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Original Article

Metamizole-associated neutropenia: Comparison of patients with neutropenia and metamizole-tolerant patients

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ABSTRACT

Reports of metamizole-induced neutropenia have increased in Switzerland and Germany over the last decades, most likely reflecting increased use of metamizole. To date, there are no effective strategies to identify patients at increased risk of metamizole-induced neutropenia. In this observational, multi-center comparative study, characteristics of patients with metamizole-associated neutropenia were compared with patients treated with metamizole without developing adverse hematological reactions. Patients with metamizole-induced neutropenia treated at the University Hospitals Basel and Bern between 2005 and 2017 were included. Tolerant comparison patients with continuous metamizole treatment (≥500 mg/day for at least 28 days) were recruited from GP offices and community pharmacies. Forty-eight patients with metamizole-induced neutropenia, consisting of 23 and 25 cases with inpatient-acquired and outpatient-acquired neutropenia, respectively, were compared to 39 metamizole tolerant comparison patients. Median latency until first diagnosis of neutropenia was 6 days (1–61 days) in inpatient cases and 19 days (2–204 days) in outpatient cases. There was no association between non-myelotoxic and non-immunosuppressive co-medication ($p = .6627$), history of drug allergy ($p = .1304$), and preexisting auto-immune diseases ($p = .2313$) and the development of metamizole-induced neutropenia. Our results suggest that autoimmune diseases, history of drug allergy, and concomitant treatment with non-myelotoxic and non-immunosuppressive drugs are likely not individual risk factors for metamizole-associated neutropenia.

1. Introduction

Metamizole (dipyrone) is a non-opioid analgesic and antipyretic drug, widely prescribed in many countries due to its good efficacy and low gastrointestinal toxicity [1–3]. Despite the favorable safety profile of metamizole, susceptible patients may experience neutropenia or agranulocytosis, a severe and potentially fatal decrease in circulating neutrophil granulocytes [1,4]. Previous studies reported incidence rates of approximately 1:1500 prescriptions in Sweden and 1 case per one million inhabitants and year in Spain [5,6]. In Switzerland, the incidence rate of metamizole-associated agranulocytosis was estimated to be 0.46–1.63 cases per million person-days of use between 2006 and 2012, whereas the incidence of metamizole-associated neutropenia is likely higher [1]. Based on reports of metamizole-induced neutropenia (MIN), metamizole has been withdrawn from the market in several countries including Sweden and the USA, but it is still available and increasingly prescribed in other countries such as Switzerland, Germany, and France [5,7]. The mechanism by which metamizole induces

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neutropenia is currently not known and there are no effective strategies to predict or prevent occurrence of MIN. Immunologic mechanisms, including T-cell mediated elimination of neutrophils, have been proposed due to clinical observations such as increased symptom-severity upon re-exposure in some patients [8–10]. Conversely, certain features such as the rapid onset within a few hours after the first few doses in some patients without known previous exposure and the observation that metamizole can also induce bi- or pancytopenia [5] are more compatible with direct toxicity on precursors of neutrophil granulocytes and other hematopoietic cells in the bone marrow. This hypothesis is supported by a recent study revealing cytotoxicity in neutrophil progenitor cells involving electrophilic intermediates of the main metamizole metabolite [11]. Additionally, genetic predisposition has been shown for various neutropenia-inducing drugs such as sulfasalazine and clozapine, which might also be present in MIN [12,13]. It has been shown that neither metamizole dose, nor treatment duration increase the risk of MIN [1]. However, various factors have been suggested to influence the development of MIN, such as co-medication with immunosuppressants, e.g. low dose methotrexate or with non-myelotoxic and non-immunosuppressive drugs, and comorbidities such as infections with hepatitis B or C or HIV [1,4,6,14–16]. However, to prevent MIN, a better understanding of factors associated with increased susceptibility is needed. By excluding at-risk patients from metamizole exposure instead of banning its use overall, metamizole could remain a valuable treatment option e.g. for patients with contra-indications for nonsteroidal anti-inflammatory drugs such as many elderly patients. Hence, the current study aimed to identify differences between patients who had experienced MIN and patients tolerating metamizole treatment without developing any adverse hematological events, which could represent potential susceptibility factors for MIN.

This study is part of an interdisciplinary collaboration investigating direct toxic and immunological mechanisms of MIN as well as genetic factors potentially associated with MIN. The current work describes the findings of the characteristics evaluated during clinical assessment of cases and comparison patients and aims to evaluate the association between potential risk factors and the development of MIN. Results of the toxicological, immunological, and genetic investigations will be published separately.

2. Methods

2.1. Setting and study design

An observational, multi-center comparative study was performed including patients with new-onset neutropenia during metamizole therapy and metamizole-tolerant comparison patients between 2005 and 2017.

The study was performed following the principles of good clinical practice according to the Declaration of Helsinki. The study was approved by the local ethics committee “Ethikkommission Nordwest- und Zentralschweiz” (protocol number EKNZ BASEC 2015–00231). Written informed consent was obtained from all study participants.

2.2. Selection and assessment of MIN cases

In order to identify patients with metamizole-associated neutropenia, two different approaches were used. In a first approach, we screened the available electronic medical records of all wards of the University Hospitals Basel and Bern for the keywords “metamizole”, “Novalgin”, or “Minalgin” in conjunction with “neutropenia”, “agranulocytosis”, or “leucopenia” for the time period between 2005 and 2017. In a second approach, neutropenia cases who were hospitalized during the recruitment period of the study (2016–2018) were reported by the treating physician per email to the study authors or by report to the pharmacovigilance center by the processing physician or pharmacist (Fig. 1).

Included patients were at least 18 years old and developed neutropenia at the earliest one day after the first metamizole intake and at the latest 2 weeks after stopping metamizole intake. Only patients were included where a causal association between neutropenia and metamizole intake was classified at least as “possible” according to the Naranjo score [17]. Patients with idiopathic neutropenia or concomitant use of cytotoxic drugs or immunosuppressants (1 case low dose methotrexate, 2 cases tacrolimus, and 1 case sirolimus) were excluded. A previous analysis of Swiss pharmacovigilance data showed that myelotoxic drugs such as methotrexate increase the risk of MIN [1], which is why we excluded cases with myelotoxic co-medication to focus on yet unknown potential risk factors. Additionally, although non-myelotoxic, immunosuppressants are known to reduce the neutrophil count as ADR [18]. Since only 3 cases were under immunosuppressive co-medication, it would have been not possible to differentiate, whether MIN was caused by metamizole alone or by the combination with the immunosuppressant. Therefore, these cases were excluded from the analysis.

Eligible patients were contacted by mail and by phone. Patients who agreed to participate were invited for a study visit, where they were again informed about the study and provided written informed consent. Neutropenia patients were subdivided into inpatient cases who developed neutropenia in an inpatient setting, or outpatient cases who developed neutropenia in an outpatient setting with subsequent hospitalization.

2.3. Selection and assessment of metamizole tolerant comparison patients

Metamizole-tolerant comparison patients were recruited by contacting local family practitioners and community pharmacies. After asking patients under metamizole treatment with a daily metamizole dose of at least 500 mg for at least 28 consecutive days for consent of potential study participation, the practitioners and pharmacists forwarded the patients' contact information to the study authors. Additionally, some control patients contacted the authors after receiving a study information letter from their practitioner or pharmacist. Tolerant comparison patients, who agreed to participate, were invited for a study visit identically to case patients, where they were informed about the study and provided written informed consent. Good clinical drug tolerability was confirmed by the absence of fever, sore throat, or mucositis during metamizole treatment. Additionally, tolerant comparison patients were required to have a medical history without any drug-related hematological complications.

2.4. Covariates

During the study visit, demographic data (age, body mass index (BMI), ethnicity), hypersensitivity reactions (“allergy”) to drugs, concomitant diseases, co-medication, dose, duration, route, and frequency of metamizole intake of cases and comparison patients were recorded identically for cases and comparison patients by interview. Based on dosage information and medical records if available, daily dose, cumulative dose, and treatment duration were calculated. For neutropenia cases, latency until diagnosis of neutropenia, as well as duration of neutropenia were calculated. In case metamizole dosage regimen or latency could not be assessed with certainty, a minimal daily dose of 500 mg or a minimal latency of one day of treatment were assumed (n = 10 of 48 cases). Laboratory values and treatment of neutropenia were obtained from the patients' inpatient medical records. Co-medication of drugs with known association with neutropenia (level 1 and 2 evidence according to Andersohn et al.) was taken into consideration when assessing adverse drug reaction (ADR) causality [16]. Blood counts consisting of neutrophil and platelet counts and hemoglobin values were recorded at the nadir of neutropenia. Neutropenia was defined as a neutrophil count below 1.5×10^9/L. Thrombocytopenia was defined as a thrombocyte count below

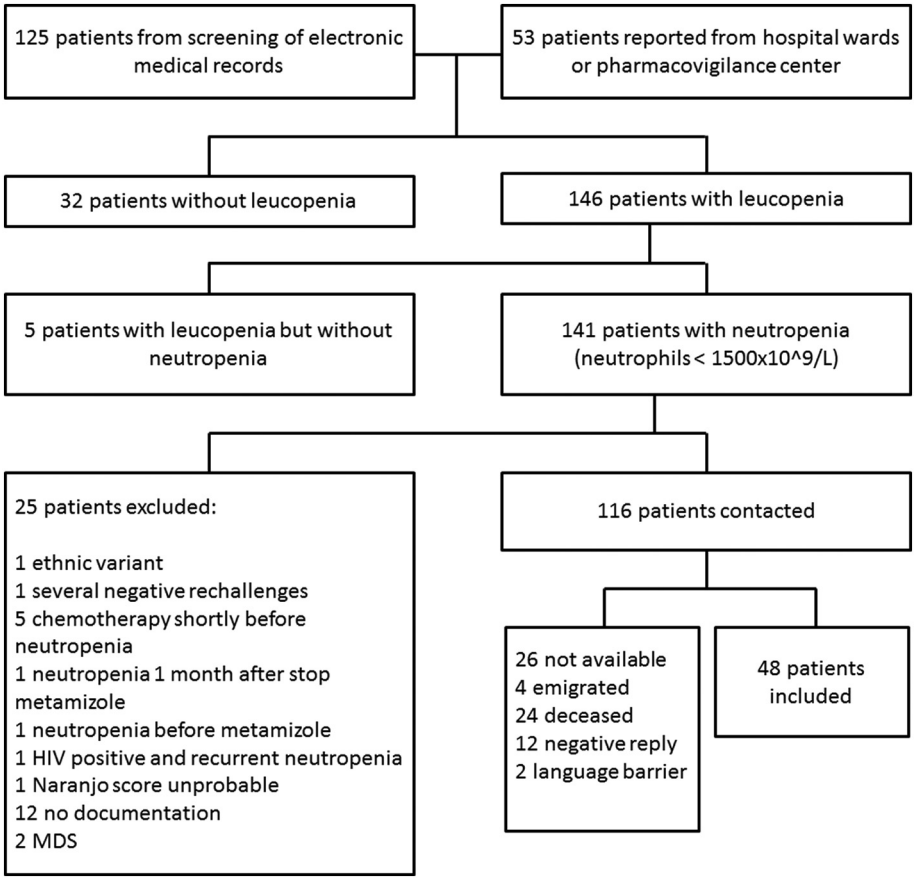

Fig. 1. Selection process of case patient recruitment.

150×10^9/L, and anemia as a hemoglobin concentration below 120 g/L and 140 g/L for women and men, respectively. For tolerant comparison patients, hematological laboratory values during metamizole treatment were evaluated if available. Additionally, a full blood count was obtained on the day of the study visit to confirm normal blood values.

Since immunologic reactions may be involved in metamizole-associated neutropenia, the allergy history of cases and comparison patients was obtained and grouped into probably T-cell mediated (delayed), anaphylactic, or non-specific allergic reactions to any drug. Details about possible T-cell mediated allergies or anaphylactic/anaphylactoid reactions were extracted from patient charts and patient history. Comorbidities were grouped according to their potential to affect neutrophil counts into chronic infections, autoimmune diseases, and other comorbidities (i.e. cardiovascular and metabolic diseases, renal insufficiency, psychiatric disorders and others).

2.5. Statistical analysis

We summarized the frequency distribution of continuous covariates and present normally distributed parameters as arithmetic mean (and standard deviation) and not normally distributed parameters as median (and range). Between-group comparisons were done using *t*-tests (for $n = 25$) and Fisher exact tests (when $n < 25$) for normally distributed variables and Wilcoxon signed rank tests for not normally distributed variables. Normality was assessed graphically. Microsoft Office Excel (Version 2010, Redmond, Washington, USA) and GraphPad PRISM (Version 7, La Jolla, California, USA) were used for analyses. Differences were considered as statistically significant when $p < .05$.

We conducted an explorative (hypothesis generating) comparative analysis using multivariable logistic regression analysis to compute odds ratios (OR) with 95% confidence intervals (CI). To increase homogeneity of study groups, we excluded all patients who had developed neutropenia in an inpatient setting, because control patients were recruited from an outpatient setting only. We compared the prevalence of potential risk factors for neutropenia between cases and comparison patients. Evaluated risk factors were considered based on their potential to influence development of neutropenia reported in previous studies. These included daily metamizole dose (< 1500 mg or ≥ 1500 mg), co-medication with level 1 evidence and level 2 evidence according to Andersohn et al., and two composite covariates including 1) autoimmune diseases and drug allergies and 2) cardiovascular and metabolic diseases (including hypertension, hypertensive cardiopathy, diabetes, and hypercholesterinemia). Covariates were dichotomized due to the limited number of included neutropenia cases ($n = 25$). We were not able to analyze acute infections and age as potential risk factors of MIN due to potential bias by the underlying indication for metamizole treatment. Several cases received short-term metamizole treatment for fever or pain during an acute infection, whereas tolerant comparison patients were required a minimum treatment duration with metamizole of 28 days, which inherently excludes patients with short-term therapy and over-samples controls with chronic diseases and long-term metamizole therapy. Multivariable logistic regression analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patients and metamizole treatment

Forty-eight patients with MIN managed at the University Hospital Basel and the University Hospital Bern between 2005 and 2017 and 39

Table 1
Patient and comparison subject characteristics.

	All cases (n = 48)	Inpatient cases (n = 23)	Outpatient cases (n = 25)	Tolerant comparison patients (n = 39)	p-value
Age (years) at neutropenia diagnosis (cases), or at last metamizole intake (comparison patients); median (range)	44 (17–77)	50 (22–77)	35 (17–76)	60 (19–91)	0.0007[a]
Women; N (%)	24 (50.0)	11 (48.0)	13 (52.0)	21 (53.8)	> 0.9999[b]
Body mass index in kg/m2; median (range)	24 (18–47)	23 (18–37)	24 (19–47)	28 (16–39)	0.0320[a]
Ethnicity; N (%)					
Caucasian	47 (97.9)	22 (95.7)	25 (100)	37 (94.9)	0.5164[b]
Other	1 (2.1)	1 (4.3)	0 (0)	2 (5)	

[a] Wilcoxon signed rank test between outpatient cases and tolerant comparison patients
[b] Fishers exact test between outpatient cases and tolerant comparison patients.

Table 2
Metamizole treatment.

	All cases (n = 48)	Inpatient cases (n = 23)	Outpatient cases (n = 25)	Tolerant comparison patients (n = 39)	p-value
Dosage (g/day); mean (SD)	1.78 (1.26)	1.91 (1.23)	1.67 (1.31)	1.64 (1.06)	0.9384[d]
Cumulative dose (g); median (range)	21 (0.5–859)	26 (0.5–196)	18 (0.5–859)	214 (23.5–13'149)	< 0.0001[e]
Latency time[a]/ treatment duration[b](days); median (range)	12 (1–204)	6 (1–61)	19 (2–204)	177 (30–5480)	< 0.0001[e]
Latency time[a]/ treatment duration[b]categorized: Patients N (%)					
1–7 days	19 (40)	12 (52)	7 (28)	n/a	
8–30 days[a]/ 28–30 days[b]	18 (38)	9 (39)	9 (36)	2 (5)	
31–60 days	8 (17)	1 (4)	7 (28)	9 (23)	
61–120 days	2 (4)	1 (4)	1 (8)	5 (13)	
121–180 days	0 (0)	0 (0)	0 (0)	4 (10)	
181–365 days	1 (2)	0 (0)	1 (4)	4 (10)	
> 365 days	0 (0)	0 (0)	1 (4)	15 (38)	
Route of application; N (%)					0.0594[f]
Oral	82	62	100	95	
Intravenous[c]	18	38	0	5	

[a] Cases.
[b] Comparison patients.
[c] Initial intravenous administration followed by per oral administration.
[d] t-test between outpatient cases and tolerant comparison patients.
[e] Wilcoxon signed rank test between outpatient cases and tolerant comparison patients.
[f] Fishers exact test between outpatient cases and tolerant comparison patients.

metamizole tolerant control patients were included. Characteristics of neutropenia patients and control subjects are summarized in Table 1. The median age of neutropenia cases was 44 years (17–77 years) and of tolerant comparison patients was 60 years (19–91 years). The majority of cases and comparison patients (> 90%) were Caucasian, reducing genetic variability of the results. The application route for metamizole was predominantly oral among tolerant comparison patients (95%) and cases (100% in outpatient and 62% in inpatient cases, Table. 2). Mean daily metamizole dose did not differ significantly between cases and tolerant comparison patients and was within the recommended maximum dose of 4 g per day (Table. 2).

The median latency between first intake of metamizole and neutropenia diagnosis among outpatient and inpatient cases was 19 and 6 days, respectively. Among all cases, 40% received metamizole for < 7 days and 38% for 8 to 30 days. Latency between 31 and 60 days and longer than 60 days was observed in 17% and 6% of cases, respectively. By definition of the study inclusion criteria, tolerant control patients took metamizole for at least 28 days. The median treatment duration in the tolerant comparison group was almost six months, with more than one third taking metamizole for more than one year.

3.2. Metamizole-associated neutropenia

According to the Naranjo scale, none of the cases met the criteria for a "definite" causality for metamizole and neutropenia (Table. 3). In half of the cases, causality was formally assessed as "probable" and the other half as "possible". Over two thirds of all included cases experienced agranulocytosis, i.e. a drop in neutrophils below 0.5×10^9 cells per liter (90% among outpatient cases and 40% among inpatient cases).

Ten patients (all inpatient cases) had a known rechallenge with metamizole, of whom 2 experienced a new episode of neutropenia whereas 5 cases had a negative rechallenge. For 3 patients, the outcome of the rechallenge was unknown. Table 4 shows that anemia was present in 19 (49%) tolerant comparison patients and in over half of these comparison patients anemia was either present before the start of metamizole treatment or could be attributed to other causes than metamizole. In contrast, 39 cases (81%) had anemia at neutropenia diagnosis and thereof almost half was of unknown cause. There was no difference between inpatient and outpatient cases.

Thrombocytopenia was less frequent among tolerant comparison patients (13%) than among cases (33%). In 80% of the tolerant comparison patients, thrombocytopenia was either already present before the start of metamizole treatment or had a known cause, whereas the cause for thrombocytopenia was only known for two of the inpatient cases and for none of the outpatient cases.

None of the cases had new onset pancytopenia, but in 33% of cases, cell counts were reduced in all three cell lines at the time of neutropenia diagnosis.

3.3. Preexisting drug-related allergies

As shown in Table 5, evidence for T-cell mediated allergies was only

Table 3
Characteristics of neutropenia.

	All cases (n = 48)	Inpatient cases (n = 23)	Outpatient cases (n = 25)
Naranjo Causality assessment; N (%)			
Definite (> 9)	0 (0)	0 (0)	0 (0)
Probable (5–8)	25 (52)	8 (35)	17 (68)
Possible (1–4)	23 (48)	15 (65)	8 (32)
Rechallenge; N (%)			
Known positive rechallenge	2 (4)	2 (9)	0 (0)
Known negative rechallenge	5 (10)	5 (22)	0 (0)
Rechallenge with unkown outcome	3 (6)	3 (13)	0 (0)
No known rechallenge	38 (79)	13 (57)	25 (100)
ADR duration in days; median (range)	5 (1–15)	3 (1–8)	7 (1–15)
Severity of neutropenia (n = 48 + 1)[a]; N (%)			
Neutrophils 1–1.5 × 10^9/l	4 (8)	4 (17)	0 (0)
Neutrophils 0.5–1 × 10^9/l	13 (27)	11 (46)	2 (8)
Neutrophils < 0.5 × 10^9/l	32 (65)	10 (42)	23 (92)

[a] One case with positive rechallenge and recorded blood values.

found in one neutropenia case and in no tolerant control. One inpatient case and one tolerant control each had a history of anaphylactic/anaphylactoid reaction to drugs (penicillin, diclofenac). In addition, one third of the tolerant comparison patients had experienced unspecific drug rashes compared to approximately 20% and 10% in the inpatient and outpatient cases, respectively.

3.4. Comorbidities

Half of the cases had experienced an infection shortly before or at diagnosis of neutropenia whereas only one quarter of the tolerant comparison patients reported a possible infection during metamizole treatment (Table 5). Eight cases with infection received metamizole to treat fever and/or pain related to the infection. There was a higher proportion of chronic comorbidities among inpatient than among outpatient cases. Self-reported autoimmune diseases were present in 8% and 15% of cases and tolerant comparison patients, respectively. Three quarters of case patients with an autoimmune disease were inpatient cases. Other diseases without any expected effect on the neutrophil count were most prevalent in the tolerant comparison group.

3.5. Co-medication

The median number of co-medications per patient was higher among the tolerant comparison group compared with all neutropenia cases (Table 5). Inpatient cases received twice as many co-medications during metamizole treatment compared with outpatient cases.

Besides metamizole, various drugs have been associated with neutropenia. According to the inclusion criteria, none of the cases had received myelotoxic or immunosuppressive co-medications. Among the tolerant comparison patients, one patient was under once weekly methotrexate treatment (10 mg/ week) and his blood values were within the normal range.

Certain non-myelotoxic and non-immunosuppressive medications have also been associated with neutropenia. Over 40% of cases and tolerant comparison patients had at least one co-medication with evidence 1 according to the classification after Andersohn et al. [16]. However, 13% of tolerant comparison patients had 2 or more evidence 1 drugs compared to 2% among cases. Inpatient cases received more evidence 1 co-medications than outpatient cases. Prevalence of drugs with evidence 2 was slightly higher among cases compared to tolerant comparison patients. Evidence 2 co-medication was twice as frequent among inpatient cases compared with outpatient cases (Table 5).

3.6. Multivariable comparison of cases and tolerant comparison patients

One third of outpatient cases and almost half of tolerant comparison patients received a median daily metamizole dose of 1.5 g or higher. The corresponding adjusted OR revealed no association of metamizole dose and the risk of neutropenia (OR 1.24, 95% CI 0.35–4.33). After multivariable adjustment, the adjusted OR for neutropenia in association with autoimmune diseases and/or any previous allergic reaction to drugs was 0.22 (95% CI 0.06–0.81). Cardiovascular and/or metabolic diseases were twice as frequent among tolerant comparison patients compared with outpatient cases. Thus, the corresponding adjusted OR revealed no association of cardiovascular and/or metabolic diseases and the risk of neutropenia (OR 0.58, 95% CI 0.18–1.84). Half of the tolerant control patients and 40% of outpatient cases had at least one co-medication with drugs associated with neutropenia of evidence level 1. Similarly, co-treatment with drugs associated with neutropenia of evidence level 2 was reported by half of the tolerant control patients and 36% of outpatient cases. The corresponding adjusted ORs showed no association between evidence level 1 (OR 0.43, 95% CI 0.13–1.41) or evidence level 2 (OR 0.54, 95% CI 0.18–1.64) co-medication and MIN (Table 6).

Table 4
Additional blood values.

	All cases (n = 48)	Inpatient cases (n = 23)	Outpatient cases (n = 25)	Tolerant comparison patients (n = 39)
Other affected cell lines; N (%)				
Anemia (w: < 120 g/L; m: < 140 g/L)	39 (81)	19 (83)	20 (80)	19 (49)
Anemia with known cause or preexisting	17 (35)	8 (35)	9 (36)	10 (26)
Thrombocytopenia (< 150 × 10^9/L)	16 (33)	9 (39)	7 (28)	5 (13)
Thrombocytopenia with known cause or preexisting	2 (4)	2 (9)	0 (0)	4 (10)
New onset pancytopenia[a]	0 (0)	0 (0)	0 (0)	0 (0)
Pancytopenia at presentation[b]	16 (33)	10 (43)	6 (24)	0 (0)

[a] New onset after metamizole treatment.
[b] With known cause or preexisting anemia or thrombocytopenia.

Table 5
Health characteristics.

	All cases (n = 48)	Inpatient cases (n = 23)	Outpatient cases (n = 25)	Tolerant comparison patients (n = 39)	p-value
Allergies to drugs; N (%)					
T-cell mediated[a]	1 (2)	1 (4)	0 (0)	0 (0)	> 0.9999[e]
Anaphylactic reactions to drugs	1 (2)	1 (4)	0 (0)	1 (3)	> 0.9999[e]
Drug rash, non-specified	8 (17)	5 (22)	3 (12)	12 (31)	0.1304[e]
Comorbidities; N (%)					
Infections[b]	23 (48)	11 (48)	12 (48)	10 (26)	0.1048[e]
Acute infections	22 (46)	10 (43)	12 (48)	9 (23)	0.0563[e]
Chronic infections	4 (8)	3 (13)	1 (4)	1 (3)	1.0000[e]
Preexisting auto-immune diseases	4 (8)	3 (13)	1 (4)	6 (15)	0.2313[e]
Cardiovascular diseases	12 (25)	5 (22)	7 (28)	14 (36)	0.5919[e]
Metabolic diseases	4 (8)	3 (13)	1 (4)	13 (33)	0.0055[e]
Psychiatric disorders	3 (6)	1 (4)	2 (8)	4 (10)	1.0000[e]
Renal insufficiency	4 (8)	1 (4)	3 (12)	0 (0)	0.0552[e]
Other	10 (21)	3 (13)	7 (28)	14 (36)	0.5919[e]
Co-medication					
Median number of medications per subject (range)	5 (0 – 20)	7 (0–14)	3 (0–20)	8 (0–20)	< 0.0001[h]
N (%) of patients with evidence 1 co-medication[c]					0.6627[e]
1 evidence 1 drug	20 (42)	11 (48)	9 (36)	16 (41)	
2 evidence 1 drugs	1 (2)	0 (0)	1 (4)	4 (10)	
> 2 evidence 1 drugs	0 (0)	0 (0)	0 (0)	1 (3)	
N (%) of patients with evidence 2 co-medication[d]					0.5732[e]
1 evidence 2 drug	21 (44)	13 (57)	8 (32)	15 (38)	
2 evidence 2 drugs	9 (19)	8 (35)	1 (4)	5 (13)	
> 2 evidence 2 drugs	1 (2)	1 (4)	0	1 (3)	

[a] According to patient chart/detailed patient history.
[b] Several infections per patient counted as one infection.
[c] Evidence 1: At least 1 ADR report with a definite relationship.
[d] Evidence 2: At least 1 ADR report with a probable relationship but no report with a definite relationship.
[e] Fishers exact test between outpatient cases and tolerant comparison patients
[h] Wilcoxon signed rank test between outpatient cases and tolerant comparison patients.

4. Discussion

In the current retrospective observational comparative study, patients with autoimmune diseases or previous allergic reactions to drugs were not at increased risk of MIN. Additionally, co-medication with non-myelotoxic and non-immunosuppressive drugs, which have previously been associated with neutropenia [16], were not associated with an increased risk of MIN.

A possible involvement of the immune system in the development of MIN has previously been suggested [19,20]. Patients who had previously experienced an immune-mediated reaction to drugs might be more susceptible to also react to other drugs. Accordingly, patients with autoimmune diseases might have a more reactive immune system, which could also react to xenobiotics. However, in the current study, autoimmune diseases and previous immune-mediated reactions to drugs were more frequent among tolerant comparison patients than in neutropenia cases, which may be due to the older age of the tolerant comparison patients. Our results therefore suggest that autoimmune diseases and prior immune mediated reactions are not a key risk factor for developing MIN. In a previous study investigating risk factors for metamizole induced leucopenia [4], history of medication allergies has been associated with an increased risk for leucopenia after metamizole treatment. This divergence to the current study may be attributable due to the different data collection methods. In the current study, patients' drug allergy history was assessed by personal interviews, whereas in the previous retrospective study, data were collected from medical records only, introducing a risk of reporting bias.

Regarding co-medication, also non-myelotoxic and non-immunosuppressive drugs have been associated with the development of neutropenia [16] and may facilitate the development of MIN or even be the main cause for neutropenia in patients treated with metamizole. However, in the current study, administration of drugs associated with neutropenia was more frequent among tolerant comparison patients compared with neutropenia cases and was not associated with increased risk for MIN after multivariable adjusting. This is in agreement with a previous study, which did not find evidence that co-medication with non-myelotoxic and non-immunosuppressive drugs is a potential risk factor for MIN [4].

Table 6
Multivariable comparative analysis of neutropenia risk factors.

	Outpatient cases (n = 25)	Tolerant comparison patients (n = 39)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Risk factor; N (%)				
Metamizole dose > 1.5 gramm	8 (32)	18 (46)	1.19 (0.42–3.35)	1.24 (0.35–4.33)
Autoimmune disease and/or any drug related allergic reaction	4 (16)	19 (49)	0.25 (0.07–0.85)	0.22 (0.06–0.81)
Cardiovascular and/or metabolic disease	8 (32)	27 (69)	0.50 (0.17–1.41)	0.58 (0.18–1.84)
Evidence level 1 co-medication	10 (40)	21 (54)	0.57 (0.21–1.58)	0.43 (0.13–1.41)
Evidence level 2 co-medication	9 (36)	21 (54)	0.59 (0.21–1.66)	0.54 (0.18–1.64)

Previous retrospective studies investigating MIN identified concomitant use of myelotoxic and immunosuppressive drugs as potential risk factor [1,4]. Since myelotoxic and immunosuppressive drugs themselves can cause neutropenia or lead to a decrease in circulating neutrophils, a high number of patients and comparison patients treated with such drugs would be needed in order to differentiate whether neutropenia was caused by metamizole, the myelotoxic or immunosuppressive co-medication, or the combination of both. Since this was not the case in the current study, we excluded patients with any myelotoxic or immunosuppressive treatment, which allowed searching for other potentially involved factors.

A previous analysis of Swiss pharmacovigilance data showed that only few patients developed neutropenia after > 28 days of metamizole treatment [1]. Therefore, tolerant comparison patients included in the current study were required to be on metamizole treatment for at least 28 days. Previous studies reported contradictory findings regarding the latency time of MIN. The median latency time of 12 days among all cases is within the latency time period of 7 to 14 days reported by Swiss pharmacovigilance data [1]. However, it is longer than the 2 days reported in a review of Andersohn et al., describing latency times of various non-chemotherapy drugs [16]. Interestingly, outpatient cases in our study had a longer median latency compared to inpatient cases. This difference may be due to the predominantly intermittent metamizole use among outpatient cases compared to the regular daily treatment in-hospital. Alternatively, the shorter latency time among inpatient cases might reflect the closer surveillance of hospital patients where a drop in the neutrophil count is detected earlier than in outpatient cases with less frequent blood counts. This could also explain the higher degree of neutropenia severity among outpatient cases, reflecting the later detection of the neutropenia and thus later metamizole discontinuation. Similar observations of lower neutrophil counts in outpatient cases compared to inpatient cases had been reported in a German case-control surveillance study [21]. In accordance with the more pronounced severity of neutropenia, the ADR duration of 7 days was longer among outpatient cases compared to 3 days in inpatient cases in our study, reflecting the time needed to restore a sufficient amount of circulating mature neutrophils from the bone marrow [22]. This is in agreement with reports of Andersohn et al., who investigated agranulocytosis and reported a median ADR duration of 8 days. In the current study, the median ADR duration of all cases was 5 days, which is similar to previously reported findings of Swiss, German and Swedish studies investigating MIN [4,5,23].

4.1. Limitations

The observations in the current study are mainly limited by the small sample size, a consequence of the rarity of MIN, as well as the difficulty of recruiting a larger number of tolerant comparison patients, who had metamizole treatment for at least 28 consecutive days. Several potential risk factors could therefore not be evaluated. The required minimum treatment duration of 28 days for metamizole tolerant comparison patients, but not for cases, resulted in different indications for metamizole treatment in cases and comparison patients. While acute diseases such as infections, pain, menstrual cramps, and migraine were predominant indications in cases, chronic diseases such as chronic lumbar spine syndrome, gout, and fibromyalgia were the most frequent indications in comparison patients. This difference between cases and comparison patients prevented the analysis of acute infections and age as potential risk factors of MIN, because they are associated with the underlying indication and would thus have resulted in biased effect estimates. Prior studies reported an increased ADR risk for other drugs in the presence of viral infections [24]. Two of the neutropenia cases had an HIV infection and one neutropenia patient had an ongoing chronic hepatitis C infection, but all with normal neutrophil counts before and after metamizole treatment. Taking into account these observations, it would be interesting to investigate the impact of viral, bacterial, and fungal infections on the risk to develop MIN. WHO and Swiss spontaneous safety reports mentioned more metamizole-associated hematological disorders in elderly people (median age close to 60 years), but without data on metamizole exposure of the specific age groups [1]. Since the median age of neutropenia cases in the current study was distinctly lower, further studies on the influence of age on the risk of MIN would be interesting. Further, the included patients represent those, who were willing to participate in the study and in case of the neutropenia patients, who survived the adverse drug reaction. The inclusion of cases with not only a “probable” but also a “possible” association according to the Naranjo scale could have led to the inclusion of a number of cases where metamizole was not the main cause of neutropenia. The recruitment of inpatient cases and tolerant comparison patients in different settings limited a direct comparison, which is why we only compared cases who developed neutropenia in an outpatient setting with tolerant comparison patients in the multivariable regression analysis. However, we cannot rule out residual selection bias due to different recruitment channels for cases and comparison patients.

5. Conclusion

Our results suggest that neither autoimmune diseases, history of drug allergies, nor concomitant treatment with drugs associated with neutropenia of evidence level 1 or evidence level 2 are associated with an increased individual risk of metamizole-associated neutropenia.

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Declaration of Competing Interest

None of the authors has a conflict of interest regarding this study.

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