Te Awakairangi Health NETWORK

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Monitoring Methotrexate in Primary Care

In 2013, 23.3 methotrexate (MTX) prescriptions were dispensed per 1,000 patients registered in general practice in New Zealand.[1] So while methotrexate is usually initiated in secondary care, many patients taking MTX will be monitored by their general practitioner, and receive repeat prescriptions in primary care.

When used and monitored correctly methotrexate can be an effective and safe treatment; however if an error occurs and it is taken as a daily dose rather than a once weekly dose it can be fatal. General practitioners should be aware of strategies for safe prescribing of this potentially toxic medicine and be familiar with the symptoms and signs of MTX toxicity (see *TeAHN Prescriber Tips: Monitoring High Risk Medicines in Primary Care - Methotrexate. June 2017*).

Table 1 outlines the recommended monitoring for patients taking methotrexate.[1] A baseline chest x-ray should also be done, but repeated only if respiratory symptoms occur (see Table 2).

Key points - Safer prescribing of methotrexate

- Advise patient of the **dose** and **frequency** and reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- Prescribe only one strength of methotrexate tablet;
- Warn the patient to immediately report onset of any feature of blood disorders (e.g. sore throat, bruising, mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, dark urine), and respiratory effects;
- Advise patient not to take any NSAIDs without asking first.

Laboratory monitoring	Frequency	What to look for	What to do
Full blood count (FBC)	Baseline Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	WBC $<3.5 \times 10^9$/L Neutrophils $<2.0 \times 10^9$/L Platelets $<150 \times 10^9$/L	Discuss with specialist team immediately.
		MCV > 105 fL	Check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality.
Liver function tests (LFTs)	Baseline Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	AST, ALT > twice the upper limit of reference range.	Withhold until discussed with specialist team. Other factors to consider: • Check alcohol intake. • Review medicines which may cause liver dysfunction, e.g. NSAIDs
Serum creatinine	Baseline Often performed at same time as LFT and FBC monitoring during dosing changes. Every three months for patients on stable treatment.	Significant deterioration in renal function	Reduce dose

Table 1: Recommended monitoring for patients taking methotrexate, adapted from Chakravarty et al, 2008.

Methotrexate acts as an inhibitor of the enzyme dihydrofolate reductase, which interferes with folic acid metabolism ie its use results in a decreased supply of folates, therefore supplementation of folic acid during MTX treatment is required.
Folic acid significantly reduces the risk of abnormal liver biochemistry and gastrointestinal side-effects (e.g. nausea, vomiting and abdominal pain), and reduces the likelihood of methotrexate discontinuation (for any reason).[2] Total weekly doses of 5 – 27.5 mg have demonstrated efficacy in decreasing methotrexate adverse effects; however, a pragmatic approach is the use of 5 mg, once weekly.[1]

Table 2 includes recommendations for managing adverse effects of methotrexate should they occur.

Symptoms	What to do
Rash or oral ulceration	Withhold methotrexate until discussed with specialist team. Folic acid mouth wash may help with mucositis.
Nausea and vomiting, diarrhoea	Giving methotrexate by subcutaneous injection is often a good way of avoiding nausea
New or increasing dyspnoea or dry cough (pneumonitis)	Withhold and discuss URGENTLY with specialist team. Arrange chest x-ray and respiratory function tests
Severe sore throat, abnormal bruising	Request immediate FBC and withhold until results available. Discuss any unusual results with specialist team

Table 2: Symptoms and actions for managing MTX adverse effects.

The patient's concurrent medicines, including OTC medicines, and alcohol use should also be checked.

- Impaired renal function can reduce the excretion of methotrexate and patients should report any use of medicines such as NSAIDs which reduce methotrexate excretion.

- Alcohol intake should ideally be no more than one to two standard drinks twice per week, although many patients admit to higher amounts without developing evidence of liver problems.

- Co-trimoxazole and trimethoprim should be avoided in patients taking methotrexate due to a theoretical increase in risk of bone marrow suppression.[1]

NOTE:

- Methotrexate Patient Guide is available from: www.saferx.co.nz/methotrexate-patient-guide.pdf
- HVDHB Rheumatology are adding the following to their clinic letters:

Before providing a repeat prescription for a DMARD (Methotrexate, Leflunomide, Sulfasalazine or Azathioprine) please ensure that monitoring blood test from within the last 12 weeks have been checked and that neutrophil and platelet counts, ALT and AST are normal.

References:

1. Best Practice Journal. 2014;64:48-52. Safer prescribing of high-risk medicines - Methotrexate: potentially fatal in overdose.
2. Ledingham J *et al*. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Oxford University Press on behalf of the British Society for Rheumatology. 2017. doi:10.1093/rheumatology/kew479.