REVIEW

Aspirin Hypersensitivity and Coronary Artery Disease: A Difficult Clinical Issue

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Abstract

Cardiovascular disease is highly prevalent in modern western societies and aspirin has been established as an irreplaceable drug in such patients. A small but non-negligible number of these patients, manifest hypersensitivity to aspirin and /or other non-steroidal anti-inflammatory drugs (NSAIDs), which can take different forms depending on the underlying pathophysiology and clinical variability. In this brief communication, we review the types of hypersensitivity to NSAIDs, the diagnostic steps and its management, focusing on desensitization protocols in patients who require coronary interventions and long-term salicylate administration. ***Rhythmos*** 2018;13(2);30-34.

Key Words: coronary artery disease; aspirin; hypersensitivity; acute coronary syndrome; myocardial infarction

Abbreviations: CAD = coronary artery disease; COX-1 = cyclooxygenase-1; NSAIDs = non-steroidal anti-inflammatory drugs; STEMI = ST elevation myocardial infarction

Introduction

Coronary artery disease (CAD) is the leading cause of death in both genders in Western societies. The prevalence of clinically overt CAD is related to age and ranges from below 1% in individuals <40 years old up to over 30% in octogenarians. [1] The incidence of ST elevation myocardial infarction (STEMI) in Europe lies between 43 and 144 per 100 000 per year, [2] while that of acute coronary syndromes between 1/80 and 1/170 per year. In all these patients who make up a considerable number, aspirin constitutes the mainstay of antithrombotic therapy; needless to say, in the acute coronary syndrome setting, its administration has to be immediate since any delay might lead to clinical deterioration and adverse outcomes especially when an emergency coronary intervention is warranted.

However, not every patient tolerates aspirin well. Hypersensitivity reactions may be observed in 0.6-5.7% of the general population, while in predisposed individuals this frequency can reach 11%. [3,4] In this brief communication, we review the pathophysiological mechanisms of non-steroidal drug hypersensitivity, and the potential preventive and therapeutic maneuvers in patients with CAD who have a strong indication for aspirin use.

Types of aspirin hypersensitivity

Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) are not rare in the general population, since their prevalence ranges between 0.6% and 2.5%, while asthmatics are affected more often (4-20%). However, depending on the specific population studied and the type of the reaction, this frequency may vary significantly. If provocation tests are used, the diagnosis is established in 21%. [3] Non-steroidal anti-inflammatory drugs are among the most common agents to produce hypersensitivity-related adverse effects, second only to antibiotics. Clinically, hypersensitivity reactions exert three main manifestations: respiratory, cutaneous and systemic, and can vary in terms of timing (immediate vs delayed) and severity. Exacerbation of respiratory disease may be noted in 4.3-20% of patients, with the high percentage observed in female patients with chronic rhinosinusitis, nasal polyps or severe asthma. [5-7] Among patients with chronic urticaria, a large portion reaching 30% may experience clinical deterioration after NSAID use. Moreover, up to 1/3 of skin reactions related to NSAIDs can be attributed to immunological mechanism. [8]

With respect to pathophysiology, either a pharmacological or immunological mechanism may be involved, although both types can exist in the same patient on different occasions. Pharmacological reactions are the result of the cyclooxygenase-1 (COX-1) pathway inhibition, while immunological/allergic reactions are mediated by the production of drug specific immunoglobulin E (IgE) or sensitized T-cells. [9-11]

Non-allergic hypersensitivity reactions are typically cross-reactive (they involve reactions to several, chemically non-related NSAIDs) because COX-1 inhibition is a common pharmacologic action shared by many chemically different NSAIDs. Cyclooxygenase catalyzes the production of prostaglandins and thromboxanes from arachidonic acid. Among the former, prostaglandin E_2 plays a vital role in stabilizing inflammatory cells. Its deprivation therefore is believed to activate these cells, especially in susceptible individuals. [12] Moreover, the 5-lipoxygenase pathway is enhanced, leading to the overproduction of leukotrienes, which can exacerbate respiratory symptoms. [13]

Non-immunologically mediated reactions can take any of the three forms: NSAIDs- exacerbated respiratory disease, NSAIDs exacerbated cutaneous disease or NSAIDs-induced urticaria/angioedema.[14]

NSAID-exacerbated respiratory disease: Formerly known as Samter or Widal syndrome, it presents mainly as dyspnea, bronchial obstruction and nasal congestion, in individuals already suffering from an underlying respiratory disease, such as asthma, nasal polyps or rhinosinusitis. It typically relates to more than one drug of the category.

NSAID-exacerbated cutaneous disease: It manifests with angioedema or wheals in relation with aspirin or other NSAID, in patients with a history of spontaneous urticaria.

NSAID-induced urticaria/angioedema: Clinical presentation is similar to the previous form, but the affected patients do not report a chronic urticaria history. Symptoms must be induced by at least two agents of the NSAID class originating from different chemical groups.

Immunologic reactions occur after the administration of one or more substances belonging to the same chemical group. Typically, patients report no previous hypersensitivity episodes with the use of other NSAIDs. Two types of allergic phenomena are described:

Single-NSAID-induced urticaria/angioedema or anaphylaxis is a rapid (within mins to 1 h) occurrence of symptoms ranging from mild urticaria to laryngeal edema and anaphylactic shock. It represents a type I allergic mechanism mediated by antigen-specific IgE antibodies.

Single-NSAID-induced delayed hypersensitivity is characterized in the majority by cutaneous manifestations (maculopapular eruptions, photosensitivity reactions, delayed urticaria, contact dermatitis, acute generalized exanthematous pustulosis, and severe cutaneous adverse reaction-SCAR). Rarely may involvement of other organs be noted (nephritis, pneumonitis).[15] This reaction is presumably a type IV immunological reaction occurring via the activation of specific CD4+ and CD8+ T cells as evidenced in several reports.[16-18] This clinical and patho-physiological classification is summarized in Table 1.

Table 1. Classification of hypersensitivity reactions to NSAIDs[10]

Reaction type	Terminology	Symptoms/ signs	Timing	Pathophysiology
Cross-reactive (non-immunologically mediated)	NSAID exacerbated respiratory disease	Bronchial obstruction, dyspnea and/or nasal congestion/ rhinorrhea	30-180 min	Cox-1 inhibition
	NSAID exacerbated cutaneous disease	Wheals and/or angioedema	30-360 min	Cox-1 inhibition
	NSAID-induced urticaria/ angioedema	Wheals and/or angioedema	15 min to hrs (usually within1 h)	Unknown probably Cox-1 inhibition
Selective (immuno-logically mediated)	Single NSAID induced urticaria/ angioedema/ anaphylaxis	Wheals/ angioedema/ anaphylaxis	Immediate (typically within 1h)	IgE-mediated
	Single NSAID induced delayed hypersensitivity reactions	Various symptoms and organs involved (e.g. fixed drug eruption, SJS/ TEN, nephritis)	Delayed onset (usually >24 h after exposure)	T-cell mediated

NSAID = nonsteroidal anti-inflammatory drugs; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis

Diagnosis

Obtaining a detailed history is fundamental, as it provides information on the suspect drug, the type of the reaction and the presence of long-term symptoms. Then, according to the suspected reaction, provocative tests can be implemented to confirm the clinical diagnosis. In more detail, in exacerbated respiratory disease, oral provocative test is a sensitive method (sensitivity 90%) to detect hypersensitivity to aspirin or other drugs. Inhalation tests or nasal challenge with lysine-aspirin are quick and safe, but less sensitive. Cutaneous disease exacerbation is also confirmed by oral provocation. Interestingly, skin tests have no place in the diagnostic work-up. NSAID-induced urticaria/angioedema is suspected when the symptoms are related to the administration of at least two chemically different NSAIDs and no history of chronic urticaria is reported. Confirmation may be provided by oral provocative test with the culprit agent and in the case of aspirin with one alternative drug as well. [14, 19,20] Allergic reactions are usually diagnosed based on history of rapid onset of symptoms after exposure to a specific NSAID. A skin test with an alternative drug may be performed to exclude cross-reactivity. For the diagnosis of delayed hypersensitivity, patch tests or intradermal skin tests can be used.[21-25]

In general, oral tests with the culprit agent are the gold standard for diagnostic confirmation. They exhibit both a high positive (almost 100%) and negative predictive value (97.8%). [20] However, they should not be performed in certain circumstances such as in severe delayed type reactions, in cases with a history of severe anaphylaxis, when the underlying chronic disease (asthma, urticaria) is uncontrolled and if concomitant disorders that could be aggravated by challenge are present. Usually the challenge is done with aspirin and an alternative drug to confirm or exclude cross-reactivity. Based on these general rules, Kowalski et al have proposed a seven-step diagnostic approach [15] which is depicted in Table 2.

Table 2. Seven steps leading to the diagnosis of NSAIDs hypersensitivity [11]

History	1. Is it a predictable or unpredictable reaction?
	2. Assess the timing of the reaction
	3. Observe the clinical manifestations and the presence of chronic underlying disease
	4. Review the history for tolerance of other NSAIDs
Tests	5. Confirm/exclude cross-reactivity to other NSAIDs by oral challenge
	6. Consider skin testing or in vitro testing in case of single reactions
	7. Consider oral provocation challenge with the culprit drug

Management

Avoidance of the agent responsible for the reaction is fundamental. In single drug reaction, alternative NSAIDs can be used but it is prudent to perform an oral challenge in order to exclude cross-reactivity. Moreover, non-acetylated salicylates such as trisalicylate or salsalate are well tolerated by most patients with respiratory disease exacerbations. [14] However, patients who suffer an acute coronary syndrome or undergo coronary angioplasty and stenting, cannot substitute aspirin as it constitutes the mainstay of antiplatelet therapy. In these cases, desensitization to aspirin can be attempted. Unfortunately, not all types of hypersensitivity are prone to desensitization procedures. These protocols have been validated in cases of exacerbation of respiratory disease and aspirin-induced urticaria/angioedema. [26-28] In exacerbated cutaneous disease the data are controversial and in immunological reactions no recommendations can be made due to the lack of evidence from prospective controlled trials. [29,30]

Desensitization

Desensitization therapy refers to the elimination of pharmacological and immunologic reactions of aspirin by slowly increasing exposure to oral acetylsalicylic acid. The result is the decrease in leukotriene production, down-regulation of cysteinyl leukotriene receptors, as well as extracellular histamine and tryptase levels after mast cell stimulation. In patients with IgE-mediated reactions, the exact mechanism is unknown, but repeated and sustained administration of aspirin leads to saturation of the specific IgE antibodies sites on basophils and mast cells. As an additive effect, cross-linking of IgE antibodies limits mast cell and basophil activation. Finally, intracellular mediators (i.e., histamine) are being depleted and the reaction gradually weakens and ceases. [31-33]

Although the available evidence supports desensitization in cases of aspirin-induced exacerbated respiratory disease and urticaria/angioedema, most patients with salicylate hypersensitivity can undergo the procedure, except for those with exacerbated cutaneous disease or induced delayed hypersensitivity. Several desensitization protocols have been used and there is no consensus yet for the use of a common methodology. Tables 3 and 4 describe the desensitization sequences implemented by Szczeklik and Stevenson, [34] Schaefer and Gore, [35] and Wong et al. [36] Silberman et al used two similar schemes in their patients who presented with acute coronary syndromes mostly treated with percutaneous intervention. The first consisted of 8 doses, starting at 1 mg and doubling every 30 minutes up to a final dose of 100 mg (total duration 3.5 hours). The second was shorter, and was completed in 5 doses of 5, 10, 20, 40, and 75 mg. [37] Christou et al reported on 11 patients with respiratory or cutaneous aspirin hypersensitivity who underwent coronary angioplasty (5 for stable angina, 3 for unstable angina, 2 for non-ST elevation myocardial infarction and 1 for STEMI). They used the protocol proposed by Wong (Table 4) with complete success. Coronary interventions were all performed on the second day of admission. [38] Rossini et al used a different rapid desensitization protocol with excellent results in 26 patients with respiratory or cutaneous manifestations undergoing percutaneous coronary intervention, which is displayed in Table 5. All patients were desensitized before intervention apart from those with STEMI who were subjected to the protocol before discharge. [39] A similar sequence was used by Schiano et al in a patient with a history of aspirin-induced urticaria/angioedema who presented with STEMI. The patient received thrombolytic therapy along with clopidogrel and heparin, and on the next day he was started on incremental doses of aspirin following a protocol lasting less than two hours (5, 10, 20, and 40 mg given at 30 min intervals up to a cumulative dose of 75 mg, which was then continued daily. [40] Alternative protocols have also been tested. [41-44] All endorse oral administration of aspirin. Only one publication has introduced intravenous desensitization with administration of aspirin in doses of 1, 2, 4, 8, 16, 32, 64, 125, 250 mg at time points 0, 30, 60, 90, 120, 150, 180, 210, 240 min respectively. Efficacy was reported in 42 out of 43 patients (97.6%) over a 12-month follow up. [45]

Table 3. Desensitization protocol used in patients with ASA-exacerbated respiratory disease [34]

Day \ Time	0	3 hours	6 hours
1	Placebo	Placebo	Placebo
2	ASA 30 mg	ASA 60 mg	ASA 120 mg
3	ASA 150 mg	ASA 325 mg	ASA 650 mg

ASA = acetylsalicylic acid

Table 4. Desensitization protocols used in patients with ASA-induced cutaneous disease [35,36]

Wong et al protocol		**Schaefer and Gore protocol**	
Time (min)	ASA (mg)	Time (h)	Placebo/ASA (mg)
0	0.1	0	Placebo
15	0.3	1	ASA 150
30	10	2	ASA 325
45	30	3	Placebo
60	40	4	ASA 325
85	81	5	Placebo
110	162	6	End
135	325		

Table 5. Rapid desensitization protocol proposed by Rossini et al. [39]

Time (min)	Aspirin dose (mg)
0	1
30	5
60	10
90	20
210	40
330	100

In a review of the available data, all studied regimens were found equally effective (success rate >97%). Reaction rate during protocol implementation did not exceed 5% and it was higher when the number of aspirin doses was <6 compared to less aggressive oral or IV protocols. Angioedema occurred in 3.4% (0.6%-6.3%) of the participants in relation with the short protocols only. [46]

Recently, the results of the ADAPTED multicenter registry were published. [47] A total number of 330 aspirin intolerant patients with stable CAD or acute coronary syndrome scheduled for percutaneous intervention were given the Rossini desensitization regimen before catheterization. In participants with STEMI (23%), desensitization was deferred until after the revascularization, and bridging therapy with IIb/IIIa inhibitors was given according to the judgment of the attending physicians. Desensitization was successful in 315 patients (95.4%) and in all patients with a history of anaphylactic reaction. In the non-responder group (15 patients-4.6%), adverse reactions were minor and were managed with corticosteroids and antihistamines. [47]

In conclusion, aspirin hypersensitivity is a relatively rare but recognizable condition which complicates the management of patients with CAD especially in cases of acute coronary syndromes requiring urgent intervention. Substituting triflusal for aspirin in dose 300 mg bid has been reported; [48] however it is seldom used. Rapid desensitization offers an attractive alternative and the literature has been encouraging so far. A variety of administration sequences with progressively increasing dose of aspirin have been tested and published with comparable, high efficacy, and this practice emerges as the most appropriate to deal with salicylate hypersensitivity when its long-term use is deemed necessary. Most protocols are completed within a few hours and can be applied before the coronary intervention. In case of STEMI, when any delay may be detrimental, primary angioplasty can be performed under IIb/IIIa inhibition and desensitization should follow. It should be also emphasized that the effect of desensitization fades away within a few days unless aspirin is uninterruptedly given thereafter, which must be taken into account when aspirin therapy is temporarily withheld as for instance in view of an upcoming surgical procedure. Although a promising method, desensitization has not been studied in large trials and its application is largely empiric or based on limited regional experience, as implied by the numerous similar protocols in use. Thus, more research is needed, which will allow for the incorporation of hypersensitivity management in current guidelines and will standardize the therapeutic approach in these patients.

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