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RESEARCH LETTER

Metamizole-induced reactions as a paradigm of drug hypersensitivity: Non-allergic reactions, anaphylaxis, and delayed-type allergy

To the Editor

Metamizole belongs to the group of non-opioid analgesics, and as for other non-steroidal anti-inflammatory drugs (NSAID) such as acetylsalicylic acid, diclofenac, or ibuprofen, both isoforms of cyclooxygenase are inhibited. Metamizole is an important trigger of non-allergic and allergic hypersensitivity reactions and has been withdrawn from the United States, Australian, and UK market due to the risk of agranulocytosis, but is still available and broadly used in many countries of Europe, Central and South America, and Asia.

We retrospectively evaluated clinical and diagnostic data from 239 consecutive patients with metamizole hypersensitivity over a period of 19 years; Table S1 shows baseline clinical parameters. Metamizole anaphylaxis was diagnosed in 75 patients (31.4%), non-allergic immediate hypersensitivity in 95 (39.7%), and delayed reactions in 69 (28.9%). (Table 1, Figure 1). The number of diagnoses per year steadily increased from 2000 to 2019 along with the prescription numbers of metamizole in Germany, which almost doubled between 2008 and 2017[1] (Figure S1A,B). The unbroken and even growing popularity of metamizole possibly reflects its otherwise favourable safety profile including a comparatively low renal, gastrointestinal, and hepatic toxicity. Indications for metamizole include severe pain following surgery or serious trauma, colic, tumour pain, and high fever. Beyond these clear-cut indications, metamizole is also used for mild and moderate pain, though alternatives with a better safety profile are available. This is in accordance with our observation of an uncritical use of metamizole for the treatment of back and joint pain (20.5%) or headache (20.5%) (Table S1).

Sixty-five out of 75 patients with metamizole anaphylaxis had a history of moderate to severe symptoms (86.7%) (Table 1; the classification of anaphylaxis is detailed in Table S2). In a mild reaction found in 10 of our 75 anaphylaxis patients (13.3%), urticaria was the most prominent feature. In more than half of the anaphylaxis cases (n = 43), the reaction occurred within 5 minutes after administration of metamizole, 66 reactions (88.0%) set in within 30 minutes, and all occurred within the first hour (Table 1). Positive results in prick and intradermal testing and in basophil activation tests suggest that anaphylactic reactions to metamizole are mediated by specific IgE antibodies.[2,3] Unmetabolized metamizole in the circulating blood is measurable for a maximum of 15 minutes following intravenous administration and cannot be detected upon oral intake due to immediate hydrolysis into the active moiety 4-methylaminoantipyrine.[4] The latter may bind to cellular or serum proteins, resulting in a complex capable to activate the immune system. The antigenic determinant is to date unknown; however, certain metamizole metabolites increase the sensitivity of basophil activation testing.[5]

Of the 69 patients with delayed reactions, 37 suffered from measles-like exanthem (53.6%), and 15 developed a fixed drug eruption (FDE) (21.7%) (Table 1). A small number of patients were diagnosed with a manifestation of the Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) spectrum (n = 5), drug reaction with eosinophilia and systemic symptoms (DRESS) (n = 4), flexural exanthem (n = 3), or agranulocytosis (n = 5). Delayed metamizole exanthem likely results from a T cell-mediated immune response, supported by the immuno-histological finding of infiltrates of activated T cells.[6,7] Several of our patients reported initial signs of the delayed reaction already within 12 hours after first intake of metamizole (Table 1). Data from medical history, however, are to a certain extent subjective, which may explain the contrast to the statement that delayed reactions regularly occur after 24-48 hours.[8]

Skin testing was performed according to international guidelines and included reading at 15 minutes in immediate reactions and additional readings on days two, three, and four in delayed reactions. The original concentration of an intravenous metamizole solution (500 mg/mL) was used for patch and prick testing, a dilution of 1:100 (5 mg/mL) for intradermal testing. A wheal of at least 3 mm in diameter with surrounding erythema was considered a positive prick test result, and a wheal of at least 6 mm was considered positive in intradermal testing. An erythematous and infiltrated plaque or eczematous lesion clearly visible and palpable on days two, three, and four was assessed as a positive delayed-type skin test reaction. Test results of the 239 patients with metamizole hypersensitivity are depicted in Table S3. Thirty-one patients with a delayed reaction showed a positive intradermal test result. In 10 cases, only the patch test yielded a positive result, whereas both prick and intradermal testings remained negative. Ten patients diagnosed as SJS/TEN spectrum (n = 5) or agranulocytosis

TABLE 1 Clinical symptoms and time interval between administration of metamizole and first symptoms

	Immediate reaction (n = 170)		
	Urticaria/AERD (n = 95)	Anaphylaxis (n = 75)	Delayed reaction (n = 69)
Immediate reaction			
NSAID-induced urticaria	27	n.a.	
NSAID-exacerbated urticaria	34		
AERD	34		
Mild anaphylaxis	n.a.	10	n.a.
Moderate anaphylaxis		38	
Severe anaphylaxis		27	
Delayed reaction			
Measles-like exanthem	n.a.	n.a.	37
Flexural exanthem			3
Fixed drug eruption			15
SJS/TEN			5
DRESS			4
Agranulocytosis			5
Time interval from administration of metamizole to first symptoms			
<1 min	0	5	n.a.
>1-5 min	7	38	
>5-30 min	35	23	
>30 min-1 h	30	7	
>1-2 h	15	n.a.	0
>2-6 h	7		3
>6-12 h	1		24
1-2 d	n.a.		23
3-6 d			5
Unclear or not sufficiently documented	0	2	14

Abbreviations: AERD, aspirin-exacerbated respiratory disease; DRESS, drug reaction with eosinophilia and systemic symptoms; n.a., not applicable; NSAID, non-steroidal anti-inflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

(n = 5) based on a highly suggestive clinical history did not undergo diagnostic skin testing (Figure 1). In 41 cases of metamizole-induced anaphylaxis (54.7%), prick testing was clearly positive after 15 minutes, and additional intradermal testing was not done in the majority of these patients. In 32 out of 75 cases with anaphylaxis (42.7%), allergic hypersensitivity could only be detected by intradermal testing, the prick test being negative (Table S3). Intradermal testing of metamizole permits an accurate diagnosis of metamizole allergy in the majority of cases. The sensitivity of skin testing for delayed reactions can be further increased by simultaneous patch testing as a combination of prick and intradermal testing occasionally reveals a (false) negative result.[6] In our group of patients, skin testing of metamizole revealed an overall sensitivity of 78.0% for delayed exanthem, and 97.3% for anaphylaxis. In a comparable study of 139 patients (132 immediate and five delayed reactions), combined skin testing, that is prick, intradermal, and patch, was positive in 62.0% of cases.[9]

Focus of our data evaluation was the diagnosis of allergic metamizole hypersensitivity which has to be differentiated from non-allergic reactions appearing either as urticaria or as an obstructive reaction of the airways.[8] In contrast to anaphylaxis, skin testing in these clinical manifestations yielded negative results in all patients and thus could discriminate allergic from non-allergic reactions. Of the 95 patients with non-allergic immediate metamizole hypersensitivity, 61 had an acute urticarial skin reaction; 34 of these reported a history of episodes of an underlying chronic urticaria and were classified as NSAID-exacerbated urticaria. In the remaining 34 patients, an acute obstructive reaction of the upper and lower airways following the intake of metamizole was diagnosed as aspirin-exacerbated respiratory disease (AERD) (Table 1). Cases with an acute airway reaction occasionally experienced flushing of face, neck, and upper trunk up to a slight periorbital oedema, but generalized urticaria never occurred. The majority of patients with non-allergic metamizole hypersensitivity

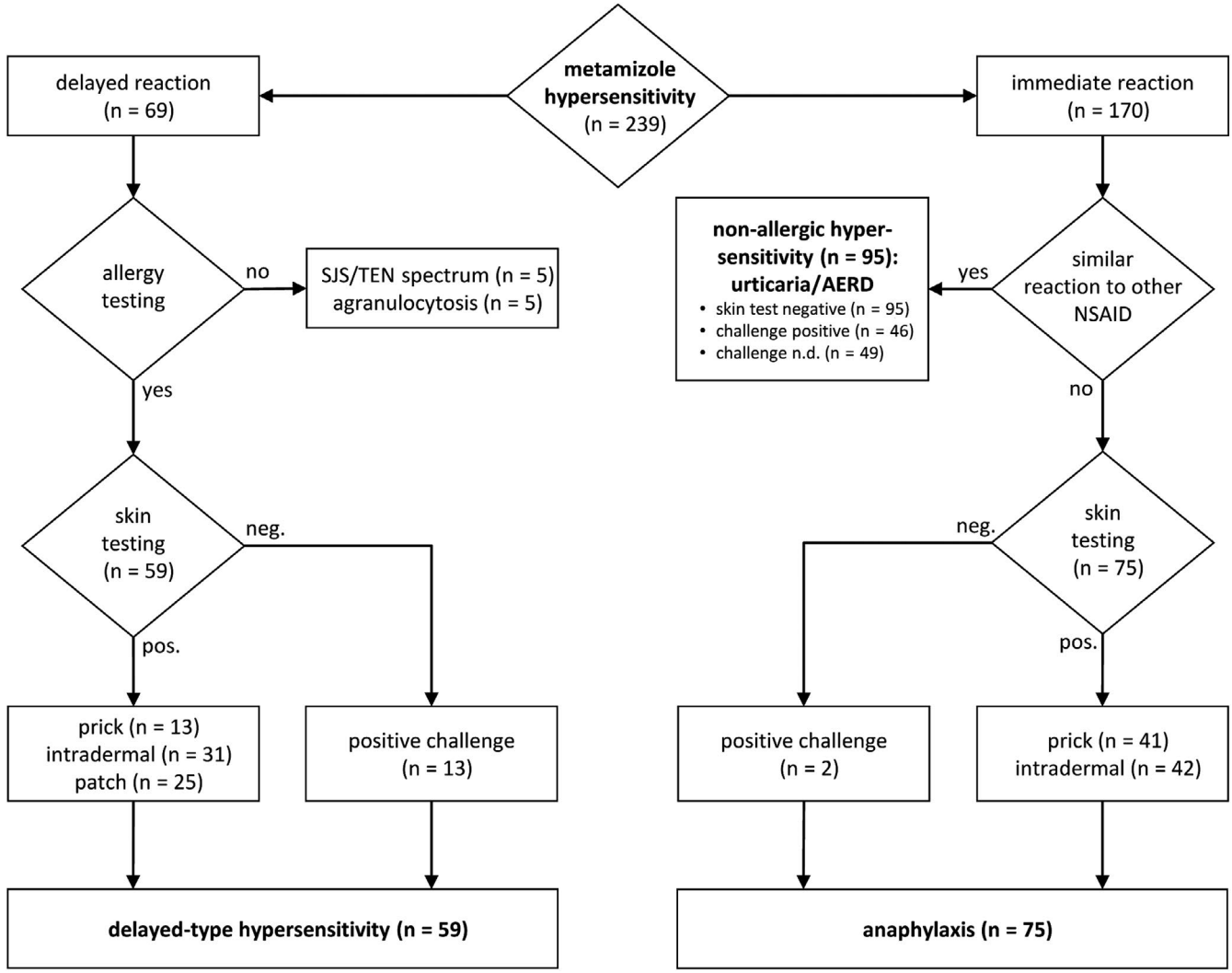

FIGURE 1 Results of allergy testing in 239 patients with metamizole hypersensitivity

had a history of similar clinical reactions to one or several NSAID, including acetylsalicylic acid, ibuprofen, and diclofenac.

Patients with suspected non-allergic or allergic metamizole hypersensitivity but negative skin test results underwent diagnostic challenge testing. General principles of our protocol are the following: (a) Concurrent urticaria was in remission, and patients had not taken any H_1-antihistamine for at least 1 week prior to metamizole challenge. (b) The administered dose of metamizole gradually increased to cumulative 1875 mg with an interval of one hour between each single dose: 125, 250, 500, and 1000 mg. (c) All patients were observed for at least four hours after the last dose and advised to present for objective examination if any symptoms developed within the next hours or days. In 46 patients, non-allergic immediate metamizole hypersensitivity was proven by positive oral challenge (Figure 1, Table S3). Thirty-five patients developed urticaria, and an AERD reaction pattern was observed in the remaining eleven. In 49 cases, the diagnosis of non-allergic NSAID hypersensitivity was based on a convincing medical history (that is at least three similar clinical episodes following the intake of different NSAID), and metamizole challenge testing was not done. Both prick and intradermal testings were (false) negative in only two out of 75 cases with metamizole-induced anaphylaxis (2.7%), and the diagnosis was confirmed by positive oral provocation of an anaphylactic reaction (Figure 1). Tolerance of acetylsalicylic acid was confirmed in both cases by negative challenge testing. In 13 skin test-negative patients, a delayed reaction was diagnosed by positive challenge testing. Eight patients developed a measles-like exanthem, four a FDE, and one a flexural exanthem.

1 | LIMITATIONS OF OUR STUDY

Data were retrospectively extracted from patient records, resulting in a certain methodological inhomogeneity; for example, not all patients were examined with all skin test methods. Only about half of the patients with non-allergic hypersensitivity were diagnosed by positive oral challenge testing. Patients with agranulocytosis do not primarily visit an allergy centre and are thus likely to be underrepresented in this cohort.

2 | CONCLUSIONS

1. Non-allergic immediate metamizole hypersensitivity may induce either an acute obstructive airway reaction or urticaria confined to the skin. IgE-mediated metamizole allergy, on the other hand, causes anaphylaxis with considerable respiratory, cardiovascular, and/or gastrointestinal involvement.
2. Delayed metamizole hypersensitivity commonly causes measles-like exanthem and may occasionally trigger other forms of a drug reaction including flexural exanthem, FDE, DRESS, or the SJS/TEN spectrum.
3. Intradermal testing of metamizole at a dilution of 1:100 (ie 5 mg/mL) is an appropriate method for the diagnosis of metamizole allergy.

KEYWORDS

agranulocytosis, aspirin-exacerbated respiratory disease, drug adverse reaction, drug allergy, drug hypersensitivity, exanthem, fixed drug eruption, urticaria

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AT initiated data evaluation; AT, KB, and JS analysed and interpreted the data; AT wrote the first draft of the article; AT, KB, and JS revised and edited the manuscript and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.