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Neutropenia following metamizole use in pediatric patients: a multicenter retrospective study

To the editor,

Neutropenia, with an absolute neutrophil count (ANC) below 1,500/mm³ or 1.5×10^9/L, significantly increases health risks, particularly when induced by drugs like metamizole—an analgesic with antipyretic and anti-inflammatory properties.[1] The pathogenesis of metamizole-associated neutropenia may involve immune responses or direct myeloid cell line toxicity.[1,2] The condition's severity and duration vary, with documented cases of agranulocytosis at high metamizole dosages, indicating dose-dependent risks.[3] Risk estimates for metamizole-induced agranulocytosis vary, with Sweden reporting 1 in 1,439 prescriptions and a German study noting a 23.6% mortality rate.[1,4] Such adverse effects prompted metamizole's withdrawal in several countries.[2] Despite these concerns, metamizole remains widely used in many countries including Turkey, especially for pediatric fever management. This multicenter retrospective study aims to investigate the incidence, clinical outcomes, and severity of metamizole-induced neutropenia in Turkish children, highlighting the drug's safety profile in pediatric care.

This multicenter retrospective study analyzed 17 cases of metamizole-induced neutropenia across 7 pediatric hematology centers in Turkey, focusing on patients whose neutropenia developed after metamizole therapy. Neutropenia was defined as an ANC below 1.5×10^9/L, with severity classifications of less than 0.5×10^9/L for severe and under 0.1×10^9/L for very severe. Data were collected via online questionnaires sent to authors at each center, capturing demographics, clinical features, laboratory findings, metamizole dosages and durations, and patient outcomes. The analysis used descriptive statistics, including frequencies, percentages, means, and medians, to summarize both discrete and continuous variables.

The cohort consisted of 17 patients (male:female, 9:8). The median age of the patients was 5 (interquartile range, 2–8) years. The most common indication for metamizole use was for antipyretic symptomatic relief in cases of upper respiratory tract infections (52.9%), followed by lower respiratory tract infections (17.6%), and abdominal pain (11.8%). Among the patients, 29.4% had ANC levels below 0.1×10^9/L, 17.6% had below 0.5×10^9/L, 41.2% presented with ANC levels ranging from 0.5 to 1.0×10^9/L, and 11.8% exhibited levels between 1.0 and 1.5×10^9/L. A comprehensive diagnostic evaluation was conducted for the cohort, including peripheral blood smear, vitamin B12 levels, and

Table 1. Demographic, clinical, and laboratory features of pediatric patients with metamizole-induced neutropenia (n=17)

Variable	Value
Age (yr)	5 (2–8)
Sex	
Male	9 (52.9)
Female	8 (47.1)
Indication	
Upper respiratory tract infection	9 (52.9)
Lower respiratory tract infection	3 (17.6)
Urinary tract infection	1 (5.9)
Acute gastroenteritis	1 (5.9)
Acute appendicitis	2 (11.8)
Others	1 (5.9)
Drug prescribed	
Metamizole	6 (35.3)
Metamizole with antibiotics	11 (64.7)
Investigations for aetiology	
Peripheral blood smear	17 (100)
Vitamin B12 level	17 (100)
Viral markers[a]	17 (100)
Autoimmune markers	14 (82.4)
Bone marrow aspiration	3 (17.6)
Genetic testing	0 (0)
Absolute neutrophil count at diagnosis	
$<0.1\times10^9$/L	5 (29.4)
$<0.5\times10^9$/L	3 (17.6)
$0.5–1.0\times10^9$/L	7 (41.2)
$1.0–1.5\times10^9$/L	2 (11.8)
Hospitalization required	8 (47.1)
Treatment	
G-CSF	3 (17.6)
Steroid	3 (17.6)
Steroid + G-CSF	2 (11.8)
Metamizole discontinued (no other treatment)	9 (52.9)
Hospital stay (day)	4.94 (1.0–15.0)
Outcome	
Complete recovery	16 (94.1)
Death	1 (5.9)

Values are presented as median (range) or number (%).
G-CSF, granulocyte-colony stimulating factor.
[a]Epstein-Barr virus, cytomegalovirus, and parvovirus B19.

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viral serologies for Epstein-Barr virus, cytomegalovirus, and parvovirus B19, indicating a standardized approach to evaluating neutropenia. Autoimmune markers were tested in 82.4% of patients, while 17.64% underwent bone marrow aspirations. Genetic testing for drug metabolism and adverse reactions was not performed. Demographic, clinical, and laboratory details are provided in Table 1.

Treatment analysis revealed granulocyte-colony stimulating factor (G-CSF) was given to 17.6% of the patients with an ANC below 0.1×10^9/L. Steroids plus G-CSF were used in 2 patients (11.8%) with an ANC below 0.5×10^9/L. Steroid monotherapy was administered to 3 patients across different ANC ranges. The median recovery times were as follows: 15 days (range, 10–30 days) for ANC $<0.1\times10^9$/L, 6 days (range, 4–8 days) for ANC $0.5–1.0\times10^9$/L and 4 days (range, 3–5 days) for ANC $1.0–1.5\times10^9$/L. For 14 patients, the average metamizole dose was 40 mg/kg/day (±20.6 standard deviation [SD]), with a mean cumulative dose of 219.4 mg/kg (±113.5 SD) (Table 2). The average duration of exposure to metamizole before the occurrence of adverse effects was 4.64±1.86 days, ranging from 2 to 7 days. The average hospital stay was 4.94 days (range, 1.0–15.0), with 94.1% of patients achieving full recovery. One patient, with ANC $<0.1\times10^9$/L, died from sepsis 11 days after hospitalization.

In our study, metamizole was most used for symptomatic relief in cases of upper respiratory tract infections, followed by lower respiratory tract infections, emphasizing its frequent application in pediatric population. The World Health Organization categorizes drug-induced agranulocytosis into 4 levels: certain, probable, possible, and unlikely.[5] Our study found that the severity of possible drug-induced neutropenia was significant, with nearly half of the cases presenting with severe neutropenia and becoming particularly alarming at counts under 0.1×10^9/L. Additionally, we recorded a mortality case due to sepsis associated with very severe neutropenia, highlighting the serious risks involved. These findings align with those from other multicenter studies and underscore the significant mortality rates associated with metamizole-induced agranulocytosis.[1,6]

Childhood respiratory infections often lead to neutropenia, usually attributed to viruses.[7] In our study, patients had negative viral serologies, suggesting the drug was the likely cause of neutropenia. Diagnostics included blood smears, B12 levels, and viral serologies, with 82.4% tested for autoimmune markers and 17.64% undergoing bone marrow aspirations, indicating thorough evaluation. Research into genetic factors like NAT2, CYP2C9, and CYP2C19 polymorphisms is crucial for understanding the role in metamizole-induced agranulocytosis and its toxicity, as evidenced by a study on 3 cases, including dizygotic twins.[8] The metabolism of metamizole is significantly influenced by cytochrome P450 enzymes, which are subject to genetic variations. These genetic differences can affect the enzyme's activity level, potentially leading to variations in how patients metabolize metamizole. This pharmacogenetic aspect could explain the variability in drug response and the incidence of adverse effects such as neutropenia. A 14-month-old male developed severe neutropenia during metamizole treatment, showing initial resistance to G-CSF and steroids but later recovered, hinting at genetic factors affecting drug response, though no genetic testing was conducted. Although our study did not directly investigate these genetic factors, acknowledging their potential impact is crucial for future research and could lead to more personalized approaches in managing pain with metamizole.

For the latency period, studies suggest a 7- to 11-day median onset after starting therapy.[2,9] In our study, among 14 out of 17 cases, the average exposure to metamizole before adverse effects occurred was 4.64±1.86 days, ranging from 2 to 7 days.

Treatment varied widely, with G-CSF for those with lowest ANC counts and steroids or their combination with G-CSF for others, reflecting diverse clinical management. The average hospital stay was 4.94 days. A notable 94.1% recovery rate underscores treatment effectiveness, yet a sepsis-related death highlights the potential severity of extreme neutropenia, emphasizing the need for early intervention. Despite low annual incidence, the grave nature of

Table 2. Distribution of ANC levels, treatment interventions, recovery days, and daily and cumulative doses of metamizole-treated patients

Parameter	ANC			
	$<0.1\times10^9$/L	$<0.5\times10^9$/L	$0.5–1.0\times10^9$/L	$1.0–1.5\times10^9$/L
Patients	5 (29.4)	3 (17.6)	7 (41.2)	2 (11.8)
G-CSF	3 (17.6)	0 (0)	0 (0)	0 (0)
Steroid	1 (5.9)	1 (5.9)	1 (5.9)	0 (0)
Steroid + G-CSF	1 (5.9)	1 (5.9)	0 (0)	0 (0)
Recovery days	15.0 (10.0–30.0)	9.0 (6.0–20.0)	6.0 (4.0–8.0)	4.0 (3.0–5.0)
Daily and cumulative doses of 14 patients				
MD (mg/kg/day)			40.0±20.6	
Cumulative MD (mg/kg)			219.4±113.5	

Values are presented as number (%), median (range), or mean±standard deviation.
ANC, absolute neutrophil count; G-CSF, granulocyte-colony stimulating factor; MD, metamizole dose.

severe cases demands aggressive treatments like G-CSF, granulocyte suspension, and short-term steroids.[10]

Metamizole remains widely used for pain and fever worldwide, including Turkey, despite safety concerns leading to its withdrawal in some countries, indicating global regulatory discrepancies.[1,4] (Supplementary Table 1). The need for stronger adverse drug reaction surveillance and reporting is critical, especially where metamizole is prevalent, to mitigate risks like neutropenia. Our study offers a detailed view of metamizole-induced neutropenia in Turkish pediatric patients, showing significant health impacts, hospitalization demands, and treatment diversity. Despite limitations like small sample size and incomplete dosage data, our findings stress the importance of further research on genetic susceptibility and understanding the long-term impact on pediatric patients who recover from metamizole-induced neutropenia.

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Footnotes

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