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

SHORT TITLE: SELECTIVE REACTIONS TO METAMIZOLE

AUTHORS: Natalia Blanca-López¹, Inmaculada Doña², José Augusto Agúndez³, Elena García-Martín³, María José Torres², José Antonio Cornejo-García⁴, James R. Perkins⁴, Miguel Angel Miranda⁵, Inmaculada Andreu⁵, Cristobalina Mayorga⁴, Gabriela Canto¹, Miguel Blanca².

AFFILIATIONS:

¹Allergy Service, Infanta Leonor Hospital, Madrid, Spain; ²Allergy Unit, Regional University Hospital of Malaga-IBIMA, UMA, Malaga, Spain; ³Department of Pharmacology, University of Extremadura, Caceres, Spain; ⁴Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain; ⁵Chemical Technology Institute, UPV-CSIC, Polytechnic University of Valencia, Valencia, Spain

Corresponding author and Address for reprint requests:

Inmaculada Doña, Allergy Unit, pabellón 6, primera planta, Hospital Regional Universitario de Málaga (Pabellon C), Plaza del Hospital Civil, 29009 Malaga, Spain.
Tel: +34 951290224. FAX: +34 951290302. E-mail: inmadd@hotmail.com

Total word count: 3170 words.

Conflict of interest: None of the authors has any conflict of interest, nor have they received any money for the present study. Research is part of their daily activities. All the authors had full access to all the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. The study was funded by FIS-Thematic Networks and Co-operative Research Centres (RIRAAF/RD012/0013 and RIRAAF/RD012/0002).
**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 24 hours 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 entity (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.
<table>
<thead>
<tr>
<th></th>
<th>SNIUAA n=132</th>
<th>SNIDHR n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yr (IR)</td>
<td>53 (41.25-63)</td>
<td>68 (31.75-75.75)</td>
</tr>
<tr>
<td>Gender n (%) female/n(%) male</td>
<td>97 (73.48)/35 (26.51)</td>
<td>4(80)/1(20)</td>
</tr>
<tr>
<td>Number of episodes reported after metamizole administration</td>
<td>2 (1-2)</td>
<td>2 (2-3)</td>
</tr>
<tr>
<td>Clinical entities n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>80 (60.60)</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>42 (31.81)</td>
<td>0</td>
</tr>
<tr>
<td>Angioedema</td>
<td>7 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Glottis oedema</td>
<td>1 (0.75)</td>
<td>0</td>
</tr>
<tr>
<td>FDE</td>
<td>2 (1.51)</td>
<td>0</td>
</tr>
<tr>
<td>MPE</td>
<td>0</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Exanthema with bullae</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Exanthema with skin desquamation</td>
<td>0</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>
Table 2.

<table>
<thead>
<tr>
<th>Organ system involved</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin+respiratory</td>
<td>Oral</td>
</tr>
<tr>
<td>n=24 (30%)</td>
<td></td>
</tr>
<tr>
<td>Skin+gastrointestinal</td>
<td>Oral</td>
</tr>
<tr>
<td>n=2 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Skin+cardiovascular</td>
<td>Oral</td>
</tr>
<tr>
<td>n=2 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Skin+respiratory +gastrointestinal</td>
<td>Oral</td>
</tr>
<tr>
<td>n=5 (6.25%)</td>
<td></td>
</tr>
<tr>
<td>Skin+transitory loss of consciousness</td>
<td>Oral</td>
</tr>
<tr>
<td>n=22 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Skin+respiratory+transitory loss of consciousness</td>
<td>Oral</td>
</tr>
<tr>
<td>n=9 (11.25%)</td>
<td></td>
</tr>
<tr>
<td>Skin+gastrointestinal+transitory loss of consciousness</td>
<td>Oral</td>
</tr>
<tr>
<td>n=9 (11.25%)</td>
<td></td>
</tr>
<tr>
<td>Skin+respiratory+gastrointestinal+transitory loss of consciousness</td>
<td>Oral</td>
</tr>
<tr>
<td>n=2 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Skin+respiratory+cardiovascular+transitory loss of consciousness</td>
<td>Intravenous</td>
</tr>
<tr>
<td>n=3 (3.75%)</td>
<td></td>
</tr>
<tr>
<td>Skin+respiratory+gastrointestinal+cardiovascular</td>
<td>Intravenous</td>
</tr>
<tr>
<td>n=2 (2.5%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.

<table>
<thead>
<tr>
<th>Methods for diagnosis</th>
<th>SNIUAA n=132</th>
<th>SNIDHR n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin test</td>
<td>37 (28.03%)</td>
<td>Not done</td>
</tr>
<tr>
<td>ID</td>
<td>45 (47.36%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Patch</td>
<td>Not done</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>BAT</td>
<td>14 (28%)</td>
<td>Not done</td>
</tr>
<tr>
<td>DPT with metamizole</td>
<td>6 (12%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Clinical history+DPT ASA</td>
<td>30 (60%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Patient number</td>
<td>Age/Gender</td>
<td>Clinical entity</td>
</tr>
<tr>
<td>----------------</td>
<td>------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Patient 1</td>
<td>46/F</td>
<td>Urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>41/F</td>
<td>Urticaria+angioedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>42/F</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Patient 4</td>
<td>33/M</td>
<td>Urticaria+angioedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>43/M</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Patient 6</td>
<td>52/F</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Patient 7</td>
<td>67/M</td>
<td>Maculopapular exanthema</td>
</tr>
</tbody>
</table>


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


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).