TITLE: ALLERGIC REACTIONS TO METAMIZOLE: IMMEDIATE AND DELAYED RESPONSES.

SHORT TITLE: SELECTIVE REACTIONS TO METAMIZOLE

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KEYWORDS: Basophil activation test; Metamizole; Drug provocation test; Selective hypersensitivity; Skin test.

ABBREVIATIONS: Non-steroidal anti-inflammatory drugs (NSAID); Single NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA); Single-NSAID-induced delayed hypersensitivity reactions (SNIDHR); Cyclooxygenase (COX); Selective responses (SR); Acetylsalicylic acid (ASA); Skin prick test (SPT); Intradermal test (ID); Basophil activation test (BAT); Drug provocation test (DPT).

ABSTRACT

Background: Pyrazolones are the most common cause of selective NSAIDs hypersensitivity. We studied a large group of patients with immediate and delayed selective responses to metamizole.

Methods: Patients with suspicion of hypersensitivity to metamizole were evaluated. We verified acetylsalicylic acid-tolerance and classified patients as immediate or delayed responders if they showed symptoms less or more than 24hours after metamizole administration. Skin tests were performed and if negative, basophil activation test (BAT) was performed on immediate responders. If this was negative, we performed a drug provocation test (DPT) with metamizole.

Results: A total of 137 patients were included: 132 reacted within 24 hours (single NSAID-induced urticaria/angioedema/anaphylaxis; SNIUAA); 5 after 24 hours (single-NSAID-induced delayed hypersensitivity reactions; SNIDHR). More specifically, 73.72% reacted within 30 minutes; 9.48% 30-60 minutes; 6.56% 1-2 hours; 6.56% 2-8 hours and 3.64% after over 24 hours. Most SNIUAA patients developed anaphylaxis (60.60%); for SNIDHR, maculopapular exanthema was the most frequent entitiy (60%). Skin testing was positive for 62.04% of all cases and BAT for 28% of SNIUAA patients with negative skin tests. In 5.1% cases DPT with metamizole was needed for establishing diagnosis. In the 22.62% of cases, diagnosis was established by a consistent and unequivocal history of repeated allergic episodes in spite of negative skin test and BAT.

Conclusions: SNIUAA to metamizole is the most frequent type of selective NSAID hypersensitivity, with anaphylaxis being the most common clinical entity. It may occur over an hour after drug intake. SNIDHR occurs in a very low percentage of cases. The

low sensitivity of diagnostic tests may be due to incomplete characterization of the chemical structures of metamizole and its metabolites.

INTRODUCTION

Adverse drug reactions constitute an important public health issue, causing 3 to 6% of all hospital admissions and occurring in 10 to 15% of hospitalized patients [1]. Non-steroidal anti-inflammatory drugs (NSAID) are the most frequent medicines involved in drug hypersensitivity reactions in both adults [2] and children [3] followed by beta-lactam antibiotics [4]. Hypersensitivity reactions to NSAIDs have been classified into different categories depending on the clinical symptoms induced, the number of NSAIDs involved and the presence or absence of underlying disease [5]. The following classification has been proposed: 1) NSAID-exacerbated respiratory disease (NERD); 2) NSAID-exacerbated cutaneous disease (NECD); 3) NSAID-induced urticaria/angioedema (NIUA); 4) Single NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA); and 5) Single-NSAID-induced delayed hypersensitivity reactions (SNIDHR).

The mechanism involved in the first three reaction types is thought to be non-immunologically mediated (cross-hypersensitivity) but related to the inhibition of the cyclooxygenase (COX-1) enzyme [5]. The last two categories involve an immunologically-mediated response that is induced by a single drug/drug-group, with subjects tolerating other chemically unrelated compounds (selective response) including strong COX-1 inhibitors [5, 6]. In SNIUAA, symptoms usually occur shortly after drug intake [5] and an IgE-mediated mechanism has been proposed [7-10]. In SNIDHR, reactions occur 24–48 h or longer after drug intake [5] and a T cell-mediated mechanism is likely [11]. As occurs with BL antibiotics, symptoms may appear at a shorter interval after drug intake [12, 13].

Most studies of hypersensitivity reactions to NSAIDs have focused on non-immunologically mediated reactions (cross-hypersensitivity) [14-17], mainly in NERD,

although there is growing interest in the cutaneous entities (NIUA and NECD) [14-19]. Although immunologically mediated reactions account for 25-30% of all NSAID hypersensitivity reactions [20], less attention has been paid to these reactions and no studies have been performed looking at large series of well-phenotyped cases. It is known that pyrazolones, particularly metamizole ([N-(1,5-dimethyl-3-oxo-2-phenylpyrazolin-4-yl)-N-methylamino] methanesulfonate, drug bank id. no. DB04817), are the most frequent drugs involved in immunologically mediated reactions [7, 20, 21]. Their use is widespread in many countries due to their analgesic, antipyretic and spasmolytic properties and therefore many patients are exposed.

Our aim was to study a large group of patients who developed selective responses (SR) to metamizole, one of the most frequently used analgesics in our population, and to establish in how many cases responses were immediate or delayed, following the classification provided by ENDA group [5]. The contribution of diagnostic tests (both in vivo and in vitro) was also assessed.

METHODS

Patients

We evaluated patients with symptoms suggestive of hypersensitivity reactions to metamizole referred to the allergy unit of the University Regional Hospital of Málaga (Málaga, Spain) and Infanta Leonor Hospital (Madrid, Spain) over a period of 3 years (2012-2014).

Inclusion criteria. Patients aged 14–80 years with a confirmed diagnosis of SR to metamizole.

The diagnosis was established according to the algorithm shown in Figure 1. The first approach was to verify tolerance to acetylsalicylic acid (ASA) if this was not known. If subjects responded to ASA, they were considered cross-hypersensitive to NSAIDs and not included in this study. If subjects tolerated ASA in a drug provocation test (DPT), they were considered as having either immediate reactions when they had the symptoms less than 24 hours after metamizole administration, or as delayed reactions when symptoms occurred more than 24 hours later. Skin tests with metamizole were performed for patients with both immediate and delayed reactions as described previously [22]. In patients with immediate reactions, if skin tests were negative, a basophil activation test (BAT) with metamizole was carried out. If skin tests or BAT were positive, the patients were confirmed as having SR to metamizole. If both skin test and BAT were negative, we considered the number of episodes suffered after metamizole administration: if the patient had at least 2 episodes, they were diagnosed as having SR to metamizole, but if the patient had only one episode, a positive DPT with metamizole was required, except in subjects with severe reactions (e.g. toxic epidermal necrolysis or anaphylactic shock).

Exclusion criteria. Patients younger than 14 years or older than 80 years of age; patients with a confirmed diagnosis of cross-hypersensitivity to NSAIDs; patients with one reported prior reaction to metamizole, with negative skin test and BAT results, where DPT with metamizole was contraindicated; patients who tolerated metamizole; patients where DPT to COX-1 inhibitor is contraindicated due to underlying disease; pregnant or breastfeeding patients; patients taking beta-blockers or ACE inhibitors or with contraindications for epinephrine administration; patients who had acute infections and/or underlying cardiac, hepatic or renal diseases that contraindicated DPT; and subjects with psychosomatic disorders.

Clinical history

Patients were questioned about the symptoms induced by metamizole administration; the time interval between drug intake and reaction onset; the number of episodes; the time interval between the last reaction and study; underlying nasal and bronchial symptoms, food allergy and the presence of underlying chronic spontaneous urticaria, either active or in remission.

Atopy status assessment

The atopy status was assessed with skin prick test (SPT) performed with a battery of 20 common inhalant allergens, including pollens, house dust mites, moulds and animal danders and a battery of 31 common food allergens that included animal, fruit and vegetable allergens (ALK, Madrid, Spain). Histamine hydrochloride 10 mg/mL and phenolated glycerolsaline were used as positive and negative controls, respectively. A positive SPT response was defined as a wheal diameter of 3 mm or larger to at least one

of these allergens. The patients were requested to stop taking any medications that contained antihistamine at least 8 days before skin testing.

Skin testing

For immediate reactions, skin prick and intradermal (ID) tests were carried out as described [22] using metamizole (Boehringer Ingelheim, Barcelona, Spain) at 40 and 400 mg/mL for SPT and at 0.4 and 4 mg/mL for ID. For those cases reporting severe reactions, ID was initially performed using 0.004 and 0.04 mg/ml. An increase in the diameter of the wheal by more than 3 mm, 20 min after testing was considered positive for SNIUAA.

For delayed reactions, patch and ID tests were carried out and evaluated after 48 hours as described [22]. For ID tests, the presence of intradermal papular induration after 48h was considered positive. Patch tests were performed by mixing powdered metamizole in petrolatum at 10% w/w. The occlusion time was 48h. Erythema with oedema, papules, vesicles or bullae 48 and/or 72 h after testing was considered positive [22].

Basophil activation test

In patients with a suspected immediate reaction, BAT was performed as described [23] using metamizole (Boehringer Ingelheim, Barcelona, Spain) at 0.25 and 2.5 mg/mL. Results were considered positive when the stimulation index (SI), calculated as the ratio of the percentage of degranulated basophils with the different haptens to the negative control, was greater than 2 in at least one of the concentrations used.

Oral drug provocation test

In order to verify tolerance to a strong COX-1 inhibitor, DPT with ASA was performed in a single blind manner, as described [20]: placebo capsules were given at different times on the first day, three doses of ASA were administered orally at intervals of 90 min (5, 30, 100 mg) on the second day, and, if negative, another two doses of ASA (150, 300 mg) on the third day. If patient had only one episode after metamizole administration and no contraindications for DPT existed, increasing doses of metamizole were administered orally at intervals of 90 min for 2 days (first day: 5, 10, 50 mg; accumulative dose 65 mg; 2nd day: 50, 150, 300 mg; accumulative dose 500 mg).

If cutaneous and/or respiratory symptoms or alterations in vital signs (rhythm alterations, decrease in peak expiratory flow (PEF) rate or hypotension) appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during drug administration, the therapeutic dose of ASA/metamizole was achieved. If tolerance occurred, this was followed by 2 days/8 hours at maximum dose, after a gap of 24 hours. ASA, metamizole and placebo were given in opaque capsules prepared by the hospital pharmacy service.

Forced expiratory volume in 1s values had to be at least 80% of predicted values, with an absolute value of at least 1.5 L. Antihistamine agents were stopped 1 week before challenge.

Statistical analysis

Data analysis was performed using Chi-squared analysis to test differences in nominal variables between groups, the Fisher test was used when there were no criteria for using the chi-square test and the Mann–Whitney test was used for quantitative variables. All reported p-values represented two-tailed tests, with values <0.05 considered statistically

significant. The analysis included age, gender, atopic status, number of episodes, clinical manifestations and methods used for the diagnosis.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethics Committees of the University Regional Hospital of Málaga. All the participants were informed orally about the study and signed the corresponding informed consent.

RESULTS

A total of 5926 patients with a clinical history of drug hypersensitivity reactions were evaluated at the Allergy units of the University Regional Hospital of Málaga and the Infanta Leonor Hospital in Madrid in 2012-2014. NSAIDs were involved in 2398 cases. In 922 cases metamizole was the NSAID involved in the episodes. Of these, a total of 137 patients were confirmed as having SR to metamizole and were included in this study. The remaining 785 patients with reactions after metamizole intake were not considered for this study due to cross-hypersensitivity (678 subjects) or unconfirmed diagnosis (107 subjects). Of these, 6 were pregnant; 101 had negative skin and BAT and could not undergo DPT to ASA and/or metamizole (40 were older than 70 years and had cardiopulmonary co-morbidities, 41 reported anaphylactic shock and 20 severe delayed reactions)

The 137 patients with confirmed SR to metamizole included in this study had a median age of 53 years [interquartile range (IR): 41–64] and 101 were women (73.72%). Fifty-seven cases (41.6%) were atopic and 35 (25.54%) had rhinitis, 10 (7.29%) had asthma, 10 (7.29%) had symptoms attributed to food allergy and 7 (5.1%) had underlying chronic urticaria.

Considering the total group and according to clinical history (see Table 1), most cases with confirmed SR to metamizole developed anaphylaxis (80; 58.39%), followed by urticaria (42, 30.65%), angioedema (7, 5.1%), maculopapular exanthema (MPE) (3, 2.18%), fixed drug eruption (FDE) (2, 1.45%) and glottis oedema, exanthema with bullae and exanthema with skin desquamation with only one patient each (0.7%). Concerning the number of previously reported episodes, patients had a median of 2 (IR: 1-2). Analyzing the time interval between metamizole administration and the onset of the reactions reported in clinical history, in a total of 101 (73.72%) patients the reaction

occurred within 30 minutes; in 13 (9.48%) patients within 30-60 minutes; in 9 (6.56%) within 1-2 hours; in 9 (6.56%) within 2-8 hours and in 5 (3.64%) more than 24 hours later. For further analysis, we classified patients as SNIUAA if the time interval was less than 24 hours after metamizole administration (132; 96.35%) and SNIDHR if the interval was more than 24 hours (5; 3.64%).

Considering the patients with anaphylaxis (n=80), in all cases there was skin involvement. We show the involvement of other organs in table 2. The respiratory involvement consisted of dyspnea, wheezing and chest tightness, the gastrointestinal consisted of abdominal cramps, vomiting and diarrhoea and the cardiovascular consisted of tachycardia and hypotension.

Analyzing the time interval in the cases of anaphylaxis, in 70 (87.5%) the reactions occurred in less than 30 minutes, in 6 (7.5%) between 30-60 minutes, in 2 (2.5%) between 1-2 hours and in 2 (2.5%) between 2-8 hours. No cases of anaphylaxis occurred beyond this time.

According to clinical history, most cases reported to have taken metamizole by oral route and 5 by intravenous one. In 2 patients there were one episode after intravenous administration and another after oral intake. In all cases, the reactions reported by the patient were more severe with the involvement of 4 organ systems (skin, respiratory, cardiovascular and gastrointestinal or transitory loss of consciousness) when the metamizole was administered by intravenous route (see table 2). In the 5 cases where the reactions occurred after intravenous administration, the symptoms appeared within 30 minutes.

No differences were found in age, gender, atopy, rhinitis, asthma, food allergy, underlying chronic urticaria and number of episodes reported when comparing SNIUAA and SNIDHR.

Most SNIUAA patients (80; 60.60%) had anaphylaxis whilst amongst SNIDHR patients the most frequent clinical entity was MPE (3; 60%).

The median time interval between the last reaction and the study was 6 months (IR: 3-24). No differences were found between SNIUAA and SNIDHR.

Of the 137 cases evaluated, 85 (62.04%) subjects gave positive skin tests (see Table 3). For SNIUAA, 37 (28.03%) were positive by prick-test and 45 (47.36%) by ID. For SNIDHR, 3 (60%) were positive by both ID and patch test (see table 2). One patient developed an immediate systemic response during SPT with metamizole although the reading was negative. In SNIUAA patients with negative skin test results (n=50), BAT with metamizole was performed, and was positive in 14 subjects (28%).

Comparing patients with positive and negative results in skin tests and BAT, the time interval between the last reaction induced by metamizole and the study was shorter in those who had positive tests (3 (IR: 3-12) vs 12 (IR: 3-36) months, p=0.023).

The results of DPT with metamizole are shown in Table 4. A total of 6 cases reported immediate reactions after metamizole administration, had negative skin tests and BAT and only one episode induced by metamizole; 1 case reported a delayed reaction after metamizole administration, had negative skin tests and only one episode induced by metamizole. In all cases DPT with metamizole induced mild symptoms: 7 patients developed pruritus and wheals localized on different parts of the body and 1 MPE with no systemic symptoms. No patient had respiratory or cardiovascular system involvement. The patients responded to a median dose of 480 (IR: 65-575) mg of metamizole. The symptoms disappeared within 1-48h of administering antihistamine and corticosteroid treatment.

In 31 patients (22.62%) with both negative skin tests and BAT, the diagnosis was achieved by clinical history as they had 2 or more episodes induced by metamizole and tolerance to ASA was confirmed by DPT (see Table 3).

DISCUSSION

We have evaluated a large group of cases with hypersensitivity to pyrazolones following the consensus guidelines published by the EAACI special interest group on NSAID hypersensitivity reactions [5]. After excluding cross-hypersensitive subjects we verified, in those confirmed SR cases, how many were SNIUAA and SNIDHR.

The diagnosis of SR patients is often complex, not risk-free, and requires trained personnel and specific resources [24]. In this study we first verified tolerance to ASA in order to exclude patients with cross-hypersensitivity to NSAIDs. Of the remaining cases, those with positive skin tests and/or BAT were confirmed as SR to metamizole, as reported previously by our group [23]. Cases with negative skin tests and BAT required a minimum history of two previous reactions after metamizole administration to be considered SR. Although in previous studies looking at cross-hypersensitivity to NSAIDs at least three episodes were required [18], in SR we have considered 2 clear episodes to be sufficient, provided that clinical history was reliable. Those patients with both negative skin tests and BAT that reported only one reaction after metamizole administration and contraindications for DPT were excluded from this study. This could contribute to some bias in this study in terms of the sensitivity of the skin tests, particularly for those with immediate reactions.

Skin testing was positive for 62.04% of the cases tested. Of the remaining cases (n=52), 28% of SNIUAA could be identified by BAT. The overall sensitivity including both tests was therefore 72.26%. Skin and *in vitro* tests have shown variable results in different studies [23, 25-27]. For immediate reactions Gamboa *et al*. [25] reported BAT sensitivity to be 42.3% and specificity 100%. Similar results were observed in a later study by Gomez *et al*. [23] in which the sensitivity of the BAT was 54.9% and the specificity 85.7%, and 62% of patients had positive skin tests to metamizole. In this

study we cannot establish the overall sensitivity of the tests because we did not perform BAT with metamizole in all patients. The time interval between the reaction and the study can affect the outcome of the tests [23] as has been shown in subjects with immediate hypersensitivity reactions to beta-lactams [28, 29]. We found differences comparing the time interval between the reaction and the performance of the tests in those who were negative and those who were positive. Another factor to take into account that can contribute to the low sensitivity of diagnostic tests is the incomplete characterization of the chemical structures of metamizole and its metabolites [30]. Four major metamizole metabolites have been described in the literature [31], however we recently demonstrated the presence of arachidonoyl metabolites in patients receiving metamizole [32], and additional metabolites, such as oxalic acid derivatives have been reported elsewhere [33]. It cannot be ruled out that in some patients, metamizole metabolites may contribute to hypersensitivity reactions.

Considering the underlying mechanism in patients with immediate SR to pyrazolone derivatives, evidence (basophil activation and skin test positivity) supports an IgE mediated mechanism [7, 23]. There are only a few experimental studies on the quantification of IgE antibodies and no detailed studies have been carried out in this field [8-10]. For delayed reactions, positive delayed intradermal and/or patch tests to the culprit drug with a characteristic T cell infiltrate have been reported [6, 34-38]. Further evidence has been provided by in vitro cellular assays [38, 39].

In the case of beta-lactams, the time interval between drug administration and the appearance of symptoms is considered crucial for evaluating allergic reactions [40]. The reactions to these drugs can be considered immediate and non-immediate. The former are induced by an IgE-mediated response, whilst for the latter, there are some controversies as to the underlying mechanism, especially for those cases where there is

an interval of between 1 and 24 hours after drug intake [41]. It has been shown that, for the so called accelerated reactions to amoxicillin, occurring between 1 and 6 hours, the mechanism is not IgE-dependent [13]. In fact, some evidence indicates that these reactions are T cell-mediated [12]. However, to our knowledge this mechanism has not yet been studied for NSAIDs. In this study, by analysing the time interval between metamizole administration and reaction onset, we observed that 13% of patients had reactions 1-24 hours after metamizole intake. When analysing basophil activation in those cases where the reaction occurred 1-8 hours after metamizole administration, we did not find any positive response in a group of 8 patients tested, suggesting that an IgE mechanism is unlikely. The time interval between drug administration and the onset of the reaction may be related to the production of different, as yet unidentified, metabolites. Metamizole metabolism occurs rapidly following intake and some of the resultant metabolites are measurable in serum, urine and other biological fluids shortly after administration [42, 43].

Metamizole has more than 20 known metabolites [31] formed by either alkaline hydrolysis or biotransformation, however only a few studies have analysed their immunogenic potential [8, 44]. The identification of the adequate metabolite may be necessary to identify the underlying mechanisms and better diagnose these patients.

The percentage of atopy is high in these patients, but less than for cross-hypersensitive ones [20]. Atopy prevalence was similar in both SNIUAA and SNIDHR, however more SNIDHR cases are needed to confirm this.

In summary, we conclude that pyrazolones contribute to the production of selective reactions to NSAIDs, of which most are immediate. Although skin tests and BAT may aid in the diagnosis of these reactions, further research is needed to help identify the

culprit metabolite and develop better diagnostic tools. To our knowledge this is the largest study of cases with allergic responses to pyrazolones to date.

363 Table 1.

		SNIUAA n=132	SNIDHR n=5
Age yr (IR)		53 (41.25-63)	68 (31.75-75.75)
Gender n (%) female/n(%) male		97 (73.48)/35 (26.51)	4(80)/1(20)
Number of episodes reported after metamizole administration		2 (1-2)	2 (2-3)
Clinical entities n (%)	Anaphylaxis	80 (60.60)	0
	Urticaria	42 (31.81)	0
	Angioedema	7 (5.3)	0
	Glottis oedema	1 (0.75)	0
	FDE	2 (1.51	0
	MPE	0	3 (60)
	Exanthema with bullae	0	1 (20)
	Exanthema with skin desquamation	0	1 (20)

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366 Table 2.

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Organ system involved	Route
Skin+respiratory n=24 (30%)	Oral
Skin+gastrointestinal n=2 (2.5%)	Oral
Skin+cardiovascular n=2 (2.5%)	Oral
Skin+respiratory +gastrointestinal n=5 (6.25%)	Oral
Skin+transitory loss of consciousness n=22 (27.5%)	Oral
Skin+respiratory+transitory loss of consciousness n=9 (11.25%)	Oral
Skin+gastrointestinal+transitory loss of consciousness n=9 (11.25%)	Oral
Skin+respiratory+gastrointestinal+transitory loss of consciousness n=2 (2.5%)	Oral
Skin+respiratory+cardiovascular+transitory loss of consciousness n=3 (3.75%)	Intravenous
Skin+respiratory+gastrointestinal+cardiovascular n=2 (2.5%)	Intravenous

368 Table 3.

Methods for diagnosis		SNIUAA n=132	SNIDHR n=5
Skin test	Prick test	37 (28.03%)	Not done
	ID	45 (47.36%)	3(60%)
	Patch	Not done	3 (60%)
BAT		14 (28%)	Not done
DPT with metamizole		6 (12%)	1 (20%)
Clinical history+DPT ASA		30 (60%)	1 (20%)

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370 Table 4.

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Patient number	Age/ Gender	Clinical entity	TIR	Dose (mg)	Symptoms
Patient 1	46/F	Urticaria	30	65	Generalized pruritus and facial angioedema
Patient 2	41/F	Urticaria+angioedema	45	575	Pruritus in hands and wheals in thorax and abdomen
Patient 3	42/F	Urticaria	60	205	Systemic pruritus, conjunctival injection and tongue oedema
Patient 4	33/M	Urticaria+angioedema	30	575	Wheals in abdomen plus pruritus
Patient 5	43/M	Urticaria	45	65	Pruritus in thorax, arms and back and wheals in thorax
Patient 6	52/F	Urticaria	720	480	Facial angiodema and pruritus and wheals in thorax
Patient 7	67/M	Maculopapular exanthema	2880	575	Maculopapular exanthema in trunk

REFERENCES

1. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. British journal of clinical pharmacology. 2011 May;71(5):684-700. PubMed PMID: 21480948. Pubmed Central PMCID: 3093074.
2. Dona I, Blanca-Lopez N, Torres MJ, Garcia-Campos J, Garcia-Nunez I, Gomez F, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. Journal of investigational allergology & clinical immunology. 2012;22(5):363-71. PubMed PMID: 23101312.
3. Zambonino MA, Torres MJ, Munoz C, Requena G, Mayorga C, Posadas T, et al. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2013 Mar;24(2):151-9. PubMed PMID: 23506290. Epub 2013/03/20. eng.
4. Antunez C, Martin E, Cornejo-Garcia JA, Blanca-Lopez N, R RP, Mayorga C, et al. Immediate hypersensitivity reactions to penicillins and other betalactams. Current pharmaceutical design. 2006;12(26):3327-33. PubMed PMID: 17017927. Epub 2006/10/05. eng.
5. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013 Oct;68(10):1219-32. PubMed PMID: 24117484. Epub 2013/10/15. eng.
6. Canto MG, Andreu I, Fernandez J, Blanca M. Selective immediate hypersensitivity reactions to NSAIDs. Current opinion in allergy and clinical immunology. 2009 Aug;9(4):293-7. PubMed PMID: 19561490.
7. Himly M, Jahn-Schmid B, Pittertschatscher K, Bohle B, Grubmayr K, Ferreira F, et al. IgE-mediated immediate-type hypersensitivity to the pyrazolone drug propyphenazone. The Journal of allergy and clinical immunology. 2003 Apr;111(4):882-8. PubMed PMID: 12704373.
8. Schneider CH, Kasper MF, de Weck AL, Rolli H, Angst BD. Diagnosis of antibody-mediated drug allergy. Pyrazolinone and pyrazolidinedione cross-reactivity relationships. Allergy. 1987 Nov;42(8):597-603. PubMed PMID: 3425858.
9. Blanca M, Perez E, Garcia JJ, Miranda A, Terrados S, Vega JM, et al. Angioedema and IgE antibodies to aspirin: a case report. Annals of allergy. 1989 Apr;62(4):295-8. PubMed PMID: 2468301.
10. Harrer A, Lang R, Grims R, Braitsch M, Hawranek T, Aberer W, et al. Diclofenac hypersensitivity: antibody responses to the parent drug and relevant metabolites. PloS one. 2010;5(10):e13707. PubMed PMID: 21060839. Pubmed Central PMCID: 2965666.
11. Posadas SJ, Padial A, Torres MJ, Mayorga C, Leyva L, Sanchez E, et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. The Journal of allergy and clinical immunology. 2002 Jan;109(1):155-61. PubMed PMID: 11799383.
12. Gomez E, Blanca-Lopez N, Salas M, Canto G, Campo P, Torres MJ, et al. Induction of accelerated reactions to amoxicillin by T-cell effector mechanisms. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2013 Apr;110(4):267-73. PubMed PMID: 23535091. Epub 2013/03/29. eng.

13. Terrados S, Blanca M, Garcia J, Vega J, Torres MJ, Carmona MJ, et al. Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. Allergy. 1995 Jul;50(7):563-7. PubMed PMID: 8588688.

14. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. The Journal of allergy and clinical immunology. 2003 May;111(5):913-21; quiz 22. PubMed PMID: 12743549.

15. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ. 2004 Feb 21;328(7437):434. PubMed PMID: 14976098. Pubmed Central PMCID: 344260. Epub 2004/02/21. eng.

16. Szczeklik A, Sladek K, Dworski R, Nizankowska E, Soja J, Sheller J, et al. Bronchial aspirin challenge causes specific eicosanoid response in aspirin-sensitive asthmatics. American journal of respiratory and critical care medicine. 1996 Dec;154(6 Pt 1):1608-14. PubMed PMID: 8970343.

17. Sanak M, Gielicz A, Bochenek G, Kaszuba M, Nizankowska-Mogilnicka E, Szczeklik A. Targeted eicosanoid lipidomics of exhaled breath condensate provide a distinct pattern in the aspirin-intolerant asthma phenotype. The Journal of allergy and clinical immunology. 2011 May;127(5):1141-7 e2. PubMed PMID: 21315430.

18. Blanca-Lopez N, M JT, Dona I, Campo P, Rondon C, Seoane Reula ME, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2013 Jan;43(1):85-91. PubMed PMID: 23278883.

19. Dona I, Blanca-Lopez N, Torres MJ, Gomez F, Fernandez J, Zambonino MA, et al. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014 Apr;69(4):438-44. PubMed PMID: 24372026.

20. Dona I, Blanca-Lopez N, Cornejo-Garcia JA, Torres MJ, Laguna JJ, Fernandez J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011 Jan;41(1):86-95. PubMed PMID: 21155908.

21. Kowalski ML, Woszczek G, Bienkiewicz B, Mis M. Association of pyrazolone drug hypersensitivity with HLA-DQ and DR antigens. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1998 Sep;28(9):1153-8. PubMed PMID: 9761020.

22. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002 Jan;57(1):45-51. PubMed PMID: 11991289.

23. Gomez E, Blanca-Lopez N, Torres MJ, Requena G, Rondon C, Canto G, et al. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2009 Aug;39(8):1217-24. PubMed PMID: 19400910.

24. Ayuso P, Blanca-Lopez N, Dona I, Torres MJ, Gueant-Rodriguez RM, Canto G, et al. Advanced phenotyping in hypersensitivity drug reactions to NSAIDs. Clin Exp Allergy. 2013 Oct;43(10):1097-109. PubMed PMID: 24074328. Epub 2013/10/01. eng.

25. Gamboa PM, Sanz ML, Caballero MR, Antepara I, Urrutia I, Jauregui I, et al. Use of CD63 expression as a marker of in vitro basophil activation and

leukotriene determination in metamizol allergic patients. Allergy. 2003 Apr;58(4):312-7. PubMed PMID: 12708979. Epub 2003/04/24. eng.

26. Gamboa P, Sanz ML, Caballero MR, Urrutia I, Antepara I, Esparza R, et al. The flow-cytometric determination of basophil activation induced by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is useful for in vitro diagnosis of the NSAID hypersensitivity syndrome. Clin Exp Allergy. 2004 Sep;34(9):1448-57. PubMed PMID: 15347380. Epub 2004/09/07. eng.

27. Sanz ML, Gamboa P, de Weck AL. A new combined test with flowcytometric basophil activation and determination of sulfidoleukotrienes is useful for in vitro diagnosis of hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs. Int Arch Allergy Immunol. 2005 Jan;136(1):58-72. PubMed PMID: 15608437. Epub 2004/12/21. eng.

28. Blanca M, Torres MJ, Garcia JJ, Romano A, Mayorga C, de Ramon E, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. The Journal of allergy and clinical immunology. 1999 May;103(5 Pt 1):918-24. PubMed PMID: 10329829.

29. Fernandez TD, Torres MJ, Blanca-Lopez N, Rodriguez-Bada JL, Gomez E, Canto G, et al. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. Allergy. 2009 Feb;64(2):242-8. PubMed PMID: 19178404. Epub 2009/01/31. eng.

30. Ariza A, Fernandez TD, Dona I, Aranda A, Blanca-Lopez N, Melendez L, et al. Basophil activation after nonsteroidal anti-inflammatory drugs stimulation in patients with immediate hypersensitivity reactions to these drugs. Cytometry Part A : the journal of the International Society for Analytical Cytology. 2014 May;85(5):400-7. PubMed PMID: 24443418. Epub 2014/01/21. eng.

31. Levy M, Zylber-Katz E, Rosenkranz B. Clinical pharmacokinetics of dipyrone and its metabolites. Clinical pharmacokinetics. 1995 Mar;28(3):216-34. PubMed PMID: 7758252.

32. Martinez C, Andreu I, Amo G, Miranda MA, Esguevillas G, Torres MJ, et al. Gender and functional CYP2C and NAT2 polymorphisms determine the metabolic profile of metamizole. Biochemical pharmacology. 2014 Dec 1;92(3):457-66. PubMed PMID: 25241292.

33. Wessel JC, Matyja M, Neugebauer M, Kiefer H, Daldrup T, Tarbah FA, et al. Characterization of oxalic acid derivatives as new metabolites of metamizol (dipyrone) in incubated hen's egg and human. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2006 May;28(1-2):15-25. PubMed PMID: 16417995.

34. Ozkaya-Bayazit E, Bayazit H, Ozarmagan G. Drug related clinical pattern in fixed drug eruption. European journal of dermatology : EJD. 2000 Jun;10(4):288-91. PubMed PMID: 10846256.

35. Gonzalo-Garijo MA, Perez-Calderon R, De Argila D, Rodriguez-Nevado I. Metamizole-induced acute generalized exanthematous pustulosis. Contact dermatitis. 2003 Jul;49(1):47-8. PubMed PMID: 14641128. Epub 2003/12/04. eng.

36. Borja JM, Galindo PA, Gomez E, Feo F. Delayed skin reactions to metamizol. Allergy. 2003 Jan;58(1):84-5. PubMed PMID: 12580814.

37. Dalmau J, Serra-Baldrich E, Roe E, Peramiquel L, Alomar A. Use of patch test in fixed drug eruption due to metamizole (Nolotil). Contact dermatitis. 2006 Feb;54(2):127-8. PubMed PMID: 16487292. Epub 2006/02/21. eng.

38. Macias E, Ruiz A, Moreno E, Laffond E, Davila I, Lorente F. Usefulness of intradermal test and patch test in the diagnosis of nonimmediate reactions to metamizol. Allergy. 2007 Dec;62(12):1462-4. PubMed PMID: 17983381.

39. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. The Journal of allergy and clinical immunology. 2011 Mar;127(3 Suppl):S67-73. PubMed PMID: 21354502.

40. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009 Feb;64(2):183-93. PubMed PMID: 19133923.

41. Bircher AJ, Scherer Hofmeier K. Drug hypersensitivity reactions: Inconsistency in the use of the classification of immediate and nonimmediate reactions. The Journal of allergy and clinical immunology. 2012 Jan;129(1):263-4; author reply 5-6. PubMed PMID: 21982115.

42. Agundez JA, Martinez C, Benitez J. Metabolism of aminopyrine and derivatives in man: in vivo study of monomorphic and polymorphic metabolic pathways. Xenobiotica; the fate of foreign compounds in biological systems. 1995 Apr;25(4):417-27. PubMed PMID: 7645307.

43. Vlahov V, Badian M, Verho M, Bacracheva N. Pharmacokinetics of metamizol metabolites in healthy subjects after a single oral dose of metamizol sodium. European journal of clinical pharmacology. 1990;38(1):61-5. PubMed PMID: 2328750.

44. Zhu D, Becker WM, Schulz KH, Schubeler K, Schlaak M. Detection of IgE antibodies specific for 1-phenyl-2,3-dimethyl-3-pyrazoline-5-one by RAST: a serological diagnostic method for sensitivity to pyrazoline drugs. Asian Pacific journal of allergy and immunology / launched by the Allergy and Immunology Society of Thailand. 1992 Dec;10(2):95-101. PubMed PMID: 1305820.

TABLES AND FIGURE LEGENDS

Figure 1. Algorithm for diagnosis of patients with reactions suggestive of hypersensitivity to metamizole.

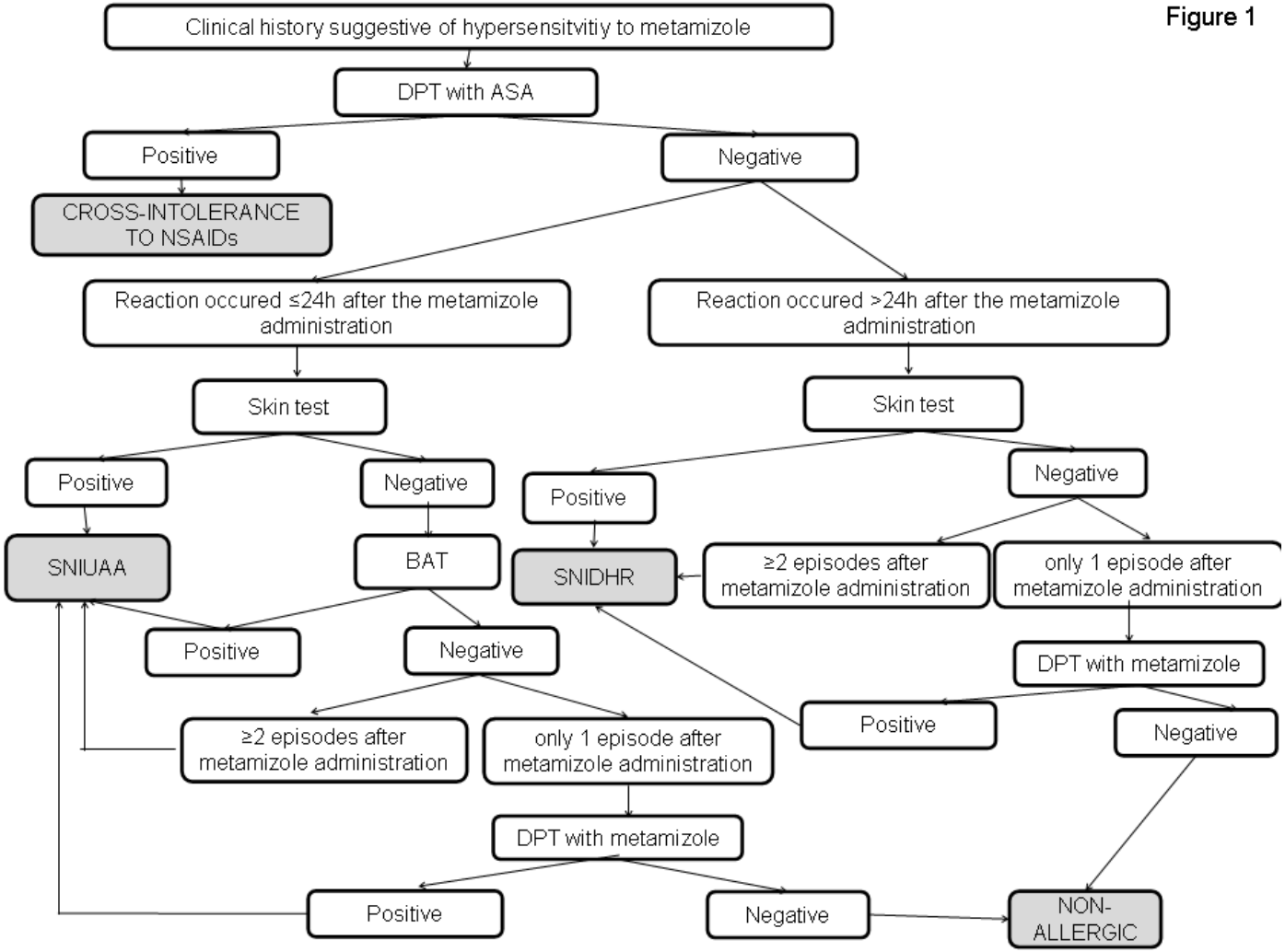
Table 1. Clinical data comparing SNIUAA and SNIDHR.

Table 2. Involvement of different organs and administration route of metamizole in patients who reported anaphylaxis.

Table 3. Methods used for diagnosis of SNIUAA and SNIDHR.

Table 4 Clinical data of patients with DPT to metamizole. F=Female. M=Male. TIR= time interval between metamizole administration and the reactions (minutes).

Figure 1


Clinical history suggestive of hypersensitvitiy to metamizole
DPT with ASA
Positive
Negative
CROSS-INTOLERANCE TO NSAIDs
Reaction occured ≤24h after the metamizole administration
Reaction occured >24h after the metamizole administration
Skin test
Skin test
Positive
Negative
Positive
Negative
SNIUAA
BAT
SNIDHR
≥2 episodes after metamizole administration
only 1 episode after metamizole administration
Positive
Negative
DPT with metamizole
Positive
Negative
≥2 episodes after metamizole administration
only 1 episode after metamizole administration
DPT with metamizole
Positive
Negative
NON-ALLERGIC

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