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# Methotrexate Side Effects: Review Article

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**Abstract**

Methotrextae (MTX) is an antifolate first developed to treat certain types of cancer. It was used at higher doses as a cancer therapy and since 1990 it is used at much lower doses to treat rheumatic diseases [1]. Side effects of MTX high dose (MTX-HD) may be life threatening, however those of various doses of oral MTX are variable because of the interindividual variability of gastrointestinal absorption of this drug. Bone marrow, gastrointestinal mucosa and hair are particularly vulnerable to the effects of MTX, secondary to their high rate of cellular turnover [2] and because MTX concentration is inversly proportianal to renal clearance [2], renal toxicity is frequent with MTX-HD.

This review aimed at exposing MTX toxicity in different organs, at explaining pathogenic mechanisms of these toxicities and their prevention or treatment.

**Keywords:** Methotrexate; Side effects; Toxicity; Prevention

## Introduction

Methotrextae (MTX) is an antifolate first developed to treat certain types of cancer. It was used at higher doses as a cancer therapy and since 1990 it is used at much lower doses to treat rheumatic diseases [1].

Side effects of MTX high dose (MTX-HD) may be life threatening, however those of various doses of oral MTX are variable because of the interindividual variability of gastrointestinal absorption of this drug. Bone marrow, gastrointestinal mucosa and hair are particularly vulnerable to the effects of MTX, secondary to their high rate of cellular turnover [2] and because MTX concentration is inversly proportianal to renal clearance [2], renal toxicity is frequent with MTX-HD.

This review is aimed at exposing MTX toxicity in different organs, at explaining pathogenic mechanisms of these toxicities and their prevention or treatment.

## Renal Toxicity

Acute renal failure due to acute tubular necrosis induced by MTX-HD is rare (2 à 4%) [3] but serious and redoubtable. This toxicity is due to the precipitation of MTX or its metabolites in the renal tubules [4-6] causing obstruction and diminition of renal clearance with consequently prolongation of MTX high levels. High MTX levels may in turn lead to ineffective rescue by leucoverin and an enhancement of MTX's other toxicities [7-9]. MTX may also acts as a direct toxin on the tubular epithelium [10] and causes vasoconstriction of the afferent arteriole [12].

MTX and its metabolites are relatively insoluble in acid urine [4,11]. An increase in the urine pH results on a greater solubility of the MTX and its metabolites. For that reason, it is recommended to monitor renal function before, during and after MTX infusion in order to control its plsamtic levels. Intravenous hydratation and urine alkalinization were made before, during and after the infusion of MTX-HD [2,3]. Clinically, patients with acute renal failure are usually asymptomatic. It consists frequently on a nonoliguric renal failure which generally disappears in two to three weeks [12-14]. Some patients may develop nausea, vomiting or diarrhea as prodroms [14,15]. Urine alkalinization and leucoverin rescue are the cornerstones of the management of the earlier signs of renal dysfunction. Peritoneal dialysis, hemodialysis and hemofiltration have been tried and may be helpful for the management of the MTX intoxication with acute renal failure. However these methods are invasive and are associated in postdialysis to a marked rebound in plasma MTX concentrations [16-19]. Thymidine, an endogenous nucleoside, has been shown to rescue cells from the MTX effects. It does not compete with MTX for transport into the cell but directed converted to thymidine monophosphate and circumvent de novo pathway blocked by MTX [8,20]. Furthermore carboxypeptidase (CPDG2) an enzyme able to reduce MTX levels by metabolising circulating MTX to the inactive metabolite DAMPA (deglutamated 4-amino-4-deoxy-$N^{10}$-methyl pteroic acid) providing another route for MTX elimination [8,15,21].

## Neurotoxicity

MTX can induce acute, subacute or chronic neurotoxicity. This toxicity is mainly observed after intrathecal or intravenous administration of MTX [22-24]. Mechanisms of toxicity are not yet fully known but many hypotheses may explain this neurotoxicity, such as interference of MTX with transmethylation reactions which are important for the formation of proteins, lipids and myelin [25]. MTX decreases also the rate of methionine and S-adenosyl methionine in cerebrospinal fluid and increases levels of S-adenosyl homocysteine and homocysteine. It was demonstrated that elevated rates of homocysteine may be responsible for the vascular phenomena of MTX neurotoxicity [26,27].

The most frequent acute neurologic manifestation is leucoencephalopathy [11]. This entity can be subclinical diagnosed only by magnetic resonance or manifested by insomnia, confusion, agitation, seizure and coma [28,29]. Headache, nausea, vomiting and aseptic meningitis are also observed after intrathecal administration of MTX [30,31]. These symptoms represent another aspect of acute MTX

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neurotoxicity. They are generally not severe, last 12 to 72 hours [31] and desappear with the discontinuation of the drug.

Paraplegia, cerebellar dysfunction, seizure are reported as a subacute MTX neurotoxicity [30] and occured a few weeks after MTX initiation [32].

Chronic neurotoxicity is observed several months to years after MTX therapy. It is an irreversible complication and it is observed especially if an encephalic radiotherapy was associated to the therapeutic protocol [2,24]. Necrotic leucoencephalopathy is the most frequent complication characterised by a slow progressive cognitive deterioration, seizures, ataxia, spasticity and/or coma [2,12,28].

MTX neurotoxicity is usually treated with aminophylline or leucoverin administration [33,34].

## Hematologic Toxicity

Hematologic toxicity is a serious complication commonly observed with MTX-HD [35]. This complication consists of a thrombocytopenia followed by a rapidly progressive leukoneutropenia [12]. Leukopenia occurs from one to three weeks and marrow recovery is generally observed within approximately 3 weeks [36].

Hematologic toxicity including thrombocytopenia, megaloblastic anemia, leukopenia and pancytopenia with MTX low doses are rare [37,38]. Their prevalence is about 3% in patients with rheumatoid arthritis treated by MTX and the incidence of pancytopenia in these subjects is approximatively 1.4% [39,40]. The frequency of pancytopenia may increase with co-administration of other drugs, folic acid deficiency, hypoalbumenia, concomitant infections, advanced age, dehydratation and renal impairment [41,42]. Pathogenesis of MTX inducing panctopenia is unclear. Pancytopenia may be acute or chronic and thought to be an allergy-like reaction [43,44]. Discontinuation of MTX represents the basis of therapy but the use of G-CSF and methylprednisolone are also beneficial [45].

## Cutaneomucous Toxicity

MTX has a variety of cutaneous side effects, particularly when it is administered at high doses. It generally occurs when recommended guidelines are ignored or renal excretion is decreased.

The most frequent mucocutaneous reactions to MTX are ulcerations of the oral mucosa, burning sensation of the skin, photosensitivity, acral erythema, multiform erythema, urticaria and vasculitis [46].

The pathogenesis of skin adverse reactions due to MTX is not well known. Skin reactions to MTX-HD seem to be due to a cytotoxic-T lymphocytes and mononuclear cells that induce apoptosis in keratinocytes expressing drug-derived antigens at their surfaces [47,48]. Hypersensitivity reactions may also explain some cutaneous side effects. It has been also suggested that MTX can induce cutaneous small-vessel vasculitis in patients with collagen vascular disease who were treated with low-dose of MTX [49].

## Gastro-intestinal Toxicity

MTX can induce a variety of gastro-intestinal disorder. Patients usually present abdominal pain, vomiting and diarrehea. These side effects may occur either with high or low MTX doses [2].

Hepatotoxicity is a common complication of long term treatment with MTX [2,50]. In rhumatoid arthritis and psoriatic arthritis, an increase in aminotransferases levels was obseserved with a frequency varing from 7, 5 to 26% [50,51]. In another hand, typical histopathologic changes in the liver were observed with MTX and have been divided into four grades according to Roenigk classification [52]; *Grade I*: mild fatty infiltration, nuclear variability, with or without portal inflammation; *Grade II* : moderate to severe fatty infiltration, nuclear variability, and portal tract expansion, inflammation and necrosis; *Grade IIIA*: mild fibrosis; *Grade IIIB*: moderate to severe fibrosis and *Grade IV*: cirrhosis.

Many risk factors may increase the occurrence of severe hepatotoxicity (*Grade III* or *IV*) such as a long duration of exposure to MTX and its cumulative dose, hepatitis B or C infection, alcoholism, diabetes, obesity and non alcoholic steatohepatitis [53,54].

The mechanism by which MTX affects the liver is unclear. Hepatic folate stores are depleted by MTX in the doses used in rhumatoid arthritis and these stores can be repleted by short-term administration of oral folinic acid [55]. A relationship between folate depletion and hepatic toxicity has not been established. However, supplementation with either folic acid 1 mg per day or folinic acid 2.5 mg per week is associated with a reduced incidence of aminotransferases elevation [56,57].

## Pulmonary Toxicity

Pneumonitis is one of the most serious but infrequent side effects of MTX low doses. Its prevalence seems about 0.9 to 1% [58,59]. Mechanism of pneumonitis is an hypersensitivity reaction to MTX mediated by activated T-cells [2,60]. In fact, MTX leads to a cytokines release by type 2 alveolar cells causing an alveolitis by recruitment of inflammatory cells [61]. MTX can also stimulate lung fibroblasts and epithelial cells to induce recruitment of eosinophils [62]. It has been also demonstrated that neutrophiles are implicated in the pathogenesis of lung fibrosis [63,64]. Clinically symptoms may occur from few days to more than a year after the begining of MTX therapy [65,66] and also several weeks after MTX discontinuation [67]. An insidious nonproductive cough is the most common symptom [66]. Fever, malaise, dyspnea may also occur [68]. Chest x-ray may show either localised or diffuse interstitiel changes [69]. Tomography has a higher sensitivity and shows commonly diffuse bilateral and patchy ground glass [70]. Peripheral eosinophilia was seen in one third of patients [69], bronchoalveolar lavage shows lymphocytosis about 33-68% with a disproportionate increase in the CD4+/CD8+ ratio [71]. Lung biopsy is not done all the times because it is an invasive method and because of the availability of tomography.

Treatment of MTX pneumonitis is based on corticotherapy and immediate discontinuation of MTX [59]. In difficult cases cyclophosphamide has been successfully used [72]. The prognosis of MTX-associated lung injury is generally favourable [73].

## Prevention and Management of MTX-HD Toxicity

To avoid MTX toxicity, there are some general aspects of MTX-HD administration and post-treatment management that are common to all regimens.

### Assessing renal function

Because MTX is eliminated essentially by the kidneys. Therefore it is mandatory to determine renal function for MTX-HD administration. In the presence of an impaired renal fuction, MTX dose adjustement is necessary. So, when creatinine clearance (CrCl) is between 30 and 60 ml/min, dose of MTX is reduced by 50% and when CrCl is between 10 and 30 ml/min, dose of MTX should be reduced by 75% [74].

### Maintaining adequate hydratation

Agressive hydration is important to promote diuresis and to prevent intratubular precipitation of MTX. Most protocols recommend at least 2.5 to 3.5 L/m$^2$ of IV fluid hydration per day, starting 4 to 12 hours prior to the initiation of the MTX infusion [2,3].

### Maintaining alkaline urine pH

MTX and its metabolite 7-OH-MTX, which is predominent with MTX-HD, show respectively 20 and 12 fold increased solubility when pH increases from 5 to 7 [4]. Renal tubular precipitation of MTX and 7-OH-MTX occurs when pH is lower than 5.7 [75]. In clinical practice, it is essential to begin the MTX infusion only after the urine pH is ≥ 7.0 and to maintain it in this range until plasma MTX levels decline to less than 0.1 μM.

### Avoiding drug interactions

Toxicity with MTX-HD may be increased when there is coadministartion of drugs having the potentiel to displace MTX from serum proteins and/or to reduce MTX clearance. The most known are interaction with trimethoprim and sulfamethoxazole (TMP-SMX) and non steroidal anti-inflammatory drugs (NSAID) [44,76,77]. Alteration of the elimination of MTX was also reported with pyrazoles, aminoglycosides, probenecid, some penicillins and macrolides [78], omeprazole [79,80], mezocilline [81], piperacillin [82], amphotericine B [83] and ciprofloxacin [84].

**Drainage of third space fluids:** The presence of a third space fluid like pleural effusions or ascites is an important contraindication to the administartion of MTX-HD. Third space fluids lead to a prolonged MTX plasma half life and subsequently to a prolonged exposure to MTX and to the risk of toxicity. Drainage of third space fluids before MTX-HD is recommended to prevent toxicity [75].

**Leucoverin rescue:** Administration of reduced folate such as leucoverin is mandatory in order to circumvent the metabolic blockage imposed by MTX [85]. Leucoverin rescue should be started within 24 to 36 hours of the start of the MTX infusion. The dose and the frequency of leucoverin rescue have been developed empirically and differ according to the regimen of MTX-HD. Rescue doses of leucoverin that are commonly given are between 10 to 15 mg/m$^2$. Leucoverin is given every six hours until plasma MTX levels are less than 0.2 μM [2].

### Monitoring plasma MTX concentration

Monitoring plasma MTX is an essentiel part of MTX-HD therapy. It aimed at identifying patients with the highest risk for MTX toxicity. MTX levels should be followed daily. Plasma MTX levels are usually measured at 24, 48, and 72 hours after starting the MTX infusion. For 24-hour infusional regimens, the initial MTX measurement may be at 36 hours. To avoid MTX toxicity, levels should be above 10 μM at 24 hours, 1 μM at 48 hours and 0.15 μM at 72 hours [86,12].

## Conclusion

Because MTX can cause many side effects and some of them are life threatening, it is important to recognize them as the drug must be discontinued immediately and rescue measures instituted. Many of these side effects can be avoided by a close monitoring and a good prevention.

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