

Short communication

Usefulness of intradermal test and patch test in the diagnosis of nonimmediate reactions to metamizol

Background: Metamizole is a pyrazolone derivative, and its most common reactions are IgE-mediated reaction and idiosyncratic reactions. Non-immediate reactions are poorly described and there are very few reports on non-immediate reactions to pyrazolones.

Materials and methods: We evaluated 12 patients (nine men) who consulted for a non-immediate reaction after metamizol administration. We performed cutaneous tests (skin prick tests and immediate and delayed intradermal tests) and epicutaneous tests, and, if necessary, an oral challenge test.

Results: All skin prick and intradermal tests, if necessary, were negative in immediate reading. Delayed intradermal tests were positive in six of 10 patients (60%) and epicutaneous tests were positive in four of 11 patients (36%). Three cases (25%), were diagnosed by a positive oral challenge test.

Discussion: Delayed-reading intradermal tests and patch tests are useful tools in the diagnosis of nonimmediate reactions to pyrazolones and should be considered the first step when evaluating these type of reactions. Intradermal test appears to be more sensitive than patch test. The positivity of skin tests suggests an immunological reaction, probably mediated by T lymphocytes, but further studies are required.

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Key words: metamizol; nonimmediate reaction;
pyrazolones.

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Accepted for publication 9 June 2007

Metamizol is a pyrazolone derivative, with analgesic, antipyretic and spasmolytic properties. Its use is widespread in Spain, for its favorable pharmacokinetic characteristics, and its antalgic effect similar to low doses of opiates. Furthermore, it is almost devoid of hemorrhagic complications and has a slight relaxing action on soft muscles. However, its use in many countries is considered in severe pain when no alternative is suitable because metamizol is associated with an increased risk of agranulocytosis and with shock. It is also the analgesic that most frequently causes hypersensitivity reactions (1, 2). The most common reactions are IgE-mediated reactions and idiosyncratic reactions, although nonimmediate reactions have also been described, including severe cutaneous reactions, such as Stevens–Johnson syndrome or necrotic epidermolysis (3) and other delayed reactions such as fixed drug eruption and contact dermatitis (4). Nonimmediate reactions are poorly described and there are very few reports on nonimmediate reactions to pyrazolones (5–9).

Cases, materials and results

We evaluated 12 patients (nine men) who consulted for a nonimmediate reaction following metamizol administra-

tion. All patients had tolerated metamizol before the reaction. Mean age was 55.7 years and their reaction had occurred between 2 hours and 35 days after first dose of treatment (Table 1).

Most of the reactions consisted of generalized maculopapular exanthemas, although one patient presented symptoms compatible with fixed drug eruption and another presented lesions of the oral mucosa. The time in which the maculopapular exanthemas resolved ranged from 24 h to a week. In the last reactions, the time of resolution was superior to a week.

Cutaneous tests were performed in accordance with the EAACI recommendations (10). Skin prick tests were performed with metamizol at 400 mg/ml. Intradermal reaction tests were performed with an 1 : 10 dilution. Histamine was used as a positive control and normal saline as a negative control. Patch tests were performed with a 10% solution of metamizol in water. The immediate reading of skin prick and intradermal test were performed at 20 min and delayed intradermal reading at 24 and 48 h. Skin prick tests were considered positive when the diameter was > 3 mm. Intradermal tests were considered positive when there was erythema and an increase in diameter by 3 mm or greater and on delayed reactions when there was an infiltrated erythematous reaction. An erythema, wheal or vesicles were considered

Table 1. Characteristics of the patients and reactions

Patient	Gender	Age	Clinical manifestations	Latency time	Days of treatment
1	M	73	Squamous erythematopapular exanthema	Unknown	3 days
2	M	42	Confluent maculopapular eruption. Facial edema and ulcerated lesions in oral mucosa	Unknown	35 days
3	F	33	Pruriginous squamous generalized maculopapular exanthema	10 h	1 day
4	M	56	Pruriginous generalized maculopapular exanthema	2 h	2 days
5	M	65	Pruriginous generalized maculopapular exanthema	Unknown	4 days
6	M	61	Fixed exanthema in lower limbs	Unknown	2 days
7	M	79	Pruriginous generalized maculopapular exanthema predominant in trunk	Unknown	4 days
8	M	22	Pruriginous squamous generalized maculopapular exanthema, fever, increase of transaminases	Unknown	2 days
9	M	78	Pruriginous generalized maculopapular exanthema predominant in trunk	6 h	3 days
10	M	54	Erythema and itching on the trunk	3–4 h	1 day
11	F	55	Maculopapular exanthema in the trunk	5–10 h	2 days
12	F	51	Maculopapular exanthema in the trunk	10 h	1 day

Table 2. Results of prick, intradermal, patch and oral challenge tests

Patient	IDR (area mm)		Patch test		Oral challenge
	24 h	48 h	48 h	96 h	
1. Maculopapular exanthema	8	7	NP	NP	NP
2. Maculopapular exanthema, ulceration of the mucosa	NP	NP	++	++	NP
3. Maculopapular exanthema	7	7	(–)	(–)	NP
4. Maculopapular exanthema	9	5	++	+	NP
5. Maculopapular exanthema	(–)	(–)	(–)	(–)	Exanthema at 48 h
6. Fixed exanthema	(–)	(–)	(++)	(++)	NP
7. Maculopapular exanthema	Erythema 20/20	Erythema 15/10	(–)	(–)	NP
8. Hypersensitivity syndrome	(–)	(–)	(++)	(++)	NP
9. Maculopapular exanthema	(–)	7/7	(–)	(–)	NP
10. Maculopapular exanthema	(–)	(–)	(–)	(–)	Exanthema at 4 h
11. Maculopapular exanthema	6	7	(–)	(–)	NP
12. Maculopapular exanthema	(–)	(–)	(–)	(–)	Exanthema at 8 h

IDR, intradermal test; NP, not performed.

as positive in delayed reading. Patch tests were read at 48 and 96 h. If skin and patch tests were negative, a single blind oral challenge with progressive doses of metamizol up to 575 mg was performed.

All skin prick tests and intradermal tests in immediate reading were negative. Intradermal tests were positive in six of 10 patients (60%) and epicutaneous tests were positive in four of 11 patients (36%). In three cases (25%), an oral challenge test was necessary to reach a diagnosis. All patients developed an exanthematic reaction after drug intake that resolved within 24–48 h. The patients responded positively to intradermal test with metamizol with a mean area wheal between 7 and 10 mm, surrounded by erythema after 24 and 48 h. One patient showed isolated erythema at 24 h, which remained after 48 h (Table 2).

Discussion

Dipyrone has more than 20 known metabolites (11), although their allergenic molecules have not been properly characterized. There are very few studies that have analyzed the immunogenic potential of the pyrazolone

and pyrazolidone metabolites (12, 13). Immediate reactions are more frequent and better known. In these cases, cutaneous tests and *in vitro* tests (FAST and CAST) have been proven useful (14). Nonimmediate reactions, however, are less frequent and less studied (5–9).

In our study, intradermal tests with delayed reading and patch tests were useful for diagnosis in nonimmediate reactions to metamizol, with a percentage of positive results for intradermal tests of 60% and 36% for patch tests. Similar results have been obtained in the evaluation of nonimmediate reactions to beta-lactam antibiotics (15). Nevertheless, in 25% of patients, an oral challenge test was necessary to reach diagnosis. All reactions were mild and reproduced the original reaction. The positivity of skin tests could indicate an immunological reaction, probably mediated by T lymphocytes.

In conclusion, delayed-reading intradermal tests and patch tests are useful tools in the diagnosis of nonimmediate reactions to pyrazolones and should be considered the first step when evaluating this type of reactions. Intradermal test appears to be more sensitive than patch test. Patients with mild symptoms, but negative allergologic work up, can be subjected to provocation tests.

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