Errors with methotrexate can be fatal

METHOTREXATE IS PRESCRIBED once weekly for rheumatoid arthritis or other autoimmune conditions. It is often initiated by a secondary care specialist, but is increasingly being initiated and prescribed 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.

The most common adverse effects of methotrexate are gastrointestinal. Folic acid is prescribed to manage these adverse effects (see opposite). Toxicity can occur with any dose of methotrexate, however, toxic effects are more frequent and more severe with increased dose or increased frequency of dosing.[1] Patients should be made aware of symptoms that may indicate methotrexate toxicity

A case report

A patient with rheumatoid arthritis presents to the general practice with a fever and chest tightness. After taking a history and examining the patient, you see in the medical record that the patient was last seen by another doctor in the practice, one week ago, for a repeat prescription of oral methotrexate.

The symptoms of chest tightness and fever could be unrelated to the methotrexate dose but should be further investigated.

Questions to ask: When did you last take your methotrexate? How many doses have you taken in the last seven days? How many tablets do you take at a time? Do you know what strength your methotrexate tablets are?

Action required: If questioning reveals that there has been an error in the methotrexate dose or frequency then the patient should be referred urgently to hospital for further tests and treatment, including chest x-ray, respiratory function tests and CBC.

If no error has occurred in the methotrexate dose or frequency, consider other causes and advise the patient not to take any more methotrexate while awaiting the results of an urgent CBC, liver function and renal function tests. Review the patient again when the results are received.

such as fever, sore throat, abdominal pain, jaundice, chest pain or shortness of breath.

Routine baseline testing prior to initiation of methotrexate usually includes a complete blood count (CBC), liver function tests, serum creatinine, a chest x-ray and respiratory function testing.

Methotrexate-related pulmonary complications

Methotrexate use may cause significant pulmonary complications such as pneumonitis and pneumonia. Patients with methotrexate-induced pneumonitis typically present with fever, dry cough, chest pain and shortness of breath. It is not clear whether methotrexate-induced pneumonitis is due to direct toxicity, a hypersensitivity reaction or an underlying viral infection.[2] As methotrexate suppresses the immune system, people taking this medicine are more susceptible to opportunistic infections caused by pathogens such as *Pneumocystis carinii*, viruses or mycobacteria.[2] Both methotrexate-induced pneumonitis and *Pneumocystis carinii* pneumonia are potentially fatal.

Folic acid co-administration

Methotrexate use results in a decreased supply of folates. Folic acid is co-administered to minimise the adverse effects of folate deficiency (stomatitis, bone marrow toxicity, abnormal liver function tests and gastrointestinal intolerance). Total weekly doses of 5 – 27.5 mg have demonstrated efficacy in decreasing methotrexate adverse effects,[3] however, a pragmatic approach is the use of 5 mg, once weekly.

Scenarios for potential error

Prescriber error: The methotrexate prescription is inadvertently prescribed as a daily dose rather than a weekly dose.

Pharmacy error: The prescription is correctly written as a weekly dose but the pharmacist dispenses and labels it incorrectly as a daily dose.

Patient error: A prescription is changed from a large number of low dose methotrexate tablets to a smaller number of higher dose tablets (to help simplify the regimen for the patient). The prescription is dispensed correctly but the patient continues to take the same number of new higher dose tablets, as their weekly dose.

All of these scenarios have occurred in New Zealand and overseas, resulting in patient deaths.

Best practice for prescribing methotrexate

"Right strength, right dose, right frequency"

- Double check prescriptions (both on screen and printed)
- Prescribe in milligrams not number of tablets
- Specify on the prescription the day of the week that the methotrexate should be taken
- Consider only prescribing 2.5 mg tablets (unless the patient is already stabilised on 10 mg tablets)
- Confirm with the patient what their individual dose in milligrams is, the strength of their tablets, the number of tablets they should take and the day of the week they should take them
- Inform the patient of possible adverse effects and what they should do if they think an adverse effect has occurred

For further information about monitoring methotrexate use, see "Recommended investigations for some commonly used DMARDs" BPJ 17 (Oct, 2008).

References

1. Pfizer New Zealand Ltd. Methoblastin. Medicine Safety Data Sheet, 2008. Available from: www.medsafe.govt.nz (Accessed Feb, 2011).
2. Balk RA. Methotrexate-induced lung injury. UpToDate 2010. Available from: www.uptodate.com (Accessed Feb, 2011).
3. Pangilian J. Does folic acid reduce the toxicity of methotrexate? Ask the experts. Medscape Today, 2009. Available from: www.medscape.com/viewarticle/588229 (Accessed Feb, 2011).