

## Delayed postoperative reactions to metamizole: a diagnostic challenge

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### Abstract

**Background:** Metamizole, a non-steroidal anti-inflammatory drug from the pyrazolone group, is a frequent cause of immediate hypersensitivity reactions and, more rarely, of delayed drug hypersensitivity reactions. Due to its favorable pharmacokinetic characteristics, metamizole is widely used in the postoperative period for pain control.

**Aim:** Evaluate the usefulness of skin tests, including intradermal and patch tests, and drug provocation tests for the diagnosis of delayed drug hypersensitivity to metamizole, in the complex postoperative multidrug setting.

**Methods:** Retrospective study of patients referred for allergological study between January 2012 and June 2022 for postoperative hypersensitivity reactions. Clinical and diagnostic data were collected through review of patients' medical records. Twenty patients with postoperative hypersensitivity reactions were referred, of which 10 presented delayed reactions. We analyzed the results of skin prick, intradermal and patch tests performed with an intravenous metamizole solution as well as provocation tests performed with metamizole and acetylsalicylic acid. Cross-reactivity to non-steroidal anti-inflammatory drugs was excluded by confirmation of clinical tolerance to non-steroidal anti-inflammatory drugs or by acetylsalicylic acid provocation test.

**Results:** In 7 of the 10 patients a delayed reaction to metamizole was diagnosed. These reactions were characterized as maculopapular exanthema, occurring in multiple postoperative settings. Skin tests were negative, except in one patient with late mild erythema in the ipsilateral upper limb and no reaction at the site of intradermal injection. Delayed hypersensitivity was demonstrated by late positive metamizole provocation tests.

**Conclusions:** This study demonstrated that for a correct diagnosis a high degree of suspicion about possible delayed hypersensitivity drug reactions to metamizole in the postoperative setting is needed. In the investigation, provocation test with metamizole was decisive for diagnostic confirmation.

**Keywords:** Allergy, delayed hypersensitivity, metamizole, non-steroidal anti-inflammatory drugs, postoperative.

**Impact statement:** Immediate reactions to metamizole are well characterized however few studies focus on delayed reactions. In this study we thoroughly characterize and emphasize the difficulty in evaluating delayed reactions to metamizole

## INTRODUCTION

Adverse drug reactions (ADR) constitute a relevant cause of hospital admissions and are estimated to occur in 10 to 15% of hospitalized patients, mainly in poly-medicated patients (1). Some of these ADR are caused by hypersensitivity reactions. Non-steroidal anti-inflammatory drugs (NSAID) are the most common cause of hypersensitivity reactions in adults in several countries and also in Portugal (2–4). They include reactions caused by immunological and non-immunological mechanisms, the latter being based on the excessive inhibition of cyclooxygenase (COX) enzymes in NSAID-sensitive patients, making these patients react to different, non-chemically related NSAID (5). Immune or allergic reactions to NSAID are usually directed to a single drug or to drugs belonging to the same chemical class (Table I) and these reactions can be classified as immediate or non-immediate reactions (2). Metamizole is a pyrazolone derivative, with significant analgesic and spasmolytic properties, frequently used in Portugal in acute and chronic pain treatment. Due to its favorable pharmacokinetic characteristics, it is widely used in the postoperative period, in multiple types of surgeries, also because metamizole is almost devoid of gastric or hemorrhagic complications seen with other NSAID. However important side-effects such as agranulocytosis or shock have been reported in several patients, some countries banning its use due to these possible side-effects (6). As a group, pyrazolone derivatives are frequently involved in hypersensitivity reactions, metamizole being one of the analgesics that most frequently causes hypersensitivity reactions (7). In a large Portuguese study based on anaphylaxis reports by allergists, metamizole was responsible for more than 10% of all drug-induced anaphylactic reactions (4).

Immediate reactions to metamizole are much more frequent and better known, in many cases involving IgE-mediated mechanisms. It has been shown that some metamizole

metabolites can be specifically recognised by IgE antibodies bound to the surface of basophils, causing anaphylactic reactions in sensitised individuals (8). On the other hand, non-immediate reactions are much less frequently described, T-cell mediated inflammatory response being frequently pointed out as the responsible mechanism in these cases.

In hypersensitivity reactions appearing in the postoperative period, we have to consider not only the possible role of drugs given during anaesthesia and surgery but especially the probable role of a significant number of different drugs, including analgesics/NSAID, antibiotics, as well as several others, that usually are being used concomitantly in the first days after surgery, making it difficult to identify, on clinical grounds alone, the culprit drug. This is true for immediate reactions but even more so to delayed drug hypersensitivity reactions (DDHR), where the beginning of the reaction can be more easily missed, being more difficult to establish a clear relationship between drugs and DDHR. In these cases, it is crucial to perform a thorough allergological work-up, with skin tests to try to demonstrate the presence of delayed reactions and with drug provocation tests (DPT) to try to replicate the DDHR.

The aim of our study was to describe, in a series of patients investigated for drug allergy in a postoperative multidrug setting, between 2012 and 2022, the usefulness of a thorough allergological investigation, with intradermal and patch tests, and drug provocation tests in the diagnosis of delayed drug hypersensitivity to metamizole.

## **MATERIAL AND METHODS**

This was a retrospective study, that analyzed clinical and diagnostic data collected through review of the medical records of patients, referred to our allergy department with suspected postoperative allergic reaction, from January 2012 to June 2022, and in whom a delayed allergic reaction to metamizole was confirmed. Reactions were classified as delayed if symptoms started more than 24 hours of metamizole administration.

Patients' data were collected from the ENDA Questionnaire regarding clinical manifestations, time between drug administration and the onset of reaction, number of postoperative reactions until diagnosis, age at first reaction, personal background of rhinitis and/or asthma, and reported hypersensitivity to other NSAID (9).

Allergological investigation was based on the results of skin tests to metamizole and DPT to metamizole as well as skin prick tests to common aeroallergens. To exclude NSAID

cross-reactivity and confirm a selective allergic reaction to metamizole, patients underwent acetylsalicylic acid (ASA) provocation test if tolerance was not known (10). Written informed consent was obtained before starting the allergological investigation. Descriptive statistics of the data was performed.

#### Atopy assessment

Skin prick tests (SPT) were performed using a battery with 23 common allergens including house dust mites, pollens, molds, animal dander and latex (Diater, Madrid, Spain). Histamine hydrochloride (10 mg/mL) and phenolated glycerol saline were used as positive and negative controls, respectively. Tests were considered positive if a wheal diameter  $> 3$  mm than the diameter of negative control was obtained. We considered atopy to be present if SPT was positive to at least one of these allergens.

#### Drug skin tests

Drug skin testing was performed according to international guidelines (11). Readings were taken at 20 minutes and additionally at 6, 48 and 96 hours. For prick tests we used the undiluted concentration of intravenous metamizole solution (400 mg/mL) and for patch tests a 10% solution of metamizole in water (12). For intradermal tests, a concentration of 4 mg/mL (1/100) was used (12). Prick tests with a wheal of at least 3 mm in diameter and intradermal tests with a papule of at least 6 mm in diameter were considered positive at 20 minutes. For delayed reactions, the presence of papular and erythematous induration in intradermal tests after 48 hours was considered positive. Verification of an eczematous-like reaction, erythema with edema, papules, vesicles, or bullae, at 48 or 96 hours in patch tests was considered a late positive reaction.

#### Drug provocation tests

Progressively higher doses of metamizole (Placebo, 25, 50, 100, 150, 250mg) and ASA (Placebo, 50, 150, 300, 500mg) were orally administered at 60-minute intervals in our day hospital, according to the DPT protocols of the department. The therapeutic dose is

reached in the first day. If after a gap of 24 hours there are no symptoms, therapeutic dose is maintained for 2 additional days.

During the first day of provocation, which took place in a day hospital, patients were closely monitored. Subsequently, symptoms surveillance was maintained on an outpatient basis for 7 days.

#### Ethical issues

The clinical part of the study as well as in vivo tests were carried out as part of the clinical routine evaluation. Patients gave oral informed consent to the use of their clinical data anonymously. The study followed the recommendations of the Ethics Committee and of the World Medical Association (Declaration of Helsinki revised in 2013).

## RESULTS

During the time of this study 88 patients with suspected perioperative allergic reactions were referred for allergological investigation, 20 patients referred for postoperative reactions. In all patients, investigation was carried out for all drugs administered during the postoperative setting, if they had not yet shown tolerance.

DDHR were reported by 10 patients, metamizole allergy being confirmed in 7 patients. In all patients, metamizole was administered intravenously. The Table II shows the demographic and clinical data of the patients with metamizole delayed hypersensitivity. Among the 7 patients with confirmed delayed allergic reaction to metamizole 4 were female. Median age at first reaction was  $62.6 \pm$  (IQR 60,64) years.

All patients described at least one previous postoperative reaction, and six patients had more than one. The number of drugs involved in the postoperative setting varied between 3 and 7. Suspected antibiotic allergy was the reason for referral in 3 patients and allergy to pantoprazole in another. Three patients were referred with no indication of a suspected drug.

All patients had maculopapular exanthema (MPE). In 5 patients the MPE was generalized. In 2 patients, the non-pruritic MPE was located on the trunk and upper limbs, evolving with intense desquamation of the hands in one patient.

MPE appeared more than 24 hours after administration of metamizole in 3 patients and more than 48 hours in 4 patients.

Only 1 patient had rhinitis and asthma with positive SPT for house dust mites.

Table III refers to metamizole skin tests and DPT.

All patients performed prick and intradermal tests and 4 patients made patch tests.

Patch tests were all negative. All patients had negative intradermal tests with metamizole, except patient 1 who had mild non-pruritic erythema in the ipsilateral upper limb at 48 hours, without injection site reaction.

In all 7 patients, metamizole DPT were positive, replicating the previous postoperative reactions. Figure 1 shows MPE after metamizole DPT in patients 4 and 1. All these DPT were positive after 24 hours, in 2 patients MPE appeared only after 5 days.

The patient with an intradermal test initially evaluated as negative (mild non-pruritic erythema in the ipsilateral upper limb and no reaction at the injection site) was also evaluated with DPT, which induced MPE with scaling of the palms (Figure 2), improving only after 15 days with antihistamines and oral corticosteroids.

Time to resolution of the reactions varied between 2 and 15 days. In 5 patients, treatment with antihistamines and oral corticosteroids was necessary for complete resolution of symptoms.

Four of the seven patients underwent ASA provocation test which was negative. The other three patients had already tolerated other NSAIDs, including ASA, after the postoperative reaction.

## DISCUSSION

Our paper describes a series of 7 patients with DDHR to metamizole: pruritic and non-pruritic MPE, generalized or limited to the trunk and upper limbs, that appeared postoperatively, more than 24-48 hours after several drugs were administered. In our patients the number of drugs varied between 3 and 7, which reflects accurately a real-world postoperative setting. All patients had previous postoperative reactions, which could have facilitated referral to a specialized allergy center, but in fact metamizole had not been previously pointed out as a possible culprit.

Although metamizole hypersensitivity is already well-known, there are not so many studies addressing delayed reactions to metamizole. Borja et al described in 2003, 3 patients with DDHR to metamizole confirmed by skin tests (13). Macias et al described

in 2007 a series of 12 patients with DDHR to metamizole but only 3 patients performed DPT (7). Blanca-Lopez et al published in 2016 a series of 137 metamizole allergic patients but only 5 patients having had a delayed reaction: MPE in 60% of these patients (12). As far as we know, the largest series on DDHR to metamizole was published in 2020, by Trautmann et al, although consisting of a retrospective analysis resulting in methodological heterogeneity and also including patients with non-selective NSAID hypersensitivity reactions (14). This German study that spanned a period of 19 years, described 239 patients with hypersensitivity reactions following metamizole administration, 69 with delayed reactions, mostly MPE; however only 13 performed DPT to confirm the DDHR to metamizole (14). In 2016, Pinho et al described a series of 14 patients diagnosed with DDHR to metamizole in a multidrug setting, in which 7 patients were diagnosed by patch test(15). It is worth mentioning that only in our study of postoperative setting and in the study by Pinho et al, it is described that the reactions that motivated the allergy study occurred in the context of multidrug administrations. Postoperative drug hypersensitivity reactions (DHR) are reactions to drugs administered after a surgical procedure. Most often DHR are immediate reactions, DDHR being much more rarely identified and reported in the postoperative setting (16–18).

Due to the multitude of different drugs administered, allergological work-up poses particular challenges and, in fact, many cases have a presumptive diagnosis only based on retrospective clinical assessments. In the investigation of many postoperative DHR skin and laboratory tests are of limited value, making DPT an important step to establish a definitive and correct diagnosis. These diagnostic difficulties are highlighted in our study by the occurrence of previous postoperative reactions to metamizole in all patients that, until a thorough allergological investigation was done, remained unsuspected.

Antibiotics are frequently involved in postoperative DHR, but it is wise to assume that any drug administered postoperatively can be the culprit. In fact, 5 of our patients had received cefazolin and/or other antibiotics, which were demonstrated to be safe by the allergological work-up.

Analgesics and NSAID were also prescribed in all our patients, and these are drugs frequently involved in DHR in any setting. Non-selective reactions are more frequently observed in NSAID hypersensitivity, and if they are demonstrated they imply the avoidance of this important group of drugs to control postoperative pain. Therefore, it was important to exclude this possibility with provocation tests with ASA and other COX-1 inhibitors. This was done in our patients, all showing tolerance to ASA and other

NSAID. On the other hand, DPT with metamizole triggered MPE in all patients, as shown in Figure 1, replicating the previous delayed reactions.

Allergologic work-up of perioperative DHR always starts with thorough history taking with the patient but it is crucial to access to the complete anaesthetic / surgical record. It is very important to document if any drugs used in the perioperative period were subsequently used and if they were tolerated or not. Latex, dyes or disinfectants should also be incorporated as a cause of immediate or delayed reactions (16,18,19).

In DDHR it is indicated to use intradermal skin tests or patch tests with readings performed at 24, 48 hours and later. Regarding the results of the skin tests, we would like to point out some differences to other studies previously mentioned. Somewhat surprisingly all our patients had negative results in intradermal tests, performed according to guidelines, except one patient with erythema on the ipsilateral upper limb but without reaction at the intradermal test site, that was therefore considered as a positive test. This is in contrast with the positivity found in 60-70% of patients with DDHR to metamizole in another studies (7,12-14). However, in these studies, if we restrict the analysis to patients with EMP, the percentage of positive intradermal tests to metamizole decreases. Two recent Spanish studies showed that only 2 out of 14 patients (15%) and 2 out of 12 patients (17%) with the suspicion of selective metamizole delayed hypersensitivity reactions had positive intradermal tests (20,21). We carried out patch tests with a 10% solution of metamizole in water on 4 patients, who had negative results. In Pinho et al study, positive patch test reactions to metamizole were observed in 7 of 14 patients, including 4 of 8 patients with MPE (15). In this study, patch tests were performed with metamizole 10% petrolatum, which may explain the discrepancy in the results of patch tests.

These results highlight the fact that it is not advisable to rely solely on skin tests in the diagnosis of DDHR to metamizole. In these very complex patients, DPT are an essential tool not only for the correct identification of the culprit drug but also for assessing tolerance to the multiple other drugs involved. In our series DPT with metamizole triggered MPE in all patients replicating the previous DDHR.

As expected, and similar to other published papers, atopy did not seem to play a role in these patients. Despite our investigation that also included latex, only one patient that also had respiratory allergy (15%) showed evidence of sensitization to aeroallergens (3).

There is a scarcity of studies analysing DDHR in the complex postoperative setting. In this way, our study is particularly relevant since it shows the importance of metamizole



as a culprit drug in DDHR in the postoperative setting. The fact that all patients underwent drug challenges with metamizole showing a reproducible DDHR pattern, adds strength to our description.

Clinical characteristics of the patients presented here, point out the challenges that postoperative drug reactions in general, and delayed postoperative reactions in particular, pose to the allergologist in charge of the investigation of these very complex patients, that in our series had already had several other previous episodes that did not lead immediately to a correct diagnosis.

As far as we know this is the largest study addressing postoperative DDHR to metamizole, a drug widely used in this context across several southern European countries due to its favourable pharmacokinetic profile. Even when other more common suspects are present, such as antibiotics or non-selective NSAID hypersensitivity, our series shows that metamizole delayed hypersensitivity needs to be considered and investigated to avoid re-expositions to metamizole while making unnecessary avoidances of “innocent” drugs.

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Table I – Main chemical groups of the different non-steroidal anti-inflammatory drugs

<b>Chemical group</b>	<b>Main drugs belonging to that group</b>
Salicylic acids	Acetyl salicylic acid, Salsalates, Salycilic acid
Acetic acids	Indomethacin, Sulindac, ketorolac, Etodolac
Propionic acids	Ibuprofen, Naproxen, Flurbiprofen, Ketoprofen
Phenylacetic acids	Diclofenac, Aceclofenac
Enolic acids	Meloxicam, Piroxicam, Tenoxicam
Fenamic acids	Mefenamic acid, Flufenamic acid
Para-aminophenol derivative	Acetaminophen
Pyridinic sulfonamide	Nimesulide
Naphtyl alkanones	Nabumetone
Pyrazolone derivatives	Metamizole, Propifenazone, Phenylbutazone
Diaryl heterocyclic acids	Celecoxib, Etoricoxib, Rofecoxib, Parecoxib, Valdecoxib

Table II - Characterization of demographic and clinical data of the patients with metamizole delayed hypersensitivity

Pts	Sex / M	Age 1 <sup>st</sup> reaction	Previous post op reactions	Clinical manifestation	Reaction time (hours)	Postoperative drugs
1	M	62	3	Nonpruritic MPE with scaling on trunk and upper limbs	> 48	CEF, ENOX, PANT, TRAM, MORF, ASA, MET
2	F	65	3	Generalized non-pruritic MPE	> 48	CEF, TRAM, MTCL, MET
3	M	62	2	Generalized pruritic MPE	> 48	PIP-TAZ, AMOX-CLAV, TRAM, PIROX, MET
4	M	58	3	Generalized pruritic MPE with scaling	> 24	NORF, CIPROF, ENOX, KET, MET
5	F	63	3	Generalized pruritic MPE	> 24	TRAM, KET, MET
6	F	45	1	Generalized nonpruritic MPE	> 24	AMOX-CLAV, TRAM, MET
7	F	83	2	Nonpruritic MPE on trunk	> 48	TRAM, MTCL, THIOC, KET, MET

Pts, patients; F, female; M, male; MPE, maculopapular exanthema; Postop, postoperative; MET, metamizole; CEF, cefazolin; ENOX, enoxaparin; PANT, pantoprazole; TRAM, tramadol; MORF, morfin; ASA, acetylsalicylic acid; MTCL, metoclopramide; PIP-TAZ, piperacillin-tazobactam; AMOX-CLAV, amoxicillin-clavulanic; PIROX, piroxicam; NORF, norfloxacin; CIPROF, ciprofloxacin; KET, Ketorolac; THIOC, thiocolchicoside

Table III - Results of the metamizole skin test and drug provocation test

Pts	Intradermal tests	Patch tests	Metamizole DPT	Reaction time after DPT (hours)	Treatment	Time to symptoms resolution (days)
1	Positive*	Negative	MPE on trunk/upper limbs with peeling palms	48h	Anti-H1; OCS	15
2	Negative	ND	MPE on trunk	72	Anti-H1; OCS	3
3	Negative	Negative	Generalized pruritic MPE	120	Anti-H1; OCS	3
4	Negative	Negative	Generalized pruritic MPE	72	Anti-H1; OCS	7
5	Negative	Negative	Generalized pruritic MPE	24	Anti-H1	2
6	Negative	ND	Generalized nonpruritic MPE	24	Anti-H1	2
7	Negative	ND	Generalized nonpruritic MPE	120	Anti-H1; OCS	5

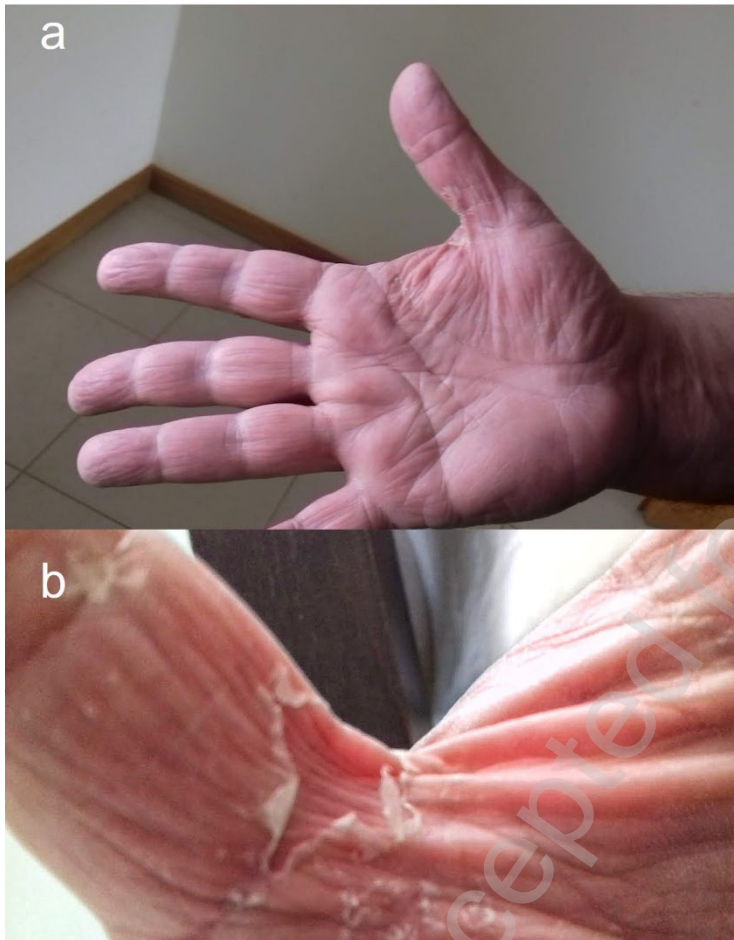
Pts, patients; DPT, Drug provocation test; MPE, maculopapular exanthema; ND, Not done; Anti-H1, 2<sup>nd</sup> generation antihistamines; OCS, oral corticosteroids

\*No reaction at injection site; erythema on the ipsilateral upper limb at 48 hours

Figure 1 - Maculopapular exanthema after metamizole provocation test; 1a - Maculopapular exanthema on the trunk of patient 4; 1b and 1c - Maculopapular exanthema on the limb and trunk of patient 1



Figure 2 - Maculopapular exanthema with peeling palms after metamizole provocation test; 2a and 2b – Aspect of intense scaling on the palms of patient 1



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