Aspirin Hypersensitivity and Desensitization in Patients with Coronary Artery Disease – Challenges and Solutions

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Aspirin or Acetyl salicylic acid (ASA), the platelet cyclooxygenase-1 enzyme (COX-1) inhibitor is the *sine qua non* of pharmacotherapy in patients with coronary artery disease (CAD). Combination therapy of Aspirin and a P2Y12 inhibitor (Clopidogrel, Prasugrel or Ticagrelor) is all the more important in patients with acute coronary syndromes and in patients who have undergone percutaneous coronary interventions (PCI) especially with drug eluting stents. Interruption of Aspirin treatment in this group of patients can cause catastrophic major adverse cardiac events, especially stent thrombosis in post PCI patients. But, some patients are unable to tolerate Aspirin due to adverse reactions, most commonly gastrointestinal intolerance and bleeding manifestations which are usually predictable and dose related. However, Aspirin can also cause a spectrum of hypersensitivity reactions, which can be very alarming and sometimes even life threatening. In this article we will be reviewing the classification, pathophysiologic mechanisms and management of the challenging problem of Aspirin hypersensitivity.

**Classification of Aspirin hypersensitivity**

Aspirin hypersensitivity reactions have been traditionally classified into three basic types depending upon the clinical manifestations.

**Type 1:** Respiratory sensitivity (Aspirin-exacerbated respiratory disease/AERD)

**Type 2:** Cutaneous sensitivity (Urticaria and / or Angioedema), and

**Type 3:** Systemic sensitivity (Anaphylactoid reaction).

Another detailed classification of Aspirin or NSAID hypersensitivity into five types was proposed by Stevenson in 2004 based upon the clinical presentation and the underlying pathophysiologic mechanisms, allowing a better understanding of the phenomenon of Aspirin hypersensitivity. (Table 1) Among the five types, Type I to III have a pharmacologic basis in which reactions induced by NSAIDs or Aspirin are dependent on inhibition of the COX-1 pathway and Type IV and V are immunologically mediated reactions, dependent on IgE production against the drug.

**Type I: Rhinitis and Asthma Induced by NSAIDs - Aspirin exacerbated respiratory disease (AERD)**

Aspirin exacerbated respiratory disease is a triad of asthma, Aspirin sensitivity, and rhinitis/nasal polyps. This condition was first described in 1922 by Widal et al. The article was published in French, and was relatively ignored for the next 45 years. It wasn’t until 1968 when Samter and Beers described patients with the symptom triad of asthma, aspirin sensitivity and nasal polyps, that this syndrome complex was recognised and came to be known as Samter’s triad.

AERD has been estimated to affect 0.3 to 2.5% of the general population. The frequency of symptoms associated with AERD published in literature is, 5–10% in patients with rhinitis, 5–30% in those with

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Aspirin hypersensitivity reactions have been traditionally classified into three basic types depending upon the clinical manifestations which are usually predictable and commonly gastrointestinal intolerance and bleeding. However, Aspirin can also cause a dose related spectrum of hypersensitivity reactions, which can be systemic sensitivity (Anaphylactoid reaction), Type I: Rhinitis and Asthma Induced by Immunologically mediated reactions, dependent on IgE production against the drug. Type II: Urticaria/Angioedema Induced by NSAIDs in patients with Chronic idiopathic Urticaria, Type III: Urticaria/Angioedema Induced by Multiple NSAIDs. Some patients without a history of underlying Chronic Idiopathic Urticaria may develop urticaria/angioedema after treatment with more than one NSAID that inhibit COX-1. These patients usually develop cutaneous manifestations only, without accompanying anaphylaxis. Desensitization can be attempted safely in this subgroup. Inhibition of the COX-1 enzyme by ASA and NSAIDs decreases the production of prostaglandins (PGs), most importantly PGE2. PGE2 is an inhibitor of 5-lipoxygenase enzyme, and decreased availability of PGE2 stimulates the 5-lipoxygenase pathway, leading to an increase in leukotrienes (LTs). Leukotrienes (especially LTC4, LTD4, and LTE4) mediate eosinophil chemotaxis, increase vascular permeability and mucus gland secretion, and precipitate bronchoconstriction.

Type IV: Urticaria/Angioedema Induced by a Single NSAID. Some patients may experience urticaria and/or angioedema to a single NSAID / aspirin. Type IV Aspirin hypersensitivity is believed to be an immunologic reaction. NSAID acts as a hapten with subsequent production of drug specific IgE antibodies against that NSAID. On repeat exposure to the same NSAID, patients may develop an immune reaction with histamine release leading on to Urticaria/Angioedema.

Type V: Anaphylaxis Induced by a Single NSAID. A single NSAID/Aspirin can induce anaphylaxis which is also presumed to be an IgE-mediated reaction. Reaction occur within minutes of ingesting the drug and is characterized by generalized pruritus, laryngeal edema, hypotension, and may progress to shock. Patients will not cross-react with other NSAIDs. Desensitization is often difficult to accomplish and can be potentially fatal and hence many authors recommend avoiding desensitization in these patients.

Patients need not always present with a specific category of reaction, but may rather develop “blended” reactions such as a predominant urticarial response with a mild respiratory tract involvement.
Table 1. Types of Reactions to Acetylsalicylic Acid and Other NSAIDs and Clinical Risk Factors

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Underlying Risk Factor</th>
<th>Cross-Reactions to Other NSAIDs</th>
<th>First Exposure Reaction</th>
<th>Mechanism of Sensitivity</th>
<th>Able to Undergo Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Rhinitis and asthma</td>
<td>Asthma, nasal polyps, sinusitis</td>
<td>Yes</td>
<td>Yes</td>
<td>COX 1 inhibition</td>
<td>Yes</td>
</tr>
<tr>
<td>II</td>
<td>Urticaria/angioedema</td>
<td>Chronic idiopathic urticaria</td>
<td>Yes</td>
<td>Yes</td>
<td>COX 1 inhibition</td>
<td>No</td>
</tr>
<tr>
<td>III</td>
<td>Urticaria/angioedema</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>COX 1 inhibition</td>
<td>Yes</td>
</tr>
<tr>
<td>IV</td>
<td>Urticaria/angioedema</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Immunologic</td>
<td>Yes</td>
</tr>
<tr>
<td>V</td>
<td>Anaphylaxis</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Immunologic</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Testing for hypersensitivity

There are no in vitro tests for aspirin hypersensitivity and cutaneous testing does not yield consistent results and is not clinically useful. A clinical diagnosis, based upon a careful history and assessment, is the key. The only definitive way to make a diagnosis is through a provocative aspirin challenge. However, an aspirin challenge should generally not be performed purely for diagnostic purposes, especially if a systemic reaction has occurred due to the possibility of a life-threatening reaction.

Clinical strategies for patients with aspirin hypersensitivity or intolerance

First of all, the necessity of aspirin therapy should be reassessed. If aspirin therapy is indeed necessary, then a lower dose can be tried, as hypersensitivity reactions may be dose dependent and patients who have not previously tolerated high doses of aspirin may tolerate a low dose. If patients are unable to tolerate aspirin despite the above measures, alternative antiplatelet strategies such as the thienopyridines can be considered. But for some patients, stopping Aspirin can be risky, for example in patients with ACS and after coronary artery stenting. Here, aspirin desensitization should be strongly considered, because there is limited evidence for nonaspirin-based antiplatelet regimens in these settings.

Aspirin desensitization

Aspirin desensitization therapy refers to the elimination of pharmacological and immunologic reactions by slowly increasing exposure to the drug. In patients with reactions related to COX-1 inhibition, desensitization therapy results in decreased leukotriene production, downregulation of cysteinyl leukotriene receptors, and decreased extracellular histamine and tryptase levels after mast cell stimulation. These changes result in a reduction in the inflammatory cascade.

In patients with IgE-mediated reactions, repeated and sustained NSAID exposure leads to saturation of anti-NSAID IgE antibodies sites on basophils and mast cells. In addition, cross-linking of IgE antibodies results in limited mast cell and basophil activation. Ultimately, there is gradual depletion of intracellular mediators (i.e., histamine) with continued exposure to the NSAID.

Approach to aspirin desensitization

An attempt should be made to ascertain if the mechanism of the reaction is pharmacological or immunological, before an appropriate desensitization regimen is selected.

Pharmacological reactions due to COX-1 inhibition tend to occur on first exposure to the drug and there is cross reactivity to other COX-1 inhibitory NSAIDs. Alternatively, IgE-mediated responses (type IV & V) lack cross reactivity with
other NSAIDs and there is a need for prior exposure to initiate an immune mediated reaction.

Desensitization should be carried out in a multidisciplinary setting where there is access to resuscitation facilities and close monitoring of the patient can be carried out. Different methods of successful aspirin desensitization protocols have been published, but there is no universally agreed standard approach. In general, patients are treated with incremental doses of Aspirin. If a positive response to aspirin occurs, it is vigorously treated and after subsequent recovery, the dose at which the response occurred is repeated until no reaction occurs. The dose is gradually increased until the maximum needed dose is reached. The desensitized state exists only as long as regular aspirin continues to be administered; an interruption of 1–5 days returns the patient to a desensitized state. 4,15

There are differences between the protocols used for patients with AERD and those with cutaneous sensitivity. Generally, the desensitization for patients with cutaneous reactions are more rapid than those for patients with AERD but starts with lower doses to provide an extra margin of safety. If reactions are of a mixed nature, protocols that initiated aspirin at a lower dose is preferred, due to the dose-dependent nature of the reaction.

**Desensitization protocol for Aspirin-exacerbated respiratory disease**

Aspirin desensitization has been recommended for AERD that can only be controlled by unacceptably high doses of systemic corticosteroids, repeated polypectomies and/or sinus surgery, or patients requiring aspirin for treatment of coronary disease.

The most famous protocol for desensitizing patients with AERD is the "Scripps Clinic Protocol," described by Szczeklik and Stevenson 16. In this protocol, small incremental oral doses of ASA is administered over the course of 2 to 3 days, until 325 to 650 mg of ASA is tolerated. The first day of placebo challenges is done to ensure airway stability and can be avoided if needed.

Table 2: Scripps Clinic Protocol Protocol for patients with AERD

<table>
<thead>
<tr>
<th>Time 0</th>
<th>Time 3 hours</th>
<th>Time 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Day 2</td>
<td>ASA 30mg</td>
<td>ASA 60mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>ASA 150mg</td>
<td>ASA 325mg</td>
</tr>
</tbody>
</table>

Another similar protocol was proposed by Hope et al from Scripps Clinic itself, where each patient received 30 mg of ASA as the starting dose and proceeded at 3-hour intervals through 45, 60, 100, 150, and 325 mg up to a final dose of 650 mg over a 2- or 3-day procedure 17. Leukotriene-modifying drugs, like Montelukast has been shown to reduce or eliminate bronchospastic reactions without blocking nasoocular reactions. Corticosteroids do not exert a similar effect. It is currently recommended that patients continue asthma-controller medications (e.g. inhaled corticosteroids) before initiation of challenge and desensitization, but anticholinergics, antihistamines, sodium cromoglycate, and short-acting beta agonists be discontinued 24 h before challenge 18.

ASA challenge should be attempted when the patient’s baseline forced expiratory volume in first minute (FEV1) value is equal to or greater than 70% of best predicted FEV1 value and above an absolute value of 1.5 L. 19

A classic positive ASA challenge reaction is described as a 20% or greater decrease in FEV1 combined with naso-ocular symptoms. Isolated asthmatic or naso-ocular symptoms can also occur.

**Aspirin - or NSAID - induced cutaneous reactions protocols**

As already mentioned, the desensitization for patients with cutaneous reactions starts with lower doses and dose escalation is more rapid.

Wong et al published a protocol for Aspirin induced cutaneous reactions in CAD patients and has been widely used since then. 20. This protocol is particularly useful in patients with unstable CAD, as it can be completed within a few hours, thus allowing for rapid desensitization. Dosing was individualized for each patient and administered at intervals of 10-30 min, in the following increasing doses: 0.1 mg, 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, 40 mg, 81 mg, 162 mg, and 325 mg.

Table 3: Protocol for ASA-Induced Cutaneous Disease ; Wong et al

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>85</th>
<th>110</th>
<th>135</th>
<th>160</th>
<th>190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin dose, mg</td>
<td>0.1</td>
<td>0.3</td>
<td>10</td>
<td>30</td>
<td>40</td>
<td>81</td>
<td>162</td>
<td>325</td>
<td>162</td>
<td>325</td>
</tr>
</tbody>
</table>
Dilutions can be prepared by dissolving a dispersible aspirin tablet in drinking water (For eg: 325 mg of aspirin in 325 ml of water will give a solution with a strength of 1 mg/1mL)

Silberman and colleagues used a similar protocol and could successfully desensitize patients rapidly when urgent percutaneous coronary intervention and stenting were required. They started at 1 mg and doubled the dose every 30 min with a final dose of 100 mg (lasting 3.5 h), or a simplified shorter version using five sequential doses (5, 10, 20, 40, and 75 mg), with the procedure lasting 2.5 h.

For patients with aspirin-induced cutaneous disease undergoing desensitization, pretreatment with an antihistamine is useful and systemic steroids can be considered depending on the patient’s clinical condition. If the patient has CIU, the antihistamine should not be stopped but tapered to the lowest effective dose before oral challenge. This is because antihistamine withdrawal may cause a flare up of the urticaria thus interfering with assessment.

Beta blockers and angiotensin converting enzyme inhibitors

Beta blockers may increase sensitivity to allergens which may result in a more serious hypersensitivity response. Also, beta blockers may reduce the response to adrenaline, if emergency treatment is needed for a severe hypersensitivity reactions. Therefore, it is recommended that beta blockers be discontinued for 24 h before desensitization is attempted. However, in patients with symptomatic coronary disease this should be decided on a case-by-case basis.

Patients with a history of angioedema unrelated to angiotensin converting enzyme (ACE) inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. It has been suggested that ACE inhibitors should be withheld prior to desensitization in order to prevent systemic reactions, although angiotensin receptor antagonists would be a reasonable alternative in most patients.

Conclusion

Aspirin hypersensitivity is a challenging clinical problem in patients with coronary artery disease especially in those who have undergone PCI. Avoiding Aspirin in all patients with suspected Aspirin hypersensitivity is unwarranted and puts the patient at an unnecessary and potentially avoidable risk of Major Adverse Cardiac Events including stent thrombosis. Aspirin desensitization is feasible and probably a much safer option in this patient population.

Allergic reactions to Aspirin form a clinical spectrum, and proper classification of the reaction is the first step when a patient with “Aspirin allergy" is encountered in clinical practice, as protocols for aspirin desensitization are different for respiratory and cutaneous reactions. Different protocols for aspirin desensitization have been published, and at present there is no single internationally agreed approach. Once desensitized, patients should be strictly maintained on regular aspirin therapy, because a break in therapy of 1–5 days may put the patient back in the sensitized state. It is generally agreed that patients who have had previous systemic anaphylactic reactions to aspirin should not undergo aspirin desensitization because of the risk of a fatal reaction.

Attempting Aspirin desensitization in patients with unstable cardiovascular disease can turn dangerous at times and more studies are required to establish the risk-benefit ratio of desensitization in hemodynamically unstable patients. Also, there is a great need for standardization of classification and treatment of Aspirin hypersensitivity for better understanding and management of this challenging problem.

References

17. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease Andrew P. Hope, MD,a,b Katharine A. Woessner, MD,b Ronald A. Simon, MD,b and Donald D. Stevenson, MD . J Allergy Clin Immunol 2009 Volume 123, Issue 2, Pages 406–410.