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IgE-mediated metamizol allergy and the usefulness of the cellular allergen stimulation test

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Summary

Metamizol is a pyrazolone-derivative nonsteroidal anti-inflammatory drug that is commonly associated with hypersensitivity reactions. Some of these reactions are IgE-mediated and potentially severe, which limits the diagnosis based on oral drug challenge. We describe 6 selective metamizol hypersensitivity cases, regarding clinical evaluation and diagnosis management, with focus on the usefulness of skin tests and the cellular allergen stimulation test (CAST). All patients were female, aged 27 to 50 years old. All had immediate reactions after metamizol administration: 3 had anaphylaxis and 3 had urticaria and angioedema. Skin prick tests with metamizol were positive in 2 patients. Intradermal tests were positive in the remaining, all with 1/100 dilution, and elicited systemic reactions in 2 of them. CAST to metamizol was negative in all cases. The patients tolerated other nonsteroidal anti-inflammatory drugs. Skin tests proved to be a good diagnostic method to identify IgE-mediated metamizol allergy, although skin tests elicited systemic symptoms in some cases. Despite this being a small sample, our results showed a very low sensitivity for CAST, which differs from data previously reported in the literature.

Introduction

Hypersensitivity to acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) is widely believed to be associated with a nonallergic mechanism, with the inhibition of the cyclo-oxygenase (COX) enzyme playing a central role (1). COX-1 inhibition leads to decreased release of protective prostaglandin E2 and in this way to an increase of unrestrained synthesis of sulphidoleukotrienes LTC4, LTD4, and LTE4, and release of other mediators by mast cells. Nevertheless, in some patients, a specific immunoglobulin E (IgE) mechanism has been proposed (2-4). These patients are generally single responders, having good tolerance to other NSAIDs from the same group or from different groups (5, 6). Pyrazolones are the most common NSAIDs involved in these immediate hypersensitivity reactions (7-9). Some of the pyrazolones induced reactions are potentially severe, which limits oral drug challenge. Intradermal tests also carry the potential risk of side effects, and can provoke large local (both immediate and late) and systemic reactions which range in incidence from 0.02% to 1.4% of patients tested (10). This being the case, in vitro tests would be of great value.

For the last 20 years, there was no in vitro diagnostic test for NSAIDs hypersensitivity (1). However, since 1993, the advent of a new sulphidoleukotriene-release test, the cellular allergen stimulation test (CAST), has been seen as an option (11-13). It is based on the determination of sulphidoleukotrienes (LTC4, LTD4, LTE4) produced by IL-3 primed basophils stimulated by allergens in vitro. This

method enables the diagnosis of immediate allergic reactions to drugs without the risks of in vivo tests. Furthermore, cellular tests are seen as candidates to replace oral challenges, since the stimulation of IgE-loaded basophils in vitro is, in principle, more representative of the pathophysiologic process occurring in vivo than simple determination of serum IgE concentrations. Prior data suggested that CAST could be a reasonable alternative in patients with metamizol hypersensitivity (13, 14).
More recently, flow-cytometric evaluation of basophil activation (flow-cytometric allergen stimulation test - Flow CAST, also known as basophil activation test - BAT) (15) has opened up new perspectives (16, 17), but unfortunately it is not yet available for clinical use in many centers.
Our aim is to describe 6 selective metamizol hypersensitivity cases, regarding clinical evaluation and diagnosis management, with focus on usefulness of available in vivo (skin tests) and in vitro (CAST) tests.

Description of cases

Case 1: A 47-year-old female, with prior history of mint allergy (18), had 2 anaphylactic reactions to metamizol. The first episode occurred 30 minutes after oral administration of 575mg of metamizol and was resolved in emergency room (ER) with intramuscular adrenaline, intravenous (IV) steroid and H1-antihistamine (AH). The second episode, which included loss of consciousness, occurred 4 months later, immediately after IV administration, and was treated with intramuscular adrenaline, IV steroid and AH. The patient's clinical history revealed that she tolerated paracetamol; oral challenges performed to other NSAIDs (diclofenac, ibuprofen and meloxicam) were negative.
Case 2: A 32-year-old female, with prior history of allergic rhinitis, sensitized to mites (*Dermatophagoides pteronyssinus* and *Lepidoglyphus destructor*) and dog, started generalized urticaria and facial edema 20 minutes after oral administration of 575mg of metamizol, which resolved after IV steroid and AH in the ER. The patient's clinical history revealed that she tolerated ASA, ibuprofen and paracetamol.
Case 3: A non-atopic 50-year-old female started generalized urticaria, edema of the tongue and dysphonia 15 minutes after oral administration of 575 mg of metamizol, which was resolved in the ER with IV steroid and AH. The patient's clinical history revealed that she tolerated ibuprofen and paracetamol.
Case 4: A non-atopic 45-year-old female started generalized urticaria, rhinitis and edema of the lips, 15 minutes after oral administration of 575 mg of metamizol, which spontaneously disappeared in 2 hours. The patient's clinical history revealed that she tolerated ASA, ibuprofen, meloxicam and paracetamol.
Case 5: A 27-year-old female, with prior history of minocycline hypersensitivity, had an anaphylactic reaction 15 minutes after oral administration of 575 mg of metamizol, which was resolved in the ER with intramuscular AH and IV steroid. The patient's clinical history revealed that she tolerated paracetamol; oral challenges performed to other NSAIDs (ibuprofen and meloxicam) were negative.
Case 6: A 42-year-old female, with prior history of allergic rhinitis, sensitized to mites (*Dermatophagoides pteronyssinus* and *Blomia tropicalis*) and olive pollen, went into anaphylactic shock 15 minutes after ingestion of 575 mg of metamizol, which was resolved in the ER with intramuscular adrenaline, IV steroid and AH. Oral challenges performed to other NSAIDs (ibuprofen, meloxicam and paracetamol) were negative.
Diagnostic procedures and results are presented in Table 1. Skin prick tests to metamizol (concentration 0.4 g/mL) were positive in 2 patients (1 and 6). When negative, intradermal tests were performed starting with 1/1000 dilution. Intradermal tests were positive in the remaining 4 patients, all with 1/100 dilution, and elicited systemic reactions in 2 of them (33% of the sample): in case 4, rhinitis, facial and back itching and rash on the neck started 17 minutes later; in case 5, oropharyngeal itching and rash on the back occurred 10 minutes after intradermal test. Both cases resolved with 10mg of cetirizine. CAST (Bühlmann Laboratories®, Schönenbuch, Switzerland) was negative in all patients. Skin tests and CAST were performed, in all cases, between 6 weeks and 1 year after the clinical reaction to metamizol.

Discussion

Pyrazolone-derivatives hypersensitivity reactions are classically separated into two groups based on their mechanism (2, 7), although some variations have also been described (6). In the group of allergic type reactions, these are most likely IgE-mediated (4, 19), and can be life-threatening. They are usually limited to a single pyrazolone drug or two drugs chemically closely related (e.g. metamizol and aminophenazone), and this strict clinical specificity is corroborated by results in experimental animals (20). Skin tests with the incriminated drug are generally positive. In

Table 1 - Clinical characteristics and results from diagnostic procedures of the 6 patients with IgE-mediated metamizol hypersensitivity.

Patient	Sex	Age	Prior history	Threshold dose	Time until symptoms	Symptoms	SPT	Intradermal tests	CAST
Case 1	F	47	Mint allergy	575 mg oral	30 min	2 anaphylactic reactions: - generalized urticaria, glottis edema with respiratory distress	Positive (11x7 mm)	Not done	Negative
				2000 mg IV	Immediately (<5 min)	- generalized urticaria, hands edema, wheezing and loss of consciousness			
Case 2	F	32	Allergic rhinitis	575 mg oral	20 min	Generalized urticaria, facial edema	Negative	Positive (11x9 mm) with 1/100 dilution	Negative
Case 3	F	50	None	575 mg oral	15 min	Generalized urticaria, tong edema, dysphonia	Negative	Positive (12x9 mm) with 1/100 dilution	Negative
Case 4	F	45	None	575 mg oral	15 min	Generalized urticaria, palms and soles itching, rhinitis, lip edema	Negative	Positive (9x7 mm) with 1/100 dilution – systemic symptoms	Negative
Case 5	F	27	Minocycline hypersensitivity	575 mg oral	15 min	Generalized malaise, face and neck flushing, pharyngeal itching, wheezing	Negative	Positive (6x5 mm) with 1/100 dilution – systemic symptoms	Negative
Case 6	F	42	Allergic rhinitis	575 mg oral	15 min	Generalized urticaria, facial, hands, feet, ears and lips edema, dysphonia, wheezing and loss of consciousness	Positive (5x5 mm)	Not done	Negative

CAST: cellular allergen stimulation test; F: female; IV: intravenous; min: minutes; mm: millimeters; SPT: skin prick tests.

about 90% of patients other NSAIDs can be taken with good tolerance (6), and asthma is present only in about one-fourth of patients (19).

All the patients reported in this study had immediate reactions to metamizol and in all, the mechanism was confirmed to be IgE mediated by means of positive skin tests. The identification of an IgE-mediated mechanism points to the absence of cross-reactivity with other NSAIDs, and so their avoidance is unnecessary. In fact, all our patients tolerated other NSAIDs, diagnosed either by prior exposure or oral challenges.

In this sample, skin tests proved, as expected, to be a good diagnostic method for IgE-mediated metamizol allergy, although physicians should be alert as symptoms after skin tests seem to be commoner than previously reported (33%). Therefore, these diagnostic procedures should only be performed in hospital setting by experienced allergists. We tried to understand if in centers where these conditions are not met, CAST could be a reliable in vitro tool for diagnosis. However, in our sample, as has also been pointed out by other authors (21), CAST showed a very low sensitivity, being negative in all cases. These results

differ from data previously reported by Gamboa PM et al (14) which found a sensitivity of 52% and a negative predictive value of 99.5% for CAST to metamizol. More studies are needed to evaluate these discrepancies.

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