Safer prescribing of high-risk medicines

Methotrexate: potentially fatal in overdose

Low-dose methotrexate is commonly used in the treatment of patients with rheumatoid arthritis and other rheumatologic diseases, as well as severe psoriasis. It is prescribed as a weekly dose and is a preferred option due to its effectiveness, predictable adverse effect profile and low cost. However, it can also be highly toxic and even fatal. Although toxicity is more likely to occur in patients taking high doses, any dosing regimen may induce toxicity.[1]

While methotrexate is usually initiated in secondary care, many patients taking methotrexate will be monitored by their general practitioner, and receive repeat prescriptions in primary care. In 2013, 23.3 prescriptions for methotrexate were dispensed per 1000 patients registered in general practice in New Zealand.[2] General practitioners therefore need to be aware of strategies for safe prescribing of this potentially toxic medicine and be familiar with the symptoms and signs of methotrexate toxicity.

The mechanisms behind the anti-inflammatory effect of methotrexate in rheumatoid arthritis are not certain, but are thought to include suppressing DNA synthesis in inflammatory cells, reducing auto-antibody levels, anti-inflammatory effects of adenosine release, and reducing cytokine levels in synovial fluid to bring about a reduction in inflammatory disease activity and joint damage.[3, 4] Methotrexate acts as an inhibitor of the enzyme dihydrofolate reductase, which interferes with folic acid metabolism. As the adverse effects (but not the anti-inflammatory effects) of methotrexate are mediated via the metabolism of folates, it is given with folic acid supplementation.

Adverse and toxic effects of methotrexate

Adverse effects of methotrexate can occur at therapeutic levels and include headache, malaise, mouth ulcers and hairfall.[5] In overdose, vomiting, diarrhoea and gastrointestinal bleeding may occur, as well as severe bone marrow suppression and disturbance of liver function. Long-term liver injury, normally accompanied by elevations of ALT and AST, can result in hepatic fibrosis. Liver toxicity is more likely in patients with pre-existing risk factors for liver disease, and in patients taking methotrexate for the treatment of psoriasis than those taking it for the treatment of rheumatoid arthritis.[6]

Methotrexate can induce acute pneumonitis, which can be fatal. Patients may present with acute shortness of breath and a dry, persistent cough, possibly with fever.[7] A chest x-ray prior to initiating methotrexate is recommended to facilitate the diagnosis of potential lung disease at a later date.

Co-administration of folic acid, typically given as 5 mg weekly, a few days after each weekly methotrexate dose, has been shown to reduce the risk of adverse effects such as abdominal pain and nausea, abnormal serum transaminase levels, and increases adherence with a methotrexate regimen.[8]

Methotrexate can be fatal

There have been documented cases of death attributable to methotrexate use in New Zealand and around the world. These have often involved patients taking methotrexate as a daily, rather than weekly dose due to patient, clinician and/

or pharmacy error. In New Zealand, fatal cases have occurred most recently in 2012 and 2006.[9, 10] In the United Kingdom, the National Patient Safety Authority released a report in 2004 on methotrexate prescribing after 25 deaths and 26 incidents of serious harm in the preceding decade.[11] In some of these cases, even once the error was identified, patients died due to ongoing deterioration after methotrexate withdrawal.

The usual cause of methotrexate-related mortality is pneumonitis, which can occur idiosyncratically (i.e. it is not dose related), even after one dose. Bone marrow suppression is another cause of mortality, with multiple organ failure and gastrointestinal bleeding occurring secondary to this.

Recommendations for managing risk

A number of common sense steps can be taken by clinicians, including pharmacists, to minimise the risk of methotrexate toxicity and potential accidental overdose. Given the number of documented fatalities which have arisen from simple errors in medicine dosing frequency, the most important lesson is to emphasise that **methotrexate should be taken as a weekly dose** and to put in place procedures, safeguards and reminders to ensure this dosage is followed by doctors, pharmacists and patients.

Steps during patient consultation to ensure weekly administration:

- Avoid writing "as directed" on prescriptions – give the specific dose and state this in mg.
- Write the day the medicine is to be taken in full on the prescription (one case of fatality occurred when a patient interpreted "Mon" as morning, resulting in a daily as opposed to weekly dose).[12]
- Highlight differences in the appearance of 2.5 mg and 10 mg tablets, especially when a patient is transferred from one tablet size to another. Prescribe only one strength of tablet at a time in order to avoid accidental ingestion of 10 mg tablets in place of 2.5 mg tablets.[12]
- Emphasise to the patient the differences between methotrexate and folic acid – cases have occurred where the two dosing regimens were inadvertently swapped by the patient.[11] A simple mnemonic tool is "Methotrexate for Monday", "Folic acid for Friday" as a means of ensuring once weekly dosing for each on different days.
- Maintain contact with the secondary care team and patient contact with rheumatology and practice nurses. Research conducted in New Zealand found significantly higher levels of patient awareness of signs and symptoms of methotrexate toxicity and awareness of weekly dosing in patients who had seen a rheumatology nurse.[13]
- If the patient has a carer, ask that they be present at consultations or that the need for accurate intake of medicines is discussed with them (with patient consent).
- In follow-up appointments specifically question patients on their medicine intake – How many tablets of methotrexate do you take? When do you take them?

Be vigilant for adverse effects, and ensure patients understand what these could be:

- Patients should be advised of key symptoms of methotrexate toxicity such as a sore throat, mouth ulcers, fever, dry persistent cough, vomiting or diarrhoea, and to report if any of these occur.
- Ensure that patient reports of adverse effects while taking methotrexate are relayed by practice staff to the patient's usual clinician.[9]

Practice steps to ensure weekly administration:

- Check that prescribing software automatically defaults to weekly prescriptions for methotrexate.[9]
- Flag the patient's notes to alert other practice staff to report any potential features of methotrexate toxicity.[9]
- Consider a short education session for practice staff on methotrexate risks and symptom awareness, and put processes in place so that methotrexate adverse effects can be reported to the treating clinician.
- Be aware of failures to report for appointments by patients taking methotrexate, and double check the reasons why.

Laboratory monitoring is essential (also see Table 1, over page):

- A full blood count, liver and renal function tests should be carried out before starting methotrexate, and repeated every two to four weeks initially, then every month to three months if results have been normal and the dose is stable.
- Ensure tests have been done within the last six weeks prior to writing repeat prescriptions.[12]
- Results showing decreased white blood cell counts or increased transaminase levels may indicate methotrexate toxicity. Discuss any abnormal results with the rheumatologist/dermatologist. See Table 1 for further details.

- Procollagen 3 (type III procollagen amino terminal propeptide, or PIIINP) may be used to monitor liver safety in patients with psoriasis. This is available as a Tier two test in the National Laboratory Test Schedule and will be arranged by a specialist. Liver biopsies may also be performed.

Check concurrent medicine and alcohol use:

- Impaired renal function can reduce the excretion of methotrexate and patients should report any use of medicines such as NSAIDs which reduce methotrexate excretion.[5]
- Alcohol intake should ideally be no more than one to two standard drinks twice per week,[5] 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.[5, 14]

Pharmacy steps to avoid weekly dosing errors:[9]

- Ensure that methotrexate labels state that dosing is weekly and give the day of the week, written in full, that the medicine is to be taken.
- Ensure software alerts are given appropriate attention.
- Contact the prescribing clinician with queries or to check that dosing is appropriate when there is doubt.
- Place prepared scripts for medicines with alerts in a different area to general, non-high risk, medicines so that alerts can be appropriately checked and addressed before handing medicines to patients.
- Where prescriptions are manually entered into a pharmacy computer system, double check that entry is correct. When filling repeats, refer back to original script rather than computer system to ensure any errors which may occur when entering prescription details into computer software are not perpetuated.
- Be wary of needing to order stock to fill a script for high risk medicines; as this may indicate that a prescribing error has occurred.
- Have a system for recording "near miss" events, as these can identify sources of error.

A Methotrexate Patient Guide is available from: **www.saferx.co.nz/methotrexate-patient-guide.pdf**

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Methotrexate is contraindicated in women who are pregnant or breast feeding

Care must be taken to avoid the use of methotrexate in women who are pregnant as it is an abortifacient and can exert teratogenic effects on the developing foetus.[15] If female patients of reproductive age are prescribed methotrexate, discuss appropriate contraception and delaying pregnancy plans. International treatment guidelines also recommend the use of contraception for male patients taking methotrexate,[14] although recent evidence suggests that paternal use of methotrexate does not increase the risk of miscarriage or birth defects.[16]

Table 1: Recommended monitoring for patients taking methotrexate, adapted from Chakravarty et al, 2008[14]

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
Chest X-ray	Baseline		Repeat if respiratory symptoms occur (see below)

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

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References:

1. Kivity S, Zafrir Y, Loebstein R, et al. Clinical characteristics and risk factors for low dose methotrexate toxicity: A cohort of 28 patients. Autoimmun Rev 2014;[Epub ahead of print].
2. bpac^{nz}. Annual Practice Report, 2013. Available from: www.bpac.org.nz/Report/2013/November/2013PracticeReportSample.pdf (Accessed Oct, 2014).
3. Lopez-Olivo MA, Siddhanamatha HR, Shea B, et al. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 2014;6:CD000957.
4. Chan ESL, Cronstein BN. Methotrexate - how does it really work? Nat Rev Rheumatol 2010;6:175–8.
5. New Zealand Formulary. NZF, V28. NZF, 2014. (Accessed Oct, 2014).
6. Menter A, Griffiths CEM. Current and future management of psoriasis. Lancet 2007;370:272–84.
7. Kremer JM, Alarcón GS, Weinblatt ME, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis. A multicenter study with literature review. Arthritis Rheum 1997;40:1829–37.
8. Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2013;5:CD000951.
9. Devonport C. Coroner's Report. Hastings: Coroner's Court 2014.
10. Smith IR. Coroner's Report. Nelson: Coroner's Court 2009.
11. National Patient Safety Agency, NHS. Toward the safer use of oral methotrexate. London: NHS, 2004.
12. Medication Alert. Oral methotrexate - once weekly dosing. Wellington, New Zealand: Health Quality and Safety Commission New Zealand, 2012. Available from: www.hqsc.govt.nz/our-programmes/medication-safety/publications-and-resources/publication/67/ (Accessed Oct, 2014).
13. Ingaram T, Highton J, Dockerty J. Proceedings of the 216th Scientific Meeting of the Otago Medical School Research Society. Identifying factors affecting patient's knowledge of methotrexate therapy and potential risk of unintentional overdose. N Z Med J 2013;126.
14. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatol Oxf Engl 2008;47:924–5.
15. Hyoun SC, Običan SG, Scialli AR. Teratogen update: methotrexate. Birt Defects Res A Clin Mol Teratol 2012;94:187–207.
16. Weber-Schoendorfer C, Hoeltzenbein M, Wacker E, et al. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. Rheumatol Oxf Engl 2014;53:757–63.