Best Practice Message

September 2021

Focus on Safety: Low dose methotrexate

Practice changing moments

- ALL patients taking methotrexate including those on low doses (25mg and under) taken once a week, require regular monitoring and vigilance for any side effects.
- Advise the patient to immediately report any mouth ulcers, sore throat, dry cough or shortness of breath, abdominal discomfort or dark urine.
- Be aware of interactions that can increase the risk of toxicity, especially trimethoprim.
- Consider flagging patient's notes to alert practice staff of any potential features of methotrexate toxicity.
- Withhold methotrexate and contact the hospital specialist team if the patient develops mucositis, unexplained cough, cytopenias or AST/ALT greater than twice the upper limit of normal.

The benefits of low dose methotrexate

Methotrexate is a folic acid antagonist, inhibiting DNA and RNA synthesis required for normal cell division.[1] When used at low doses, 25mg and under, it can treat inflammatory conditions such as psoriasis, vasculitis and Crohn's disease. It is the most widely used first- line DMARD in the treatment of rheumatoid arthritis.[2]

Methotrexate used correctly in this manner is generally safe and effective and side effects are usually predictable and reversible. The vast majority of patients will use this medication without harm and with significant improvement in their condition and quality of life.

Methotrexate can be fatal

Methotrexate is however classified as a 'High-risk medicine' by The Health Quality and Safety Commission New Zealand (HQSC). This is due to the risk of liver failure, bone marrow suppression, lung injury and death due to methotrexate toxicity. This is more likely to occur in the setting of high dose use in chemotherapy but should not be forgotten in low dose use.

Medication interactions can contribute to the risk of methotrexate toxicity and death. The risk of toxicity is also increased by incorrect use - such as wrong strength, dose or frequency – as well as abnormal liver and kidney function.

Monitoring

Low dose methotrexate, requires regular monitoring and vigilance for any side effects. The blood tests required are: **FBC, LFT, UEC and CRP.**

From initiation or dose change until dose and monitoring are stable for 6 weeks.	Once Patient has been stable for 6 weeks.	Once patient has been stable for a year.
Test every 2 weeks.	Test monthly.	Test every three months.

Adverse and toxic effects of methotrexate

What to watch for:	What to do about it:
Gastrointestinal:	
Ulcerative stomatitis (mouth ulcers). • This is often the earliest indications of toxicity. • Can occur in 2 to 10% of patients.[3]	This should trigger a review of treatment.
Nausea, vomiting and diarrhoea. • Occurs in around 10% of patients.[3]	May require interruption of therapy, dose reduction, folic acid dose review or symptomatic management.
Infections:	
RA patients have increased incidence of infection compared to the general population[2]. The risk is increased if the patient: • Is also on other immunosuppressive agents. • Has comorbidities, particularly pre-existing lung disease.	Caution should be taken if using methotrexate in patients with active infection. In short courses of antibiotics such as UTIs the course may be too short to withhold methotrexate, but the patient should be closely monitored. In patients requiring longer treatment with antibiotics, withhold methotrexate until the patient has finished antibiotics and is well again.
Cytopenias:	
Minor changes in blood count parameters. • This can occur in around 3-10 % of patients[3].	This is usually temporary or reversible with dose adjustment or interruption of therapy.
Severe bone marrow suppression and a significant reduction in platelets or white blood cell count. • Can occur rarely but abruptly. • The risk is increased with concomitant use of other anti-folate medicines, such as trimethoprim.	Neutrophils <2.0 x 10^9/L; Platelets <150 x 10^9/L; WBC <3.5 x 10^9/L; requires immediate discontinuation of methotrexate and discussion with the hospital specialist.
Pulmonary Toxicity:	
Pneumonitis. • This is rare (1%)[3]. • The risk of lung disease is higher in those who smoke tobacco and who have pre-existing lung disease.	Withhold treatment and discuss with the hospital specialist involved.
Neurotoxicity:	
Headaches, dizziness, fatigue, and problems concentrating. • These symptoms often develop gradually and may not initially be picked up as side effects of treatment.	May require dose reduction, and in some patients will require drug discontinuation.
Hepatotoxicity:	
Increased liver enzymes. • Can occur in up to 15% of patients[3]. Liver cirrhosis. • Rare but has been reported. • Is more likely in patients with pre-existing liver disease or risk factors.	ALT <2x upper limit of normal is usually accepted as appropriate to continue treatment. Readings higher than this should be discussed with the hospital specialist involved and interruption of treatment considered. Alcohol should be minimised or if possible avoided, to reduce the risk of liver toxicity developing.
Skin complications:	
Photosensitivity reactions • This can occur in around 3-10 % of patients. Long term risk of non-melanoma skin cancers whilst on immunosuppression.	Patients should be warned to avoid unprotected exposure to sunlight or tanning beds. Recommend a skin check every 1-2 years.

Renal function:	
Methotrexate is not nephrotoxic, but it is mainly excreted by the kidney. Changes in renal function can lead to an increased risk of side effects and toxicity from methotrexate.	Methotrexate use should be considered carefully and doses reduced in anyone with eGFR <30ml/min/1.73m^2.
Congenital abnormalities:	
Increased risk of foetal malformation and miscarriage.	Both men and women of childbearing potential must have effective contraception during and for at least 3 months post-treatment cessation. In case of accidental pregnancy, please notify hospital specialist.

Prescribing advice

The HQSC has some guidelines around safe methotrexate prescribing. These include that:

- The prescription specify the day of the week written in full that the dose is to be taken.
- Only one strength of tablets generally be prescribed.
- The required laboratory monitoring is documented and who is responsible for this.
- No script is issued unless the patient has had a FBC and LFTs in the previous six weeks.
- All prescriptions are double checked for the right strength, dose, frequency and day and that they are correct for the clinical indication.

Potential interactions

Methotrexate can interact with a wide range of medications, increasing the risk for toxicity or adverse effects and can lead to fatalities. If a patient on methotrexate requires a change in medication or a short course treatment consider the potential for toxicity to occur, even if the patient has tolerated the combination previously. Some interactions to consider are:

- Trimethoprim or co-trimoxazole: Concomitant use of methotrexate and trimethoprim products greatly increases the risk of bone marrow aplasia, even with short courses or low doses. Fatalities have occurred because of this combination.
- Probenecid can increase the risk of methotrexate toxicity by increasing methotrexate serum concentrations.
- Other antibiotics: Some other antibiotics have had occasional case reports of pancytopenia, monitoring is recommended. In general if the patient is unwell enough to require antibiotics, with the exception of short courses, it is recommend to withhold methotrexate until the course of antibiotics is finished and the patient is well again.
- NSAIDs[5]: Non-steroidal anti-inflammatory agents are commonly co-prescribed with low dose methotrexate therapy, particularly in arthritis. It is important to monitor renal function regularly and consider adjustment of treatment if renal function decline occurs. The risk appears greatest in the elderly or those who already have some form of renal impairment.
- Live vaccines: The effectiveness of vaccines may be reduced and infection with the vaccine agent may occur whilst on immunosupressants[5]. In general, live vaccines should be avoided, but varicella zoster vaccine is considered safe if the patient is on low dose methotrexate and on no other immunosuppressants. Influenza vaccination should be encouraged for those on immunosuppressants[6].

Tools available:

'Interaction' section on NZF: https://nzf.org.nz/interactions/stockleys/of/10029041000116107

Patient resources:

- http://www.open.hqsc.govt.nz/assets/Open-for-better-care/Medication/PR/factsheet-methotrexate-Feb-2015.pdf
- https://www.mymedicines.nz/home/sheet/Methotrexate-(for-inflammatory-conditions)?format=pdfA4&inline=true
- http://www.saferx.co.nz/assets/Documents/3fe06fa9a3/methotrexate-patient-guide.pdf
- https://www.sunsmart.org.nz/

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