

## METHOTREXATE - SAFE PRESCRIBING - ONCE A WEEK!

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- ▶ ERRONEOUS PRESCRIBING AND DISPENSING CAUSE THE MOST HARM
- ▶ ALWAYS DOUBLE-CHECK PRESCRIPTIONS
- ▶ ENSURE THERE'S A MONITORING PLAN
- ▶ ADVISE PATIENTS TO REPORT SYMPTOMS OF ADVERSE REACTIONS
- ▶ IT'S A USEFUL AND EFFECTIVE MEDICINE WHEN USED CORRECTLY

### METHOTREXATE IS A USEFUL AND EFFECTIVE MEDICINE IF USED CORRECTLY

Low-dose oral methotrexate therapy, i.e. less than 25mg taken as a single dose once a week, is generally safe when prescribed for non-neoplastic diseases that are characterised by inflammation, such as rheumatoid arthritis<sup>1,2</sup>. Compared to second-line disease-modifying anti-rheumatic drugs (DMARDs), methotrexate is usually well tolerated<sup>3</sup> and its side-effects predictable<sup>1</sup>. Even though 60-70% of patients may experience adverse reactions during the first year of therapy, these side-effects are often not severe enough to warrant discontinuation<sup>4</sup>.

Methotrexate is a useful and effective medicine when it is used correctly<sup>1,2</sup>. However, it is considered to be a 'high-risk' medicine because when it is not used correctly it is associated with a high rate of adverse reactions and toxicities. These may cause serious illness and significant patient harm, including death<sup>2,5</sup>.

### METHOTREXATE PRESCRIBING AND DISPENSING ERRORS CAUSE THE MOST HARM

The most common cause of significant patient harm reported in the medical literature (from Europe<sup>2</sup>, Australia<sup>6</sup> and US<sup>3</sup>) occurs when a medical practitioner unintentionally prescribes methotrexate to be taken **daily** rather than **once a week**, followed by a pharmacist dispensing the methotrexate accordingly<sup>2,5,6</sup>.

The danger of this pattern of misadventure with methotrexate is well known to health professionals. As recently as 2006, a New Zealand woman died after taking

her weekly methotrexate dose on a **daily** basis, after it was prescribed and dispensed as such<sup>7</sup>.

Harm may also occur when the wrong strength of methotrexate tablet is dispensed, or because of labelling errors<sup>2,5,7</sup>.

### ALWAYS DOUBLE-CHECK WHEN PRESCRIBING AND DISPENSING

Regulatory authorities have tried to develop strategies to reduce the harm from these errors. A simple (and obvious) way to improve patient safety is to exercise caution when prescribing and dispensing oral methotrexate (including the management of repeat prescriptions)<sup>2,5,6</sup>.

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

Prescribers are also advised to consult the full prescribing information for methotrexate to double-check for drug interactions between methotrexate and any concomitant medications<sup>8</sup>.

### ADVISE PATIENTS TO REPORT SYMPTOMS OF ADVERSE REACTIONS; ENSURE THEY KNOW WHAT THEY ARE DOING

The most common side-effects of low-dose oral methotrexate therapy are gastrointestinal symptoms; these symptoms can be managed with oral folic acid without affecting methotrexate's efficacy<sup>9</sup>. However, methotrexate may cause serious side-effects which can occur in the absence of overdose and without dose error<sup>3</sup>.

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Patients are more at risk of side-effects, especially haematological toxicity, if they are prescribed medicines that interact with methotrexate (e.g. cotrimoxazole), or have renal dysfunction. Elderly patients, those with renal impairment, and patients taking concomitant medicines which predispose them to toxicity (e.g. non-steroidal inflammatory drugs - NSAIDs) may require dose modification and/or more attentive monitoring<sup>8</sup>.

Health professionals should advise patients to be alert for any signs or symptoms suggestive of methotrexate toxicity, and to report these without delay<sup>2</sup>. The major side-effects are bone marrow suppression (e.g. fever, sore throat, mouth ulcers), symptoms suggestive of hepatotoxicity (e.g. abdominal pain, jaundice), or pulmonary toxicity (e.g. new or increasing dyspnoea, chest pain, hypoxaemia, dry cough)<sup>8</sup>.

The unusual weekly dosing schedule can be confusing for patients and it has promoted medication errors, some of which have been fatal<sup>5</sup>. Health professionals can improve methotrexate safety by providing patients with clear instructions about how and when to take their methotrexate (i.e. the strength and number of tablets per dose and nominating a specific day of the week) and by avoiding combinations of the two different tablet strengths at the same time<sup>2,5</sup>. In some instances, it may be safer to use only the 2.5mg strength tablet so that no possibility exists of taking an overdose with the 10 mg tablet strength.

Patients should be made aware of the risks of methotrexate therapy, and about avoiding "as needed" self-medication<sup>5</sup>. Women of child bearing potential, or men taking methotrexate whose partner is of child bearing potential should use effective contraception during treatment and for six months after cessation<sup>8</sup>.

Written patient information resources may help with promoting effective self-management<sup>10</sup>. A special effort may be needed when methotrexate is prescribed when English is not the first language.

### ENSURE THERE'S A MONITORING PLAN

Inadequate monitoring of patients on long-term methotrexate is another common cause of serious events that have resulted in patient harm<sup>2</sup>.

bpac<sup>NZ</sup> has published an excellent resource with the recommended investigations for a range of DMARDs, including methotrexate: [www.bpac.org.nz](http://www.bpac.org.nz) (keyword "dmard"). They note that local guidelines may vary, and that it is important to follow the advice of the treating specialist, in particular about the frequency of testing<sup>1</sup>.

Full blood counts, renal and liver function tests, and possibly chest x-rays and respiratory function tests are required 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 prevent methotrexate toxicity<sup>2</sup>.

In all cases, ensure there is clarity about the prescribing and monitoring responsibilities for each patient. An agreed management plan should be in place specifying who takes primary responsibility for changes to dosing, and for arranging, reviewing, and acting upon laboratory investigations (especially when care is shared between primary and secondary care teams or specialists)<sup>1,2</sup>.

### A REMINDER ABOUT ORAL METHOTREXATE FOR NEOPLASTIC CONDITIONS

Methotrexate is also indicated in the treatment of neoplastic disease, such as leukaemia. For these conditions it may be prescribed in daily doses. It should be noted that **folinic acid** (as opposed to **folic acid**) is used to prevent toxicity<sup>2</sup>.

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### ACKNOWLEDGMENTS

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### REFERENCES

1. best practice journal; Issue 17, Oct 2008. [http://www.bpac.org.nz/magazine/2008/october/docs/bpj17\\_rheumatoidarthritis\\_pages\\_22-26.pdf](http://www.bpac.org.nz/magazine/2008/october/docs/bpj17_rheumatoidarthritis_pages_22-26.pdf) [accessed on 23 Jan 2009]
2. Improving compliance with oral methotrexate guidelines; Patient safety alert, 13. National Patient Safety Agency (NPSA), 1 June 2006. In: <http://www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/oral-methotrexate/> [accessed on 23 Jan 2009]
3. Grove M, Hassell A, Hay E, Shadforth M. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. *Quart J Med* 2001;94:309-319
4. Aronson J. *Meyler's Side Effects of Drugs*. 15th ed. Elsevier Science, Amsterdam;2006:2277
5. Methotrexate overdose due to inadvertent administration daily instead of weekly; Medication Safety Alert! Institute for Safe Medication Practices (ISMP), December 3 2002. <http://www.ismp.org/hazardalerts/ha.pdf> [accessed on 23 Jan 2009]
6. ADRAC. Methotrexate misadventures – a need for care and counselling. *Aust Adv Drug React Bull* 1999;18(4):14. <http://www.tga.gov.au/adr/aadrb/aadr9912.pdf> [accessed on 27 Jan 2009]
7. MedTech refutes safety allegation. *New Zealand Doctor Online*, 25 August 2008. <http://www.nzdoctor.co.nz/news?article=d74947fa-70de-41e1-b8a9-ef6bcb24c02b> [accessed on 23 Jan 2009]
8. Pfizer New Zealand Limited. Methoblastin tablets data sheet 22 August 2008. <http://www.medsafe.govt.nz/profs/datasheet/m/Methoblastintab.htm> [accessed on 23 Jan 2009]
9. 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. *Br J Rheumatol* 1997;36:535-540
10. Tsai A, Morton S, Mangione C, Keeler E. A Meta-analysis of Interventions to Improve Care for Chronic Illness. *Am J Manag Care* 2005;11(8):478-488

For further information on other high-risk medicines visit our website at: [www.saferx.co.nz](http://www.saferx.co.nz)

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DISCLAIMER: This information is provided to assist primary care health professionals with the use of prescribed medicines. Users of this information must always consider current best practice and use their clinical judgement with each patient. This information is not a substitute for individual clinical decision making. Issued by the Quality Use of Medicines Team at Waitemata District Health Board, email: [feedback@saferx.co.nz](mailto:feedback@saferx.co.nz)