



Aspirin Desensitization in Acute Coronary Syndrome and Concurrent Aspirin Hypersensitivity; A Case report from Saudi Arabia

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Background: Aspirin is one of the most widely prescribed drugs in clinical practice. Patients with ischemic heart disease need prolonged therapy with this antiplatelet. Patients with history of ASA hypersensitivity are usually denied receiving this treatment. **Methods:** 6-steps ASA desensitization procedure was performed on a patient with asthma and ASA hypersensitivity who presented with acute coronary syndrome, after failure of alternative monoantiplatelet therapy. **Results:** The patient tolerated the desensitization procedure successfully with no adverse outcomes. He is currently maintained on daily aspirin and clopidogrel with no further hypersensitivity reactions or cardiac events. **Conclusion:** This report describes the first ASA desensitization procedure in our institution. ASA desensitization is generally safe, effective, and well tolerated procedure.

INTRODUCTION

Aspirin, acetylsalicylic acid (ASA), is a non-steroidal anti-inflammatory drug (NSAID). It works by irreversibly inhibiting thromboxane A₂ on the active site of cyclooxygenase-1 (COX-1) enzyme, thereby inhibiting the synthesis of prostaglandins, and subsequently preventing platelet aggregation and activation.^{1,6,8}

The role of ASA in treating patients with acute coronary syndrome (ACS) have been well established clinically to reduce the recurrence of acute coronary syndrome, including both ST segment elevation and non-ST segment elevation myocardial infarction. Moreover, ASA also has a role in preventing in-stent thrombosis in patients undergoing percutaneous coronary intervention (PCI), unless contraindicated.¹

ASA remains the first-choice and the most used medication for lifelong administration after myocardial infarction for secondary prevention purpose. Moreover, dual antiplatelet therapy has led to significant improvement in the outcomes of patients with myocardial infarction, in spite of the added risk of bleeding.⁵

Hypersensitivity to aspirin is one of its contraindications in ACS. Alternative antiplatelets may have lower effectiveness than that of aspirin's in ACS.⁵ A recent review showed that among 9565 patients with coronary artery disease, 1.5% of them reported a reaction to aspirin.³ In Saudi Arabia, the precise prevalence of aspirin hypersensitivity is unknown.

Hypersensitivity to NSAIDs, including aspirin, can be categorized based on the mechanism of hypersensitivity into two main categories;

allergic and pseudo allergic reactions. Pseudo allergic reactions are nonimmunologic reactions that are related to the cyclooxygenase-1 (COX-1)-inhibiting properties of the drug, producing moderate amounts of leukotrienes, which leads to mast-cell degranulation and the release of histamines and cytokines. Pseudo allergic reactions can be usually induced by multiple different NSAIDs and are further subdivided into four types; type (1) NSAID-induced asthma and rhinosinusitis; type (2) NSAID-induced urticaria/angioedema in patients with chronic urticaria; type (3) NSAID-induced urticaria/angioedema in otherwise asymptomatic individuals; and type (4) Blended (mixed respiratory and/or cutaneous) reactions in otherwise asymptomatic individuals.¹⁷

Allergic reactions are mediated by immunoglobulin E (IgE) antibodies and are usually induced by a single NSAID. Allergic reactions can be further divided into two types; Type (5) Urticaria/angioedema to a single NSAID; and Type (6) anaphylaxis to a single NSAID.¹⁷

Hypersensitivity reactions to ASA that are mediated by pharmacological mechanisms as a result of COX-1 inhibition can occur on first use and don't require previous exposure. Also, there is usually cross reactivity with other COX-1 NSAIDs. On the other hand, IgE-mediated reactions require previous exposure to the drug and there is lack of cross reactivity with other NSAIDs.¹³

Drug desensitization is more appropriately to be described as a temporary induction of drug tolerance. Induction of drug tolerance can involve many mechanisms, including IgE mediated mechanisms; non IgE mediated mechanisms, pharmacologic mechanisms, and unknown mechanisms. All methods to induce drug tolerance include administering incremental doses of the drug. These methods will induce a temporary state of tolerance to that drug. This state of tolerance is only

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maintained as long as the patient continues to take that drug without disruption.¹⁸

The aim of desensitization is to modify the patient's response to the medication to briefly allow its administration safely. Drug desensitization is only indicated in situations where a substitute non-cross-reacting drug is not available.¹⁸

ASA desensitization is a method of pharmacological induction of tolerance. As with all other procedures of induction of drug tolerance, this state of tolerance to ASA is temporary and is only maintained as far as the patient continues to take ASA without disruption. After the desensitization procedure, loss of tolerance usually reappears in 2 to 4 days after disruption of continuous ASA therapy.¹⁸

ASA desensitization, followed by daily ASA intake to maintain the drug tolerance, is indicated in patients with aspirin exacerbated respiratory disease (AERD) if aspirin is deemed necessary for treatment. ASA desensitization is also indicated for other conditions, such as rheumatological or cardiac diseases, peripheral arterial disease, cerebral ischemia, and atrial fibrillation.¹

The underlying mechanism for ASA desensitization is not yet fully understood. It is thought that administration of small incremental doses of ASA induces a metabolic shift through several mechanisms, including decrease in leukotrienes production, downregulation and internalization of cysteinyl leukotriene receptors, reduction in urinary leukotriene E4, and decrease in tryptase and histamine release from mast cells.^{3,9,12}

Precautions during ASA desensitization must include frequent monitoring of lung functions and preparation for management of severe bronchospasm and systemic allergic reactions.¹³

Data on the optimal aspirin desensitization strategies and populations who may receive the highest beneficence is not sufficient and almost absent in Saudi Arabia. In favor of this, the authors present a case of a patient who suffered ST-elevation myocardial infarction (STEMI) and aspirin hypersensitivity, whom was successfully desensitized using aspirin desensitization protocol.

CASE PRESENTATION

A 62 years male, known to have bronchial asthma with aspirin sensitivity, presented to the emergency department at King Abdulaziz University Hospital with acute chest pain. Investigations confirmed diagnosis with S-T elevation myocardial infarction (STEMI), and so he was rushed to have primary percutaneous coronary intervention (PCI).

As the patient denied any drug allergy initially, aspirin was initiated. However, within a few minutes of the first dose, he developed dyspnea, cough, headache and urticarial rash. He was treated with epinephrine, inhaled bronchodilators, and intravenous anti histamines.

Current AHA/CCS/ESC guidelines recommend dual antiplatelet in the setting of STEMI with ASA plus clopidogrel or Ticagrelor.⁵ Because of his ASA hypersensitivity, Aspirin was discontinued, and the patient was kept only on clopidogrel as mono antiplatelet therapy. Unfortunately, the patient developed in-stent thrombosis after 2 weeks. Since mono antiplatelet therapy with clopidogrel failed to prevent secondary thrombosis, ASA was paramount to be reinstituted to reduce recurrent in-stent thrombosis. ASA desensitization protocol was successfully performed in the coronary care unit (CCU) Table (1). Since then, the patient continued to take ASA daily without any symptoms. He also didn't develop any cardiac events since then.

His bronchial asthma was diagnosed 10 years ago. The patient has been controlled on Budesonide/formoterol twice daily and Montelukast

once daily. His last emergency visit for asthma exacerbation was more than 3 years ago.

Table 1 6-steps ASA desensitization protocol

Step	Day	Time (h)	ASA Dose (mg)	Cumulative dose (mg)
1	1	0	20 mg	20 mg
2	1	3	40 mg	60 mg
3	1	6	60 mg	120 mg
4	2	0	100 mg	220 mg
5	2	3	160 mg	380 mg
6	2	6	325 mg	705 mg

His first aspirin hypersensitivity attack occurred 10 years ago, when he was prescribed aspirin for primary prevention for ischemic heart disease. He developed shortness of breath, tachycardia, and hives within an hour of ASA ingestion. These symptoms resolved with the help of oral antihistamine and inhaled albuterol. Since then, the patient had similar but milder reactions with ibuprofen on several occasions that also responded to albuterol. He does not have any chronic or recurrent nasal symptoms. He also did not have history of chronic urticaria or angioedema.

DISCUSSION

We herein describe a case of successful ASA desensitization in a patient from Saudi Arabia with asthma and concurrent aspirin hypersensitivity who developed ST-elevation myocardial infarction (STEMI).

Currently, there are no in-vitro tests for ASA hypersensitivity that have been adequately validated. Similarly, in-vivo skin testing does not produce consistent results and so is not useful clinically.¹⁴ Thus, the most reliable tool for clinical diagnosis of ASA hypersensitivity remains careful clinical history and assessment. So far, the only way to make a definitive diagnosis of ASA hypersensitivity is through provocation challenge, including oral, nasal, or bronchial routes. However, provocation challenge should not be done solely for diagnostic purposes, especially if there is a history of previous systemic reaction, due to the possibility of a life-threatening reaction¹³

The patient's previous reactions to aspirin are immediate with respiratory and cutaneous involvement. This was re-demonstrated during re-administration of ASA in hospital. Moreover, he also reacted to other NSAIDs, indicating that his hypersensitivity to ASA is mostly pseudo allergic of type 4 comprising mixed respiratory and cutaneous reactions. Administration of the alternative antiplatelet clopidogrel proved to be inferior to ASA in this case, as the patient developed in-stent thrombosis. Hence, ASA desensitization was performed and was well tolerated safely.

Hypersensitivity to ASA is reported in approximately 1.5% of patients with coronary artery disease. However, many of those "ASA allergic" patients had in fact experienced side-effects and therefore can still receive ASA safely.² In a retrospective computer analysis that included 9,565 of patients with coronary artery disease, previous history of aspirin allergy was recorded in 142 patients. Of these 142 patients, only 30 (21%) provided clinical history compatible with cutaneous and/or respiratory reactions. The remaining patients described adverse effects to aspirin, mostly gastrointestinal manifestations such as intolerance and or bleeding.³

The incidence of side-effects of ASA desensitization is generally low. Only faster protocols had an increased rate of wheals/angioedema.⁷ Up to our knowledge, there are no reported fatalities attributed to ASA desensitization to date, demonstrating the safety of aspirin

desensitization. Two systematic reviews collectively included 256 patients underwent ASA desensitization. Of these patients, 238 (96.7%) were able to complete the desensitization procedure successfully, indicating an overall high success rate and low risk of ASA desensitization.^{7,15}

There are several protocols for aspirin desensitization that have been published. However, these protocols are highly variable, with no universally accepted approach. For example, a systematic review by Bianco et al., included eleven studies with a total of 283 patients. This systematic review showed that there were no significant differences among the oral protocols in terms of efficacy. However, higher incidence of rash and angioedema was reported for protocols with fewer than 6 doses escalation.⁷ Interestingly, despite the previous safety data on ASA desensitization, only 42 % of cardiologists in these trials proceeded with desensitization for ASA allergic patients, with the remaining 58% of cardiologists chose to switch to alternative anti platelet or anti-inflammatory agents.⁷

The presumed underlying mechanism of hypersensitivity to ASA in the patient and his clinical characteristics are helpful for the design of an appropriate desensitization protocol for each patient. Thus, in view of the likely underlying hypersensitivity mechanism in our patient and his cardiac condition, we used the protocol that was previously described by Stevenson DD et al.¹⁶

Informed consent about the risks of the desensitization procedure, including anaphylaxis, was obtained from the patient. The procedure was carried out in a monitored setting, the coronary care unit (CCU). A premedication course was started 5 days before the desensitization day. This course included Montelukast Sodium 10 mg once daily, and Budesonide/ Formoterol (Symbicort) 1 puff twice daily. This course was continued until patient fully tolerated the maintenance dose of ASA.

Before starting the desensitization procedure, a baseline spirometry was performed. Spirometry was also repeated every hour during and at the end of the protocol. Bedside medications to treat allergic reactions were available, including epinephrine, Salbutamol inhaler, and diphenhydramine.

CONCLUSION

In summary, with rare exceptions, patients with hypersensitivity to ASA who need it for cardiac indications will be able to take it safely through desensitization procedure. Despite the various protocols of ASA desensitization that have been described in the literature, the success rate is high with only little associated morbidity.

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