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REVIEW

Coronary Artery Disease and Aspirin Intolerance: Background and Insights on Current Management

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ABSTRACT

Aspirin is one of the most widely used medications across the global healthcare system and is the foundation in treating ischemic heart disease, as well as secondary prevention for ischemic and valvular heart disease. Challenges arise in treating patients with cardiovascular disease who have concomitant aspirin intolerance. Through an extensive review of the literature, we provide a comprehensive background on the pharmacology of aspirin, the mechanisms behind aspirin intolerance, the importance of aspirin in cardiovascular disease, and the management of aspirin intolerance in both acute coronary syndrome and stable coronary artery disease. Our review includes a multidisciplinary approach from the internist, allergist/immunologist, and cardiologist when evaluating this important patient population.

Keywords: Aspirin intolerance; Acute coronary syndrome; Coronary artery disease

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Key Summary Points

Aspirin is the foundation of medical management in cardiovascular disease.

Aspirin intolerance can be challenging in patients presenting with, or previously known, ischemia.

Several protocols exist in managing aspirin intolerance, but ultimately early evaluation by an allergist/immunologist should be incorporated in the treatment approach.

We recommend early aspirin desensitization to be pursued in those with a history of aspirin intolerance and risk factors for cardiovascular disease, with continuation to prevent need for repeat desensitization.

INTRODUCTION

Aspirin is well known for being the most common medication consumed by adults, especially among the sexagenarian and older populations. Equally, the role of aspirin as a preventative medication in those who have suffered from a myocardial infarction, stroke, or other ischemic events is unarguable [1]. The exact prevalence of aspirin intolerance is unknown but ranges from 4 to 44% in those with aspirin induced asthma [2]. Despite its efficacy, dilemmas arise in patients who develop intolerance or frank "allergy", to aspirin. Of utmost concern are the hypersensitivity reactions ranging from cutaneous manifestations to abject anaphylaxis [3]. In our extensive review of the literature, we evaluate the pharmacology of aspirin, the mechanisms behind aspirin intolerance, the importance of aspirin in cardiovascular disease, and the management of aspirin intolerance in both acute coronary syndrome and stable coronary artery disease. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PHARMACOLOGY AND UNDERSTANDING OF ASPIRIN INTOLERANCE

In order to understand the broad-based application of aspirin, it is important to understand its specific mechanisms of action. In general, aspirin inhibits proinflammatory prostaglandins through the uniquely irreversible inhibition of the prostaglandin-forming cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) enzymes. The utility of the cyclo-oxygenase (COX) enzyme inhibition relies on its role of converting the substrate of arachidonic acid to prostaglandin H2 and further end products of thromboxane A2 (TXA2), prostacyclins, and other prostaglandins [4]. These products are precursors to inflammation, fever, and pain, and are involved with gastric cytoprotective actions, and are directly involved with platelet activation and aggregation cascade [5].

With the oral administration of aspirin, absorption is rapid in both the stomach and the proximal small intestine. Intestinal absorption occurs at a much quicker rate; however this absorption is dependent on multiple factors including type of tablet, gastric contents, and gastric pH with enteric coating delaying the absorption. The rate of renal salicylate excretion is variable with dependence on urinary pH. The renal clearance of salicylic acid increases markedly with increasing urine pH, which is important to consider when levels are elevated in the setting of an overdose [6]. When discussing aspirin intolerance, it is important to note that there are hypersensitivity reactions specifically to non-steroidal anti-inflammatory drugs (NSAID), and then there are hypersensitivity reactions to aspirin. Mechanisms behind NSAID-induced hypersensitivity reactions are usually referred to as pseudoallergic (non-immunological) and allergic (immunologic). Pseudoallergic reactions are caused by COX-1 inhibition whereas allergic reactions are immunoglobulin E (IgE) mediated. Current

literature describes four types of pseudoallergic reactions and two types of allergic reactions to NSAIDs.

First, type 1 pseudo allergy (non-immunologic) is also known as NSAID-induced asthma and rhinosinusitis. Clinical manifestations of this type of reaction include rhinorrhea, nasal congestion, conjunctiva, bronchospasm, or laryngospasms. Typical reactions occur within 30–120 min. Asthma, chronic rhinosinusitis with nasal polyposis, and NSAID pseudo allergy patients are considered to have NSAID-exacerbated respiratory disease (NERD). In the setting with aspirin use, this is labeled as aspirin-exacerbated respiratory disease (AERD). Second, type 2 NSAID-induced urticaria/angioedema pseudo allergy is specifically in patients with chronic urticaria, while type 3 pseudo allergy is without chronic urticaria. Clinical manifestations include acute or worsening angioedema and urticaria [7, 8]. Lastly, type 4 pseudo allergy is known as a mixed reaction in otherwise asymptomatic individuals. Type 4 causes both respiratory and cutaneous symptoms. The next type of reaction, allergic (immunologic) reactions, are considered to be IgE mediated and include type 5, which is single NSAID agent-induced urticaria or angioedema, and type 6, which is single agent NSAID-induced anaphylaxis. Reaction onset is usually between minutes to an hour after ingestion [8].

MECHANISMS OF ASPIRIN INTOLERANCE

The mechanisms behind aspirin-induced hypersensitivity reactions may be pharmacological, such as anaphylactic or immunologic. Pharmacological hypersensitivity reactions to aspirin occur when COX-1 inhibition increases leukotrienes, which are proinflammatory molecules, and decreased prostaglandin E2, which are anti-inflammatory molecules, causing symptoms such as respiratory, cutaneous, or even systemic appearing reactions [9]. Immunological reactions to aspirin are mediated by drug-specific IgE production against aspirin. No "aspirin-specific" IgE or T cell production has been identified within the current literature [7].

Thus, hypersensitivity reactions to aspirin may be grouped into three categories: (A) respiratory such as rhinitis and asthma, (B) cutaneous such as urticaria or angioedema, and (C) anaphylactoid reactions [3] (Fig. 1).

Respiratory Reactions

AERD is a common term used to describe symptoms of recurrent sinusitis with nasal polyps, asthma, and sensitivity to aspirin and NSAIDs. Patients with AERD after ingesting aspirin products or NSAIDs are noted to experience worsening of nasal and respiratory symptoms. The mechanisms by which these adverse reactions occur are triggered by COX-1 inhibition rather than IgE-mediated reactions. Aspirin-induced COX-1 inhibition decreases the levels of prostaglandin E2, a mast cell stabilizer, and increases levels of 5-lipoxygenase. Ultimately, this results in a rise in cysteinyl leukotrienes. Leukotrienes, an inflammatory molecule, when vastly accumulated, can have detrimental reactions such as bronchoconstriction in a patient with prior poorly controlled asthma [10].

Cutaneous Reactions

Cutaneous reactions to aspirin such as angioedema and urticaria have been documented to occur frequently in atopic patients and may exacerbate chronic idiopathic urticaria symptoms. The same mechanism, an increase in leukotrienes from the inhibition of COX-1, is involved for the cutaneous reactions occurring from aspirin. This proposed mechanism is further supported by the improvement in urticaria and angioedema reactions with pre-treatment with any leukotriene-receptor antagonists [11, 12].

Anaphylactoid Reactions

Currently, patients with documented angioedema with hypotension, pruritus, tachypnea, laryngeal edema, and unconsciousness within

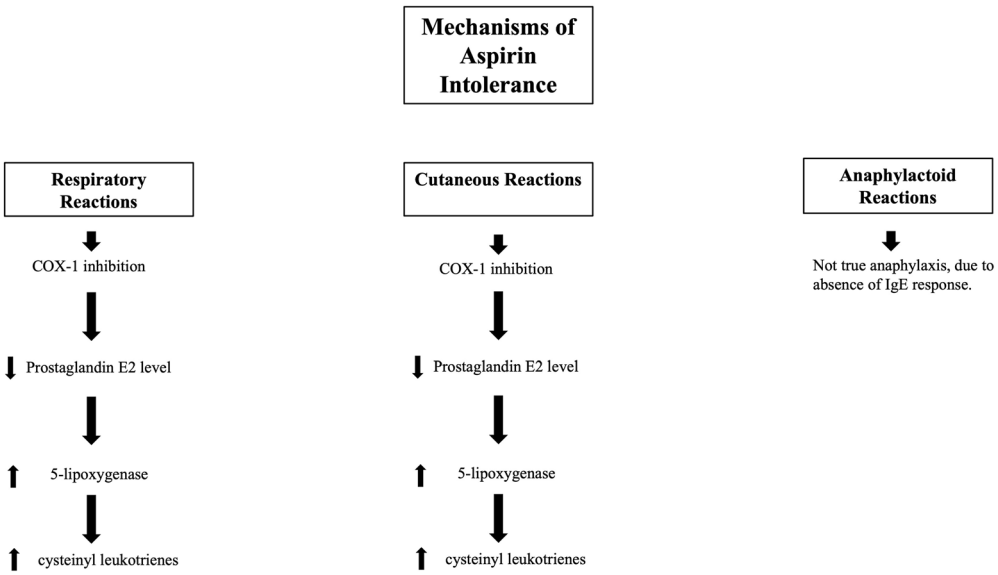

Fig. 1 Brief overview of mechanisms of aspirin intolerance

minutes of aspirin ingestion are classified as anaphylactoid-type reactions. On the contrary, these reactions are not considered anaphylactic reactions, as there has been no known discovered IgE-mediated responses towards aspirin. Given that the symptoms are detrimental, approach to treatment revolves on a presumption of anaphylaxis [3].

Despite the high number of reported adverse reactions to aspirin, the overall benefit in coronary artery disease (CAD) patients is clearly demonstrated, and we believe aspirin desensitization protocols serve as an excellent method of inducing aspirin tolerance in the CAD patients.

ASPIRIN IN MANAGEMENT OF PRIMARY AND SECONDARY PREVENTION OF CORONARY ARTERY DISEASE

Aspirin's role in primary prevention of coronary artery disease is constantly up for debate as there is controversy on its efficacy in preventing primary cardiovascular events [13]. In 2019, the ACC/AHA released guidelines on the primary prevention of cardiovascular disease. The overall takeaway points were that in patients who are at increased risk of bleeding, aspirin should not be used in primary prevention. Aspirin should also not be used for primary prevention routinely in those who are septuagenarian and older. Shared decision-making should be made in starting aspirin in primary prevention in those who are less than 70 years of age with assessment of atherosclerotic cardiovascular disease risk factors. Furthermore, emphasis should equally be placed on non-pharmacological interventions such as tobacco cessation, exercise, and dietary modifications [14].

On the other hand, there is a preponderance of data to support the use of aspirin in secondary prevention of coronary artery disease despite the concurrent bleeding risks. Aspirin helps reduce the formation of blood clots by inhibiting the platelet-clotting cascade, therefore it prevents worsening of atherosclerotic process and ischemic complications such as stent thrombosis after recent stent placement [15]. With endothelial injury of blood vessels, the physiological response of recruiting platelets to adhere at the injury site contributes to the buildup of atherosclerotic plaques. Although the progression of this response results in a formation of a platelet plug, it can also cause vascular occlusion and intraluminal thrombus formation consequently [16].

MANAGEMENT OF ASPIRIN INTOLERANCE IN ACUTE CORONARY SYNDROME AND STABLE CORONARY ARTERY DISEASE

What are the options for patients with ACS if they are intolerant to aspirin?

Treatment options for patients with aspirin allergy include antithrombotic agents not containing aspirin or desensitization to aspirin [17]. Clopidogrel, prasugrel, and ticagrelor are all antithrombotic agents that do not contain aspirin that can be used, however, the safety of any of these single agents has not been studied. In patients with ACS, there can be a risk of instent thrombosis or recurrent ischemic events. Lastly, combined use of ibuprofen and clopidogrel in a study of 42 ACS patients showed some benefit in inhibiting platelet aggregation (lower value of max % platelet aggregation to arachidonic acid) rather than monotherapy alone [18]. On the contrary, there is ambivalence and present concern of non-steroidal anti-inflammatory use when considering overall cardiovascular outcomes [19]. Dipyridamole, a platelet phosphodiesterase inhibitor, has been used in treating coronary artery disease although it has fallen out of favor in contemporary ischemic heart disease treatment protocols [20]. Although desensitization protocols exist as mentioned later in this review, in patients with ACS, the immediate need of aspirin and its antiplatelet benefit surpasses the necessity to categorize patients as aspirin intolerant or not [10].

Most aspirin challenges or desensitization protocols have excluded patients with ACS. In a retrospective review performed at Kaiser Permanente Los Angeles Medical Center, inpatient allergy consults for aspirin intolerance with cardiovascular indication were reviewed to compare the efficacy and safety of high- vs. low-dose aspirin desensitization protocols. Higher starting dose patients (median dose 40.5 mg aspirin) received no pre-medication and low-dose patients (dose 0.1 mg at 20 to 30-min intervals) received combination pre-medication regimen (antihistamine + corticosteroid + leukotriene receptor antagonist). All patients with anaphylaxis or similar reactions underwent a low-dose regimen. Low-dose protocol included the following doses (mg)— day 1: 0.1, 0.3, 1, 3, 10, 20, 40, 81; day 2: 81, 162, 325. High-dose protocol included the following doses (mg)— day 1: 20.25, 40.5, 81, 162, 325. The study found high efficacy at 98.6% for the higher starting dose and 100% for the lower starting dose group. This study showed that high starting-dose protocols for aspirin allergic or intolerant ACS patients without history of anaphylaxis is safe and just as effective as lower starting-dose protocols [21].

In general, there are many desensitization protocols available for patients. The type of aspirin desensitization protocol chosen is generally based on which type of hypersensitivity reaction the patient has had to previous exposure to aspirin or NSAIDS. There are four types of hypersensitivity allergic reactions as the following: type I—caused by IgE antibodies and subsequent mast cell degranulation, type II—cytotoxic reaction caused by IgG or IgM antibodies, type III—caused by immune complexes, and type IV is a delayed reaction that is caused by T-cellular response [22, 23].

Around 1–2% of patients with CAD develop aspirin hypersensitivity [24, 25]. As previously explained, aspirin desensitization involves exposing the patient to increasing doses of oral aspirin [26]. In general, this procedure can be safely performed in patients with stable CAD. Reportedly, it is successful in patients with type I, III, and IV hypersensitivity reactions and it is not recommended in patients with anaphylaxis. Several effective protocols can be used and there are no known controlled trials to compare the efficacy and safety between the protocols. The major difference among these protocols is the time required to complete the process, the first dose, and the target dose [27]. In the paragraphs to follow, we will briefly go over some of the more well-known aspirin desensitization protocols.

Scripps Clinic protocol is the oldest and theoretically safest, as it is performed over 3 days. The starting dose is 30 mg and the target dose is 650 mg. The interval is typically 3 h, and

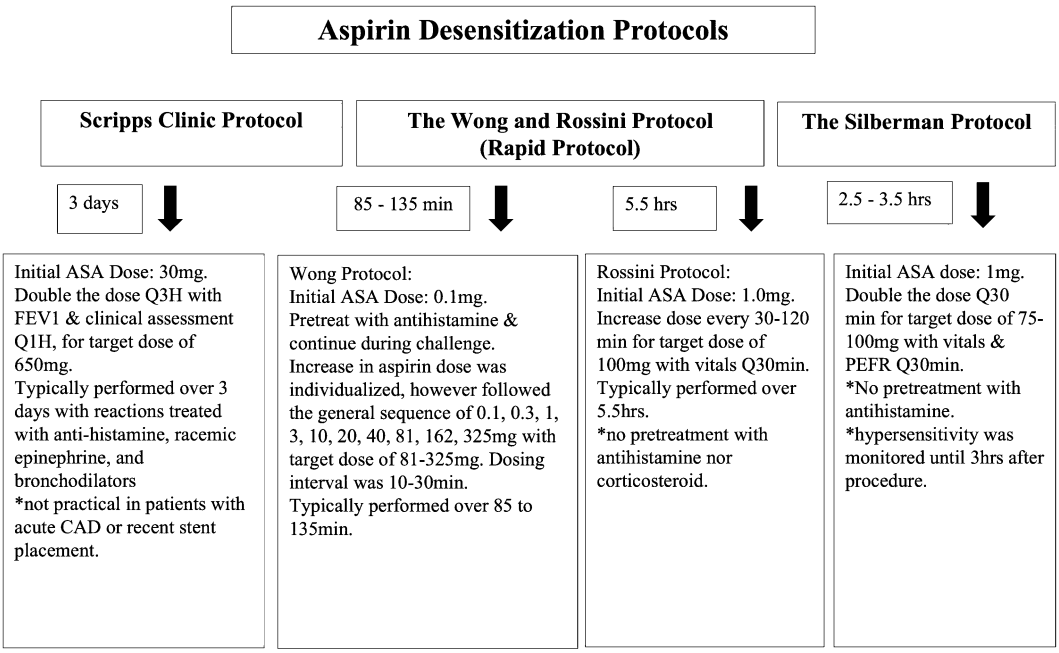

Fig. 2 Aspirin desensitization protocols

the dose is doubled on each interval. Forced expiratory volume-1 (FEV1) and clinical assessment is used every hour. Reactions are treated with different medications including antihistamine, racemic epinephrine, and bronchodilators. This protocol should be implemented mainly in patients with aspirin-exacerbated respiratory disease given their instability and higher probability of having reactions. However, it is not practical in patients with acute coronary artery disease or recent stent placement [27, 28].

The Wong and Rossini protocols were developed for patients with aspirin-induced urticaria and angioedema. In the Wong protocol, the initial dose was 0.1 mg and target dose was 81–325 mg. The dosing interval was 10–30 min. Therefore, it can be interpreted to be a rapid protocol. The time required to complete the protocol ranges between 85 and 135 min. The majority of patients undergoing this protocol receive antihistamine as a pretreatment [29]. In the Rossini protocol, 1 mg is the starting dose and with subsequent doses increased every 30–120 min to reach the target dose of 100 mg. The overall time of the procedure is around 5.5 h. This protocol is designed to be completed without the need for antihistamine or corticosteroid pretreatment. Blood pressure, pulse, and oxygen saturation should be measured every 3 min in this protocol [24].

The Silberman protocol was performed in 16 patients with acute coronary artery disease and aspirin hypersensitivity. The starting dose was 1 mg and the target dose was 75–100 mg. The dose was doubled every 30 min. Antihistamine pretreatment was not given to patients. Blood pressure, pulse, and peak expiratory flow were measured every 30 min. Hypersensitivity manifestations such as cutaneous, naso-ocular, or pulmonary reactions were monitored until 3 h after the procedure [30]. We have summarized the aforementioned protocols in Fig. 2.

Due to the vast majority of reported adverse reactions to aspirin weighed with the overall benefit of aspirin in CAD patients, we believe aspirin desensitization protocols serve as an excellent method of allowing CAD patients to be more tolerable to aspirin [31], but with early involvement of the allergist/immunologist [32]. Furthermore, it is prudent that once a patient is desensitized that they continue aspirin due to the recurrence of sensitization if they remain off aspirin for 1–5 days [33]. The management

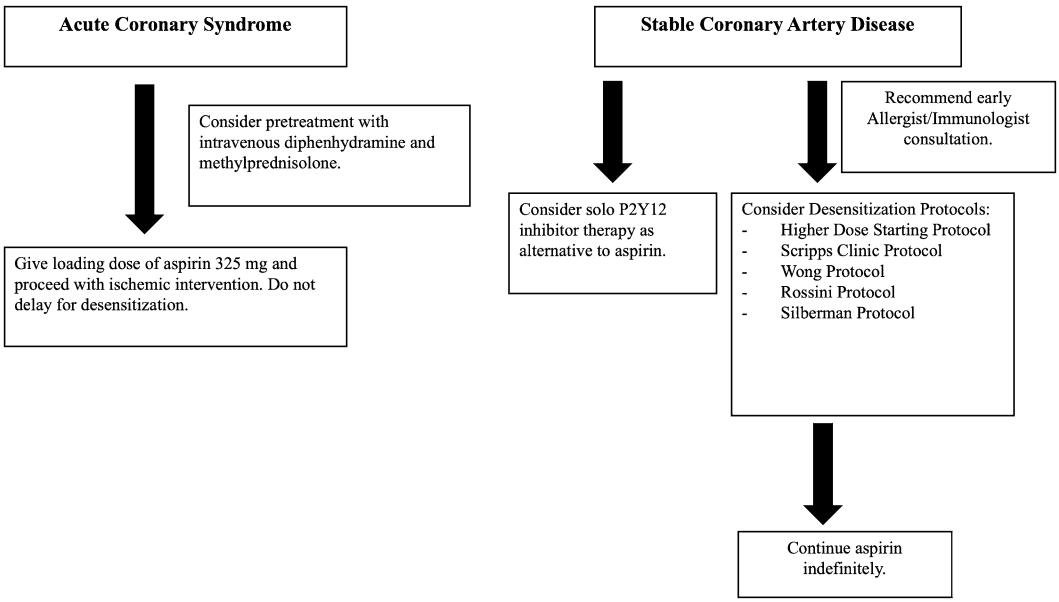

Fig. 3 Proposed algorithm in managing aspirin intolerance in ischemic patients

approach to cardiovascular patients with a reported history of aspirin intolerance is outlined in Fig. 3.

CONCLUSIONS

Aspirin in an important medication in the armament of physicians treating ischemic heart disease. Aside from our proposed algorithm, we also advocate for early aspirin desensitization and allergist consult/referral in patients with significant coronary artery disease risk factors such as hypertension, hyperlipidemia, diabetes mellitus, history of smoking, obesity, and family history of early myocardial infarction [34].

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