlusion of the infarcted artery from 18.4 to 11.7 compared to aspirin alone.⁴

A patient who first received rapid oral aspirin desensitization at Hartford Hospital is a prime example of the importance of aspirin desensitization. This 64-year-old woman had evidence of ischemia on a positive stress test, underwent a coronary angiogram and subsequently had a drug-eluting stent (DES) placed in her left anterior descending artery. Because she had an aspirin allergy, clopidogrel and ticlopidine were prescribed concurrently even though they have similar mechanisms of action. She developed a subacute stent thrombosis within 72 hours causing a large anterior wall acute myocardial infarction (AMI) leaving her with an ejection fraction of only 45%. In order to minimize the risk of a subsequent AMI, this patient underwent rapid, oral aspirin desensitization in the coronary care unit at Hartford Hospital under the direction of allergists at Connecticut Asthma and Allergy Center. This patient continues to tolerate dual antiplatelet therapy with aspirin and clopidogrel 12 months later with no coronary events.

Patients unable to tolerate aspirin due to allergy as evidenced by asthma, rhinitis, urticaria, angioedema, or an anaphylactoid reaction are often prescribed clopidogrel instead. However, dual antiplatelet therapy is clearly

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indicated in the conditions described in the previous paragraph. In these situations, a procedure to rapidly desensitize patients allowing subsequent aspirin therapy is a consideration.

Mechanism of Action for Aspirin Desensitization

The exact mechanisms of aspirin sensitization as well as desensitization remain unclear. Evidence exists that the pathogenesis of aspirin intolerance is not IgE-mediated but related to the greater cysteinyl leukotriene production and the over-expression of cysteinyl leukotriene receptor CysLT1 on inflammatory cells.⁵ The elevated expression of the CysLT1 receptor on these cells may augment the effects of cysteinyl leukotrienes on noninflammatory target cells resulting in bronchospasm, plasma exudation, vasoconstriction, and secretion of mucus.⁶ Sousa et al demonstrated a significant reduction in the percentage of leukocytes expressing CystLT1 receptor in the nasal mucosa of patients undergoing aspirin desensitization. The reduction in CystLT1 may contribute to the therapeutic effects of desensitization by reducing the activation of proinflammatory cells by cysteinyl leukotrienes.

Published Protocols on Rapid, Oral Aspirin Desensitization

Wong et al published their experience with 11 patients who had aspirin-related urticaria or angioedema and received rapid, oral challenge and desensitization.⁷ All patients had CAD and would benefit from aspirin therapy. Nine of the 11 patients completed the desensitization without adverse effects. One had a history of chronic idiopathic urticaria and developed chest tightness with aspirin 10 mg and the last patient experienced urticaria and angioedema. Symptoms resolved in both of these patients with discontinuation of aspirin therapy. Details about premedication and dosing are provided in Table 1.

More recently, Silberman et al described a series of 16 patients who underwent rapid, oral desensitization. Each patient had aspirin allergy and yet required aspirin therapy.⁸ Fourteen patients tolerated the escalating aspirin doses without event. One patient developed edema shortly after the procedure but tolerated rechallenge successfully two days later. The other patient experienced shortness of breath and nasal swelling but aspirin rechallenge was not performed. Table 1 lists parameters concerning premedication and dosing.

Hartford Hospital's Protocol on Rapid, Oral Aspirin Desensitization

The protocol at Hartford Hospital was initially developed by Drs. Marshall Grodofsky, Robert Bedard, Jason Lee, and Jasmine Abbosh at the Connecticut Asthma and Allergy Center. It is based predominantly on the protocol published by Wong et al, described earlier, with variations specific to our patient population and institution. The primary difference between the protocols is the consistent use of premedications. Patients are initially identified as potential candidates by their cardiologist based on history of aspirin allergy and need to use aspirin as dual antiplatelet therapy to prevent thrombosis post-PCI. Informed consent is signed by each patient.

The patients are admitted to the cardiology floor or coronary intensive care (CCU) depending on clinical stability. Patients are given premedications, prednisone 30 mg and montelukast 10 mg 12 hours prior and cetirizine 10 mg one hour prior to starting the procedure. At this point the patient is transferred to the coronary care unit if not already there. Baseline spirometry is performed by the respiratory therapist. The CCU nurse records blood pressure, heart rate, oxygen saturation and lung and skin examination results prior to starting the procedure as well as between each of 11 doses. The first dose is 1 mg (1 mg/mL) of aspirin suspension with

Table 1.—Comparison of Hartford Hospital's Aspirin Desensitization Protocol to other Published Protocols.

Parameter	Hartford Hospital	Wong et al ⁷	Silberman et al ⁸	
			(Patients 1–7)	(Patients 8–16)
Premedication	Consistent use of montelukast, prednisone, and ceterizine	10/11 patients received an antihistamine; 1/11 patient received 2 x 60 mg prednisone	None	None
Initial Aspirin Dose (mg)	1	0.1–10	1	5
Ending Aspirin Dose (mg)	325	10(1*), 81(1), 162(3), 243(1), 325(5)	100	75
Time to Complete Desensitization (Min)	210	90–180	210	150

*Patient had chest tightness at the 10 mg dose.

increasing doses each 15 minutes of 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 50 mg, then 81 mg chewable tablet. The last three doses of 121 mg (81 mg tablet plus 40 mg/mL suspension), 162 mg (2x 81 mg tablets), and finally a 325 mg tablet occur at 20, 30, and then 40 minute intervals. If the patient develops any symptoms of rhinorrhea, urticaria, angioedema, wheezing, respiratory distress, or anaphylaxis, the nurse holds the next dose of aspirin and may administer subcutaneous epinephrine and/or intravenous diphenhydramine. The nurse notifies the physician of any of these symptoms.

After completing this desensitization protocol, the patient must remain on aspirin 325 mg by mouth daily. The patient is instructed to take the aspirin every day and if, perchance, misses more than two days of therapy, should contact his/her cardiologist before resuming therapy in view of concerns about resensitization.

To date, 12 of 13 patients have successfully completed the Hartford Hospital rapid, oral aspirin desensitization protocol. A research study approved by Hartford Hospital's Institutional Review Board (IRB) is ongoing to provide 12-month follow-up for those patients who have completed rapid, oral aspirin desensitization under this protocol.

Conclusions

Hartford Hospital has developed a protocol for rapid, oral aspirin desensitization, a needed service for patients with aspirin allergy who require dual antiplatelet therapy prior to PCI. This procedure should minimize adverse cardiovascular events in patients who otherwise would not tolerate aspirin therapy.

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