LETTER TO THE EDITOR

Selective hypersensitivity to metamizole: role of specific IgE in the evaluation of immediate reactions

Josefina Vieira[1,2#], Sofia Cosme Ferreira[1,2#], Diana F. Santos[3,4], Marisa Paulino[2], Susana L. Silva[2,3,5]

[1]Serviço de Imunoalergologia, Hospital Dr. Nélio Mendonça, SESARAM, Funchal, Portugal
[2]Serviço de Imunoalergologia, Unidade Local de Saúde de Santa Maria, Lisbon, Portugal
[3]GIMM - Gulbenkian Institute for Molecular Medicine, Lisbon, Portugal
[4]Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
[5]Clínica Universitária de Imunoalergologia, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
#Authors contributed equally to this work

Key words

Metamizole; SNIUAA; NSAIDs hypersensitivity; specific IgE; drug allergy.

To the Editor,

Single nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria/angioedema/anaphylaxis (SNIUAA) is an immunologically mediated response induced by a single drug/drug group within the first hour after drug intake. SNIUAA accounts for 25–30% of all NSAID hypersensitivity reactions. Pyrazolones, metamizole included, are among the most common culprit drugs (1-2). Patients with metamizole-SNIUAA typically tolerate other chemically unrelated compounds, including strong COX-1 inhibitors (1).

Metamizole-SNIUAA diagnosis is based on detailed anamnesis combined with skin testing and drug provocation test, which remains the gold standard (3). Intradermal testing is a suitable method for metamizole allergy diagnosis (4). However, skin testing sensitivity is ≤50% (3, 5), carries a risk of eliciting systemic reactions (1) and is time consuming. On the other hand, *in vitro* tests for pyrazolones hypersensitivity also feature moderate sensitivity, namely Basophil Activation Test – BAT (up to 42.3-65%) and Cellular Allergen Stimulation Test – CAST (up to 52%) (5-7). Importantly, studies addressing serum specific IgE (sIgE) to pyrazolones, have only accounted for pyrazolone derivatives (8-9).

We aimed to establish the sensitivity and specificity of metamizole-sIgE determination in serum, in patients with selective hypersensitivity to metamizole. We included 18 patients followed in a tertiary Allergy Centre, with metamizole-SNIUAA diagnosis based on consistent history of allergic reactions within the first hour after metamizole intake (at least two episodes,

or one episode with positive skin testing); in association with negative drug provocation test with acetylsalicylic acid (ASA) or self-reported good tolerance to other strong COX-1 inhibitors. Patients with cross-intolerance to different NSAIDs or with delayed reactions after NSAIDs intake were excluded. As controls, we selected age and gender-matched subjects, with good tolerance to both metamizole and ASA/another strong COX-1 inhibitor. Demographic characterization of patients and controls, as well as clinical and skin tests details supporting metamizole-SNIUAA diagnosis are presented in Table I.

Skin prick tests were performed with 400mg/mL metamizole (1:1), and 1:1000, 1:100 and 1:10 dilutions were used in intradermal tests (10). Only patients were submitted to skin tests, given the risk of sensitization. In our cross-sectional evaluation, skin tests were positive in 9/18 patients, and interestingly, 3 other patients (patient 2, 8 and 11) reported positive skin tests in a previous evaluation more than 12 months before.

Metamizole-sIgE was determined in serum (ELISA System, Astra Biotech), being detectable ($\geq$0.35 kU/L) in 4/18 patients and 1/13 controls. Patients with positive metamizole-sIgE were all atopic and featured significantly higher median total serum IgE than those with undetectable sIgE (respectively 756 [465-1314] kU/L and 54.7 [27.2-111.5] kU/L; $p<0.01$). No other significant difference was found between the 2 groups regarding demographic features, clinical evaluation or allergy tests (Table II).

We then compared the performance of metamizole-sIgE with BAT and CAST to metamizole, obtained in patients and controls (Supplementary Table 1). Serum metamizole-sIgEs featured the highest specificity (92%), in comparison with BAT (54%) and CAST (40%). We thus highlight the high positive predictive value of metamizole-sIgE (80%), which might allow to waive the need for further *in vivo* evaluation in selected cases.

On the other hand, sIgEs featured the lowest sensitivity (22%), as compared with BAT (71%) and CAST (59%), mirroring current literature on the subject (5-7). Future studies should consider including pyrazolone metabolites in this assay, to improve sensitivity of serum sIgE assay in metamizole-SNIUAA diagnosis (9). In addition, it is noteworthy that, in our patients, sensitivity of skin tests combined with metamizole-sIgEs determination improved up to 79%.

Determination of sIgEs in serum is a widely accessible technique, easier to standardize and less time-consuming than other *in vitro* tests available to investigate drug-induced hypersensitivity. Although in a limited sample, our extensive evaluation of patients with metamizole-SNIUAA argues in favour of the combined use of skin testing and serum metamizole-sIgE determination when investigating this condition.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Table I. Patient and control groups' characterization: reaction severity, skin testing and laboratory evaluation.

	Gender [Age], years	Atopy	Reactions to metamizole			Skin Tests			
			Number	Type/severity*	Last reaction, months**	Result	Maximum dilution positive	Total serum IgE, KU/L	Metamizole-sIgE, KUA/L
Patient Group									
1	**F [51]**	**Yes**	**1**	**Anaphylaxis grade 3**	**5**	**+**	**PT 400mg/mL**	**1003**	**6.83**
2	F [57]	No	1	Urticaria	60	- (#)	-	110	<0.10
3	F [50]	No	2	Urticaria	13	N/A	N/A	16.7	<0.10
4	F [56]	No	2	Anaphylaxis grade 4	108	+	IDT 40mg/mL	52.6	<0.10
5	F [52]	No	2	Anaphylaxis grade 5	46	+	IDT 40mg/mL	98.8	<0.10
6	F [67]	No	2	Anaphylaxis grade 3	85	+	IDT 40mg/mL	56.7	<0.10
7	F [41]	No	1	Urticaria + angioedema	7	+	IDT 0.4mg/mL	112	<0.10
8	**F [59]**	**Yes**	**1**	Anaphylaxis grade 3	**90**	N/A (#)	N/A	**509**	**1.77**
9	**F [51]**	**Yes**	**2**	**Urticaria**	**216**	**-**	**-**	**2247**	**3.25**
10	M [42]	No	2	Anaphylaxis grade 5	60	N/A	N/A	132	<0.10
11	F [37]	No	1	Anaphylaxis grade 5	50	- (#)	-	4.7	<0.10
12	F [48]	No	1	Urticaria	11	+	IDT 40mg/mL	202	<0.10
13	F [29]	No	1	Anaphylaxis grade 5	17	+	IDT 4mg/mL	33	<0.10
14	F [48]	No	1	Anaphylaxis grade 5	11	+	PT 400mg/mL	149	<0.10
15	F [57]	No	1	Urticaria	108	+	IDT 40mg/mL	7.1	<0.10
16	F [61]	No	2	Anaphylaxis grade 5	180	-	-	33.2	<0.10

17	F [41]	Yes	2	Anaphylaxis grade 5	56	N/A	N/A	25.3	<0.10
18	**M [63]**	**Yes**	**2**	Anaphylaxis grade 3	**43**	**-**	**-**	**334**	**0.49**
Control Group									
1	M [73]	No						89.2	<0.10
2	**F [28]**	**Yes**						**120**	**0.40**
3	F [46]	No						16.3	<0.10
4	F [43]	No						18.1	<0.10
5	F [66]	No						314	0.31
6	F [59]	No						214	<0.10
7	M [56]	No						43.9	<0.10
8	F [48]	Yes						82.7	<0.10
9	F [49]	No						38.6	<0.10
10	F [46]	No						8.3	<0.10
11	M [28]	Yes						631	<0.10
12	M [60]	Yes						335	<0.10
13	M [21]	Yes						221	<0.10

Abbreviations: F – female; M – male; PT – prick test; IDT – intradermal test; IgE - immunoglobulin E; sIgE - specific IgE; + positive; - negative; N/A – not assessed; *Anaphylaxis Severity Scale for WAO Anaphylaxis Guidance 2020. **time since last reaction. (#) Patients with positive skin tests to metamizole reported in clinical files more than 12 months before inclusion.
Reference values: sIgE < 0.35 KUA/L; total serum IgE <100 kU/L

Table II. Comparison between Metamizole-SNIUAA patients with positive and negative sIgE: skin testing and laboratory evaluation.

	N	Age mean±SD, years	Female %	Atopy %	Last reaction median [IQR], months	Positive skin test %	Total serum IgE median [IQR], kU/L	Metamizole-sIgE median [IQR], kU/L
Positive sIgE	4	56±6	75	100	67 [34-122]	25	**756 [465-1314]**	2.5 [1.5-4.1]
Negative sIgE	14	49±10	93	7	53 [14-79]	57	**54.7 [27.2-111.5]**	<0.10

Abbreviations: N – number; % - percentage; SD – standard deviation; IQR – interquartile range; ST – skin test; sIgE - specific immunoglobulin E**.** Reference values: sIgE < 0.35 KU/L; total serum IgE <100 kU/L.

Supplementary Table 1. *In vitro* tests for metamizole-induced Hypersensitivity – complementary Basophil Activation Test (BAT) and Cellular Allergen Stimulation Test (CAST).

Case number	**Total serum IgE**, KU/L	**sIgE**, KUA/L	**BAT**, %	**CAST**, pg/mL
Patient Group				
1	**1003**	**6.83**	**34**	**154**
2	110	<0.10	<1	13
3	16.7	<0.10	22	68
4	52.6	<0.10	37	84
5	98.8	<0.10	N/A	N/A
6	56.7	<0.10	16	39
7	112	<0.10	51	220
8	**509**	**1.77**	**8**	**53**
9	**2247**	**3.25**	**13**	**<1**
10	132	<0.10	6	<1
11	4.7	<0.10	100	258
12	202	<0.10	<1	<1
13	33	<0.10	73	149
14	149	<0.10	100	220
15	7.1	<0.10	21	612
16	33.2	<0.10	19	56
17	25.3	<0.10	<1	<1
18	**334**	**0.49**	**11**	**41**
Control Group				
1	89.2	<0.10	9	25
2	**120**	**0.40**	**28**	**177**
3	16.3	<0.10	13	165
4	18.1	<0.10	25	84
5	314	0.31	100	597
6	214	<0.10	<1	<1
7	43.9	<0.10	<1	<1

8	82.7	<0.10	59	97
9	38.6	<0.10	100	178
10	8.3	<0.10	<1	<1
11	631	<0.10	<1	N/A
12	335	<0.10	<1	N/A
13	221	<0.10	<1	N/A

Abbreviations: F – female; M – male; IgE - immunoglobulin E; sIgE - specific immunoglobulin E; + positive; - negative; N/A – not assessed. Reference values: sIgE < 0.35; total serum IgE <100 kU/L; BAT <10%, CAST <50pg/mL. CAST® ELISA BÜHLMANN Laboratories AG, Switzerland. Flow CAST® (CCR3, CD63) BD Biosciences, USA.