



CASE REPORT

Methotrexate overdose induced acute kidney injury and pancytopenia: a case report

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ARTICLE INFO ABSTRACT



Received 04 September 2023;
Revised 22 October 2023;
Accepted 21 November 2023.

Keywords:
Dose, Adverse Drug
Reactions, Rash

Introduction: Methotrexate is a folic acid antagonist. Dose of methotrexate is ranging from 7.5 mg–30 mg per week. In rheumatoid arthritis (RA), a low dose of methotrexate is used.

Case presentation: A 48-year-old female patient suffering from RA, was admitted to a tertiary care hospital. The patient was taking methotrexate 15 mg daily instead of once weekly dosing schedule mistakenly (cumulative dose of 105 mg). The patient presented with a diffuse ecchymotic rash over both extremities with oral mucositis associated with dysphagia. Upon investigation, pancytopenia (TLC= 3400 / μ L, RBC= 1.85 Lac/ μ L, Platelets= 6000/ μ L) with microcytic hypochromic anemia (Hb= 4.3 g/dl) with acute kidney injury (Urea= 78 mg/dl, Creatinine= 2.26 mg/dl) was found. Elevated C-reactive protein (9.8 mg/dl) and dyslipidemia (Triglyceride= 218 mg/dl) were also evident. The case was suspected to be methotrexate toxicity and reported in the suspected Adverse Drug Reaction (ADR) form(v1.4).

Management: The patient was advised to stop methotrexate and manage with injectable folic acid (25 mg thrice Daily for 3 days) and clotrimazole mouth paint locally (thrice daily for two weeks). ADR was assessed as Probable/Likely (WHO-UMC scale), Probable (Naranjo scale), Severe (Modified Hartwig's Severity scale), and Preventable (Schumock and Thornton scale).

Conclusion: Such case report being the first line of evidence for recognizing unexperienced ADR, should be reported for 'signal detection' to improve patient care and safety. Prescription Audit Guidelines (under National Health Mission) should be followed for drug dispensing.

An official publication of the Global Pharmacovigilance Society.

Introduction

Methotrexate is a folic acid antagonist, widely used in cancer therapy and several chronic inflammatory diseases. It has anti-inflammatory and immunosuppressive effects (Tayci et al., 2017). Dose of methotrexate is ranging from

7.5 mg–30 mg per week (Roening et al., 1988). In lower doses, methotrexate has been used in autoimmune diseases including rheumatoid arthritis, psoriasis, lupus, sarcoidosis, and eczema (Rajnic et al., 2017).



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It interferes with cellular proliferation which predominantly affects the cells with the highest turnover or reduced half-life. Daily accidental ingestion instead of a weekly dose leads to acute methotrexate toxicity (Czarnecka-Operacz et al., 2014). The mechanism of acute toxicity due to methotrexate is by inhibiting DNA synthesis in rapidly proliferating cells i.e., gastrointestinal (GI) tract, and hematopoietic cells. There are no such data regarding the acute cumulative dose causing acute toxicity as well as the duration to achieve acute cumulative toxic dose and there are also various reasons for wrong dosing of methotrexate in Indian patients. A prescription audit tool which is a quality improvement process that seeks to improve patient care, can play an important role in avoiding misuse of drugs and improves rational uses of drugs (Bandyopadhyay et al., 2017).

Case report

A 48-year-old female patient who had a known case of Rheumatoid arthritis had complaints of diffuse ecchymotic rashes involving both the upper and lower extremities with oral mucositis. She had wrongly taken methotrexate at 15 mg daily for one week. On admission, the patient was conscious and oriented and her blood pressure was 118/84 mm of Hg. Oral cavity examination showed ulcerated reddish mucosa, also reddish black lesions were present over both the upper and lower limbs. The patient was also complaining of dysphagia. She was advised to stop methotrexate. Blood count was suggestive of pancytopenia (total leucocyte count= 3400/ μ l, Red blood cell 1.85 lac/ μ l, Platelets= 6000/ μ l) and peripheral blood smear showed microcytic hypochromic anemia with hemoglobin 4.3 g/dl. Upon further investigation, it was reported as elevated serum urea(78 mg/dl) and creatinine(2.26 mg/dl). Elevated c-reactive protein (9.8 mg/dl) and triglyceride(218 mg/dl) were also evident. A dermatologist's opinion was sought.

Keeping with the history, clinical presentation of mucocutaneous lesions with pancytopenia and elevated urea and creatinine, methotrexate toxicity was suspected. The patient was managed with intravenous fluid and injection of folinic acid (25 mg thrice daily for 3 days). Also, clotrimazole mouth paint was advised as thrice daily for two weeks for local application. The case was reported in suspected Adverse Drug Reaction (ADR) form (v1.4).

The images of erythematous lesions are presented in Figures 1,2,3 and 4.



Figure 1: Erythematous lesions over lower limbs



Figure 2: Reddish black lesions with ulceration over lower limbs



Figure 3: Erythematous lesions over the upper limb



Figure 4: Oral mucosal inflammation with ulceration

Discussion

Methotrexate in low weekly doses is considered a first-line therapy for inflammatory diseases such as moderate to severe psoriasis and rheumatoid arthritis. It is generally administered at doses ranging from 7.5-25mg/week (Knoll et al., 2016). Cutaneous ulcerations being rarely reported and poorly characterized, play a crucial role in indicating impending systemic overdose and pancytopenia (Weidmann et al., 2014). In our case, daily intake of methotrexate instead of weekly resulted in acute toxicity. Adverse drug event was assessed using the WHO-UMC scale as "Probable/Likely". According to the Naranjo scale, it was found to be "Probable" (score 5) (Naranjo et al., 1981). Severity was assessed as "Severe" using Modified Hartwig's severity scale (level 5) (Hartwig et al., 1992). In Schumock and Thornton scale, it was found to be "Definitely preventable" (Schumock et al., 1992). This case report also suggests the importance of prescription audits as per national guidelines so that the dispensing of medicine can be proper to avoid misuse or overdosing of the prescribed medicine.

Conclusion

Such case report represents the first line of evidence for recognizing unexperienced Adverse Drug Reactions (ADR) thus improving patient care and safety. Drugs should be dispensed according to Prescription Audit Guidelines under the National Health Mission to improve patient safety. ADR should be reported for 'signal detection'. Detailed counseling regarding the course of disease, dosing schedule, and consequences of methotrexate overdosing should be mandatory for all patients receiving methotrexate therapy to reduce possible adverse effects and life-threatening consequences.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

We thank the Indian Pharmacopoeia Commission for providing a platform to detect and monitor this case as reported.

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