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Rapid desensitization to acetylsalicylic acid in patients with ischemic heart disease: 10-year experience of a Portuguese Allergy Department

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Key words

Acetylsalicylic acid; hypersensitivity; rapid drug desensitization; ischemic heart disease; percutaneous coronary intervention.

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Impact statement

The present study reports a 10-year experience with a rapid desensitization protocol to acetylsalicylic acid (ASA) in Portuguese patients with ASA hypersensitivity undergoing coronary angiography, demonstrating its safety and efficacy regardless of the hypersensitivity reaction and timing of the procedure (before or after percutaneous coronary intervention), in both short and long terms.

Summary

Background. *Managing acetylsalicylic acid (ASA) hypersensitivity (HS) in patients with ischemic heart disease (IHD) is a challenge. Data on rapid desensitization (RD) to ASA is scarce. We aimed to report the outcomes of our 10-year experience with RD to ASA.* ***Methods.*** *Retrospective, observational, single-center study of patients with ASA HS and suspected IHD who underwent RD to ASA between March 2009 and February 2019.* ***Results.*** *Fifty patients were included. ASA HS presentation ranged from urticaria (56%) to anaphylaxis (32%). Regarding cardiologic diagnoses, 40 patients (80%) had acute coronary syndrome and 10 (20%) stable angina. The majority of patients (n = 36.72%) underwent percutaneous coronary intervention. RD to ASA was successful in all patients. Two patients presented a mild HS reaction during the RD, which was promptly treated, and subsequent daily doses of ASA 100 mg were tolerated.* ***Conclusions.*** *In our cohort, RD to ASA in patients with ASA HS and IHD was very effective and safe.*

Introduction

Dual antiplatelet therapy with acetylsalicylic acid (ASA) and a P2Y12 inhibitor (*i.e.*, clopidogrel, ticagrelor, prasugrel) is considered the mainstay of treatment in ischemic heart disease, leading to a significant decrease in cardiac events after percutaneous coronary intervention (PCI), particularly reducing the risk of stent re-stenosis (1, 2).

ASA hypersensitivity (HS) is reported in 1.5-2.6% of patients presenting with cardiovascular disease (3), which represents a complex clinical challenge. History of previous HS reactions to other non-steroidal anti-inflammatory drugs (NSAID) as well as timing and severity of the reaction(s) should always be assessed given its importance in patient's risk stratification. According to the European Academy of Allergy and Clinical Immunology (EAACI), and considering clinical manifestations, the presence of an underlying disease, and cross-reactivity with other cyclooxygenase (COX)-1 inhibitors, NSAID hypersensitivity reactions can be classified into two major groups: non-immunologically mediated (cross-reactive), which includes NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous disease (NECD) and NSAIDs-induced urticaria/angioedema (NIUA); and immunologically mediated (non-cross-reactive), comprising single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) and single-NSAID-induced delayed hypersensitivity reactions (SNIRD) (4).

Collaboration between cardiologists and immunoallergologists is crucial and should be encouraged to ensure optimal patient management (5). ASA desensitization is an effective and safe treatment strategy in patients presenting ASA HS, although it has been implemented in only 24-42% of the cases (6). This procedure consists of gradual administration of increasing doses of ASA to induce a state of transient tolerance to the drug, which is only maintained by the daily intake of ASA. Patient compliance is mandatory as this state of tolerance is lost within 2-5 days of interruption of therapy (5). Desensitization is not recommended in patients with severe anaphylactic reactions, as it carries significant risk (7), and is absolutely contraindicated in patients who have experienced severe, life-threatening immunocytotoxic reactions, vasculitis or bullous skin diseases like Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) (8).

There are several ASA desensitization protocols available, although in the context of ischemic heart disease rapid desensitization protocols are preferred, as they are completed in a few hours with reported success rates above 90% and favorable safety outcomes (3, 7, 9-21). Concerning the timing of ASA desensitization, current practice European guidelines recommend to perform the procedure before coronary angiography except for urgent situations, such as ST-segment elevation myocardial infarction (STEMI), where in order to avoid further myocardial damage, the temporary use of an alternative antiplatelet drug (*i.e.*, clopidogrel) along with a platelet glycoprotein IIb/IIIa inhibitor (*i.e.*, abciximab, eptifibatide, tirofiban) is considered a safer choice, postponing ASA desensitization to be performed within 12-72 hours (7).

The aim of the present study was to describe the outcomes of rapid desensitization to ASA in patients with ischemic heart disease, performed in our Portuguese Allergy Department over a 10-year period.

Materials and methods

Study design, population and data collection

A retrospective, observational, single-center study was conducted. Between March 2009 and February 2019, the charts of all patients undergoing ASA desensitization in our Allergy Department were reviewed. Inclusion criteria were age over 18 years-old, presence of a well-established or suspected ischemic heart disease requiring coronary intervention study, and a suspected ASA or NSAID hypersensitivity. Patients with history of delayed severe hypersensitivity reactions, such as bullous exanthemas, DRESS, SJS, TEN and acute generalized exanthematous pustulosis, were excluded, as well as patients reporting class A ASA intolerance, such as gastrointestinal symptoms or bleeding. The study was conducted in accordance with the principles contained in the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients' medical records were assessed to collect demographic and clinical data. Detailed information on initial hypersensitivity reaction to ASA and other NSAIDs, allergology and cardiology personal history, local and timing of ASA desensitization procedure, breakthrough hypersensitivity reactions during the desensitization protocol and coronary angiography were recorded.

All but one patient were followed up for at least 12 months to assess late ASA hypersensitivity reactions, compliance with ASA therapy and causes of withdrawal (if it occurred), and major adverse cardiac events (defined as non-fatal re-infarction, recurrent angina pain, re-hospitalization for cardiovascular-related illness, stent thrombosis, unscheduled coronary revascularization, stroke or cardiac death (22)).

ASA desensitization protocol

The ASA desensitization protocol in use in our Allergy Department was adapted from the Silberman's protocol (10) and included the administration of increasing oral doses, every 30-60 minutes, starting with a dose of 2.5 mg until the target dose of 152.5 mg was reached, within a total time of 4.5 hours (**table I**). When a load dose of 250 mg ASA was required for

patients with acute ischemic heart disease, an additional 100 mg was provided 60 minutes after the last dose of the protocol, reaching a cumulative dose of 252.5 mg. Before each dose administration and 1 h after the end of the protocol, vital signs, symptoms suggestive of ASA hypersensitivity reaction and peak flow measurements were assessed. Pretreatment with steroids, antihistamines or anti-leukotrienes was not administered. Therapy with beta-blocker agents was suspended the day before the ASA desensitization.

Statistical analysis

Continuous variables were presented as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions, and categorical variables as frequencies and percentages. Normal distribution was confirmed using Shapiro-Wilk test or Skewness and Kurtosis. Categorical variables were compared using Fisher's exact test or the Chi-square test, as appropriate. P-values lower than 0.05 were considered statistically significant. Analyses were performed with the use of IBM SPSS software (version 25.0).

Table I *- Acetylsalicylic acid desensitization protocol.*

Step	Time (min)	Dose (mg)	Cumulative dose (mg)
1	0	2.5	2.5
2	15	5	7.5
3	30	10	17.5
4	60	20	37.5
5	90	40	77.5
6*	150	75	152.5

*When a load dose was required, an additional 100 mg was provided 60 minutes after step 6 (cumulative ASA dose: 252.5 mg).

The protocol was performed by an immunoallergologist, trained in desensitization procedures and the treatment of potential breakthrough HS reactions. When the procedure was considered urgent/emergent, desensitization was performed at patient's bedside, in the Cardiology, Medicine or Intensive Care Unit where the patient was admitted. In cases of an elective procedure, the desensitization was performed in our Allergy Day-Care Unit, as it has a fully equipped emergency cart. The ASA desensitization protocol was approved by the Ethics Committee and all patients provided their written informed consent to participate in the study, which was conducted in accordance with the principles contained in the Declaration of Helsinki and Good Clinical Practice guidelines.

Outcomes

Safety and efficacy of our rapid ASA desensitization protocol were the study's two major outcomes. Safety was evaluated based on the presence of breakthrough hypersensitivity reactions during the desensitization protocol, considering frequency, severity and treatment management. Efficacy relied on the ability to complete the desensitization protocol and maintain ASA 100 mg daily intake without any HS reaction.

Secondary outcomes were patient compliance (daily ASA 100 mg intake) and the presence of major adverse cardiac events during the 12-month follow-up.

Results

Patient characterization

From March 2009 to February 2019, 50 patients underwent ASA desensitization with our Allergy Department's rapid desensitization protocol, mean age 68.1 ± 9.9 years (47-88 years), 29 of them male (58%). Demographic and Clinical characterization of the study population is presented in **table II**.

Regarding allergologic features, ASA HS reaction was described as urticaria and/or angioedema in 28 patients (56%), of whom two had chronic spontaneous urticaria, anaphylaxis in 14 patients (32%), respiratory sensitivity (asthma exacerbation, bronchospasm, rhinitis) in 7 patients (14%) and non-immediate cutaneous reaction in one patient (2%). History of multiple NSAID hypersensitivity was reported in 10 patients (20%). Considering NSAID classification criteria and based on the available background information, 4 of these patients had NERD reactions and 6 had NIUA reactions. Of the 40 patients with hypersensitivity reactions to ASA only, we also assumed NERD reactions in 3 patients (history of asthma and rhinosinusitis, and asthma exacerbation after ASA intake). Lack of sufficient information on prior NSAID use and background history of chronic urticaria, asthma or nasal polyps did not allow us to differentiate between immunological/non-immunological reactions in the remaining 37 patients.

Table II *- Demographic and clinical characterization of the study population.*

Baseline characteristic	n (%)
Total number of patients	50
Age, mean ± SD (range), years	68.1 ± 9.9 (44-88)
Sex, male/female	29 (58)/ 21(42)
Allergological characterization	
ASA hypersensitivity reaction	
Urticaria/Angioedema	28 (56)
Anaphylaxis	14 (32)
Asthma exacerbation/Bronchospasm/Rhinitis	7 (14)
Cutaneous non-immediate reactions	1 (2)
Multiple ASA/NSAID hypersensitivity reactions	10 (20)
Cardiological characterization	
Presentation	
Stable angina	10 (20)
Unstable angina	8 (16)
NSTEMI	15 (30)
STEMI	17 (34)
Multivessel disease	20 (40)
Left ventricular ejection fraction	
Good (> 50%)	40 (80)
Moderate (30-50%)	9 (18)
Poor (< 30%)	1 (2)
Previous PCI	7 (14)
Previous CABG	4 (8)

ASA: acetylsalicylic acid; CABG: coronary artery bypass graft; NSAID: non-steroidal anti-inflammatory drugs; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST segment elevation myocardial infarction.

Concerning cardiological characterization, 10 patients (20%) presented stable angina while 40 patients had an acute coronary syndrome: 8 (16%) had unstable angina, 15 (30%) had NSTEMI and 17 (34%) had STEMI. Multivessel disease was identified in 20 (40%) patients. Left ventricular ejection fraction was good (> 50%) in the majority of patients (n = 40, 80%), only one patient had a score below 30%. Previous PCI was reported in 7 patients (14%) and previous CABG in 4 (8%).

Efficacy and safety outcomes

The study's outcomes are presented in **table III**. ASA desensitization was performed at the Cardiology Department in 23 patients (46%), Cardiology's Intensive Care Unit in 12 patients (24%), Allergy Day-Care Unit in 11 patients (22%) and Medicine Department in 4 patients (8%). The procedure was executed before coronary angiography in 28 patients (56%) and after coronary angiography in 22 patients (44%).

The cardiologic presentation of patients desensitized after coronary angiography was acute coronary syndrome: unstable angina (n = 3), NSTEMI (n = 8) and STEMI (n = 11). Regarding cardiologic treatment, the majority of patients (n = 36, 72%) underwent PCI: one patient (2%) was treated with simple balloon angioplasty, 8 patients (16%) with bare-metal stent and 27 patients (54%) with drug-eluting stent. Coronary Artery Bypass Graft (CABG) was the treatment option in 5 patients (10%), while 9 patients (18%) received medical treatment only.

Breakthrough hypersensitivity reactions during the desensitization protocol were observed in two patients, both of them 30 minutes after the completion of the desensitization protocol,

Table III *- Allergological and cardiological outcomes.*

Outcome	n (%)
Total number of patients	50
ASA desensitization	
Local	
Cardiology Department	23 (46)
Cardiology's Intensive Care Unit	12 (24)
Allergy Day-care Unit	11 (22)
Medicine Department	4 (8)
Timing	
Before coronary angiography	28 (56)
After coronary angiography	22 (44)
Allergological outcomes	
Hypersensitivity reaction(s) during ASA desensitization	2 (4)
Hypersensitivity reaction(s) after ASA 100 mg intake	0 (0)
ASA 100 mg daily intake (12 months)*	47/49 (96)
Cardiological outcomes	
Treatment	
Medical management	9 (18)
PCI with simple angioplasty	1 (2)
PCI with bare-metal stent	8 (16)
PCI with drug-eluting stent	27 (54)
CABG	5 (10)
Major adverse cardiac events (12 months)**	4 (8)

ASA: acetylsalicylic acid; CABG: coronary artery bypass Graft; PCI: Percutaneous coronary intervention; *1 missing value; **myocardial infarction: n = 3; cardiac death: n = 1.

corresponding to a cumulative ASA dose of 152.5 mg (**table IV**). Both patients were male (75 and 62 years-old, respectively) and reported previous history of hypersensitivity reactions to multiple NSAID. Patient 1 had a personal history of NERD, and his previous ASA/NSAID reactions were characterized by asthma exacerbations. He presented with a NSTEMI and was treated with PCI with drug-eluting stent. ASA desensitization was performed after PCI and the breakthrough hypersensitivity reaction was characterized by dry cough, dyspnea, wheezing, nasal congestion and ocular hyperemia. Patient 2 had a personal history of rhinitis with pollen sensitization, reporting previous ASA/NSAID reactions usually characterized by facial angioedema, dyspnea and rhinitis. He presented with a stable angina and was treated with PCI with drug-eluting stent. ASA desensitization was performed before PCI and the breakthrough hypersensitivity reaction was characterized by eyelid angioedema, dyspnea, nasal congestion and ocular hyperemia. Both patients were treated with short-acting beta-agonists, corticosteroids and antihistamines with full recovery in less than 1 hour, tolerating the ASA 100 mg intake the day after the procedure and during the next 12-month follow-up. The incidence of hypersensitivity reactions in our NERD cohort did not differ significantly when comparing to the other patients (p = 0.263).

ASA 100 mg intake was tolerated by all patients the day after the procedure and there were no subsequent hypersensitivity reactions in a short term. Patients desensitized only after coronary angiography did not demonstrate a lower protocol's efficacy (p = 0.691). All patients were discharged with dual antiplatelet therapy including ASA.

Considering the 12-month of follow-up, one patient was not Portuguese, he was on vacation when he presented with a STEMI and was admitted in our hospital, so he was subsequently referred to his cardiologist in England and we could not complete the follow-up. Of the remaining 49 patients, only one patient discontinued ASA, although by self-initiative. This patient suffered another myocardial infarction 11 months after the first one and had to undergo a new ASA desensitization. All other patients complied with the ASA 100 mg daily intake during the 12-month follow-up without any hypersensitivity reaction reported.

Major adverse cardiac events were reported in 4 patients (8%): cardiac death (n = 1) and myocardial infarction (n = 3). Regarding the fatality, the patient was 88 years-old and presented with a STEMI and severe left ventricular dysfunction that was considered refractory to medical therapy. He underwent successful desensitization before the coronary angiography and tolerated subsequent ASA 100 mg intake without any evidence of a hypersensitivity reaction. He died afterwards during the hospital hospitalization. Three patients suffered a myocardial infarction, one already mentioned above, who discontinued ASA without medical indication. In the other two patients, these new cardiac

***Table IV** - Characterization of the patients with hypersensitivity reactions during ASA desensitization.*

Patient	Age (years)	Sex	ASA HSR	Multiple NSAID HSR	Cardiological presentation	Cardiological treatment	ASA desensitization before PCI	HSR during desensitization	Cumulative dose of ASA at which HSR occurred (mg)	Management of HSR	MACE (12 months)
1	75	Male	Asthma exacerbation	+	NSTEMI	PCI + drug-eluting stent	0	Asthma exacerbation Rhinoconjunctivris	152.5	SABA, Corticosteroids, Antihistamines	0
2	62	Male	Facial angioedema Dyspnea Rhinitis	+	Stable angina	PCI + drug-eluting stent	+	Eyelid angioedema Dyspnea Rhinoconjunctivitis	152.5	SABA, Corticosteroids, Antihistamines	0

ASA: acetylsalicylic acid; HSR: hypersensitivity reaction; MACE: major adverse cardiac events; NSAID: non-steroidal anti-inflammatory drugs; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SABA: short-acting beta-agonists.

events occurred in different coronary territories, without evidence of stent re-stenosis, and were once again successfully treated by PCI. Of note, ASA desensitization had been performed after coronary angiography. Both patients were previously compliant with the ASA treatment and were therefore maintained on their daily ASA with no further allergologic intervention.

Discussion

Our study confirms the efficacy and safety of rapid desensitization to ASA in patients with ischemic heart disease. The key findings of the present study were: 1) the bedside rapid desensitization protocol to ASA used in our Allergy Department's was effective and safe in patients with suspected or established ischemic heart disease even when performed after PCI; 2) acute hypersensitivity reactions were uncommon and responded quickly to treatment, not compromising the protocol's effectiveness; and 3) the great majority of patients were compliant with ASA 100 mg daily intake and no hypersensitivity reactions were observed in the long term (12 months).

Notably, the use of rapid desensitization protocols – protocols less than 5.5 hours in duration – is crucial due to the urgent antiplatelet need of patients with acute ischemic heart disease. In the last few years, several rapid protocols have been applied oftentimes, demonstrating favorable efficacy and safety outcomes (3, 6, 9-11, 14, 15, 17-21). A recent metanalysis of 15 studies which included a total of 691 patients presenting with coronary artery disease and history of ASA hypersensitivity who underwent ASA RD protocols reported high pooled protocol success rates among these patients (98.3% (97.2 to 99.5)) with zero hypersensitivity reactions at follow-up (between 1 and 46 months, mode 12 months) (16). The cumulative adverse events rate was 8.4% (3.2 to 13.6) and included cardiac deaths, heart failure, gastrointestinal bleeding and events requiring repeat PCI, thrombolysis, and CABG procedures (16). However, one important limitation of this metanalysis was the retrospective, nonrandomized, small cohort nature of the vast majority of the clinical literature available on ASA desensitization for these patients.

Two large multicenter prospective studies recently published have reinforced the success of these rapid protocols, providing strong evidence for its use in real-world practice. The ADAPT-ED registry (13) prospectively examined the use of a standardized 6 dose, 330 minutes, rapid ASA desensitization protocol in 330 patients undergoing coronary angiography regardless of the class of hypersensitivity. ASA desensitization was performed prior to coronary angiography unless patients presented with STEMI in which case desensitization was deferred until after PCI. Desensitization was successful in 95.4% of patients including those with a history of anaphylactic shock or respiratory sensitivity. Cortellini *et al*. (7) reported a consensus-based 10-step, 300 minutes, ASA desensitization protocol from 10 allergy centers belonging to the European Network on Drug Allergy (ENDA)/European Academy of Allergy and Clinical Immunology (EAACI) Drug Allergy Interest Group, in a total of 147 patients, with a success rate of 98.6%. According to the authors, a standard rapid ASA desensitization protocol is advised to start with very low dose (0.1-10 mg), due to the possibility of IgE-mediated reactions, and to continue with short time intervals (20-30 min) until the cumulative dose of 40 mg is reached. Subsequent time intervals, in particular in patients with NERD/NECD (considering the risk of reactions mediated by the inhibition of cyclooxygenase-1), may be longer (60-90 min), until a cumulative dose between 75 and 150 mg is reached.

Our results are in accordance with those previously mentioned. In fact, our protocol was effective in all patients desensitized, without severe hypersensitivity reactions implicating desensitization failure, and none of the patients followed-up within the 12 months discontinued ASA due to hypersensitivity reactions. Collaboration between Allergy and Cardiology Departments has been crucial to the success of the procedure.

In the last 5 years, ASA desensitization has been consistently performed in our institution, as recommended by the guidelines (7), before coronary angiography, with exception of some cases of STEMI given its urgent character and risk of further myocardial damage. In fact, the evidence suggests that patients who do not receive ASA before PCI are at higher risk of mortality and stroke (23). However, considering the 10 years of our study, 22 patients (44%) performed ASA desensitization after coronary angiography, 3 of them with unstable angina and 8 with NSTEMI. The desensitization protocol was equally successful, and no stent restenosis was recorded, although 2 of them experienced a myocardial infarction in another coronary territory 9 months later. For the majority of the patients who performed ASA desensitization after coronary angiography in the first 5 years of the study, allergologic evaluation and intervention (ASA rapid desensitization) was only requested after PCI. A closer collaboration between Cardiology and Allergology Departments of our institution has allowed us to better plan the patients' management. Moreover, taking into account that ASA has been proven to be a more cost-effective treatment in patients with coronary artery disease compared with a regimen of thienopyridine alone (24), and based on our results, we believe that ASA desensitization should always be considered, regardless of the timing of the procedure.

Although a higher risk of reactions has been reported in patients with a history of chronic idiopathic urticaria and NERD reactions (7, 16), in our Allergy Clinic, the protocol was not modified in these particular situations and there were no more reactions in these groups when compared to other patients. This is possibly due to the fact that our protocol already contem-

plates a 60-minute interval after the cumulative dose of 77.5 mg. Nevertheless, this should be interpreted with caution given the low number of patients with those characteristics desensitized in our cohort.

The present study has strengths and limitations. As strengths, we highlight the fact that it is the first Portuguese report on ASA desensitization in patients with ischemic heart disease, with a rapid protocol that was effective in all patients desensitized. Concerning limitations, its retrospective and single-center design limits generalization of the results. Furthermore, considering the relatively small cohort, allied to the fact that only 2 patients out of 50 had a breakthrough reaction during the desensitization protocol, our statistical results should be interpreted with caution, as type 2 errors cannot be excluded (more studies with larger samples are needed to confirm these results). Additionally, the definition of ASA hypersensitivity was patient-reported and not confirmed by an oral challenge, therefore, in some situations the desensitization was empirical, as some patients might not have had a true ASA hypersensitivity. Nevertheless, according to the current European recommendations (7), in patients with known/suspected ischemic heart disease needing coronary angiography with an unclear history of ASA hypersensitivity, desensitization is considered safer than challenge. Finally, lack of sufficient data on prior NSAID use and background history of chronic urticaria, asthma or nasal polyps did not allow us to differentiate between immunological/non-immunological reactions in the majority of patients. Therefore, we could not confirm if our protocol was equally effective and safe in patients with NECD and NERD reactions.

We herein presented our Allergy Department's 10-year experience with a rapid desensitization protocol to ASA in patients with ASA hypersensitivity undergoing coronary angiography, demonstrating its safety and efficacy regardless of the type of ASA hypersensitivity reaction and timing of the procedure (before or after PCI), in both short and long terms. We emphasize the importance of a close collaboration between cardiologists and immunoallergologists to a successful and optimal management of these patients.

Fundings

None.

Contributions

RB, JC, EP: study design. RB, JC: data collection. RB: data analysis and writing – original draft. JC, EP: writing – review and editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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