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TITLE: Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance.

AUTHOR LIST: Natalia Blanca-Lopez MD, PhD¹, Maria J Torres MD, PhD²,
Inmaculada Doña MD, PhD², Paloma Campo MD, PhD², Carmen Rondón MD PhD²,
M Elena Seoane Reula MD, PhD¹, María Salas MD², Gabriela Canto MD, PhD¹,
Miguel Blanca MD, PhD²

DEPARTMENTAL AND INSTITUTIONAL AFFILIATIONS:

¹Allergy Service, Infanta Leonor Hospital, Madrid, Spain

²Allergy Service, Carlos Haya Hospital, Malaga, Spain

CORRESPONDING AUTHOR:

Natalia Blanca-López

Servicio de Alergia

Hospital Infanta Leonor

Calle Gran Vía del Este, 80

28031 Madrid, Spain

Tel: +34 911918000; Fax: +34 911919092.

e-mail: Natalia.blanca@gmail.com

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ABSTRACT

Background: Multiple NSAID-induced urticaria/angioedema is the most common manifestation of hypersensitivity reactions to NSAIDs. Diagnostic evaluation is based on the clinical history and a drug provocation test.

Objective: To evaluate the role of the clinical history in the diagnosis of multiple NSAID-induced urticaria/angioedema.

Methods: We studied a group of patients with an unequivocal history of urticaria and/or angioedema after NSAID intake. Subjects had to have had at least two episodes of cutaneous symptoms with two different COX-1 inhibitors. The diagnosis was confirmed in all cases by a drug provocation test with ASA. Multivariate analysis was done by analyzing different variables, including number of drugs involved, episodes and time elapsed between drug intake and symptom onset.

Results: Out of the total group of 75 cases with multiple NSAID-induced urticaria/angioedema diagnosed according to the clinical history, 76% developed a positive drug provocation test with ASA. The risk for having hypersensitivity was 17 times higher in patients who developed symptoms within the first 60 minutes after drug intake, 13 times higher in those who experienced reactions with more than two non-chemically related NSAIDs, and 10 times higher in women.

Conclusions: Drug provocation testing with ASA confirms the diagnosis of multiple NSAID-induced urticaria/angioedema in up to 92% of cases with an unequivocal clinical history when reactions occur within one hour and more than two different NSAIDs are involved.

KEYWORDS: NSAID hypersensitivity, urticaria, angioedema, cross-intolerance, clinical history, diagnosis, ASA drug provocation test.

ABBREVIATIONS:

NSAIDs:	Non-steroidal anti-inflammatory drugs
CI:	Cross-intolerance
SR:	Selective responders
COX:	Cyclooxygenase
ASA:	Acetyl salicylic acid

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the drug groups most frequently causing drug hypersensitivity (1-3), accounting for approximately 21-25% of these reactions (2). Reports exist of hypersensitivity to all NSAIDs, regardless of their chemical structure or their anti-inflammatory potency (4-10).

Hypersensitivity reactions to NSAIDs have been classified in different categories depending on the clinical symptoms induced, the number of NSAIDs involved and the presence or absence of underlying disease. The following classification has been proposed: 1) NSAID-exacerbated respiratory disease, presently designated as aspirin exacerbated respiratory disease; 2) NSAID-exacerbated cutaneous disease for urticaria and angioedema in patients with chronic idiopathic urticaria. Analogous to aspirin exacerbated cutaneous disease, this has been identified as aspirin-exacerbated cutaneous disease; 3) Multiple NSAID-triggered urticaria/angioedema in patients without pre-existing chronic urticaria; 4) Urticaria and/or angioedema, and anaphylaxis induced by a single NSAID (11). A fifth group has been proposed for those instances where the selective response can involve a T-cell mechanism (4). Typical reactions in this last group include maculo-papular exanthema, fixed drug eruption, acute exanthematic pustulosis and more severe reactions like toxic epidermal necrolysis. Groups 1 and 3 can be associated and have, in fact, been considered as blended reactions in which both respiratory and cutaneous symptoms

may appear (11).

These clinical entities can be grouped in two major categories: one where the symptoms are induced by different NSAIDs that are not chemically related, denominated cross-intolerance (CI) (3) or non-allergic hypersensitivity (11), and a second category where the clinical symptoms are induced by a single NSAID group or even an individual drug from a specific group, like pirazolones, diclophenac, mefenamic acid, ibuprofen, paracetamol as well as others, but there is good tolerance to other chemically-unrelated NSAIDs, with these patients classified as selective responders (SR) (13-15).

A recent study showed that up to 76% of patients diagnosed with NSAID hypersensitivity have CI, with the skin being the organ most frequently involved after excluding patients with underlying chronic urticaria (1). As CI is not mediated by specific immunological mechanisms, neither skin testing nor *in vitro* immunological assays based on the presence of drug IgE-specific antibodies are useful (1,4,13). In addition, recent assays based on basophil activation and leukotriene release have yet to be validated (16,17). Consequently, the diagnosis of hypersensitivity reactions to multiple NSAIDs is currently based on a detailed clinical history plus a drug provocation test when indicated (1, 4,18).

The criteria in the clinical history for a CI reaction to be considered include the clinical manifestations (e.g., urticaria and/or angioedema), the time interval between drug intake and onset of the reaction (usually within hours), the number of drugs involved (usually two or more different non-chemically related NSAIDs), the number of episodes, and the absence of chronic urticaria (5). Although a reliable clinical history is the first approach for establishing the diagnosis, basing the diagnosis solely on this evaluation may lead to overdiagnosis (4,19).

In many cases when the clinical history is not unequivocal a drug provocation test may be necessary to confirm or exclude the diagnosis (4). Drug provocation testing has been used extensively for aspirin exacerbated respiratory disease, with the

nasal or bronchial provocation test recommended (3,20), but this approach is not appropriate when the skin is the affected organ (21). In fact, subjects with skin involvement do not respond to nasal challenge with acetyl salicylic acid (ASA) (21). Therefore the oral drug provocation test with ASA is considered the gold standard procedure (1, 4, 19). However, questions remain as to whether in multiple NSAID-triggered urticaria/angioedema the clinical history is really sufficient to establish the diagnosis or whether drug provocation testing with ASA is needed for confirmation.

The aim of this study was to assess the value of the clinical history in the diagnosis of patients with multiple NSAID-triggered urticaria/angioedema using as a gold standard the drug provocation tests with ASA for the final confirmation of the cases evaluated. Different variables such as gender, age, interval between drug intake and appearance of the reaction, type of reaction, number of drugs involved, and number of episodes were all analyzed.

METHODS

Patients

We studied a group of patients aged 14-80 years with an unequivocal history of multiple NSAID-triggered urticaria/angioedema. They were evaluated in the allergy departments of two clinical centers in Spain (Carlos Haya Hospital, Malaga and Infanta Leonor Hospital, Madrid) between January and December 2010. In all cases the diagnosis was established first by the clinical history, after which it was reassessed in all cases with a drug provocation test.

Inclusion criteria. Patients who experienced at least two episodes of urticaria and/or angioedema indicative of hypersensitivity reactions to NSAIDs with two or more different chemically-unrelated strong COX-1 NSAIDs.

Exclusion criteria. Patients younger than 14 years or older than 80 years of age; patients with chronic urticaria or acute recurrent urticaria not attributed to NSAID intake.

This included physical urticaria as well as dermographism; pregnant or breastfeeding patients; patients taking beta-blockers or angiotensin converting enzyme inhibitors, or with contraindications for epinephrine administration; patients who had acute infections, autoimmune and/or underlying cardiac, hepatic or renal diseases that contraindicated a drug provocation test; subjects with psychosomatic disorders; patients with one or more episodes to one NSAID with unknown tolerance to others; and patients who tolerated different unrelated NSAIDs.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the relevant Ethics Committees (PI11/01416). All participants were informed orally about the study and signed the corresponding informed consent.

Clinical history

A detailed clinical history was done including the following data: age, gender, atopy (measured by skin test to a standard battery of 30 common inhalant aeroallergens, including pollens, house dust mites, moulds and animal danders (ALK, Madrid, Spain) as described [1]), number of episodes, clinical symptoms reported (urticaria, angioedema, or both), drug involved in each episode, time interval between the episode and the clinical evaluation (days) and the time elapsed between drug intake and the onset of symptoms (minutes) in each episode.

Oral drug provocation test

This was carried out in all patients in a single-blind procedure following the previously described protocol (1), with some modifications. On the first day, placebo capsules were administered in all cases, and on the second day one week later increasing doses of ASA (50, 100, 150 and 200 mg) were administered orally at 90 min intervals. If cutaneous, respiratory or systemic symptoms appeared the procedure was stopped, the symptoms evaluated and appropriate treatment administered. If no symptoms occurred during the drug provocation test procedure, the therapeutic dose was reached.

This was followed 24 hours later by a dose of 500 mg of ASA every 12 hours for two days.

Statistical analysis

Comparisons for quantitative variables without normal distributions were made by the Mann-Whitney test and between qualitative variables by the chi-square test. All reported P values represented two-tailed tests, with values <0.05 considered significant. A backward logistic regression analysis was performed to establish the characteristics associated with a positive drug provocation test. The following variables were analyzed: gender, age, atopy, interval between drug intake and the onset of the reaction, type of cutaneous reaction, interval between drug reaction and study, number of non-chemically related NSAIDs involved, and number of episodes. In the multivariate analysis the continuous variables were categorized in different intervals: age in years (14-25, 26-50, 50-80), drug-reaction interval in minutes (<60, >60), and reaction-study interval in days (<30, 31-180, 181-365, >365).

RESULTS

We evaluated 75 patients (40 from Infanta Leonor Hospital and 35 from Carlos Haya Hospital) with an unequivocal history of multiple NSAID-triggered urticaria/angioedema. Of the 75, 42 (56%) were female and 33 (44%) male, 29 (38.7%) had developed urticaria and angioedema, 25 (33.3%) urticaria, and 21 (28%) angioedema. In 40 cases (53.3%) two NSAIDs from unrelated chemical groups were implicated, and in 35 (46.7%) three or more. Regarding the number of episodes, 17 patients (22.66%) had two episodes, 12 (16%) three, 12 (16%) four, and 34 (45.33%) five or more episodes; overall, 77% of the cases had three or more episodes. The median age at evaluation was 37 years (IR: 27-46), the reported time interval between drug administration and the onset of the reaction was 30 minutes (IR: 30-120), and the time elapsed between the last reaction and the study was 180 days (IR: 30-1080).

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Of the 75 patients with multiple NSAID-triggered urticaria/angioedema diagnosed according to the clinical history, 57 (76%) developed a positive drug provocation test with ASA and were therefore confirmed as having hypersensitivity. Dividing the whole group into those cases who had two episodes and those with three or more resulted in 40 cases in the first group, in 25 (63%) of whom the drug provocation test was positive, and 35 cases in the second group, in 32 (92%) of whom the drug provocation test was positive. The NSAIDs involved in those cases finally confirmed as hypersensitive were: ibuprofen (n=42; 36.2%), ASA (n=30; 25.9%), dypirone (n=13; 11.2%), paracetamol (n=10; 8.6%), diclofenac (n=11; 9.5%), dexketoprofen (n=5; 4.3%), naproxen (n=3; 2.6%) and propifenazone (n=2; 1.7%). The NSAIDs involved in those cases finally confirmed as non-hypersensitive were: ibuprofen (n=11; 33.3%), ASA (n=5; 15.2%), dypirone (n=6; 18.2%), paracetamol (n=6; 18.2%), diclofenac (n=2; 6.1%), dexketoprofen (n=2; 6.1%) and naproxen (n=1; 3%) (data not shown in the table). Significant differences between both groups were only found with paracetamol (p=0.038), with higher involvement in the non-hypersensitivity group. The reasons why patients took the NSAIDs were osteoarticular problems, abdominal pain, dysmenorrhoea, headache, pharyngoamygdalitis, toothache, and in just 3 cases for fever.

Table 1 shows the clinical characteristics of the patients with a positive drug provocation test. Twenty cases (26.67%) developed angioedema, 24 (32%) urticaria and 16 (21.33%) urticaria and angioedema. No patient developed anaphylaxis, with the symptoms limited to the skin in all instances. The median cumulative dose of ASA to which the patients reacted was 300 mg and the interval between the last dose and the reaction was 111.33 minutes (IR: 60-120). Eleven patients (14.67%) did not need any treatment in order to recover, 5 (7.14%) were treated with antihistamines, 35 (46.67%) with antihistamines and steroids and 2 (2.7%) were given epinephrine to alleviate the skin symptoms.

In the 18 cases (24%) who had a negative drug provocation test with ASA, the

provocation with the culprit drugs involved in the reaction as reported by the patients was also negative, except in two cases that responded to ibuprofen but had good tolerance to the other drugs implicated (one to diclofenac and the other to paracetamol). The other 16 cases where two drugs were implicated had good tolerance to both drugs. According to the clinical history in these 16, the drugs involved in each episode were: 11 ibuprofen and paracetamol, 3 diclofenac and paracetamol and 2 ASA and piroxicam.

In order to determine the contribution of each variable to the final outcome of having multiple NSAID-triggered urticaria/angioedema we performed bivariate analysis. Table 2 shows the clinical characteristics of the patients confirmed as hypersensitive by drug provocation testing and those who were non-hypersensitive with good tolerance after challenge, as well as the bivariate analysis of each of the variables considered in the study. Significant differences were found between the two groups, with a higher percentage of females, number of episodes, number of non-chemically related NSAIDs involved and a shorter time interval between drug intake and reaction in those patients diagnosed with multiple NSAID-triggered urticaria/angioedema. Concerning atopy, although differences were seen in the percentage of patients finally considered as having multiple NSAID-triggered urticaria/angioedema and those who had a negative drug provocation test, these differences did not reach significance ($P=0.06$). A more detailed analysis of the allergen involved showed that within the 82% of cases who were skin test positive, house dust mites were responsible in 48% of cases, grass pollen in 15%, the remaining allergens used in the standard panel in 24%, and a combination of positivity to two or more of the allergens tested in the remaining 13%. Clinical entities reported by the patients were rhinitis in 20% of the cases, asthma in 7%, rhinitis plus asthma in 10%, and atopic dermatitis in 4%. The remaining subjects were skin test positive without clinical symptoms.

In order to determine the contribution of the different variables to the outcome we also performed multivariate logistic regression analysis (See Table III). In those patients having a positive ASA drug provocation test, and therefore confirmed as

hypersensitive, the analysis of the contribution of the different variables analyzed in the clinical history showed that the risk of a positive outcome was 16 times higher in those who developed symptoms within 60 minutes after drug intake, 13 times higher in those developing reactions with more than two non-chemically related NSAIDs, and 10 times higher if the patient was a woman. No significant associations were found for the other variables, and there was no interaction between variables.

DISCUSSION

Several studies show that multiple NSAID-triggered urticaria/angioedema is the most common clinical entity in the evaluation of NSAID-induced hypersensitivity reactions, followed by those reactions induced by a single drug, in which a specific immunological mechanism has been imputed as responsible (1,4,13). Because patients with multiple NSAID-triggered urticaria/angioedema react to several NSAIDs with a strong COX-1 enzyme inhibiting capacity, correct diagnosis needs to be established in order to recommend a safe alternative (4). In addition, in patients with multiple NSAID-triggered urticaria/angioedema, skin tests to assess IgE-mediated reactions are not useful and in vitro methods have not been sufficiently validated (16,17). Consequently, the clinical history is essential to establish the diagnosis. Questions remain, however, as to whether, when and how the clinical history by itself is appropriate and informative enough to confirm the diagnosis (1,4,19).

In hypersensitivity reactions with airway involvement, for a long time identified as aspirin-induced asthma and later also as aspirin exacerbated respiratory disease, although a well-defined clinical history may raise suspicions of ASA sensitivity, diagnosis based solely on this is not advisable, and a drug provocation test is necessary to establish a definitive diagnosis (3).

Recently, Dursun et al. (22) evaluated a large group of asthmatic patients and analyzed whether the clinical characteristics and the prior number of reactions could predict the diagnosis of aspirin exacerbated respiratory disease. They concluded that

the chance of having a positive drug provocation test was 100% in those patients who had had a severe attack of asthma associated with NSAIDs, 86-88% in those with a prior mild or moderate asthma attack but with multiple episodes, and 73-79% when the asthma attack was mild or moderate with only one prior reaction. Nevertheless, other studies recommend drug provocation testing to confirm or exclude hypersensitivity only in those cases that do not have a clear clinical history (4).

Whether this approach can be applied to multiple NSAID-triggered urticaria/angioedema needs to be verified. A recent review of the EAACI/ENDA and GA2LEN/HANNA (4) recommended that in cases of multiple NSAID-triggered urticaria/angioedema the diagnosis should be confirmed with a drug provocation test, although the indications for this procedure and its diagnostic value in these patients have not been established. Data supporting this statement are limited (1,19) and further research is needed for this purpose.

A study carried out in a large group of patients with CI to NSAIDs without underlying disease concluded that a drug provocation test may be needed in order to recommend safe alternative NSAIDs, and that it was not strictly necessary for establishing the diagnosis when the clinical history was consistent enough (1). In this work, of the total group of 503 patients previously diagnosed as CI by clinical history, drug provocation testing was only done to establish the diagnosis in 10% of the patients whereas diagnosis was achieved in 90% by the clinical history alone. In order to validate the consistency of the clinical history, a drug provocation test was carried out in a representative sample of 50 patients classified by clinical history as CI with the minimum criteria of having had at least two episodes with two different non-chemically related NSAIDs with an unequivocal history, with the challenge being positive in all cases. Another study carried out by Viola et al. (19) considered that the clinical history was not a valid procedure for the diagnosis of NSAID hypersensitivity, with a drug provocation test being necessary in most instances to establish the diagnosis. In this work the authors evaluated 304 patients with a clinical history of hypersensitivity

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reactions to one or more NSAIDs (126 with immediate reactions and 178 with delayed reactions), of whom 13 were diagnosed by positive skin test and 16 by clinical history of a severe adverse reaction. A drug provocation test was carried out in the remaining patients, with only 22.2% of the cases showing a positive result. Reasons for these differences can be attributed to the fact that in this study selective reactions and CI reactions were considered together, with immunological (IgE or T-cell dependent) or pharmacological (inhibition of COX-1 cyclooxygenase) mechanisms being included, resulting in a classification bias impeding accurate results. Furthermore, no details were given in the CI group as to whether the patients had respiratory, cutaneous or mixed symptoms or whether any underlying chronic disease co-existed, adding further limitations to the study. In the study carried out by Doña et al, of the total group of patients validated by drug provocation testing, most had three or more episodes, although two episodes was the minimum number considered (1). Therefore, the question of whether two episodes was confirmatory or not remained open.

For this reason we considered undertaking this study and found that in the group of patients evaluated with a clinical history indicative of CI (considered to be at least two episodes with two non-chemically related NSAIDs), all of whom were confirmed by a drug provocation test, 76% of the cases had a positive response and were therefore confirmed as being hypersensitive.

Regarding the number of NSAIDs implicated, we found that when two drugs were involved the drug provocation test was positive in 63% of cases, rising to 92% in those with three or more NSAIDs. These data differ from those of a previous study carried out by our group (1), where it was considered that if two NSAIDs were involved the diagnosis could be achieved with the clinical history and the patient confirmed as having hypersensitivity based only on this. Accordingly, in the present study we considered that establishing the number of drugs as well as other variables was crucial for the diagnosis. For this purpose we challenged a large number of patients with a clinical history indicative of CI to NSAIDs and divided them into two groups: one with

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involvement of two drugs and another involving three or more drugs. Considering the type of NSAID involved, significant differences were only found for paracetamol, which was higher in those patients finally confirmed as not being hypersensitive compared to those confirmed to be hypersensitive. This can be explained by the good tolerance that this drug has in subjects with multiple NSAID-triggered urticaria/angioedema (23).

In the group of patients confirmed as being non-hypersensitive just two cases were diagnosed as selective reactors to ibuprofen, with good tolerance in the drug provocation test to the other drug reported in their clinical history (one case to diclofenac and the other to paracetamol). The remaining 16 cases where two drugs were involved had good tolerance after drug provocation testing to both drugs. This indicates that after excluding multiple NSAID-triggered urticaria/angioedema the patient may be a selective responder, and this diagnosis therefore needs to be ruled out.

We also analyzed other variables, such as gender, age, atopy, interval drug-reaction, type of reaction, interval reaction-study, number of drugs involved and number of episodes presented, in order to establish whether they were risk factors for multiple NSAID-triggered urticaria/angioedema. The results showed that female gender, a higher number of NSAIDs involved and a shorter interval between drug intake and the onset of the reaction were risk factors, with a risk 16 times higher when the reaction occurred within one hour after drug intake, 13 times higher when more than two drugs were involved, and 10 times higher if the patient was a woman. On the other hand, although there were significant differences in the number of episodes in the bivariate analysis this was not shown in the multivariate analysis, probably because the number of episodes depended on the number of drugs involved. Concerning atopy, although several studies have shown a different degree of association with multiple NSAID-triggered urticaria/angioedema (1), in this study the association was almost significant and probably with a higher number of cases this would have reached significance. Results of the high association with atopy are similar to those previously reported by our group (1) and further studies are in progress to understand this association.

We did not find any significant differences when we analyzed the remaining variables, such as number of episodes, time interval between the reaction and the study, type of reaction or age.

Summarizing, we conclude that in patients with multiple NSAID-triggered urticaria/angioedema the diagnosis can be made in more than 90% of cases based on the clinical history when more than two different NSAIDs are involved. In those cases involving just two drugs, even if the number of episodes is more than two, a drug provocation test must be considered to establish the diagnosis. In this situation based on two drugs, even with an unequivocal clinical history, 40% of cases may fail to be confirmed if these criteria are considered. Finally, in 8% of the cases where more than two different NSAIDs were involved but which had a negative drug provocation test with ASA, the possibility exists that subjects may be either tolerant or selective responders to the drugs implicated. In these circumstances a control challenge could be considered if any of the specific NSAIDs involved are required.

Conflict of interests

The authors declare no conflict of interests.

REFERENCES

1. Doña I, Blanca-López N, Cornejo-García JA et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011; 41(1):86-95.
2. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005; 5:309-316.
3. Szczeklik A, Nizankowska E, Sanak M. Hypersensitivity to aspirin and non-steroidal anti-inflammatory drugs. In: Adkinson NF, Bochner BS, Busse WW, Holgate S,

Lemanske RF, Simons FE, eds. Middleton's allergy, principles and practice, 7th edn. Philadelphia: Mosby, 2009; 1227-43.

4. Kowlaski ML, Makowska JS, Blanca M et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)- classification, diagnosis and Management: review of the EAACI/ENDA and GA2LEN/HANNA. Allergy 2011; 66:818-829.

5. Schneider CH, Kasper MF, de Weck AL et al. Diagnosis of antibody-mediated drug allergy. Pyrazolinone and pyrazolidinedione, cross-reactivity relationships. Allergy 1987; 42:597-603).

6. Blanca M, Pérez E, García JJ et al. Angioedema and IgE antibodies to aspirin: a case report. Ann Allergy 1989; 62:295-8.

7. Himly M, Jahn-Schmid B, Pittertschatscher K et al. IgE mediated immediate-type hypersensitivity to the pyrazolone drug propyphenazone. J Allergy Clin Immunol 2003; 111:882-8.

8. Scala E , Giani M, Pirrotta L et al. Selective severe anaphylactic reaction due to ketorolac tromethamine without non-steroidal antiinflammatory drug intolerance. J Allergy Clin Immunol 2001; 107:557.

9. del Pozo MD, Lobera T, Blasco A. Selective hypersensitivity to diclofenaco. Allergy 2000; 55:412-3.

10. del Paramo BJ, Gancedo SQ, Cuevas M et al. Paracetamol (acetaminophen) hypersensitivity. Ann Allergy Asthma Immunol 2000; 85:508-11.

11. Sanchez-Borges M. NSAID Hypersensitivity Respiratory, Cutaneous, and Generalized Anaphylactic Symptoms. Med Clin N Am 2010; 94: 853-863.

12. Stevenson DD, Sánchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann Allergy Asthma Immunol 2001; 87:177-80.

13. Canto MG, Andreu I, Fernández J, Blanca M. Selective immediate hypersensitivity reactions to NSAIDs. Curr Opin Allergy Clin Immunol 2009; 9:293-297.

14. Gómez E, Blanca-López N, Torres MJ et al. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. *Clin Exp Allergy* 2009; 39 (8): 1217-24.
15. Posadas SJ, Padial A, Torres MJ et al. Delayed reactions to drugs show a Th1 profile and levels of perforin, granzyme B and Fas-L related to disease severity. *J Allergy Clin Immunol* 2002; 109:155-61.
16. Sanz ML, Gamboa PM, Mayorga C. Basophil activation test in the evaluation of immediate drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2009; 9:298-304.
17. Kowalski ML, Ptasinska A, Jedrzejczak M et al. Aspirin-triggered 15-HETE generation in peripheral blood leukocytes is a specific and sensitive Aspirin-Sensitive Patients Identification Test. *Allergy* 2005; 60:1139-1145.
18. Aberer W, Bircher A, Romano A et al. European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; 58:854-63.
19. Viola M, Rumi G, Valluzi RL et al. Assessing potential determinants of positive provocation test in subjects with NSAID hypersensitivity. *Clin Exp Allergy* 2010; 41:96-103.
20. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L et al. EAACI/GA2LEN guideline: aspirin provocation test for diagnosis of aspirin hypersensitivity. *Allergy* 2007; 62:1111-1118.
21. M.Blanca, P.Campo, C.Rondon et al. Response to Nasal challenge with Lysine-aspirin in subjects with hypersensitivity reactions to NSAIDs with respiratory versus cutaneous involvement. *J Allergy Clin Immunol* 2011; 127 (2):192.
22. Dursun AB, Woessner KA, Simon RA et al. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008; 100:420-425.

23. Doña I, Blanca-López N, Jagemann LR, Torres MJ, Rondón C, Campo P, et al. Response to a selective COX-2 inhibitor in patients with urticaria/angioedema induced by nonsteroidal anti-inflammatory drugs. *Allergy* 2011;66:1428-33.

Table 1. Results of positive drug provocation test with ASA.

Pat	Cumulative Dose (mg)	Interval Drug-Reaction (min)	Symptoms	Treatment administered	Time to recovery (min)
1	50	90	AE	ST+aH1	120
2	300	120	URT	NO	180
3	300	300	AE	NO	960
4	150	90	AE	aH1	120
5	300	60	URT	ST+aH1	60
6	300	120	URT	ST+aH1	40
7	500	60	URT	ST+aH1	40
8	300	90	URT+AE	ST+aH1+Epi	180
9	300	60	URT	ST+aH1	120
10	300	60	URT	ST+aH1	60
11	500	120	AE	aH1	240
12	300	60	URT	ST+aH1+Epi	120
13	300	120	URT	NO	120
14	300	120	AE	NO	720
15	150	60	URT+AE	ST+aH1	150
16	300	120	URT+AE	ST+aH1	120
17	300	45	URT+AE	ST+aH1+Epi	240
18	300	90	AE	ST+aH1	120
19	500	120	AE	ST+aH1	120
20	300	120	URT	NO	180
21	300	60	URT	ST+aH1	120
22	300	30	URT	ST+Ah1+Epi	180
23	300	120	URT+AE	ST+aH1	120
24	350	30	URT	ST+aH1	20
25	300	120	AE	NO	720
26	500	240	URT+AE	ST+aH1	180
27	300	120	URT	ST+aH1	240
28	300	120	AE	ST+aH1	180
29	500	480	URT+AE	ST+aH1	90

30	50	90	AE	ST+aH1	100
31	50	90	AE	NO	1440
32	50	60	URT	NO	360
33	50	60	URT+AE	ST+Ah1+Epi	180
34	50	45	URT	ST+aH1	90
35	50	30	AE	ST+aH1	120
36	300	120	URT	ST+aH1	60
37	500	240	AE	aH1	240
38	300	90	URT	NO	120
39	150	100	URT	ST+aH1	
40	300	120	URT+AE	ST+aH1	120
41	300	45	URT+AE	ST+aH1+Epi	240
42	300	100	URT+AE	ST+aH1	120
43	150	90	AE	ST+aH1	120
44	50	30	AE	ST+aH1	90
45	300	60	URT	ST+aH1	60
46	500	240	AE	aH1	60
47	300	120	URT	NO	120
48	150	45	URT+AE	ST+Ah1+Epi	320
49	300	60	URT+AE	ST+aH1	140
50	300	45	URT	ST+aH1+Epi	260
51	300	80	URT+AE	ST+aH1	120
52	300	75	AE	ST+aH1	240
53	150	120	URT	ST+aH1	180
54	500	360	URT	ST+aH1	60
55	500	100	AE	aH1	240
56	500	340	URT	NO	90
57	300	120	AE	ST+aH1	100

AE: angioedema, URT: urticaria, ST: steroids, aH1: antihistamines, Epi: epinephrine

Table 2. Comparisons between those confirmed as allergic and non allergic.

Characteristics	CI N=57	Tolerant N=18	P
Gender, N (%)			0.007
Female	30 (52.6)	3 (16.7)	
Male	27 (47.4)	15 (83.3)	
Age, mean (IR)	36 (26-45)	41.50 (36-51.25)	0.156
Atopy, N (%)			0.063
Yes	47 (82.5)	11 (61.1)	
No	10 (17.5)	7 (38.9)	
Interval drug-reaction in min, mean (IR)	30 (30-60)	120 (30-270)	0.01
Type of reaction N (%)			0.307
Angioedema	17 (29.8)	4 (22.2)	
Urticaria	20 (35.1)	5 (27.8)	
Angioedema-urticaria	20 (35.1)	9 (50)	
Interval reaction-study in days, mean (IR)	180 (30-1080)	135 (15-247.50)	0.224
Number of drugs, N (%)			0.003
2	25 (43.9)	15 (83.3)	
>3	32 (56.1)	3 (16.7)	
Number of episodes, N (%)			0.004
2	10 (17.5)	7 (38.9)	
3	6 (10.5)	6 (33.3)	
4	11 (19.3)	1 (5.6)	
>5	30 (52.6)	4 (22.2)	

Table 3. Multivariate analysis using a logistic regression model based on a positive drug provocation test.

Characteristic	OR	95% CI	P value
Gender	10.057	1.637-61.796	0.013
Interval drug-reaction <60min	16.013	2.934-87.407	0.001
Number of NSAIDs involved >2	13.043	2.086-81.565	0.006