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CASE REPORT

A study of the clinical toxicity of methotrexate in the Taif region: a case report

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ABSTRACT

Background: The first report, written by Sidney Farber in 1948, detailed his success in the use of methotrexate (MTX) for the treatment of leukemia in children. The drug was used for the first time in 1951 for the treatment of rheumatoid arthritis and psoriasis. MTX classical antifolate, also known as amethopterin, is 4-amino-4-dcoxy-Na-methyl folic acid. The correlation between toxic reactions and the pharmacokinetics of MTX discloses certain time- and concentration-dependent relationships that appear to determine which target tissue is at risk for toxicity, whether toxicity will occur and the severity of MTX toxicity. A high dose of MTX (HDMTX) is defined as more than 500 mg/m² or if given intravenously.

Case Presentation: HDMTX can cause significant toxicity, including myelosuppression, mucositis, hepatotoxicity and, in severe cases, may cause multiorgan failure.

Conclusion: An early understanding of the causes and risk factors for MTX toxicity may be beneficial in reducing the occurrence of MTX toxicity in the Taif region.

Keywords: Methotrexte, toxicity, high dose, hepatotoxicity, rheumatoid arthritis.

Background

Methotrexate (MTX) is a common drug. Farber et al.'s [1] initial report in 1948 was on using it to treat pediatric leukemia. MTX was used to treat psoriasis and rheumatoid arthritis (RA) in 1951 [2]. Several years later, its efficacy and superiority over placebos were reported in patients with chronic and severe RA [3]. The European League Against Rheumatism (EULAR) recommends MTX with low-dose glucocorticoids for RA. MTX may boost the efficacy of disease-modifying antirheumatic drugs (DMARDs) and has lower doses than other synthetic DMARDs. These results show the superiority of MTX and why it is preferred over DMARD for RA [4].

The mechanism of MTX enters the cell and undergoes polyglutamation, which is mediated by the enzyme folylpolyglutamate synthetase. MTX is maintained in cells long after being polyglutamated. By inhibiting the dihydrofolate reductase (DHFR) enzyme, MTX and its polyglutamate (MTXGlu) principally limit de novo nucleotide synthesis by depriving cells of reduced tetrahydrofolate cofactors [5]. Since it affects DNA synthesis, repair, and cell replication, MTX also has anti-inflammatory and immunomodulatory properties [6]. MTX is cell-cycle specific for the S phase of the cycle. Low-dose MTX (<1 mg) arrests leukemic myeloblasts in

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the S phase for about 20 hours and does not have a direct effect on cells in the G1, G2, or M phases of the cell cycle [4]. Higher doses of MTX (HDMTXs) (>30 mg) arrest human myeloblasts in phase S for more than 48 hours and slow the entry of cells [7]. Reduced folates are also needed as cofactors in the conversion of homocysteine to methionine and glycine to serine. By interfering with these amino acid interconversions, MTX can also inhibit protein formation. This effect might be the method by which high-dose MTX "arrests" cells in the G1 phase. Decreased folates are also required for the metabolism and normal synthesis of neurotransmitters in the central nervous system [8]. The reduction in decreased folates by MTX may cause neurotoxic effects, especially when MTX is immediately injected into the cerebrospinal fluid [8].

The pharmacokinetics of MTX and toxic responses are correlated, and this connection reveals interactions correlated with time and concentration that seem to define which target tissues are at risk of toxicity and how toxic MTX will be [9]. The severity of MTX toxicity is determined by the degree to which the time threshold is exceeded [10]. HDMTX, defined as a dose more than 500 mg/m^2, is used to treat a of adult and childhood cancers [11]. HDMTX can cause significant toxicity, including liver toxicity, myelosuppression, and mucositis. In severe instances, it may cause multiorgan failure [12]. This study is a case report in the city of Taif in Saudi Arabia to determine the incidence of MTX-poisoning cases and to help healthcare professionals reduce and prevent the occurrence of MTX toxicity in the future.

Case Presentation and Results

Case report 1

The patient was a 56-year-old woman. She was admitted to the emergency department with dyspnea, gastrointestinal symptoms such as nausea and vomiting, abdominal pain, dyspepsia, and mouth sores from the previous 4 days. The symptoms worsened over time. She had been using MTX continuously for 14 days, according to the analysis of the medications she had consumed. The patient's background was investigated while searches were performed to determine why the patient was taking MTX. She came to her appointment in the cardiology clinic and then the cardiologist wrote for her to take MTX 2.5 mg once a day instead of metolazone 2.5 mg. She had used MTX 2.5 mg for 14 consecutive days. At admission, her vital signs were: blood pressure = 90/60 mmHg, pulse rate = 82/minute, respiratory rate = 12/minute, and temperature = 38.2°C. She showed her mucocutaneous lesions during a physical examination at the time of presentation. The results of the laboratory tests on admission were as follows: hemoglobin = 9.1 g/dl, WBC = 3,200/mm^3, platelet counts = 50,000/mm^3, blood urea nitrogen (BUN) = 81 mg/dl, creatinine = 1.8 mg/dl, aspartate aminotransferase (AST) = 18 IU/l, alanine aminotransferase (ALT) = 17 IU/l, prothrombin time (PT) = 14 seconds, partial thromboplastin tim (PTT) = 36 seconds, international normalized ratio (INR) = 1.14, bilirubin total = 1.2 mg/dl, and bilirubin direct = 0.3 mg/dl. She was admitted to the intensive care unit (ICU). Platelets and antibiotics were administered and dermatology care was considered for her. Finally, she died of pulmonary edema resulting from her underlying cardiac disease, 7 days after admission.

Case report 2

The 72-year-old patient was suffering from an advanced stage of kidney disease and had been on continuous dialysis for 3 years. She was diagnosed in the rheumatology clinic with chronic RA with reference to clinical and laboratory data, and, accordingly, MTX treatment was prescribed at a dose of 15 mg/week plus prednisolone folic acid 5 mg/day. The patient was admitted to the emergency room, complaining of difficulty swallowing and severe fatigue. Upon examination, it was found that she was suffering from painful ulcers in the mouth and throat and had difficulty swallowing. Due to taking MTX, she was admitted to the health isolation room under the care of the internal staff. The patient was prescribed antibiotics, a drug that stimulates white blood cells, and other treatments. After her stay in hospital for 4 weeks, the blood components returned to normal and the ulcers in her mouth improved as well as her ability to swallow and eat. The blood culture was for bacteria. Before the patient was flagged for discharge, she took responsibility for discharging herself from hospital, as she refused to begin treatment with warfarin blood thinner, which a cardiologist prescribed to prevent clots that may be caused by chronic heart palpitations, which the patient had been suffering from for several years. Five days after discharge from hospital, the patient entered the emergency department due to a sudden loss of consciousness and difficulty speaking. In the emergency department, acute cardiac and respiratory arrest occurred and she was treated several times and then admitted to the ICU. The patient received granulocyte colony stimulating factor (G-CSF), blood transfusions, folinic acid, and dialysis when MTX was withdrawn, but died 3 days later from multiorgan failure.

Case report 3

Plaque psoriasis affected a 55-year-old man. Topical corticosteroids were ineffective. Oral MTX 10 mg/week was prescribed. He was hospitalized 4 days. Fever, dysphagia, mouth ulcers, and erosions are common symptoms as are pre-existing psoriasis plaques. Laboratory tests revealed a high level of liver enzymes in the blood and a low platelet count. Direct interrogation uncovered that the patient was taking 10 mg of MTX daily. Folinic acid 15 mg/day was shown to be helpful. Treatment began with folic acid and was subsequently switched to folinic acid 5 mg/day. Consequently, the results of the tests and the appearance of skin lesions improved.

Table 1 below reveals the clinical characteristics, laboratory tests, and treatment of these three cases:

Table 1. *The clinical characteristics, laboratory tests, and treatment of the three cases.*

Treatment	Laboratory findings	Clinical findings	Concomitant diseases	MTX dose taken	Dose prescribed	Medication prescribed	Gender	Age
Folinic acid	AST 18 U/l ALT 17 U/l Hb 9.1 g/dl PLT 50,000/dl WBC 3,200/mm^3 CR 1.8 mg/dl	Mucocutaneous lesions Oral ulcers	Hypertension	2.5 mg daily	2.5 mg daily	Metolazone	Female	56
Folinic acid, G-CSF, meropenem, dialysis	AST 146 U/l ALT 220 U/l ALP 111 U/l WBC 2,000/mm^3	Ulcers in the mouth and throat Difficulty swallowing Severe fatigue	RA Renal insufficiency	15 mg daily	15 mg weekly	MTX	Male	72
Folinic acid, antibiotics	Hb 10.70 g/dl PLT 128,000/dl WBC 4,000/mm^3 CR 0.93 mg/dl	Ulcers in the mouth and throat Difficulty swallowing Fever	Plaque psoriasis	10 mg daily	10 mg weekly	MTX	Male	55

Discussion

The FDA has authorized MTX to treat moderate to severe psoriasis and T-cell lymphomas of the skin, but it is also used to treat bullous autoimmune diseases, atopic dermatitis, autoimmune collagen disorders, and other inflammatory dermatologic problems [13]. Due to its effectiveness and long-term safety profile, EULAR recommended MTX as the initial therapy option for patients with RA [14]. In dermatologic indications, the normal dose ranges from 7.5 to 25 mg/week (once). These modest doses, compared to those used for oncologic purposes, can have direct anti-inflammatory effects by raising adenosine levels through the intracellular production of MTXGlu [15]. MTX works as an antimetabolite in highly mitotically active cells in high doses by blocking DHFR, a key enzyme in DNA synthesis [16].

However, in patients taking MTX therapy, common side effects include toxicities in various organs or systems. From administration, absorption, metabolism, and excretion, most of them are based on the pharmacological and pharmacokinetic mechanisms of MTX. Because most of these adverse effects involve immunologic, inflammatory, or lymphoproliferative problems, they are not completely separated.

The skin, gastrointestinal mucosa, liver, kidneys, and bone marrow of patients are affected by MTX toxicity. Because hyperproliferative psoriatic plaques absorb more MTX than normal skin, skin ulcerations caused by MTX toxicity are limited to psoriatic plaques. The third case had ulceration on psoriasis plaques that had already occurred. In the second case, renal dysfunction, infection, folic acid insufficiency, hypoalbuminemia, and advanced age were all linked to MTX-induced pancytopenia. Within the first 10 days of MTX toxicity, pancytopenia develops.

Renal function impairment, pharmacokinetics, heavy alcohol intake, infections, and advanced age are other risks. In the cases discussed, the most frequent cause of acute MTX toxicity was overdose related to medication errors (daily instead of weekly dosage). Patients with low cognition, elderly patients taking many drugs or living alone, patients with linguistic difficulty, and psychiatric patients should avoid this drug.

As a result of a lack of facilities, the authors were unable to measure the drug level of MTX. However, accidental administration of MTX, which is a major contributory factor in toxicity, was a common aspect of all of them. Drugs can decrease renal elimination of MTX (aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs), cyclosporine, sulfonamides, salicylates, penicillin, colchicine, probenecid, cisplatin, and other renotoxic drugs) or displace MTX from protein-binding sites in plasma (aminoglycosides, cyclosporine, NSAIDs, salicylates, sulfonamides, barbiturates, phenytoin, probenecid, retinoids, sulfonylureas, and tetracyclines). In the fourth case, an NSAID used for joint pain contributed to MTX toxicity.

Self-administration of MTX, as in the third case, must be avoided. The patient would be well advised not to use the medications without consulting a dermatologist and not to combine them with other drugs without the consent of the doctor. The third case consumed MTX without adhering to standard investigative and therapeutic

protocols. In one patient, MTX was withdrawn and intravenous folinic acid was begun. Furthermore, due to the worsening of leucopenia, G-CSF was administered in the second case. Platelet transfusion and romiplostim injections were used to treat severe thrombocytopenia and bleeding.

Serious complications, including death, can result from a lack of awareness of the condition, medication combinations, and nonadherence to the treatment plan. Primary-care physicians should also be aware of the various causes of toxicity, as most of them can be prevented with continuous monitoring and appropriate guidance. In addition, a complete history of the patient's condition should be produced to determine the therapeutic dose of MTX and choose the right medications.

Conclusion

When making a treatment choice for MTX, consider the increasing prevalence of comorbidities and polypharmacy. Although MTX has a long history of use in dermatology, the substantial morbidity, and probable death associated with acute MTX toxicity explain the need for patient education and careful monitoring. To avoid errors in administration, patients must be carefully chosen, and appropriate explanations and written or graphic instructions on prescription patterns must be provided. Although low-dose MTX is considered a generally safe drug, dermatologists must be aware of the characteristics, management, and prevention of MTX toxicity, as it can be life threatening.

Conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication
Due permission was obtained from the patients/guardians of the patients to publish the case and the accompanying images.

Ethical approval
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