*ejpmr, 2022, 9(8), 491-493*

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Case Study

ISSN 2394-3211

EJPMR

# A CASE REPORT ON METHOTREXATE OVERDOSE INDUCED ORAL ULCERATIVE MUCOSITIS AND PANCYTOPENIA

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**Article Received on 31/05/2022** **Article Revised on 20/06/2022** **Article Accepted on 10/07/2022**

## ABSTRACT

**Background**: Methotrexate is a folic acid antagonist commonly used for Cancer therapy and for the management of several chronic inflammatory diseases. It functions by interfering with the cellular profileration and at high doses can cause increased risk for bleeding, infections and cytopenias. **Case Presentation**: In this case, a female patient aged 58 was admitted in the general medicine department with complaints of oral ulcer, mucositis and difficulty in food intake. She had a history of rheumatoid arthritis and was on treatment with methotrexate and folic acid. She had accidentally overdosed on 7.5mg of methotrexate twice daily for 1 week. She was managed with intravenous antibiotics, Inj Leucovorin 100mg intravenous every 6 hourly along with antacids and supportive care. **Conclusion**: The symptoms associated with accidental overdosing of Methotrexate was managed appropriately with administration of Leucovorin. The ulcerative mucositis and stomatitis was managed efficiently and the blood methotrexate level was below toxicity level. Patient had improved therapeutic outcome with the management provided.

**KEYWORDS**: Methotrexate toxicity, Mucositis, Oral ulcer, Pancytopenia, Leucovorin.

## INTRODUCTION

Methotrexate is a folic acid antagonist commonly used for Cancer therapy and for the management of several chronic inflammatory diseases. It is usually used for the management of autoimmune diseases such as psoriasis, lupus, rheumatoid arthritis, eczema and sarcoidosis.[1]

It functions as a folate antimetabolite that binds to an enzyme called dihydrofolate reductase, which results in an inhibition of DNA synthesis. At higher doses (0.5-12g/$m^2$), it is used as an anticancer drug and at lower concentration (1-40mg/$m^2$) it is used for inflammatory diseases such as psoriasis, rheumatoid arthritis and Eczema.[2]

It acts mainly by interfering with the cellular profileration and at high doses can cause increased risk for bleeding, infections, macrocytic erythrocytes and cytopenias.[1] The Gastrointestinal side effects associated with methotrexate toxicity includes nausea, vomiting, ulcerative mucositis, stomatitis and secondary anorexia, pharyngitis, enteritis, diarrhea and can even cause pneumonitis and hepatitis.

It can also cause headache, dizziness, fatigue and at higher doses, toxicity occurs in the bone marrow leading to pancytopenia. Dysregulation of the immune system leads to fever which can result in an increased risk and incidence of infections.[3]

## CASE PRESENTATION

A 58 year old female patient was admitted in the general medicine department with features of oral ulcer, mucositis and difficulty in food intake. She had a history of rheumatoid arthritis, hypertension, Type II diabetes mellitus and was on treatment with methotrexate and folic acid for rheumatoid arthritis. On examination of the patient's history and enquiry it was found that she had accidentally overdosed on 7.5mg of methotrexate twice daily for 1 week. Her blood investigation revealed a low WBC count (2000 cells/mm3), low Hb level (9.1 g/dl), low neutrophil level (27.1%), low platelet count (1.2 lakh/microlitre) indicating pancytopenia, elevated ESR (134mm/hr) and an elevated CRP (285mg/L). The patient also had a slightly elevated Bilirubin levels and liver enzymes indicating mild liver impairment due to methotrexate toxicity.

She was managed with intravenous antibiotics (Piperacillin Tazobactum 4.5g, Metronidazole 500mg), Inj Leucovorin 100mg intravenous every 6 hourly to manage methotrexate toxicity and to prevent further

complications. Tab sodium bicarbonate 500mg thrice daily in addition to Syp Mucaine gel (Oxetacaine+ Aluminium Hydroxide+Milk of Magnesia) 10ml TDS, Syp Gaviscon (Sodium alginate+ Sodium bicarbonate+ Calcium carbonate) 15ml TDS and Inj Pantoprazole 40mg BD were given. Inj Methylprednisolone 40mg was given intravenously Q8H. T.Folic acid 5mg 1-0-1 and multivitamins and minerals were also given to manage the condition. Metronidazole ointment was given for local application in mouth.

## DISCUSSION

Methotrexate toxicity can lead to side effects which affects various organ systems in the body. The adverse effects are usually produced by methotrexate inhibition on folate synthesis and on the transmethylation reaction and purine synthesis. It usually affects the highly proliferative and replicative cells such as blood stem cells and mucosal tissues.[4] If Methotrexate toxicity is suspected, the drug must be stopped and blood level must be measured to evaluate the extent of toxicity and for the administration of Leucovorin.[5]

The patient was treated with intravenous antibiotics (Piperacillin Tazobactum 4.5g, Metronidazole 500mg), Inj Leucovorin 100mg intravenous every 6 hourly to manage methotrexate toxicity and to prevent further complications. Leucovorin is a biologically active S-form of racemate folic acid and is indicated particularly for methotrexate toxicity. It should be given intravenously every 6 hours and it helps in replenishing the intracellular levels of reduced folate bypassing dihydrofolic acid reductase and provides substrates required for purine and thymidylate synthesis.[6] Tab sodium bicarbonate 500mg was given thrice daily and its administration helps to improve and promote the methotrexate excretion by urine alkalinization along with adequate hydration. Due to the poor solubility of methotrexate in acidic solutions, raising the PH of urine helps in increasing its excretion.[7]

Syp Mucaine gel (Oxetacaine+Aluminium Hydroxide+Milk of Magnesia) 10ml TDS and Syp Gaviscon (Sodium alginate+ Sodium bicarbonate+ Calcium carbonate) 15ml TDS and Inj Pantoprazole 40mg BD were given to reduce gastric irritation and to minimize the impact of stomatitis that occurs with methotrexate toxicity.[8] Inj Methylprednisolone 40mg was given intravenously Q8H to help reduce the effects of oral ulcer, mucositis and stomatitis.[9]

Metronidazole ointment was given for local application in mouth to manage the oral ulcer and to prevent further oral infection and complications. Folic acid supplement was also given to avoid the folic acid deficiency that had occurred with methotrexate toxicity and to replenish the normal level of folic acid in the body which is essential for DNA synthesis and cellular replication.[10] The blood methotrexate level after treatment with Leucovorin and supportive care was found to be within normal levels. Patient's condition was improved and hence was discharged.

## CONCLUSION

The symptoms associated with accidental overdosing of Methotrexate was managed appropriately with measurement of the blood methotrexate level and administration of Leucovorin. The ulcerative mucositis and stomatitis was managed efficiently and the blood methotrexate level was below toxicity level. Patient had adequate and improved therapeutic outcome with the management provided.

## DECLARATION OF CONFLICTING INTERESTS

The author(s) declare that there is no conflict of interest.

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