Patch testing in the investigation of non-immediate cutaneous adverse drug reactions to metamizole

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Metamizole [INN; dipyrone (BAN, USAN)] is a pyrazolone derivative and one of the most commonly prescribed analgesics worldwide (1). Along with non-steroidal anti-inflammatory drugs (NSAIDs), metamizole is very frequently involved in hypersensitivity reactions (2). Immunologically mediated hypersensitivity reactions to metamizole can be immediate (IgE-mediated) or non-immediate (T cell-mediated) (2, 3). Although immediate cutaneous adverse drug reactions (CADRs) are frequent and well known, non-immediate CADRs to metamizole, other than fixed drug eruptions, are less common and have been poorly described in the literature (3, 4). The usefulness of patch testing in the investigation of non-immediate CADRs to metamizole has not been extensively studied. The following study was performed to evaluate the value of patch testing in the setting of non-immediate CADRs imputable to metamizole.

Methods

Fourteen patients (mean age, 56.9 years; 6 males and 8 females) who had been diagnosed with non-immediate CADRs related to metamizole intake were retrospectively analysed. In these patients, patch tests were performed from 2013 to 2015, according to European Society of Contact Dermatitis/European Network for Drug Allergy guidelines (5, 6). All patients were tested with the European baseline series, with an NSAID series, and with metamizole 10% pet., prepared from the powder of Nolotil® capsules. Tests were occluded for 48 h with Finn Chambers® on Scanpor® tape, and read on day (D) 2 or

Table 1. Characterization of patients with non-immediate CADR related to metamizole intake

Age (years)/sex	Year	NI-CADR pattern	Patchtested culprits	Relevant reactions Readings at D2/D3 or D4/D7
36/M	2013	MPE	Metamizole Ceftriaxone Levofloxacin	Metamizole*, ++/++
84/M	2013	SJS	Metamizole Allopurinol	Metamizole, +/+
82/F	2013	DRESS	Metamizole Diclofenac	NRRs
82/F	2014	DRESS	Metamizole Allopurinol	Metamizole†, +/+
72/M	2014	MPE	Metamizole Cefoxitin Metronidazole	Metamizole†, ++/++
14/M	2013	DU	Metamizole Ketorolac	NRRs
81/F	2013	MPE	Metamizole Amoxicillin	NRRs
42/M	2015	MPE	Metamizole Cefoxitin Clindamycin	Metamizole, +/+
19/F	2015	MPE	Metamizole Cefatrizine Benzylpenicillin Clarithromycin Levofloxacin	Metamizole, ++/++
61/M	2015	DRESS	Metamizole Amoxicillin Imipenem Vancomycin	Metamizole†, ++/+ Amoxicillin, ++/++
74/M	2015	DU	Metamizole Cefuroxime	NRRs
32/F	2015	MPE	Metamizole Flupirtine	NRRs
57/F	2015	MPE	Metamizole Etodolac	NRRs
60/F	2015	MPE	Metamizole Flupirtine Etodolac	NRRs

DRESS, drug reaction with eosinophilia and systemic symptoms; DU, delayed urticaria; F, female; M, male; MPE, maculopapular exanthema; NI-CADR, non-immediate cutaneous adverse drug reaction; NRR, non-relevant reactions; SJS, Stevens–Johnson syndrome.

*Biopsy of the test.

†Positive accidental reintroduction.

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D3 and D4 to D7. Nineteen persons exposed to other analgesics or NSAIDs, and 35 patients without analgesic exposure, were tested with the same metamizole preparation as controls.

Results

Positive patch test reactions to metamizole were observed in 7 of 14 patients (mean age, 56.6 years; 4 males and 3 females) (Table 1). These included 4 of 8 patients with maculopapular exanthema, 2 of 3 patients with drug reactions with eosinophilia and systemic symptoms (DRESS), and 1 patient with Stevens–Johnson syndrome (SJS); neither of the 2 patients with delayed urticaria reacted to metamizole. In all cases, there was another possible culprit: in 7 cases, antibiotics (mainly β-lactams); in 5 cases, other analgesics or NSAIDs; and in 2 cases, allopurinol. Two of the patients who showed positive patch test reactions to metamizole had experienced a positive accidental re-exposure. One patient with DRESS reacted to both metamizole and amoxicillin. In this patient, skin biopsies of the positive patch test reactions to metamizole and to amoxicillin showed histopathological features of allergic contact reactions. Similar histopathological features were observed for another positive patch test reaction to metamizole in a patient with DRESS. No further culprit was identified by patch testing in the patients who did not react to metamizole in the patch test. None of the 54 controls reacted to the same metamizole preparation.

Discussion

The occurrence of a positive patch test reaction to metamizole exclusively in suspected cases, namely 2 with a positive re-exposure and 2 with histopathology compatible with a T cell-mediated reaction, shows that metamizole can be involved in non-immediate CADRs. Thus, patch testing can be considered to be an important tool with which to investigate these reactions, as shown in a previous study showing positive patch test reactions to metamizole in 4 of 11 (36%) patients with non-severe non-immediate CADRs (4). In our series, patch testing was also useful for confirming drug imputability in 3 of 4 (75%) patients with severe CADRs, such as DRESS or SJS. Metamizole is rarely considered to be the main culprit in non-immediate CADRs, especially when other drugs such as antibiotics, other NSAIDs or allopurinol are also possible culprits. As we were able to collect 7 cases in a single department in the course of 3 years, we suspect that the role of metamizole in non-immediate CADRs is often overlooked.

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References

1 Kötter T, da Costa B R, Fässler M et al. Metamizole-associated adverse events: a systematic review and meta-analysis. *PLoS One* 2015: **10**: e0122918.

2 Ariza A, García-Martín E, Salas M et al. Pyrazolones metabolites are relevant for identifying selective anaphylaxis to metamizole. *Sci Rep* 2016: **6**: 23845.

3 Kowalski M L, Asero R, Bavbek S et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013: **68**: 1219–1232.

4 Macías E, Ruiz A, Moreno E et al. Usefulness of intradermal test and patch test in the diagnosis of nonimmediate reactions to metamizol. *Allergy* 2007: **62**: 1462–1464.

5 Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015: **73**: 195–221.

6 Brockow K, Garvey L H, Aberer W et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013: **68**: 702–712.

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