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Waitemata District Health Board
Best Care for Everyone

METHOTREXATE - SAFE PRESCRIBING - ONCE A WEEK!

- ALWAYS DOUBLE-CHECK PRESCRIPTIONS - PRESCRIBING AND DISPENSING ERRORS CAUSE THE MOST HARM
- CLEARLY EXPLAIN THE DOSING SCHEDULE TO PATIENTS
- TELL PATIENTS TO REPORT ADVERSE REACTIONS AND CONTRAINDICATIONS
- BE AWARE OF INTERACTIONS THAT INCREASE THE RISK OF TOXICITY
- ENSURE THERE IS A MONITORING PLAN

Low-dose (less than 25mg) oral methotrexate therapy, taken as a single dose **once a week**, is generally safe when prescribed for conditions such as severe psoriasis and rheumatoid arthritis.[1,2] Compared to second-line disease-modifying anti-rheumatic drugs (DMARDs), methotrexate is usually well tolerated[3,4] and its side-effects are predictable.[1]

ALWAYS DOUBLE-CHECK PRESCRIPTIONS - PRESCRIBING AND DISPENSING ERRORS CAUSE THE MOST HARM

The most common cause of significant patient harm reported from methotrexate occurs when a medical practitioner unintentionally prescribes methotrexate to be taken **daily** rather than **once a week**, followed by a pharmacist dispensing the methotrexate according to the prescription.[2,4,5,7]

Harm may also occur when the wrong strength of methotrexate tablet is dispensed, or because of labeling errors.[2,5,8,9] Always exercise caution when prescribing and dispensing oral methotrexate.

Please double-check prescriptions:
right strength ✓ right dose ✓ right frequency = weekly ✓

Prescribers are advised to specify a **day of the week** (written in full) on which the dose should be taken **and** to recommend the **strength** to be dispensed (eg consider specifying only 2.5mg tablets to be dispensed). The day of the week, in full, should also be printed on the label by the pharmacy.[10]

CLEARLY EXPLAIN THE DOSING SCHEDULE TO PATIENTS

The unusual weekly dosing schedule can be confusing for patients and has promoted medication errors, some of which have been fatal.[5] Health professionals can improve safety by providing patients with clear instructions about how and when to take their dose.

Written patient information resources may help with promoting effective self-management;[11] see the patient guide available on www.saferx.co.nz, which also includes information about handling the tablets. A special effort may be needed when methotrexate is prescribed and English is not the patient's first language.

TELL PATIENTS TO REPORT ADVERSE REACTIONS AND CONTRAINDICATIONS

Adverse reactions

Many of the side-effects of low-dose oral methotrexate are due to the inhibition of folate metabolism and include nausea, stomatitis and bone marrow suppression. These symptoms can be reduced with oral folic acid tablets (5mg once a week, on a different day to methotrexate) without affecting the efficacy of methotrexate[4,12,13] and should be prescribed for all patients.

Health professionals should advise patients to be alert for **any** symptoms suggestive of methotrexate toxicity, and to report these to their GP or specialist without delay.[2] Toxicity may present as symptoms of bone marrow suppression (eg fever, sore throat, mouth ulcers), hepatotoxicity (eg abdominal pain, jaundice), or pulmonary toxicity (eg new or increasing dyspnoea, chest pain, hypoxaemia, dry cough). Pulmonary toxicity can progress rapidly, it may not be fully reversible and is potentially fatal.[14] Diarrhoea and ulcerative stomatitis can progress to potentially fatal haemorrhagic enteritis and intestinal perforation if methotrexate is continued.[14] See Table 1 for more information.

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METHOTREXATE

Contraindications

Contraindications to treatment include active infection, alcoholism, peptic ulcer disease, poor nutritional status and recent exposure to chicken pox or herpes zoster infection.[15] Advise patients to inform their GP or specialist if these conditions occur.[14,15]

Methotrexate should be avoided during pregnancy and breastfeeding. Ensure women of child-bearing age are not pregnant before starting methotrexate. Effective contraception should be used during, and for at least 3 months after treatment in both men and women.[14]

BE AWARE OF INTERACTIONS THAT CAN INCREASE THE RISK OF TOXICITY

Methotrexate can be hepatotoxic, especially at higher doses or with prolonged therapy. Liver function should be checked prior to the initiation of treatment and monitored every fortnight for the first six weeks and then monthly.[16] Concomitant use of methotrexate with other hepatoxic agents (including alcohol) will increase the risk of toxicity, which can progress to cirrhosis in severe cases. It is not known precisely what level of drinking is safe with methotrexate, however there is general agreement that one to two standard alcoholic drinks once or twice a week is unlikely to cause a problem. Drinking more than four standard alcoholic drinks on one occasion, even if infrequently, is strongly discouraged.[17]

Methotrexate accumulates in the presence of renal impairment. Doses of methotrexate should be reduced in cases of poor renal function, whether caused by concomitant medications (such as non-steroidal anti-inflammatories (NSAIDs) and diuretics), dehydration, or kidney disease.[1] Advise patients to ask their specialist or GP before self-medicating with NSAIDs.

The risk of methotrexate toxicity can also be increased if it is taken together with some antibiotics. **Trimethoprim and cotrimoxazole significantly increase the risk of bone marrow aplasia and concurrent use with methotrexate should be avoided**. The risk of toxicity can also be increased taken together with penicillins and tetracyclines. Live vaccines should be avoided; however inactivated vaccines may be given eg the influenza vaccination.[1]

For a more comprehensive list of interactions with methotrexate, consult the full prescribing information[14] or the 'Interaction' function on *New Zealand Formulary* online.[18]

ENSURE THERE IS A MONITORING PLAN

Inadequate monitoring of patients on long-term methotrexate is another cause of serious events that have resulted in patient harm.[2]

A full blood count, renal and liver function tests, and in some cases chest X-ray and respiratory function, need to be checked before treatment is started. Laboratory monitoring needs to be repeated at regular intervals until the patient is stabilised, and then on an ongoing basis so that the patient can be clinically evaluated, and to identify methotrexate toxicity.[2] Repeat prescriptions for methotrexate should not be provided without a full blood count and liver function test having been performed within the previous 4 to 8 weeks.[4,10,16]

See Table 1 for more details, but please note that local guidelines may vary; follow the advice of the treating specialist about the frequency of testing.[1]

In all cases, an agreed management plan should be in place for each patient specifying who takes primary responsibility for changes to dosing, and for arranging, reviewing and acting upon laboratory investigations.[1,2,10]

Note: Methotrexate is also indicated for the treatment of neoplastic diseases, such as leukaemia. For these conditions it may be prescribed in daily doses. **Folinic acid** (as opposed to **folic acid**) is used to prevent toxicity in these patients.[2]

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REFERENCES

1. Highton J, Harrison A, Grainger R. Rheumatoid arthritis – monitoring of DMARDs. Best practice journal 2008; 17:22-26 www.bpac.org.nz/magazine/2008/october/docs/bpj17_rheumatoidarthritis_pages_22-26.pdf (Accessed 04-05-12)
2. Improving compliance with oral methotrexate guidelines; Patient safety alert, 13. National Patient Safety Agency (NPSA) 2006. www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/oral-methotrexate/ (Accessed 04-05-12)
3. Grove M, Hassell A, Hay E, Shadforth M. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. The Quarterly Journal of Medicine 2001;94:309-319
4. Harrison A. Disease-modifying Anti-rheumatic Drugs (DMARDs) for Rheumatoid Arthritis: Benefits and Risks. Prescriber Update 1999; 18:4-12 www.medsafe.govt.nz/profs/puarticles/dmards.htm (Accessed 18-04-13)
5. Methotrexate overdose due to inadvertent administration daily instead of weekly; Medication Safety Alert! Institute for Safe Medication Practices (ISMP), December 3 2002. www.ismp.org/hazardalerts/ha.pdf (Accessed 04-05-12)
6. Yeoh S, Siderov J. Methotrexate misadventure – a case for counselling. Rheumatology 2001;40:230-32 rheumatology.oxfordjournals.org/content/40/2/230.full.pdf+html (Accessed 04-05-12)
7. Pharmacist not to blame for death, says coroner. 20-10-09. www.stuff.co.nz/national/health/2983300/Pharmacist-not-to-blame-for-death-says-coroner (Accessed 04-05-12)
8. Bookstaver PB, Norris L, Rudisill C et al. Multiple toxic effects of low-dose methotrexate in a patient treated for psoriasis. Americal Journal o fHealth-System Pharmacy 2008;65(22):2117-21 www.ajhp.org/content/65/22/2117 (Accessed 19-04-13)
9. Blinova E, Volling J, Koczmara C, Greenall J. Oral methotrexate: Preventing inadvertent daily administration. Canadian Journal of Hospital Pharmacy 2008;61(4):275-77
10. Health Quality and Safety Commission. Methotrexate - once weekly dosing. Medication alert 14, April 2012. www.hqsc.govt.nz/assets/Medication-Safety/Alerts-PR/Oral-methotrexate-Alert-final.pdf (Accessed 04-05-12)
11. Tsai A, Morton S, Mangione C, Keeler E. A Meta-analysis of Interventions to Improve Care for Chronic Illness. American Journal of Managed Care 2005;11(8):478-488
12. Bologna C, Viu P, Picot MC, Jorgensen C and Sany J. Long-term follow-up of 453 rheumatoid arthritis patients treated with methotrexate: an open, retrospective, observational study. British Journal of Rheumatology 1997;36:535-540
13. Best Practice Advisory Centre. Recommended Investigations for some commonly used DMARDs. Best Practice Journal 2008;17:29-32 www.bpac.org.nz/magazine/2008/october/docs/bpj17_dmards_pages_29-32_pf.pdf (Accessed 19-04-13)
14. Hospira New Zealand Limited. DBL Methotrexate injection and tablets data sheet 14-09-12. www.medsafe.govt.nz/profs/datasheet/d/dblmethotrexateinjmayne.pdf (Accessed 18-04-13)
15. The New Zealand Formulary, methotrexate. www.nzf.org.nz/nzf_4548.html?searchterm=methotrexate (Accessed 18-04-13)
16. Best Practice Advisory Centre. Errors with methotrexate can be fatal. Best Practice Journal 2011; 34:16-17 www.bpac.org.nz/magazine/2011/february/docs/bpj_34_methotrexate_pages_16-17_pf.pdf (Accessed 19-04-13)
17. The Australian Rheumatology Association. Patient information, methotrexate; August 2012. www.rheumatology.org.au/community/PatientMedicineInformation.asp (Accessed 23-08-13)
18. The New Zealand Formulary, interactions. www.nzf.org.nz/interactions (Accessed 18-04-13)

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Table 1

Methotrexate Monitoring Recommendations[13]

(Adapted from BPAC 2008;17:29)

Monitoring	Frequency	Parameters	Action
Complete blood count (CBC)	Baseline, then every 2 weeks until stable for 6 weeks; thereafter every 4-8 weeks	WBC <3.5 x 10^9/L Neutrophils <2.0 x 10^9/L Platelets <150 x 10^9/L	Discuss with specialist team immediately
		MCV > 105 fL	Check vitamin B_{12}, folate, TSH and treat abnormalities
Liver function tests (LFTs)	Baseline, then every 2 weeks until stable for 6 weeks; thereafter every 4-8 weeks	AST, ALT > twice the upper limit of reference range	Withhold, discuss with specialist and check: alcohol intake NSAID intake and other medication
		Unexplained decrease in albumin (in absence of active disease)	Withhold and discuss with specialist
Serum creatinine	Baseline, then every 2 weeks until stable for 6 weeks; thereafter every 4-8 weeks	Significant deterioration in renal function	Reduce dose
Rash or oral ulceration	Inform patient to report immediately if occurs		Withhold, discuss with specialist. Try folinic acid mouthwash for mucositis
Nausea and vomiting, diarrhoea	Inform patient to report immediately if occurs		Consider subcutaneous route to avoid nausea if other causes excluded
Dyspnoea or dry cough (pneumonitis)	Baseline chest X-ray and respiratory function tests may be advised		Discuss URGENTLY with specialist. Arrange chest X-ray and respiratory function tests
Severe sore throat, abnormal bruising	Inform patient to report immediately if occurs		Immediate CBC, withhold methotrexate until results available. Discuss abnormal results with specialist

WBC = White blood cells
MCV = Mean cell volume
TSH = Thyroid stimulating hormone
NSAID = Non-steroidal anti-inflammatory drugs
AST = Aspartate transaminase
ALT = Alanine transaminase