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Case Report

Life threatening acute kidney injury in a patient of rheumatoid arthritis, is it drug or disease related?

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ABSTRACT

Even low-dose MTX therapy for treatment of rheumatic diseases is claimed to cause impairment in renal function. We report an insidious and progressive deterioration of renal function of patient with RA on low-dose MTX in a 41-year-old woman. We suggest that patients on low-dose MTX therapy should be periodically monitored for creatinine levels.

Keywords: Nephrotoxicity, Low dose methotrexate, Rheumatoid arthritis

INTRODUCTION

Methotrexate (MTX) has become the most commonly prescribed disease-modifying anti-rheumatic drug now a day.[1] However, permanent discontinuation of therapy occurs in 1 patient out of 10 due to its toxic side effects. Kidney biopsy revealed advanced kidney fibrosis with extensive interstitial and glomerular fibrosis and vascular sclerosis. RA is a chronic systemic auto inflammatory disease with so many acute complications. It affects joint function and also affect many vital organ systems, including the cardiovascular, pulmonary, gastrointestinal, musculoskeletal, haematological, renal, neurological, and dermatological systems.[2] Many complications can arise from MTX which is used to treat RA. Serious medication-related adverse events are an important issue when selecting appropriate therapies for individual patients who may be at higher risk than others. The necessity to adapt the dosage of MTX therapy for renal function disorders due to other causes however has first priority. Non-steroidal anti-rheumatic drugs (NSAIDs) are also a problematic nephrotoxic group of substances and change for therapeutic armamentarium for rheumatoid arthritis (RA) should be instigated.[3]

CASE REPORT

A 41 years old female patient came to tertiary care hospital with chief complain of fever, nausea, vomiting, itching, weakness, pain in lower limb, skin lesion over face & neck. On the day of admission patient was conscious and well oriented with normal temperature, Pulse: 72/min, BP:126/72 mm hg, RR 16/min, SPO2 99% on room air. Laboratory findings on day of admission included: creatinine 24.5 mg/dl (0.7-1.3), CRP 215 mg/l (<5), K^+ 6.8 mmol/l (3.5-5.5), Na^+ 134 mEq/l (132-146), Ca^{+2} 8.6 mg/dl (8.6-10.3). USG abdomen showed mild hepatomegaly, increase cortical echogenicity in Kidney & B/L renal parenchymal changes. Patient was known case of Rheumatoid Arthritis since 3 months. Her rheumatoid factor RA was 16 IU/ml. So she was taking tablet Methotrexate 15 mg/week, tablet Hydroxychloroquine 200 mg PO BD, tablet Naproxen 500 mg PO BD for rheumatoid arthritis. Patient had also

taken ayurvedic medication (Sargavo, Tulsi, Ashwagandha, Suddha Sallaki) for 10 days before 15 days of admission. Patient do not have diabetes, hypertension and had no past history of jaundice or tuberculosis or any other disease. Patient was suspected to have acute kidney injury due to methotrexate use. Patient was started on dialysis therapy for 4 days along with Inj. Sulbactam & Cefoperazone 1.5G/100 CC NS IV, Inj. Meropenem 500 mg IV TDS, Inj. Fluconazole 200 mg IV OD, Tablet Prednisolone 70 mg PO OD & Injection Lasix 400 mg IV 1-1-1-1. After 5 days of treatment patient's urine output started increasing and serum potassium (3 mmol/l) and serum creatinine (5.17 mg/dl) started decreasing. Patient was in recovery phase till last follow up.

Table 1: Serum creatinine levels in patient at different time intervals.

Duration	Serum creatinine (mg/dl)
Day 0	24.5
Day 3	7.48
Day 4	6.7
Day 5	5.17

This suspected adverse drug reaction (ADR) of "Methotrexate induced acute kidney injury" was reported to PvPI with unique ID no IN-IPC-300642712. Causality assessment of this ADR is "possible" based on WHO causality assessment scale because of temporal relationship between administration of Ayurvedic drugs, NSAIDs and Acute kidney injury also along with Methotrexate.

DISCUSSION

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that blocks de novo nucleotide synthesis. It is used in the treatment of many conditions ranging from autoimmune disease to malignancies, with doses ranging from 20 mg/m^2 per week to 1000-33,000 mg/m^2 depending on indication.[4] Methotrexate (MTX) use can be associated with a variety of adverse effects over a wide range of severity; the risk of most side effects is influenced by the MTX dose and treatment regimen. In rheumatoid arthritis (RA) and other disorders, MTX is administered as long-term, low-dose therapy, usually 7.5 to 25 mg weekly.[5] The etiology of MTX-induced renal dysfunction is believed to be mediated by the precipitation of MTX and its metabolites in the renal tubules or via a direct toxic effect of MTX on the renal tubules.[6] More than 90% of MTX is cleared by the kidneys. MTX is poorly soluble at acidic pH, and its metabolites, 7-OH-MTX and DAMPA, are six- to tenfold less soluble than MTX, respectively. An increase in the urine pH from 6.0 to 7.0 results in a five- to eightfold greater solubility of MTX and its metabolites, a finding that underlies the recommendation of hydration and urine alkalinisation prior to, during, and after the administration of MTX.[7] Before starting treatment, liver and kidney disease should be excluded, and screening done for alcohol use. Pre-treatment investigations should include baseline complete blood count, assessment of liver and renal function, chest radiograph and pregnancy test (in women of childbearing age). Complete blood count, creatinine and liver function test should be assessed every 2–4 weeks for the first 3 months, then 8–12 weeks for the following 3-6 months, and every 12 weeks thereafter.[8] Co-administration with nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the plasma concentrations and toxicities of methotrexate. The proposed mechanism is NSAID inhibition of the renal elimination of methotrexate and its metabolite, 7-hydroxymethotrexate. Displacement of methotrexate binding to serum albumin by certain NSAIDs may also play a secondary role.[9] methotrexate at dosages of 7.5 to 15 mg/week has been used without apparent problems in patients with rheumatoid arthritis who also received constant dosage regimens of NSAIDs. However, there have been occasional reports of stomatitis, pneumonitis, bone marrow toxicity, and fatality in patients receiving low-dose weekly methotrexate with daily NSAIDs.[10] Naproxen may increase the blood levels and side effects of methotrexate. You may be more likely to experience this interaction if you have kidney disease. The risk may be less if you are using methotrexate once a week. Close monitoring for signs and symptoms of bone marrow suppression, nephrotoxicity, and hepatotoxicity is recommended during treatment.[11] Patients should be advised to contact their physician if they develop stomatitis, nausea, vomiting, diarrhea, rash, anorexia, jaundice, dark urine, dry cough, shortness of breath, and/or signs and symptoms of myelosuppression such as pallor, dizziness, fatigue, lethargy, fainting, easy bruising or bleeding, fever, chills, sore throat, body aches, and other influenza-like symptoms. Patients should also be counselled to avoid any other over-the-counter NSAID products. Vomiting and diarrhea during or shortly after the administration of MTX have been observed in patients who developed MTX toxicity but the majority of patients with renal dysfunction are initially asymptomatic, and most present with nonoliguric renal dysfunction. The lack of early clinical symptoms predicting the development of renal dysfunction emphasizes the need for routine monthly monitoring of plasma MTX concentrations and serum creatinine after the administration of MTX. Patients should take folic acid (1 mg) on days they are not taking methotrexate to prevent folate depletion. . Leucovorin (2.5 mg to 5 mg once weekly) can be given to mitigate adverse effects when folic acid has fails. It treats toxicity by bypassing methotrexate inhibition of dihydrofolate reductase, the enzyme required to reduce folate to tetrahydrofolate.[12]

CONCLUSION

Our case indicates that low dose MTX treatment (15 mg weekly) may significantly impair kidney function which has to be considered particularly in situations in combine treatment with other potentially nephrotoxic substances.

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