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Article type : Letter to the Editor

TITLE:

ACETYLSALICYLIC ACID CHALLENGE OPTIMAL DOSE IN NONSTEROIDAL ANTI-INFLAMMATORY DRUGS HYPERSENSITIVITY DIAGNOSIS

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14175](https://doi.org/10.1111/ALL.14175)

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To the Editor,

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed and consumed drugs worldwide in all ages, being reported as the main cause of drug hypersensitivity reactions (DHRs). Indeed, in some populations NSAIDs are the culprit drugs in around 50% of all confirmed DHRs (1), representing an important problem for health care systems.

Two different pathophysiological mechanisms have been described in NSAIDs-hypersensitivity (2). The first one is immunological (mediated by specific IgE antibodies or by T cells), and leads to selective reactions (SRs) because patients react to a single NSAID or to several NSAIDs from the same chemical group and tolerate strong cyclooxygenase (COX)-1 inhibitors other than the reaction triggers (3). The second one is pharmacological (*ergo* dose-dependent), and leading to cross-reactive hypersensitivity reactions (CRs) as patients develop episodes after the intake of chemically unrelated NSAIDs, especially strong COX-1 inhibitors. Patients from this group must avoid all NSAIDs (3). Although not included in this classification, mixed or blended reactions have been largely described. Such reactions are characterized by the simultaneous involvement of skin and respiratory tract and/or gastrointestinal system, being frequently indistinguishable from anaphylactic allergic reactions (4).

At present, there is not a single standardized diagnostic protocol for the different types of NSAIDs-induced hypersensitivity reactions. Consequently, a high proportion of misdiagnosis exists, and patients could be unnecessarily recommended to avoid all NSAIDs, significantly reducing their therapeutic alternatives. Skin and *in vitro* tests, like basophil activation test, are not useful for diagnosis, with exception of metamizole-induced SRs, although the sensitivity of both tests is low (5, 6). Therefore, challenge or drug provocation test (DPT) is recommended as the gold standard for diagnosis and to differentiate SRs and CRs (3, 7, 8, 9). Although in most studies an accumulated challenge dose of ASA of 500 mg is achieved controversy exists if this dose is enough, as the underlying mechanism in CRs is pharmacological and, consequently, dose-dependent. Thus, patients who tolerate 500 mg of ASA should be included into the SRs group; however, it cannot be ruled out the possibility that these patients could react to a higher dose of

ASA and, consequently, should be better included into the CR group. This may be especially helpful when DPT with the culprit is contraindicated due to the severity of the reaction.

In the present study, we aimed to evaluate if doses higher than 500 mg of ASA in DPT are required to differentiate between SRs and CRs. For this purpose, from January to June 2019 we prospectively selected all consecutive patients with a confirmed diagnosis of SRs, based on a negative DPT to 500 mg of ASA and on a two-day course of 500 mg every 8 hours at home. At least two weeks after achieving diagnosis, in order to check the potential role of doses higher than 500 mg of ASA in the differential diagnosis in SRs, these patients were further re-evaluated and a new DPT to ASA was performed to a cumulative dose of 1000 mg, followed by a two-day course of 1000 mg of ASA every 8 hours at home.

All the procedures were approved by the hospital ethical committee as they are part of usual clinical practice.

We included 11 patients with confirmed SRs (Table 1) on the basis of a positive placebo single blind DPT with the culprit(s) NSAIDs, which reproduced previously reported symptoms. Patients' median age was of 38.27 years (IR: 24-61), being 7 of them female.

Nine patients presented SRs only to arylpropionic acid derivatives (7 females and 2 males), developing isolated palpebral/facial angioedema. The median number of episodes was 2.9 (5 patients presented 2 episodes, 2 patients 3 episodes, and 2 patients 5 episodes). Concerning the culprit and the time interval between drug intake and the onset of the reaction, 9 patients reacted to 600 mg of ibuprofen with a median interval of 102.2 minutes (IR: 20-240), and 2 patients also reacted to 550 mg of naproxen 60 and 360 minutes, respectively, after the intake.

The remaining 2 patients presented SRs to multiple NSAIDs: (i) the first one developed urticaria 5 minutes after the intake of 575 mg of metamizole and, years apart, another similar episode with 1000 mg of paracetamol; (ii) the second one developed 3 episodes of urticaria 60 minutes after taking 1000 mg of paracetamol, and another similar episode after the intake of 600 mg of ibuprofen.

None of the patients reacted after the second and higher dose of ASA during the re-evaluation.

Despite the limited number of patients included in this study, we confirmed that DPT with a dose of 500 mg of ASA is sufficient to achieve an accurate diagnosis of CRs and SRs, particularly in infrequent phenotypes such as isolated angioedema by SRs and multiple SRs, which may be misdiagnosed as CRs. This procedure is useful not only for reducing the number of

patients who are unnecessary avoiding NSAIDs but also for extending their therapeutic possibilities. Although such accurate diagnosis requires facilities and trained personal in this field, it will improve the allergological work-up and, consequently, patients' management.

Table I. Clinical characteristics of patients.

Patient No.	Gender	Age (years)	Culprit NSAID	Number of episodes	Interval of reaction (minutes)	Symptoms
Multiple SRs						
1	Male	60	Metamizole	1	5	Generalized urticaria
			Paracetamol	1	5	
2	Male	35	Paracetamol	3	60	
			Ibuprofen	1	60	
SRs to arylpropionic derivatives						
3	Female	24	Ibuprofen	1	60	Isolated angioedema
			Naproxen	1	60	
4	Female	32	Ibuprofen	1	240	
			Naproxen	2	360	
5	Male	40	Ibuprofen	2	30	
6	Female	28	Ibuprofen	2	180	
7	Female	44	Ibuprofen	3	60	
8	Female	43	Ibuprofen	2	20	
9	Male	24	Ibuprofen	2	60	
10	Female	30	Ibuprofen	5	30	
11	Female	65	Ibuprofen	5	240	

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Conflict of Interest disclosure statement

The authors declare no conflict of interest.

Funding:

This study has been supported by the Institute of Health Carlos III of the Spanish Ministry of Science, Innovation and Universities (grants cofounded by European Regional Development Fund: RETIC ARADyAL RD16/0006/0001 and PI17/1593); and the Spanish Society of Allergology (Fondo de Investigación de la Fundación de la SEAIC convocatoria 2016 and convocatoria 2018 Ref 18: B02). N Pérez-Sánchez is a researcher from the Rio Hortega Program (Ref CM17/00141), Gádor Bogas from the Juan Rodés Program (JR18/00054), and JA Cornejo-García from the Miguel Servet Program (Ref CP14/00034). I Doña is a Clinical Investigator (B-0001-2017) from Consejería de Salud of Junta de Andalucía.