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# Metamizole Related Granulocytopenia and Agranulocytosis: An Analysis of 13 Children

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**Abstract**

**Objectives:** Metamizole sodium (Novalgin®) is an effective, widely used analgesic and antipyretic agent in several countries. In spite of its availability and common usage, it has serious and potentially fatal adverse effects like agranulocytosis and aplastic anemia. Objectives of this study are to evaluate incidence, severity, and clinical significance of metamizole related neutropenia and agranulocytosis, and to study recovery duration of neutropenia and agranulocytosis in children exposed to metamizole.

**Material and Methods:** Thirteen cases of neutropenia and/or agranulocytosis secondary to metamizole usage have been evaluated retrospectively. Duration and cumulative doses of metamizole, degree of neutropenia, recovery from neutropenia, and other complications related to neutropenia were evaluated.

**Results:** Overall, thirteen granulocytopenic patients were recorded for 12 months after metamizol usage. Mean metamizole exposure duration was 4,64 (2-7) days; mean daily total metamizole dose was 40 (15,6-78) mg/kg; mean metamizole cumulative dose was 219,4 (58,8-468) mg/kg; mean neutropenia duration was 9,4 (1-30) days; and mean absolute neutrophil count was 690 (30-1300)/mm$^3$. Four patients who used ≥ 30 mg/kg daily doses of metamizole for 4-7 days (≥ 217 mg/kg cumulative dose) had agranulocytosis. All of the patients recovered fully after metamizol cessation. The shortest recorded recovery duration from granulocytopenia was 2 days while the longest recorded recovery duration was 30 days.

**Conclusion:** Physicians should be aware of the toxic effects of metamizole and should not prefer metamizole as a first line antipyretic agent. Neutropenia and agranulocytosis risks should be kept in mind in the application of metamizole particularly over long periods of time and in large doses in children.

**Key Words:** Metamizole; Granulocytopenia; Agranulocytosis; Childhood.

## Metamizol İlişkili Granulositopeni ve Agranülositoz: 13 Çocuğun Değerlendirilmesi

**Özet**

**Amaç:** Metamizol sodyum (Novalgin®) birçok ülkede yaygın olarak kullanılan etkili bir analjezik ve antipiretik ilaçtır. Yaygın kullanımına ve kolay elde edilebilirliğine rağmen agranülositoz ve aplastik anemi gibi ağır ve ölümcül olabilecek yan etkileri olabilir. Çalışmamızın amacı metamizol kullanan çocuklarda metamizol ilişkili nötropeni ve agranülositoz sıklığını, ağırlığını, klinik önemini ve nötropeni ve agranülositozdan çıkma sürelerini değerlendirmektir.

**Gereç ve Yöntemler:** Metamizolle ilişkili 13 nötropeni ve agranülositoz vakası metamizol kullanım süresi, kümülatif dozu, nötropeniden çıkma süresi ve nötropeni ile ilişkili diğer komplikasyonlar açısından retrospektif olarak değerlendirildi.

**Bulgular:** Metamizol kullanımı sonrası granülositopeni veya agranülositoz gelişen toplam 13 hasta tespit edildi. Ortanca metamizol kullanım süresi 4.64 (2-7) gün, ortanca günlük doz 40 (15.6-78) mg/kg, ortanca metamizol kümülatif dozu 219.4 (58.8-468) mg/kg, ortanca nötropeni süresi 9.4 (1-30) gün, ortanca mutlak nötrofil sayısı 690 (30-1300)/mm$^3$ olarak tespit edildi. 4-7 gün 30 mg/kg/gün'den (≥ 217 mg/kg kümülatif doz) fazla metamizol kullanan dört hastada agranülositoz geliştiği ve bütün hastaların metamizol kesildikten sonra tam olarak düzeldikleri tespit edildi. En kısa granulositopeniden çıkma süresi 2 gün, en uzun süre ise 30 gündü.

**Sonuç:** Klinisyenler metamizolün toksik etkilerinden haberdar olmalı ve metamizolü ilk sıra antipiretik ajan olarak tercih etmemelidirler. Özellikle uzun süreli ve yüksek dozlarda kullanımında nötropeni ve agranülositoz gelişebileceği akılda tutulmalıdır.

**Anahtar Kelimeler:** Metamizol; Granülositopeni; Agranülositoz; Çocukluk Dönemi.

## INTRODUCTION

Agranulocytosis and other blood dyscrasias, such as aplastic anemia, are rare but have potentially life-threatening adverse reactions to many drugs. Metamizole sodium (dipyrone) is an effective, widely used analgesic and antipyretic agent in several South American, Asian, and European countries. However, it was banned in Sweden in 1974, and then in the United States of America in 1979 because of its association with agranulocytosis. Since then, more than 30 countries (including Japan, Australia, Iran, and several European Union member nations) have banned this drug (1).

Consumption and frequency of usage of metamizole differs from country to country. The usual pediatric dosage of metamizole is 10-12 mg/kg tid, up to 20 mg/kg qid (2). In spite of its availability and common usage, it has serious and potentially fatal adverse effects like agranulocytosis and aplastic anemia (3).

Metamizole related granulocytopenia or agranulocytosis can occur idiosyncratically or in a dose dependent way.

The first case of agranulocytosis associated with the use of metamizole was reported by Blake et al. (4) in 1935. After that, 51 additional cases were reported until 1964 (5). Bäckström et al. (6) have reported that the risk of agranulocytosis was 1/31,000 metamizole-treated inpatients, and 1/1400 metamizole-treated outpatients. International Agranulocytosis and Anemia Study (IAAAS) has reported that metamizole-induced agranulocytosis incidence rate as 1 per million (7). Differences in the methods used in various pharmacovigilance studies and concurrent drug use probably account for the widely differing estimates of the risk of blood dyscrasias associated with metamizole (8). Variations in the incidence rates are also considered to be related to geography, genetics, age range, and underlying conditions of the patients.

Turkey is one of the several countries where metamizole is used. Despite its widespread usage, we do not know the real incidence of metamizole-induced agranulocytosis or blood dyscrasias in Turkey. The main clinical manifestations of agranulocytosis are fever, tonsillitis, pharyngitis, sepsis, stomatitis, and pneumonia. Historically, the mortality rate of agranulocytosis was about 10%. Today this rate has been decreased to about 5% with effective supportive therapies.

The purpose of this study is to evaluate neutropenic and agranulocytopenic adverse effects of metamizole in child patients in our center and to create awareness about these adverse effects of metamizole.

## MATERIAL AND METHODS

All possible metamizole associated neutropenic patients were evaluated retrospectively within the past 12 months in our center. The diagnostic criteria for neutropenia and agranulocytosis were defined as agranulocytosis; granulocyte $<500/mm^3$, and neutropenia; granulocyte count $<1500/mm^3$ (8, 9). Patients who were assumed to have any other causes of neutropenia (use of chemotherapy, radiotherapy, immuno-suppressants, having hematologic, neoplastic diseases, or systemic diseases that are known to cause neutropenia or pancytopenia such as lupus, hypersplenism) were excluded from the study.

In the study, an index day was defined for all subjects as the first day on which granulocytopenia was detected. Metamizole exposure was defined as any use of metamizole during the week before the index day. This definition of exposure was decided taking into account that, in metamizole-induced agranulocytosis, the interval between ingestion of the first dose of the drug and onset of the blood dyscrasias or infection is usually less than seven days (9). Thirteen patients who had granulocytopenia within a week after starting metamizole were detected. The subjects were evaluated for fever duration, metamizole dose and usage duration, severity of neutropenia, neutropenia duration, and accompanying disorders. Adverse drug reactions are classified by WHO-UMC case causality assessment categories as certain, probable, possible, and unlikely (avaible at: http//www.who-umc.org/DynPage.aspx?id_22682). The clinical and laboratory findings of our patients were consistent with the descriptions of possible (event or laboratory test abnormality within reasonable time after drug intake could also be explained by disease or other drugs) drug-induced neutropenia and agranulocytosis according to the WHO-UMC classification.

Statistical analyses were performed using the Scientific Package for the Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA).

## RESULTS

Between August 2011 and August 2012, 13 patients whose ages ranged from 14 months to 11 years (median 5 years) were identified as having possible metamizole related neutropenia. Seven of the patients were male and six were female. Mean fever duration was 5.6±3.9 (1-15) days; mean metamizole exposure duration was 4.64±1.86 (2-7) days; mean daily total dose of metamizole was 40±20.6 (15.6-78) mg/kg; mean metamizole cumulative dose was 219.4±113.5 (58.8-468) mg/kg; mean neutropenia duration was 9.4±7.7 (1-30) days; mean white blood cell count was 3030±841 (1400-4420)/$mm^3$; and mean absolute neutrophil count was 690±453 (30-1300)/$mm^3$. Most patients have used metamizole every day. None of the patients had leukopenia history. The majority of neutropenias appeared within 4-5 days. The shortest recorded recovery duration from granulocytopenia was 2 days while the longest recorded recovery duration was 30 days. There were no aplastic anemia cases. Mean hemoglobin was 11.6±2.1 (8.8-15.7) g/dl; mean platelets count was 288±126 (184-616)x$10^9$/L. Four of the patients who used ≥ 30 mg/kg/day doses of metamizole for 4-7 days (≥ 217 mg/kg cumulative dose) had agranulocytosis. One patient had sinusitis, 2 patients had fever of unknown origin, 1 patient had appendicitis, 4 patients had upper respiratory tract infection, 3 patients had pneumonia, and 2 patients had diarrhea as accompanying disorders at diagnosis. 84.6% of metamizole prescriptions were prescribed by family practitioners. The neutropenia treatment included rapid withdrawal of metamizole, use of antibiotics for accompanying infections, and in one more severely affected patient, administration of granulocyte-colony stimulating factor (G-CSF). All of the patients recovered fully. No fatal complications were seen in any of the patients with agranulocytosis. The demographic and laboratory findings of the patients and metamizole doses are shown in Table 1.

We calculated possible pediatric metamizole related agranulocytosis incidence for our hospital as 1/10.000 admission per year. However, we could not calculate the agranulocytosis incidence rate attributable to metamizole exposure (the number of cases per user in the children population) because we did not know the exact total number of patients who used metamizole during one year.

## DISCUSSION

Metamizole has severe hematologic advers effects, the most important ones being agranulocytosis and aplastic anemia. Only a few adult studies are available in the literature that report the risk of agranulocytosis associated with metamizole. The majority of the data is expressed as the number of cases per user population.

**Table I.** The demographic, laboratory, and clinical findings of the patients and metamizole doses. F indicates females; M, males; MD, metamizole dose; WBC, white blood cell count; ANS, absolute neutrophil count; Hgb, hemoglobin; Plt, platelet count; FN, febrile neutropenia, URTI, upper respiratory tract infection; FP, family practitioner; P, pediatrician.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 | Case 12 | Case 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (years old) | 5.5 | 4 | 5 | 1.5 | 6 | 2 | 1.5 | 6 | 11 | 10 | 2 | 10.5 | 5 |
| Sex | F | F | F | M | M | F | M | M | M | M | M | M | F |
| Fever duration (day) | 1 | 10 | 7 | 7 | 3 | 7 | 7 | 15 | 4 | 2 | 7 | 2 | 2 |
| MD (mg/kg/day) | 29.4 | 33.3 | 31 | 45 | 75 | 65 | 41 | 22.2 | 15.6 | 78 | 35 | 16 | 33 |
| MD (cumulative) (mg/kg) | 58.8 | 233 | 217 | 225 | 225 | 390 | 208 | 155 | 128 | 468 | 245 | 64 | 235 |
| Metamizole usage duration | 2 | 7 | 7 | 5 | 3 | 6 | 5 | 7 | 4 | 2 | 7 | 4 | 4 |
| WBC ($mm^3$) | 2900 | 2610 | 1400 | 3800 | 3070 | 3520 | 3800 | 3660 | 2800 | 2870 | 4420 | 2840 | 1700 |
| ANS ($mm^3$) | 1100 | 30 | 200 | 1000 | 570 | 140 | 1000 | 1300 | 1200 | 1000 | 530 | 800 | 100 |
| Hgb (g/dl) | 12.4 | 9.7 | 10.6 | 8.8 | 11.5 | 11.1 | 8.8 | 12 | 14.8 | 13.2 | 12.1 | 15.7 | 10.1 |
| Plt ($mm^3$) x $10^9$/L | 206 | 616 | 414 | 184 | 214 | 290 | 184 | 306 | 244 | 208 | 276 | 189 | 420 |
| Neutropenia start time | 2nd day | 7th day | 7th day | 5th day | 3th day | 6th day | 5th day | 7th day | 4th day | 2nd day | 7th day | 4th day | 4th day |
| Neutropenia end time | 1 | 30 | 6 | 6 | 7 | 20 | 7 | 3 | 14 | 6 | 6 | 8 | 9 |
| Accompanying diseases | Sinusitis | FN | Appendicitis | URTI | Pneumonia | Pneumonia | URTI | URTI | Diarrhea | URTI | Pneumonia | URTI | Diarrhea |
| Prescriptioner | FP | FP | FP | FP | P | FP | FP | FP | P | FP | FP | FP | FP |

Although the IAAS reported metamizole-induced agranulocytosis as 1 per million (7), it was found to be 1 per 1439 prescriptions in Sweden (10). A population-based study in the Netherlands describes a 23-fold increased relative risk of agranulocytosis associated with metamizole use (11). Worldwide, metamizole is associated with an estimated 7000 cases/year of agranulocytosis (12). Although this study is not an incidence study, we found the pediatric incidence of possible metamizole related agranulocytosisis as 1/10.000 hospital admission/year for our instutition in Elazığ. This rate is much higher than that of the IAASG's report (1 per million) (7). This result shows us that metamizole is commonly used in our region. Therefore, it is required to inform physicians and parents in this regard. Some genetic factors are also important for risk of agranulocytosis from metamizole. Vlahov et al. (13) have shown significant differences between the metamizole related agranulocytosis patients and healthy population in the frequencies of human lymphocyte antigen (HLA) alleles and chromosome aberrations.

The duration between the ingestion of the first dose and onset of the blood dyscrasias in agranulocytosis associated with metamizole use vary widely in the lietrature. The clinical features can generally appear after a few days and normally no later than 1-3 months after the initiation of drug administration (14). In our patients, we observed neutropenia and agranulocytosis within 2-7 days. These results indicate that metamizole related granulocytopenia or agranulocytosis in our patients occurred in a dose dependent way and not idiosyncratically. Drug-induced agranulocytosis may be type 1 (involving the drug, antibodies, and neutrophils), type II (associated with accumulated drug toxicity in hypersensitive persons), or type III (representing different etiologies induced by immune and toxic mechanisms) (15). Most of the metamizole-induced agranulocytosis is generally thought to be an immune-mediated reaction by creating a novel antigen when one of its metabolites binds to the neutrophil membrane. The resultant immune response causes both peripheral and bone marrow cell lysis (16).

The symptoms of agranulocytosis or neutropenia may involve sudden onset of high fever, sore throat with ulcerative angina, or stomatitis. In the present study, 1

patient had sinusitis, 2 patients had fever of unknown origin, 1 patient had appendicitis, 4 patients had upper respiratory tract infection, 3 patients had pneumonia, and 2 patients had diarrhea as accompanying disorders at diagnosis. Treatment of metamizole-induced agranulocytosis or neutropenia involves immediate withdrawal of the drug; agranulocytosis was normally expected to ameliorate within a month after stopping metamizole (15). Granulocyte colony stimulating factor (G-CSF) has been available for the treatment of neutropenia since the beginning of the 1990s. G-CSF was given to patients with agranulocytosis who did not recover spontaneously within few days as well as to those with more severe blood dyscrasia and infections. A case of bone marrow recovery after treatment with steroids has been reported in the pediatric literature (17). All of our patients recovered fully. No fatal complications were seen in any of the patients having agranulocytosis. However, one patient with agranulocytosis developed febrile neutropenia which required G-CSF and antifungal treatment. Another patient developed appendicitis. Because neutrophil count of this patient was low, clinical and radiological signs of appendicitis were masked, and, consequently, we could only have a late appendicitis diagnosis. However, the patient could be operated without any complications. Our data suggests that neutropenia and agranulocytosis are the only manifestations of metamizole-induced blood dyscrasia in our study population. We did not find any metamizole toxicity on erythropoiesis and thrombopoiesis.

Correct dosing of metamizole is another important issue. In a study from Brazil, it was found that most of the patients who received metamizole were given an incorrect dose; 15.2% received too little metamizole while 84.8% received too much (18). In the present study, four agranulocytosis patients used ≥ 30 mg/kg doses of metamizole for 4-7 days (≥ 217 mg/kg cumulative dose). The most common reason for using metamizole was fever.

We did not have any patients who were exposed to metamizole in hospitals by intra venous routes. Our patients had been exposed to oral formulation only. It was considered that the treatment duration with metamizole in hospitals have been short for sensitisation to occur. These data show that short-term low dose consumption of metamizole is relatively safe. However, it is recommended that practitioners should avoid long-term or high dose administrations. The vast majority of patients had the medication through family practitioner prescription. This shows that most of the family practitioners are not aware of the potential toxicity of metamizole. Therefore family practitioners should be informed in this regard urgently.

## CONCLUSIONS

The results of this study show that metamizole can cause granulocytopenia and severe agranulocytosis, which are more common than we usually think they are. These side effects occur mainly in home users of young children by oral intake. Granulocytopenia is generally normalized within ten days, however life-threatening complications secondary to agranulocytosis might be seen. In the light of this information, all physicians are adviced to keep the toxic effects of metamizole in mind and against preferring metamizole as a first line antipyretic agent. Physicians also should be familiar with the considerable number of metamizole containing brands and preparations on the market. Public health authorities must remain active in discouraging its use, as well as promoting the use of safer alternatives to metamizole.

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