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AN OVERVIEW ON METHOTREXATE TOXICITY IN CLINICAL PRACTICE

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ABSTRACT

Background: Methotrexate, the folic acid analogue is a highly efficacious drug that is commonly prescribed for a wide range of diseases like rheumatoid arthritis, severe psoriasis, Crohn's disease and some cancers. Since the drug has a narrow therapeutic index and once weekly dosage regimen, high doses or accidental overdose can result in potential life threatening toxicity. Due to the potential toxicity, the drug needs to be continuously and carefully monitored for the serious toxic events including bone marrow suppression, liver toxicity etc. **Methods:** Previously published literatures regarding the use and toxicity of methotrexate was collected and reviewed. **Observations:** The widely prescribed drug methotrexate poses large range of toxic events related to overdose. The toxicities include bone marrow suppression, hepatotoxicity, hematologic toxicities, nephrotoxicity, neurotoxicity, dermatologic toxicities including ulceration during treatment of severe psoriasis, oral mucositis and also gastrointestinal toxicities. Methotrexate overdose has complex toxicokinetics characteristics and produces clinical conditions that are of less severity but the occurrence of organ damage due to bone marrow suppression, nephrotoxicity, hepatotoxicity, neurotoxicity can be fatal. As per the quote "prevention is better than cure" proper patient education and rational treatment can avoid the toxic effects due to methotrexate overdose.

KEYWORDS: methotrexate, overdose, toxicity.

INTRODUCTION

Methotrexate, a folic acid antagonist is a highly efficacious drug that belongs to therapeutic categories like antineoplastic, DMARD, immunosuppressant. Methotrexate interferes with the growth of certain rapidly reproducing cells like cancer cells, bone marrow cells and skin cells.

Methotrexate acts by blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). It has cell cycle specific action- kills cells in S phase. It also inhibits thymidylate synthase so that DNA synthesis is primarily affected. Methotrexate, the DMARD also has effect on the adenosine pathway thus poses anti-inflammatory effects.[1] The inhibition of transformylase leads to increased level of adenosine, which is a potent inhibitor of inflammation and also induces vasodilation.[2]

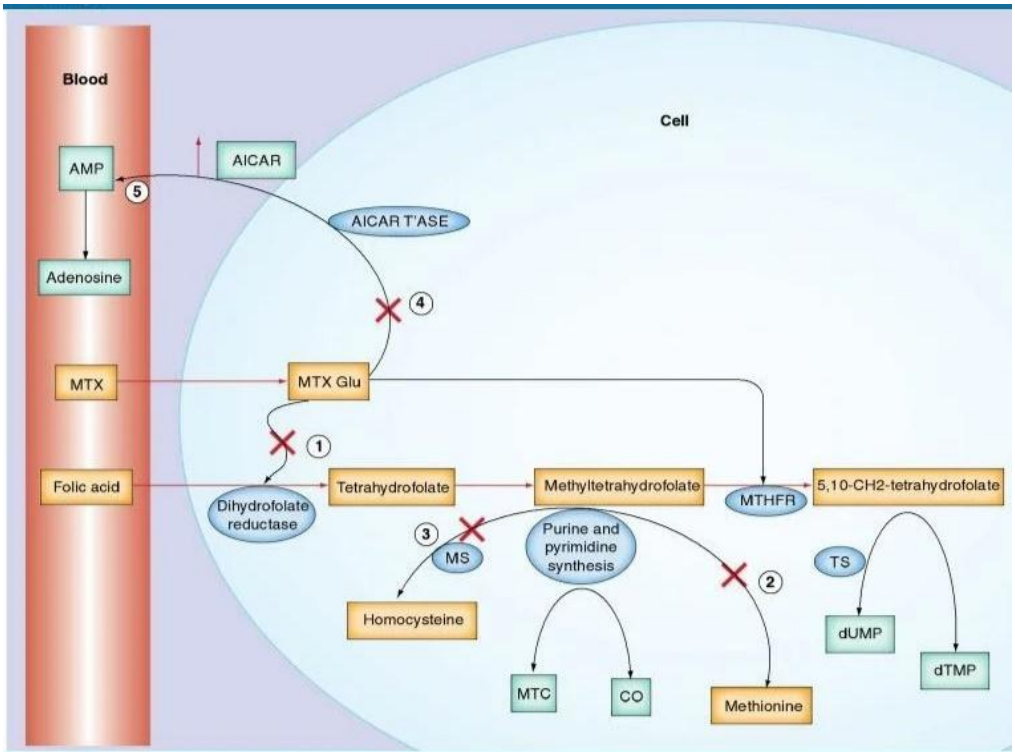

Figure 1: Mechanism of action of methotrexate.

Major indications of the drug includes Neoplasms, Meningeal Leukaemia, Osteosarcoma, Rheumatoid Arthritis, Psoriasis, cancer of head, breast and neck, cutaneous T-cell lymphoma etc.

Methotrexate is a drug with narrow therapeutic index and hence an unusual high dose can result in fatal toxicity.[3] The intracellular polyglutamination of the drug prolongs its intra

cellular presence and thus leads to toxicity. Also the drug has an unusual once weekly dosage regimen, hence the patient can mistakenly take it on a daily basis which will results in toxicity. The drug has variable and complex toxicokinetic characteristics and hence can poses adverse events that can be less sever to fatal in condition. Even though the drug is highly efficacious, it poses a number of adverse effects which can be due to increased patient susceptibility during treatment, excessive parenteral or intrathecal administration, therapeutic errors by patient, intentional overdoses etc. The risk factors leading to methotrexate toxicity includes[4]:

a. increased free plasma drug levels due to displacement of protein bound methotrexate by other drugs(sulphonamides, aspirin etc.) or displacement by protein deprivation.
b. Decreased renal elimination due to old age, pre-existing renal failure, drugs like salicylates, cyclosporine etc.

The systemic adverse events of the drug include mucositis, nausea, vomiting, hepatotoxicity, pancytopenia, nephrotoxicity and cutaneous adverse events include hyperpigmentation, epidermal necrosis, ulceration in psoriatic plaques, erythema recall after discontinuation of PUVA therapy. The drug is contraindicated during the period of pregnancy and lactation. The toxic effects produced by the drug can be quickly progressive and fatal.[2] During the treatment with methotrexate the patient must be clearly monitored and adequate patient information should be provided to avoid the toxicity.

METHODOLOGY

A literature review was carried on the topic methotrexate overdose in clinical practice. A number of good quality articles are reviewed to identify the various toxic events due to methotrexate overdose, their severity, management, their rate of occurrence, fatality etc. Various articles were collected and reviewed using PubMed, which provides high quality articles on current clinical practice.

Methotrexate induced nephrotoxicity

Methotrexate induced nephrotoxicity can results in delayed methotrexate elimination and eventually leads to fatal toxicities. The impact of high dose of methotrexate in renal impairment can be of different dimensions. The reviewed studies conclude that administration of a fairly high dose of methotrexate results in decrease in glomerular filtration rate even used in nontoxic courses. Studies also suggest that urine alkalinisation with sodium bicarbonate while hydration is remained constant will not alter the plasma

methotrexate decay.[5] Continuous monitoring of the serum creatinine and drug level after methotrexate administration will help in the execution of rescue measures. The systemic toxicity associated with methotrexate induced renal impairment can be avoided by the administration of leucovorin and thymidine. In some critical conditions of overdose where leucovorin alone cannot control the condition, carboxypeptidase- G2 was recommended as it hydrolyzes the drug to non-toxic metabolites.[5]

Methotrexate induced cutaneous ulceration

Methotrexate is a highly efficacious drug in the treatment of chronic psoriasis but has been noticed to develop cutaneous ulcerations. The ulceration can develop during the onset of the therapy or during long term therapy or due to an accidental overdose. The incidence of methotrexate induced cutaneous ulcerations are found to be rare. Most cases of cutaneous ulceration following methotrexate administration was found to occurred in psoriatic patients receiving low dose of the drug and the incidence of ulceration in cancer patients receiving high dose methotrexate was found to be rare.

Studies show that there are mainly 2 patterns of methotrexate induced cutaneous ulcerations[6]:

- Type 1- superficial ulceration of existing psoriatic plaque
- Type 2- ulceration on non-psoriatic region

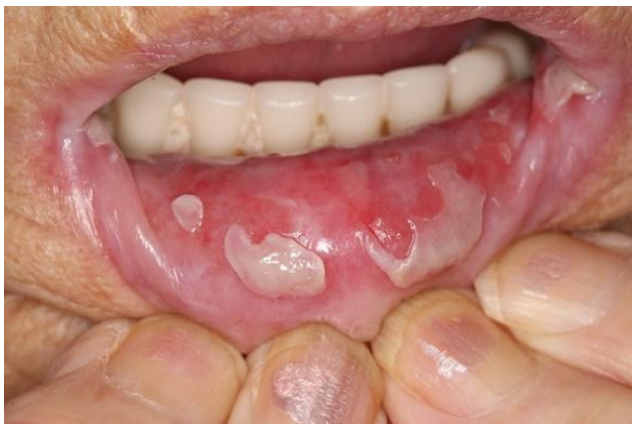

Figure: 2 Ulceration in psoriatic lesion.

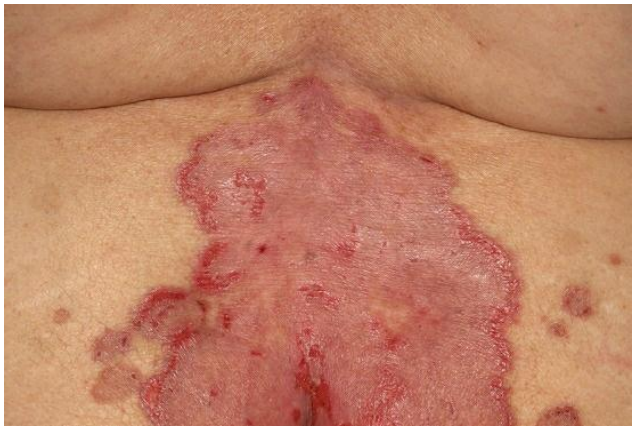

Figure: 3 Ulceration in psoriatic lesion.

The lesions can be painful, erythematous and superficially eroded. Some studies shows that addition of some drugs to methotrexate therapy has results in such cutaneous ulceration which can be manifested as drug interaction. Such drugs include amiodarone, furosemide, trimethoprim, NSAIDs etc.[7]

The cutaneous ulceration induced by methotrexate can be managed by the administration of standard rescue agent leucovorin. Also withdrawal of methotrexate with support of skin therapy can results in rapid improvement in ulceration.[8] In case of ulceration in patients with cancer receiving high dose methotrexate glucarpidase can be used which aids in the clearance of methotrexate by enhancing its hydrolysis.

Methotrexate induced hematologic toxicity

Myelosuppression, thrombocytopenia, megaloblastic anaemia and leukopenia are the most common haematological toxicities that appear late in patients receiving low dose methotrexate.[9] Hematologic toxicity induced by methotrexate is the most serious and fatal problem. It is more dangerous in the elderly patients since the risk of bone marrow suppression is higher. The risk of hematologic toxicity often increase in the presence of precipitating factors like folic acid deficiency, advanced age, renal damage etc. The pancytopenia developed due to the toxicity can lead to neutropenic sepsis.

Low dose methotrexate induced severe pancytopenia in uremic patients

Methotrexate when used for the treatment of RA in patients with uraemia and undergoing dialysis has an increased chance to develop severe pancytopenia. Generally it occurs following administration of low dose oral methotrexate. Incidence rate of pancytopenia is found to be low. The risk factors for development of pancytopenia in uremic patients taking

low dose methotrexate include impaired renal function, advanced age, hypoalbuminemia, concurrent administration of drugs like NSAIDs, clotrimazole etc[10], low serum folate levels etc. Along with pancytopenia there is development of eosinophilia in patient receiving methotrexate. Proper therapeutic monitoring and routine blood examination can help in early diagnosis and management of pancytopenia.

Methotrexate induced neurotoxicity

Methotrexate induced neurotoxicity includes leukoencephalopathy, seizure, ataxia and stroke like symptoms, hemiparesis etc.[11] Mainly neurotoxicity occurs in patients receiving high dose of the drug. The mechanism involved in development of neurotoxicity include homocysteine toxicity, altered folate homeostasis, direct neuronal damage by drug etc. Chronic encephalopathy develops slowly following high dose methotrexate and can lead to permanent neuronal damage. The neurotoxicity due to methotrexate can be managed by the administration of aminophylline (competitive inhibition of adenosine), dextromethorphan, and also intrathecal administration of Carboxypeptidase G2.[11]

Methotrexate induced hepatotoxicity

Long term use of methotrexate results in development of hepatotoxicity with development of chronic liver injury, progressive cirrhosis, fibrosis etc. The predisposing factors in development of liver impairment include obesity, alcoholism, hepatitis B or C, non-alcoholic steatohepatitis, diabetes etc. Hepatotoxicity induced by methotrexate is often manifested by an increase in serum aminotransferases level.[12] The mechanism of liver injury by the drug is through the inhibition of RNA and DNA synthesis and leading to cell arrest. Administration of folic acid can help to prevent this elevation of aminotransferases.

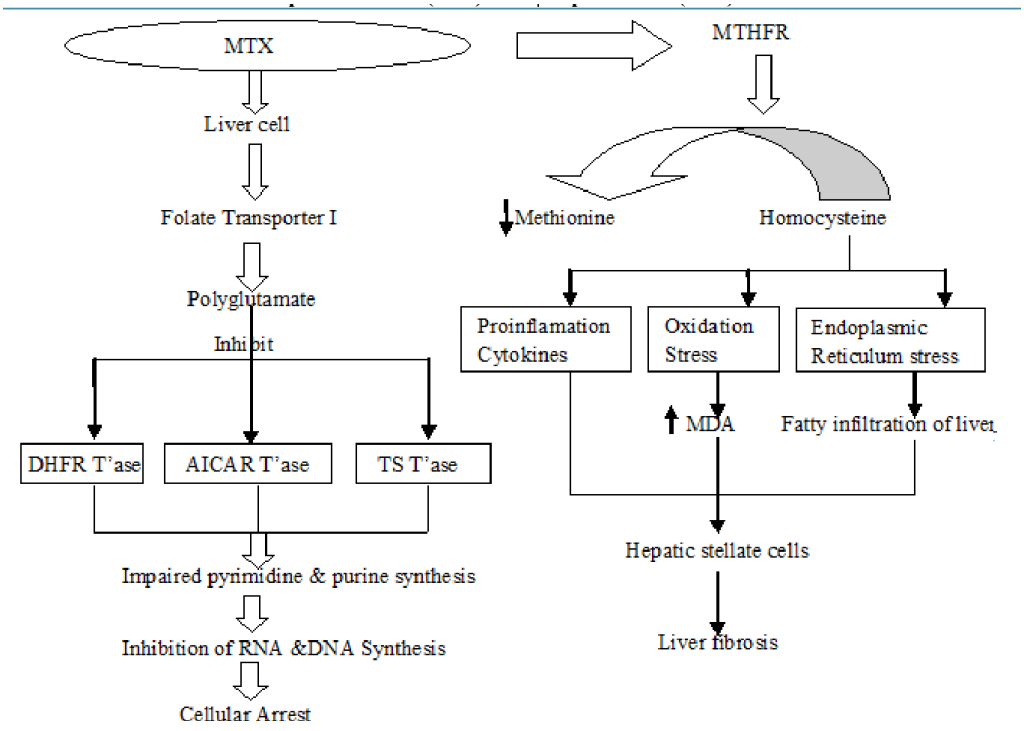

Figure 4: Mechanism of hepatotoxicity.

Methotrexate induced pulmonary toxicity

Chronic uses of methotrexate can result in conditions like pneumonitis, lung fibrosis etc. Pneumonitis occurs mainly due the activated T cell mediated hypersensitivity reactions, direct drug toxicity to lung tissues, immunosuppression etc. The drug stimulates lung fibroblast and epithelial cells that induce recruitment of eosinophils.[13] The risk factors associated with the development of pulmonary toxicity includes advanced age, hypoalbuminimia, diabetes, previous DMARD therapy etc.[14] Cessation of the methotrexate is commended. If not possible treatment with corticosteroids has found to be effective in controlling the symptoms.

DISCUSSION

The folate antagonist, methotrexate is a drug with large therapeutic indications including neoplasms, RA, psoriasis etc. The drug is highly efficacious but because of narrow therapeutic index and unusual once weekly dosage regimen the overuse of drug has resulted in a number of toxic events including nephrotoxicity, hepatotoxicity, hematologic toxicity and dermatological reactions. The nephrotoxicity is usually associated with a decreased glomerular filtration rate and the urine alkalinisation will not result in the decay of methotrexate. The haematological toxicities mainly include bone marrow suppression, thrombocytopenia, leukopenia, megaloblastic anaemia etc.

Low dose methotrexate induces severe pancytopenia when used in arthritis patients with uraemia and undergoing dialysis. In case of psoriatic patients low dose methotrexate is found to induce cutaneous ulceration which may be painful, erythematous and eroded. Long term use of methotrexate results in hepatic complications mainly in patients with risk factors like alcohol consumption, diabetes, any hepatic disease etc. The neurotoxicity due to methotrexate is mainly characterised by ataxia, encephalopathy, seizure etc. and can be managed by aminophylline, dextromethorphan etc. The pulmonary toxicity due to methotrexate occur from chronic use and it includes pneumonitis, fibrosis etc. methotrexate also interact with certain drugs like amiodarone, NSAIDs, furosemide which results in cutaneous ulceration.

Methotrexate is a drug with complex toxicokinetic characteristic and is of narrow therapeutic index. Hence a continuous monitoring is required for the safe use of the drug and thereby preventing the toxic events. The management options of methotrexate toxicity include leucovorin, carboxypeptidase-G2, thymidine etc. In case of severe pulmonary toxicity ventilation can be provided. Also care should be taken to maintain the nutritional status of the patient.

CONCLUSION

Methotrexate, a DMARD is a folate antagonist that has immense clinical importance due to its efficacy. Even though the drug poses some toxic effects including bone marrow suppression, ulceration, pneumonitis, neurotoxicity, hepatotoxicity, nephrotoxicity etc., it is well tolerated if monitored correctly. For this adequate patient information should be provided and the physicians and other health care persons should be aware of the possible complications and recommendations.

CONFLICT OF INTEREST

The author(s) declared no conflict of interest with respect to the authorship, research or publication of the article.

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