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Clinical approach on challenge and desensitization procedures with aspirin in patients with ischemic heart disease and nonsteroidal anti-inflammatory drug hypersensitivity *

Background. Hypersensitivity to acetylsalicylic acid (ASA) constitutes a serious problem for subjects with coronary artery disease. In such subjects, physicians have to choose the more appropriate procedure between challenge and desensitization. As the literature on this issue is sparse, this study aimed to establish in these subjects clinical criteria for eligibility for an ASA challenge and/or desensitization.

Methods. Collection and analysis of data on ASA challenges and desensitizations from 10 allergy centers, as well as consensus among the related physicians and an expert panel.

Results. Altogether, 310 subjects were assessed; 217 had histories of urticaria/angioedema, 50 of anaphylaxis, 26 of nonimmediate cutaneous eruptions, and 17 of bronchospasm related to ASA/nonsteroidal anti-inflammatory drugs (NSAID) intake. Specifically, 119 subjects had index reactions to ASA doses lower than 300 mg. Of the 310 subjects, 138 had an acute coronary syndrome (ACS), 101 of whom underwent desensitizations, whereas 172 suffered from a chronic ischemic heart disease (CIHD), 126 of whom underwent challenges. Overall, 163 subjects underwent challenges and 147 subjects underwent desensitizations; 86 of the latter had index reactions to ASA doses of 300 mg or less. Ten subjects reacted to challenges, seven at doses up to 500 mg, three at a cumulative dose of 110 mg. The desensitization failure rate was 1.4 %.

Conclusions. In patients with stable CIHD and histories of nonsevere hypersensitivity reactions to ASA/NSAIDs, an ASA challenge is advisable. Patients with an ACS and histories of hypersensitivity reactions to ASA, especially following doses lower than 100 mg, should directly undergo desensitization.

Key words: aspirin, challenge procedure, desensitization procedure, nonsteroidal anti-inflammatory drugs hypersensitivity.

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Cardiovascular and ischemic heart diseases (IHDs) affect 50 % and 35 % [1] of the general population, respectively, whereas hypersensitivity to cyclooxygenase (COX-1) inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs) affects around 0,6–5,7 % of it [2, 3]. It is therefore relatively common to see hypersensitivity to acetylsalicylic acid (ASA, aspirin) or to COX-1 inhibiting NSAIDs in patients who require an urgent assessment due to an acute coronary syndrome (ACS) or an elective investigation due to chronic IHD (CIHD).

The application of drug eluting or noneluting stents under coronary angiography requires a dual antiplatelet therapy for 6–12 months with ASA and thienopyridine drugs (selective, irreversible ADP receptor/P2Y12 inhibitors) [4], which can be problematic in patients with NSAID hypersensitivity, even though the recommended dose of ASA is 100 mg or less daily. In effect, the CURRENT-OASIS 7 trial [5] demonstrated that in patients with an ACS, who were referred for an invasive strategy, there was no significant difference between higher-dose ASA (300–325 mg daily) and lower-dose ASA (75–100 mg daily), with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke.

Therefore, the collaboration between allergists and cardiologists is essential [6, 7] for two reasons: (i) to ensure these patients get the best therapy, rather than going for a second choice, namely coronary artery bypass grafting; (ii) to decide which of the following procedure is applicable: an ASA challenge test, which is a diagnostic procedure aiming to verify the tolerability of ASA at an antiplatelet dose of 100 mg (or 150 mg, in the acute phase) [8] or an ASA desensitization, which is a procedure aimed at inducing a pharmacological or immunological tolerance to ASA.

The literature on this topic is currently insufficient and uneven with regard to the procedures used [6, 7, 9–14].

It also does not explain the clinical indications for when to use the tolerance (challenge) test or, instead, desensitization to ASA. In particular, the published series differ in terms of number of patients studied, antihistamine premedication, intervals between ASA doses, total time of administration, cumulative dose reached and time of observation after procedure is finished [15–27] *(Table 1)*.

Moreover, the medical history is frequently unclear, in both cardiological (e.g. CIHD or ACS) and allergological (presence of either anaphylactic symptoms, or skin reactions only, or NSAID-exacerbated respiratory disease – NERD) terms.

Therefore, in the first phase, this study collected data on ASA challenges and desensitizations in subjects with CAD and histories of ASA/NSAID hypersensitivity reactions, who were assessed in 10

Table 1
Rapid protocols of acetylsalicylic acid (ASA) desensitization

No. of patients Author treated		Total time, min	Starting dose, mg	Final dose, mg	Cumulative dose, mg	No. of protocol steps	Time interval between doses (min)	Success rate %
Wong et al. [15]	11	100–300	0.1–10	81–325	155.4–642.4	10	10–30	81.8
Silberman et al. [16]	7	210	1	100	227	8	30	85.7
	9	150	5	75	150	5	30	100.0
Alijotas-Reig et al. [17]	4	135	0.1	100–125	254.4–279.4	9*	15	100.0
Hobbs and Lyle [18]	13	210	1	325	799	11	15–40	92.3
Rossini et al. [19]	26	330	1	100	176	6	30–120	88.5
Dalmau et al. [20]	5	120–240	0.1	100	189.3	8	15–20	100.0
Ortega-Loayza et al. [21]	3	240	0.5	100	227.5	9	30	66.7
Cristou et al. [22]	11	135	0.1	325	648.4	8	15–25	100.0
Cortellini et al. [23]	31	220	0.1	50	151.6	12	20	90.3
De Luca et al. [24]	43	240	1	250	502	9	30	97.6
Lee et al. [25]	24	120	5	80	155	5	30	83.3
McMullan and Wedner [26]	26	90–120	1	325	636	7	15–20	88.5
Cordoba-Soriano et al. [27]	24	105	0.1	100	189.4	8	15	100.0†

* If no adverse effects appeared, the ASA dose of 100 or 125 mg was repeated the next day.
† Actually, one patient experienced an urticarial reaction after the 10-mg dose and completed the protocol in about 4 h.

Table 2
Demographic characteristics of the 310 patients and types of reactions to ASA

	Number (%)	Challenge (%)	Desensitization (%)	Pearson v^2/t-test P
Total number of patients	310	163	147	
Average age, years [SD]	63.9	60.4 [14.2]	67.9 [10.1]	<0.001
Males	141/310 (45.5)	50/141 (35.5)	91/141 (64.5)	<0.001
Females	169/310 (54.5)	113/169 (66.9)	56/169 (33.1)	<0.001
Urticaria/angioedema	217/310 (70.0)	118/163 (72.4)	99/147 (67.3)	0.333
Anaphylaxis	50/310 (16.1)	22/163 (13.5)	28/147 (19)	0.185
Asthma	17/310 (5.5)	7/163 (4.3)	10/147 (6.8)	0.333
Cutaneous nonimmediate reactions	26/310 (8.4)	16/163 (9.8)	10/147 (6.8)	0.339
Hypersensitivity only to ASA*	106/310 (34.2)	38/163 (23.3)	68/147 (46.3)	<0.001
Multiple ASA/NSAID hypersensitivity †	204/310 (65.8)	125/163 (76.7)	79/147 (53.7)	<0.001
Symptoms after ASA dose				
≤ 300 mg ‡	119/310 (38.4)	33/163 (20.2)	86/147 (58.5)	<0.001
> 300 mg §	191/310 (61.6)	130/163 (79.8)	61/147 (41.5)	<0.001

ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; P, correlation coefficient.
* Patients with histories of hypersensitivity reactions only to ASA.
† Patients with histories of hypersensitivity reactions to ASA and at least one other NSAID.
‡ Patients with histories of hypersensitivity reactions to ASA at doses of 300 mg or less.
§ Patients with histories of hypersensitivity reactions to ASA at doses higher than 300 mg.

allergy centers. In the second phase, the collected data were analyzed and discussed in a meeting to establish a consensus on the clinical criteria for eligibility for an ASA challenge or desensitization among the related physicians and an expert panel, and create a common protocol for ASA desensitization. In the third phase, this protocol was applied by all centers.

Methods

A multicenter study was performed from October 2013 to April 2015. In the first phase, data on ASA challenges and desensitizations from each of the 10 enrolled centers were collected. Each center belonged to the European Network on Drug Allergy (ENDA) / European Academy of Allergy and Clinical Immunology (EAACI) Drug Allergy Interest Group.

The inclusion criteria were aged over 18 years and the presence of a well-established IHD or a suspect IHD requiring a coronary study, as well as a history of ASA or NSAID hypersensitivity. The exclusion criterion was a history of severe anaphylactic reactions to ASA.

Data concerning heart diseases, culprit NSAIDs, types of ASA/NSAID hypersensitivity reactions, and allergological and cardiological outcomes were also collected *(Tables 2 and 3)*.

In the second phase, the collected data were analyzed and discussed in a consensus meeting (during the ENDA autumn meeting, October 2014, Florence, Italy), in which the physicians of the 10 centers and an expert panel participated. The key points in consensus were as follows: (i) to create homogeneous cardiological and allergological criteria to decide which patients are eligible for the challenge procedure and which are eligible for the desensitization (primary endpoint); (ii) to create a common, simple protocol for desensitization procedures (secondary endpoint); and (iii) to understand and determine allergological and cardiological outcomes of both procedures (secondary endpoint).

In the third phase, from November 2014 to April 2015, the 10 centers applied a common desensitization protocol.

Statistical analysis

Statistical analysis (absolute and percentage frequency, average data, and standard deviation) was performed. Data were analyzed with the STATA package (Stata Statistical Software: Release 10; StataCorp. 2007, College Station, TX, USA). The continuous variables are expressed as the mean (SD) and were compared using a t-test. Categorical data are given as numbers of cases and percentages and were compared using a chi-square test. A P-value of 0.05 or less indicates statistical significance.

Table 3
Cardiological characteristics of the 310 patients and both allergological and cardiological outcomes

	Number (%)	Challenge (%)	Desensitization (%)	Pearson v^2/t-test P
Total number of patients	310	163	147	
Cardiological characteristics				
Acute coronary syndrome (ACS)	90/310 (29.0)	23/163 (14.1)	67/147 (45.6)	<0.001
ACS and myocardial infarction	48/310 (15.5)	14/163 (8.6)	34/147 (23.1)	<0.001
Chronic ischemic heart disease	172/310 (55.5)	126/163 (77.3)	46/147 (31.3)	<0.001
Stenting				
Medicated	56/310 (18.1) <0.001	8/163 (4.9)	48/147 (32.7)	<0.001
Not medicated	20/310 (6.5)	8/163 (4.9)	12/147 (8.2)	0.244
Simple angioplasty	11/310 (3.5)	4/163 (2.5)	7/147 (4.8)	0.273
Allergological outcome				
Symptoms during the procedure*	22/310 (7.1)	10/163 (6.1)	12/147 (8.2)	0.487
Desensitization failure	–	–	2/147 (1.4)	
12-Month cardiological outcome				
Major adverse cardiac events (MACE)	26/310 (8.4)	12/163 (7.4)	14/147 (9.6)	0.493

* Hypersensitivity reactions experienced by the patients during challenge or desensitization procedures.

We examined the following variables: gender, type of reactions to ASA/NSAIDs (urticaria/angioedema, anaphylaxis, asthma, and cutaneous nonimmediate reactions), single reactor to ASA, reactors to ASA and other NSAIDs, index reactions at 300 mg or lower dose of ASA, index reactions at a dose higher than 300 mg, heart disease (ACS, ACS and myocardial infarction, CIHD), cardiological procedures (medicated stenting, not-medicated stenting, and simple angioplasty), allergological outcome (symptoms during the procedure), and cardiological outcome (cardiovascular accidents, death) *(Tables 2 and 3)*.

Results

Clinical features

The clinical characteristics of patients are shown in Tables 2 and 3. Altogether, 310 subjects were assessed; 163 underwent challenges and 147 desensitizations. The average age of subjects desensitized was significantly higher than that of subjects who underwent challenges. Among subjects who were desensitized, the number of males was significantly higher than that of females (91 vs 56; $P < 0.001$) *(Table 2)*.

Of the 310 subjects, 217 had histories of urticaria/angioedema, 50 of anaphylaxis, 26 of nonimmediate cutaneous eruptions, and 17 of bronchospasm related to ASA or NSAID intake. Of the 106 subjects with histories of hypersensitivity reactions only to ASA, 104 had experienced urticarial and/or angioedematous or anaphylactic reactions and, according to Kowalski et al. [28], were classified as having had a single-NSAID-induced urticaria/angioedema or anaphylaxis, whereas two suffered from asthma and rhinosinusitis, had experienced bronchospasm after ASA intake, and were classified as having had a NERD.

In the desensitization group, the number of subjects with histories of hypersensitivity reactions only to ASA was significantly higher than the one of the challenge group *(Table 2)*.

According to the clinical histories, a dose of 300 mg or less of ASA was able to induce symptoms in 119 patients (38.4 %), while in the remaining 191 patients (61.6 %) symptoms were caused by a dose of ASA higher than 300 mg *(Table 2)*.

The number of subjects with histories of hypersensitivity reactions to ASA at doses of 300 mg or less who underwent desensitization was significantly higher than that of patients challenged. On the other hand, the number of subjects with histories of hypersensitivity reactions to ASA at doses higher than 300 mg who underwent challenges was significantly higher than that of patients desensitized *(Table 2)*.

Table 4
Acetylsalicylic acid (ASA)* challenge protocol

Minutes	ml of L-ASA solution	ASA dose, mg	Cumulative dose, mg
0	0 (placebo)	0	0
20	1	10	10
65	2.5	25	35
110	2.5	25	60
155 †	5	50	110
200 †	5 ‡	50 ‡	160 ‡

* Two hundred and eighty-eight milligram of lysine acetylsalicylate (L-ASA), equivalent to 160 mg of ASA, dissolved in 16 ml of water were used.
† One to two hours observation after procedure.
‡ The default cumulative dose is 110 mg; in case of specific request by cardiologist, it becomes 160 mg.

With regard to the cardiological characteristics, 138 (44.5 %) of the 310 subjects had an ACS, whereas 172 (55.5 %) suffered from CIHD. The number of subjects with an ACS desensitized was significantly higher than that of patients challenged (101 vs 37; $P < 0.001$) *(Table 3)*.

Of the 138 subjects with an ACS, 87 underwent angioplasty and/or coronary stent placement (drug-diluting, nondiluting, and simple angioplasty in 56, 20, and 11 cases, respectively). The other 51 patients underwent simple coronarography, without angioplasty or stent placement.

In the group with stable CIHD, the number of subjects who underwent challenges was significantly higher than that of patients desensitized *(Table 3)*.

As far as challenges are concerned, 143 subjects underwent them before the consensus meeting: 95 subjects at ASA doses up to 160 mg, and 48 at doses up to 500 mg, whereas 20 were challenged after the consensus meeting, all at a cumulative dose of 110–160 mg, according to the protocol of the present study *(Table 4)*. Overall, 10 subjects reacted to challenges, seven at doses up to 500 mg, three at a cumulative dose of 110 mg. Three of the 10 subjects positive to ASA challenges had a history of anaphylaxis (cutaneous and respiratory symptoms) and were effectively treated with ASA desensitization. The remaining seven patients, with a history of urticaria/angioedema, had to stop the study for clinical reasons or personally decided to interrupt *(Table 3)*.

With regard to desensitizations, 92 subjects were treated before the consensus meeting, 82 (all Italians) with the protocol by Cortellini et al. [23], the remaining 10 with the protocol by Wong et al. [15], with slight modifications and a final ASA dose of 162 mg. Fifty-five subjects were desensitized after the consensus meeting, all with the protocol of the present study *(Table 5)*.

Table 5
Acetylsalicylic acid (ASA)* desensitization protocol

Minutes	ml of L-ASA solution	ASA dose (mg)	Cumulative dose (mg)
0	0 (placebo)	0	0
20	0.01	0.1	0.1
40	0.1	1	1.1
60	0.2	2	3.1
80	0.3	3	6.1
100	0.4	4	10.1
120	0.5	5	15.1
140	1	10	25.1
180	1.5	15	40.1
240	2.5	25	65.1
300 †	3.5	35	100.1

* Two hundred and eighty-eight milligram of lysine acetylsalicylate (L-ASA), equivalent to 160 mg of ASA, dissolved in 16 ml of water were used.
† One to two hours observation after procedure.

During desensitizations, only 12 patients (8.2 %) had hypersensitivity symptoms; 10 of them reached an effective ASA 100 mg tolerance, while the other two had to stop the procedure *(Table 3)*.

Regarding cardiovascular outcomes, the procedure of desensitization was significantly associated with stenting. With regard to the 12-month cardiological outcomes, there was no difference in major adverse cardiac events (MACE) between subjects desensitized and subjects challenged *(Table 3)*.

Recommendations

General

On the basis of the analysis of the data on ASA challenges and desensitizations collected in the first phase of the study, as well as of literature data [15–27] and the expert panel opinion, there was a consensus that the access to procedures of both challenge and desensitization should be implemented in every clinical subset of acute hypersensitivity to NSAIDs provided by the position paper on 'Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs' [28]. Moreover, there was a consensus that the challenge procedure is safe and has to be implemented in patients with stable CIHD and a history of hypersensitivity to ASA at an anti-inflammatory dose (over 300 mg), as well as at an antiplatelet dose (75–100 mg), and nonsevere clinical symptoms (e.g. urticaria). Challenge steps are determined on the basis of literature data [23, 29–34], and the cumulative ASA dose should be 110–160 mg.

On the other hand, the desensitization procedure should be chosen as a safer alternative in patients with: (i) ACS and NSAID hypersensitivity; (ii) a previous positive ASA challenge at an antiplatelet dose; and (iii) a history of nonsevere anaphylaxis due to ASA or other NSAIDs *(Fig. 1)*.

Clinical subsets

1) Regarding the challenge procedure for patients with:

a) Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease and b) NSAID-exacerbated cutaneous disease (NECD), the procedure is well documented in the EEACI/GA2LEN guidelines [30];

c) Nonsteroidal anti-inflammatory drug-induced urticaria/angioedema (NIUA), the procedure is well documented in the aforesaid EEACI/GA2LEN guidelines [30] and in some studies which evaluated subjects with histories of hypersensitivity reactions to ASA/NSAIDs [29, 31–34]. On the basis of studies performed by some members of the expert panel on large samples of such subjects, including subjects with NIUA [32, 34], it was agreed that more than 50 % of patients with NIUA might tolerate an ASA dose lower than 100 mg;

d) Single-NSAID-induced urticaria/angioedema or anaphylaxis, there is a higher level of risk for the challenge procedure, which is not recommended in patients with a history of severe anaphylaxis.

2) Regarding the desensitization procedure, taking also into account the recommendations of the aforesaid position paper [28] and those of another position paper regarding general considerations on rapid desensitization for drug hypersensitivity [35]:

a) it was agreed that the challenge procedure is risky in subjects with an ACS *(Table 3)* and that desensitization is the option of choice in ACS patients with:

i) an unclear history of ASA hypersensitivity, desensitization being safer than challenge;

ii) a history of hypersensitivity to NSAIDs and/or ASA at anti-inflammatory doses, but it is not mandatory. In effect, in these patients, desensitization may be unnecessary, but due to time pressure, it is better to be done instead of a challenge.

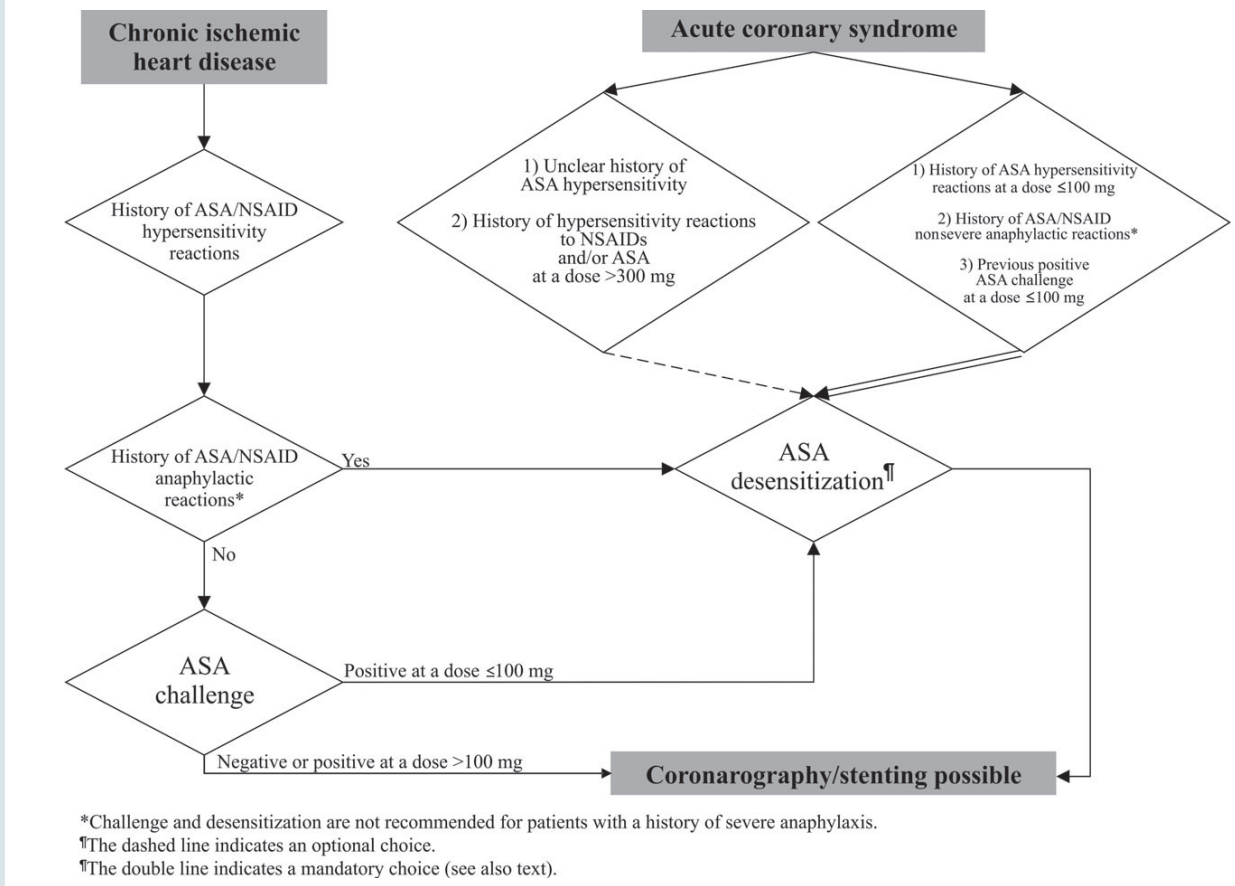

Figure 1. **Flowchart for patients with coronary artery disease and histories of hypersensitivity reactions to acetylsalicylic acid (ASA) who need ASA therapy**

b) Desensitization is mandatory in patients with:

i) an ACS and a history of hypersensitivity to ASA at an antiplatelet dose;

ii) an ACS and a history of nonsevere anaphylactic reactions to ASA/NSAIDs;

iii) a previous positive ASA challenge at an antiplatelet dose *(Fig. 1)*.

c) Desensitization is not recommended in subjects with histories of severe anaphylactic reactions.

It was agreed that patients with NERD and NECD generally need a desensitization procedure with longer intervals between the doses to reach the cumulative dose [19, 24, 25]. However, such longer intervals are impractical for subjects with unstable CAD [15].

The expert panel recommended choosing a single homogeneous procedure protocol for each patient regardless of cardiological or allergological features. This procedure could be suitable especially for cardiologists or other physicians who have no experience in drug allergy.

In a patient without a clear clinical history, hospitalized for an ACS in the coronary intensive unit *(Table 3)*, it is also imperative to perform the desensitization procedure as soon as possible.

The panel of allergists suggests to choose a very low starting dose 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, may be longer (60–90 min), preferably within a cumulative time of administration of 300 min.

Steps: On the basis of literature data *(Table 1)*, the desensitization procedure can vary between 5 and 12 steps; in the present study, the majority of patients of the 10 centers underwent desensitization in 10 steps *(Table 5)*. The time interval between steps was 20–30 min until the dose of 40 mg was reached and 60–90 min thereafter until the dose of 100 mg was reached.

Starting dose: Because of the possibility of IgE-mediated reactions [36], a low starting dose is advisable. According to literature data [15–27] *(Table 1)*, such dose varies between 0.1 and 10 mg; in the present study, a starting dose of 0.1–1 mg was used.

Cumulative dose: According to the literature data [15–27] *(Table 1)*, it ranges between 150 mg [16] and 799 mg [18]. On the basis of a cardiological consensus [8], the ENDA-EAACI expert panel suggests reaching a cumulative dose between 75 and 150 mg.

Desensitization in «primary PCI (percutaneous coronary intervention)»: In the case of an ACS *(Table 3)*, in patients with ST-segment elevation (ACS-STEMI), the primary percutaneous coronary intervention (pPCI) is a safe and effective therapeutic strategy. For this feature, it is mandatory to perform the desensitization procedure in a very short time (< 2 h) to diminish further myocardial damage. The oral dose of ASA to reach is 150 mg [8].

However, in patients with ACS-STEMI, usually there is not enough time for performing an ASA desensitization procedure before the pPCI. Therefore, according to the expert panel opinion and literature data [27, 37, 38], a safe choice would be using an alternative antiplatelet drug (e.g. clopidogrel, an adenosine diphosphate receptor antagonist) along with a platelet glycoprotein IIb/IIIa inhibitor (i.e. abciximab, eptifibatide, or tirofiban), as a temporary measure before performing an ASA desensitization. Then, within 12–72 h, an ASA desensitization with the normal schedule can be performed.

In effect, the aforesaid glycoprotein IIb/IIIa inhibitors block the final common pathway leading to platelet aggregation, thus reducing thrombotic complications in patients with ACS-STEMI undergoing pPCI [37]. Most data regard abciximab [39–42]; in some comparison studies [43–45], however, no differences in outcome [i.e. 30-day mortality, reinfarction at 30 days, postprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and ST-segment resolution] have been found between standard-dose abciximab (i.e. a bolus of 0.25 lg/kg and a maintenance infusion of 0.125 lg/kg/min over 12 h) and a high-loading dose of tirofiban (i.e. 25 lg/kg over 3 min) followed by a 12-h infusion of 0.15 lg/kg/min. In particular, a meta-analysis by De Luca et al. [43] showed among STEMI patients undergoing pPCI similar results between abciximab and tirofiban, as well as between abciximab and eptifibatide, in terms of angiographic, electrocardiographic, and clinical outcome.

In our case series, we had four ACS-STEMI patients who underwent a successful desensitization procedure after pPCI with a course of tirofiban therapy.

Summary

Acetylsalicylic acid therapy is mandatory for all patients who need a coronary angiography, possibly followed by stenting. Collaboration between cardiologist and allergist is fundamental in cases with these clinical features. However, on this topic, there is a lack of guidelines for cardiologists, allergists, and specialists in internal medicine to support their clinical decisions. Therefore, a consensus on this topic in an expert panel was desirable.

According to the consensus reached in the present study, the procedure of desensitization must be implemented in all cases of in-hospital patients with hypersensitivity to ASA/ NSAIDs and ACS.

It is recommended that, before any evaluation procedures, patients with an ACS and a history of anaphylactic reactions when exposed to antiplatelet doses of ASA to be assessed by an allergist, who together with the cardiologist can decide the appropriate procedure *(Fig. 1)*.

In any case, in high-risk ACS patients, the desensitization procedure appears to be the best and safest choice, even in those with histories of nonsevere anaphylactic reactions to ASA/NSAIDs.

In patients with stable CIHD, a challenge test is advisable. However, considering the results of the CURRENT-OASIS 7 trial [5], it is crucial to identify subjects with histories of hypersensitivity to ASA doses higher than 100 mg, as such subjects might not need any further allergological workup.

With regard to the common desensitization protocol of the present study *(Table 5)*, the low starting ASA dose is due to the documented possibility of IgE-mediated reactions [36]. Regarding these rare conditions, the suitable schedule may be of brief (20–30 min) incremental steps, reaching the cumulative dose of 40 mg of ASA. On the other hand, longer intervals are advisable to diminish the risk of reactions mediated by a pharmacological mechanism in subjects with NERD, NECD, or NIUA, which represent the cross-reactive types of nonallergic NSAID hypersensitivity [28]. The pathogenic mechanism of these reactions has been associated with the inhibition of COX-1. In fact, NSAIDs – such as ASA, pyrazolones, indomethacin, ketoprofen, ibuprofen, piroxicam, and ketorolac – inhibit the constitutive isoform of COX-1 and thus reduce the generation of protective prostaglandin (PG)E2, as well as increase the unrestrained synthesis of cysteinyl leukotrienes (Cys-LTs) and the release of mediators such as PGD2 from mast cells and eosinophils. This mechanism, which is well established in ASA-induced asthma [46], has also been supported by biochemical observations in ASA-induced urticaria [47]. Specifically, Mastalerz et al. [47] found that baseline urinary LTE4 levels, believed to reflect global cys-LTs biosynthesis, were markedly increased in patients with both NERD and NECD and that ASA released PGD2 in patients with both NERD and NECD. In effect, the risk of reactions mediated by a pharmacological mechanism increases in patients with NERD at an ASA dose of 40 mg [48]. With regard to these hypersensitivity reactions, after reaching this dose, it is reasonable to use longer steps (60–90 min) to reach the cumulative dose of 100 mg. In any case, the procedure has to be quick and has to finish within 6 h, including the subsequent clinical observation.

A limitation of our study is the absence of randomization of the patients. However, in the first phase, the study was set as a collection of real-life data in the enrolled centers. Moreover, randomization was not approved for this study, because it would have been unethical.

In conclusion, we state that desensitization with ASA is a safe procedure in subjects with an ACS and ASA/NSAID hypersensitivity, while in patients with stable CIHD and ASA/NSAID hypersensitivity, a provocation test is the option of choice.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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G. Cortellini [1], A. Romano [2, 3], A. Santucci [1], A. Barbaud [4], S. Bavbek [5], D. Bignardi [6], M. Blanca [7], P. Bonadonna [8], M.T. Costantino [9], J.J. Laguna [10], C. Lombardo [8], L.M. Losappio [11], J. Makowska [12], A. Nakonechna [13], O. Quercia [14], E.A. Pastorello [11], V. Patella [15, 16], I. Terreehorst [17], S. Testi [18], J.R. Cernadas [19], робоча група Європейської академії з алергології та клінічної імунології (EAACI) з переносності та процедур десенситизації ацетилсаліцилової кислоти в пацієнтів з ІХС (J. Dionicio Elera [10], D. Lippolis [1], S. Voltolini [6], D. Grosseto [20])

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ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

Клінічний підхід до оцінювання переносності та процедур десенситизації ацетилсаліцилової кислоти в пацієнтів з ішемічною хворобою серця та гіперчутливістю до нестероїдних протизапальних препаратів

Гіперчутливість до ацетилсаліцилової кислоти (АСК) – значна проблема для пацієнтів із захворюванням коронарних артерій. У таких випадках лікарі мають обрати більш відповідну процедуру між оцінюванням переносності та десенситизацією. У літературі це питання висвітлено недостатньо, тому метою дослідження було встановити клінічні критерії для вибору між оцінюванням переносності та/або десенситизацією в таких пацієнтів.

Методи. Збір та аналіз даних про досвід оцінювання переносності та десенситизації АСК, отриманих у 10 центрах із лікування алергії, а також консенсус серед відповідних лікарів та експертної групи.

Результати. Усього проаналізовано дані 310 пацієнтів; 217 із них мали в анамнезі крапельну/ангіоневротичну анемію, 50 – анафілаксії, 26 – відтерміновані шкірні висипання та 17 – бронхоспазм, пов'язані зі споживанням АСК/нестероїдних протизапальних препаратів (НПЗП). Зокрема, 119 осіб мали реакцію на дози АСК менше 300 мг. У 138 із 310 пацієнтів був гострий коронарний синдром, серед них 101 пройшли десенситизацію, тоді як 172 страждали на хронічну ішемічну хворобу серця, у 126 з яких оцінили переносність АСК. У цілому в 163 осіб провели оцінювання переносності, а у 147 – процедури десенситизації АСК; 86 з останніх мали реакції на дозу АСК 300 мг або менше. Десять пацієнтів відреагували на оцінювання переносності АСК, сім – у дозах до 500 мг, три – в сумарній дозі 110 мг. Частота невдалої десенситизації становила 1,4 %.

Висновки. У пацієнтів зі стабільною ішемічною хворобою серця та нетяжкими реакціями гіперчутливості до АСК/НПЗП в анамнезі оцінювання переносності АСК є доцільним. Пацієнти з гострим коронарним синдромом та реакціями гіперчутливості до АСК в анамнезі, особливо в дозах менше 100 мг, повинні одразу пройти десенситизацію.

Ключові слова: ацетилсаліцилова кислота, оцінювання переносності, десенситизація, гіперчутливість до нестероїдних протизапальних препаратів.

G. Cortellini [1], A. Romano [2, 3], A. Santucci [1], A. Barbaud [4], S. Bavbek [5], D. Bignardi [6], M. Blanca [7], P. Bonadonna [8], M.T. Costantino [9], J.J. Laguna [10], C. Lombardo [8], L.M. Losappio [11], J. Makowska [12], A. Nakonechna [13], O. Quercia [14], E.A. Pastorello [11], V. Patella [15, 16], I. Terreehorst [17], S. Testi [18], J.R. Cernadas [19], рабочая группа Европейской академии аллергологии и клинической иммунологии (EAACI) по переносимости и процедурам десенситизации ацетилсалициловой кислоты у пациентов с ИБС (J. Dionicio Elera [10], D. Lippolis [1], S. Voltolini [6], D. Grosseto [20])

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ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

Клинический подход к оценке переносимости и процедур десенситизации ацетилсалициловой кислоты у пациентов с ишемической болезнью сердца и гиперчувствительностью к нестероидным противовоспалительным препаратам

Гиперчувствительность к ацетилсалициловой кислоте (АСК) – большая проблема для пациентов с заболеванием коронарных артерий. В таких случаях врачи должны выбрать более подходящую процедуру между оценкой переносимости и десенситизацией. В литературе этот вопрос освещен недостаточно, поэтому целью исследования было установить клинические критерии для выбора между оценкой переносимости и/или десенситизацией у таких пациентов.

Методы. Сбор и анализ данных об опыте оценки переносимости и десенситизации АСК, полученных в 10 центрах по лечению аллергии, а также консенсус среди соответствующих врачей и экспертной группы.

Результаты. Всего проанализированы данные 310 пациентов; 217 из них имели в анамнезе капельную/ангионевротическую анемию, 50 – анафилаксии, 26 – отсроченные кожные высыпания и 17 – бронхоспазм, связанные с потреблением АСК/нестероидных противовоспалительных препаратов (НПВП). В частности, 119 лиц имели реакцию на дозы АСК менее 300 мг. У 138 из 310 пациентов был острый коронарный синдром, среди них 101 прошли десенситизацию, тогда как 172 страдали хронической ишемической болезнью сердца, у 126 из которых оценили переносимость АСК. В целом у 163 лиц провели оценку переносимости, а у 147 – процедуры десенситизации АСК; 86 из последних имели реакции на дозу АСК 300 мг или меньше. Десять пациентов отреагировали на оценку переносимости АСК, семь – в дозах до 500 мг, три – в суммарной дозе 110 мг. Частота неудачи по десенситизации составила 1,4 %.

Выводы. У пациентов со стабильной ишемической болезнью сердца и нетяжелыми реакциями гиперчувствительности к АСК/НПВП в анамнезе, оценка переносимости АСК целесообразна. Пациенты с острым коронарным синдромом и реакциями гиперчувствительности к АСК в анамнезе, особенно в дозах меньше 100 мг, должны сразу пройти десенситизацию.

Ключевые слова: ацетилсалициловая кислота, оценка переносимости, десенситизация, гиперчувствительность к нестероидным противовоспалительным препаратам.