Upper Respiratory Tract Infection Symptoms as a Herald Sign of Metamizole-Induced Neutropenia

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Abstract

Metamizole is an analgesic and antipyretic drug commonly prescribed in various countries. In young adults living in overcrowded conditions, such as soldiers in training camps, upper respiratory tract infection (URTI) symptoms are common and metamizole is frequently used for treatment. This report describes a severe metamizole-induced neutropenia in a 19-year-old infantry recruit who presented with non-specific URTI symptoms. The article briefly reviews the adverse reaction and describes its incidence as reflected in various studies. The aim is to raise awareness among healthcare providers regarding the possible early symptoms that may indicate the development of this idiosyncratic adverse reaction following metamizole consumption.

Keywords: Metamizole, neutropenia, agranulocytosis, idiosyncratic reaction

Background

Metamizole was previously reported to be among 11 drugs that accounted for more than 50% of drug-induced (non-chemotherapy related) agranulocytosis cases[1] and was banned in the USA in 1977, followed by similar restrictions in Japan, New Zealand, Singapore and other countries. Nevertheless, it is still available in some countries as an over the counter (OTC) drug[1]. Numerous studies worldwide have examined the incidence of the phenomenon, suggesting that only a minority of cases (around 10%) occur in children and young adults and almost double in women[2]. The results are quite consistent, with the exception of a Swedish study from the early 2000s that demonstrated significantly higher incidence of approximately 1 case per 1 400 treated patients. However, it was later noted that the study was based on inaccurate sales data from local pharmacies and, therefore, it was unclear how reliable the results were[3]. Recent studies demonstrated drug-related agranulocytosis incidence ranging from 0.46 to 1.63 cases per 1 000 000 person-days of use[2].

History

A 19-year-old infantry recruit at the Israeli Defense Forces (IDF), was admitted to a medic with symptoms including general weakness, diffuse headache and sore throat for the past three days accompanied by a 39.6°C fever. The patient was generally healthy, with no regular medications nor reported sensitivity or allergy to past substances or drugs. The medic consulted by phone with a physician that was based in a remote post and was instructed to follow the patient's symptoms and to administer analgesics that were at his disposal. The patient was administered one tablet of metamizole by the medic. It is important to note that in Israel, metamizole is considered an OTC drug and can be purchased with no prescription. Military medics can administer up to four tablets of metamizole at once without consulting a physician. Upon receiving the tablets, medics instruct the patients to keep at least six hours between each tablet consumption and advise not to consume more than one tablet at a time. The next day, the patient returned to the medic with no relief and accompanied with a 40°C fever. Due to the lack of improvement in the patient's symptoms and the ongoing fever, the medic consulted again with the physician who instructed him to refer him to the nearest emergency room/department (ER/ED) for further investigation and treatment.

Examination and clinical findings

The patient represented to the ER with the same above-mentioned symptoms and a normal physical examination except for general weakness. Measured blood pressure was 97/47 mmHg with a heart rate of 86. Fever of 39.1°C was measured and blood oxygen saturation was normal. Chest x-ray imaging and general urine test were normal. Laboratory finding indicated normocytic anaemia (HB 9.7 gr/dL, HCT 28.9%, RBC 3.9 *10^6/ul) and neutropenia

(WBC 0.47 *10^3/ul, NEUT 0.01 *10^3/ul) with a slight INR extension (1.6). Platelet count was normal (164 *10^3/ul). During his hospitalisation, a bone marrow examination was performed, showing a hypocellularity of 1% (normal range 30–70%), without an indication of bone marrow blasts. A manual blood smear test was also performed without any sign for peripheral blood blasts. The patient was admitted to the intensive care unit (ICU) due to a suspected maturation arrest of the blood lines, resulting in deep neutropenia accompanied by fever of unknown origin and hemodynamic instability, and was placed in protective isolation. Serology tests for common viruses including HIV were negative. Blood, stool and urine cultures were negative, and nasal swab for common respiratory viruses was also negative. Abdominal ultrasound and a second chest x-ray were performed and returned normal. Later physical examination revealed minor bilateral enlarged cervical lymph nodes without lymphadenopathy at any other site. In consultation with an ear, nose and throat (ENT) specialist, and in view of the anamnesis and physical examination, it was agreed that the patient may suffer from acute tonsillitis/pharyngitis. The patient was administered Filgrastim (granulocyte colony stimulating factor [G-CSF]), and started a doxycycline, ceftriaxone and meropenem regimen. Nevertheless, no fever reduction within the next 24 hours was achieved. At the family's request, the patient was transferred to a hospital closer to his home and was examined again by an ENT specialist who concluded he was suffering from acute pharyngitis, without any sign for peritonsillar abscess. Laboratory exams still pointed to leukopenia (0.7 *10^3/ul), with neutropenia (0.02 *10^3/ul), anaemia (10 gr/dL) and increased C-reactive protein (CRP) (217 mg/L). A chest and sinuses computational tomography (CT) scan returned normal with no sign for deep infection nor an abscess formation. An antifungal treatment (Fluconazole) was started concurrently with Filgrastim. The following day, the fever was gone and laboratory tests showed hyperleukocytosis (HB 11.17 gr/dL, WBC 31.45 *10^3/ul, NEUT 25.6 *10^3/ul, PLT 828 *10^3/ul). During hospitalisation and later ambulatory follow-ups, blood lines returned to normal. It was concluded that due to the proximity of the metamizole consumption, the patient suffered from an idiosyncratic drug-induced severe neutropenic event. In a thorough anamnesis, the family mentioned that at the age of 14, the patient suffered from a similar event of fever and neutropenia that led to hospitalisation and extensive investigation, concluding a drug-induced adverse reaction due to the consumption of metamizole several days before symptoms occurred. It is important to note that during that 5-year time period, the patient reported metamizole consumption several times without any adverse reaction.

Discussion and conclusions

Idiosyncratic drug reaction (IDR) is an 'adverse reaction that does not occur in most patients treated with a drug and does not involve the therapeutic effect of the drug… (the adverse reaction) is unpredictable and often life threatening'[4]. It is a Type B (hypersensitivity) adverse drug reaction (ADR), representing 10–15% ADRs and is independent of drug dosage. The mechanism remains unclear and reflects multifaceted interactions of metabolic factors and genetic predispositions. Neutropenia is defined as an absolute neutrophil count (ANC) <1500/microL while agranulocytosis is defined as ANC = 0. ANC is calculated as WBC [cells/microL] X % [polymorphonuclear neutrophils (PMNs) + bands]) ÷ 100. Agranulocytosis is a rare condition with a reported incidence ranging from 1–5 cases per 1 000 000 persons per year with 70% of cases related to drug consumption. The onset is usually delayed and can occur as late as one month after the drug has been discontinued. Clinical presentation is usually oral ulcerations, and/or a sore throat with or without fever. Neutrophil count usually returns to normal within several weeks of drug withdrawal[1]. Metamizole is an analgesic, spasmolytic and antipyretic drug commonly in use since the 1920s. The drug can induce production of antineutrophil antibodies and induce direct toxicity towards the progenitor cells in the bone marrow[5]. When taking into consideration the common pharmaceutical alternatives to metamizole, mainly acetaminophen and various NSAIDs derivatives, other factors beside the risk of neutropenia should be considered. A comparison between short-term treatment with aspirin, diclofenac, acetaminophen and metamizole showed that mortality risk due to agranulocytosis, aplastic anaemia, anaphylaxis and upper gastrointestinal complications was similar between metamizole and acetaminophen and substantially lower than the risk with aspirin and diclofenac (7 and 23 times less, respectively)[6]. There is insufficient information in the literature regarding the teratogenic effects of metamizole in pregnancy and other pregnancy outcomes, but evidences suggest that, particularly in comparison to NSAIDs, it does not appear to be teratogenic[7]. Therefore, while metamizole is an efficient analgesic and antipyretic drug; drug-induced neutropenia should be kept in mind when prescribing this medication. The drug's severe adverse reactions and associated mortality rate are significantly lower than those of the various acetaminophen and NSAIDs derivatives are. However,

although it is very rare, the chance of developing neutropenia due to the consumption of the drug is higher compared to acetaminophen and NSAIDs. Due to its idiosyncratic nature, it is not possible to predict when a patient will develop the phenomenon and under what dosage, whatsoever. Although there is no effective way to detect the patients whom are at high risk for metamizole-induced neutropenia – previous neutropenic episodes put the patient at higher risk for a recurrent future event. Moreover, it is suggested that treatment duration should be kept as short as possible and that patients should seek medical attention if they develop fever, sore throat or mouth sores. Upon being examined by a physician, it should be considered whether an urgent blood test is needed for excluding acute neutropenia. In addition, the case demonstrates the importance of electronic medical records (EMRs) sharing among healthcare organisations as in the case of the Israeli military computerised patient records (CPR) and other civilian EMRs. Should the electronic records be shared, the previous neutropenic event of the patient might have been easily detected.

List of abbreviations

ADR – Adverse drug reaction

ANC - Absolute neutrophil count

CPR – Computerised patient records

CT – Computational tomography

EMR – Electronic medical record

ENT – Ear, nose and throat

ER – Emergency room

ICU – Intensive care unit

IDF – Israeli Defense Forces

IDR – Idiosyncratic drug reaction

INR – International normalised ratio

NSAID – Non-steroidal anti-inflammatory drug

OTC – Over the counter

PMN – Polymorphonuclear neutrophils

URTI – Upper respiratory tract infection

WBC – White blood count

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