Perils and pitfalls of methotrexate prescription

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Methotrexate is a folic acid antagonist which can be used as an antineoplastic drug or as an immunomodulator. While it has a well established role in specialist oncology practice, it is increasingly being used in general medical practice for immunomodulation. Methotrexate is prescribed as a 'steroid-sparing' drug for conditions in which glucocorticoids have been used to suppress inflammatory activity. These conditions include rheumatoid arthritis, asthma, psoriasis, inflammatory bowel disease, myasthenia gravis and inflammatory myositis. This list of indications continues to grow.

Methotrexate is used in an attempt to minimise the dose of long-term oral corticosteroids and reduce their adverse effects. However the somewhat atypical dose regimen for low-dose methotrexate has presented some difficulties. The toxic adverse-effect profile of methotrexate is well known. However, the weekly dosage regimen of low-dose therapy (e.g. 7.5–10 mg) has caused confusion and errors for prescribers and patients. The risk of misadventure is increased by the current tablet formulations available.[1]

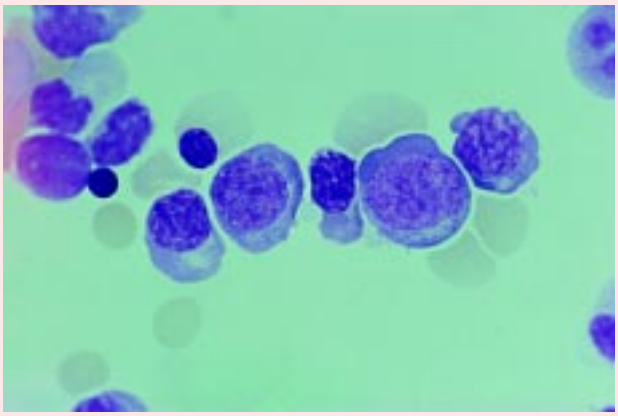
There have been six reports to the Adverse Drug Reactions Advisory Committee (ADRAC) of serious consequences resulting from toxic doses of methotrexate. Three of these patients died from complications of bone marrow suppression. Four of the six people were more than 70 years old and three of them misunderstood clear written instructions about taking the drug **weekly**, instead of daily. One patient took extra doses to relieve arthritic symptoms. Two of the cases were patients in a hospital and the methotrexate dose was incorrectly charted and/or dispensed daily, instead of weekly.

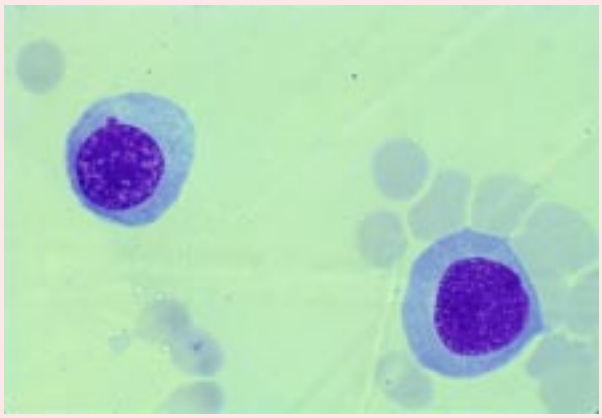
In elderly patients, other factors can contribute to the adverse outcome. Sensory and cognitive impairment may increase the chance of patient-related errors. In one of the cases cited above, there was clearly a misunderstanding of the mechanism of effect of methotrexate; it is not for symptom relief. The drug is renally cleared and may therefore accumulate in the older patient with reduced renal function.

So what can both the prescriber and 'the system' do to reduce the chance of adverse effects due to errors? Common sense measures include the following:

- give clear written instructions that **name a specific weekday** for taking the tablet[2]
- prepare instructions in big print to assist people with poor eyesight
- have a clear protocol for monitoring appropriate clinical and blood parameters such as full blood count, liver and renal function tests
- take special care in those with known renal/hepatic impairment
- ensure the patient has a good understanding of how and when to take the drug and the dangers of taking too much
- explain that extra or irregular doses are dangerous

Photomicrographs illustrating features of red cell precursors in bone marrow rendered megaloblastic by treatment with methotrexate. Normal red cell precursors on the left (slide 1) are a mixture of larger immature cells, and smaller mature forms with red cytoplasm and very dark small round nuclei. In the bone marrow of the patient affected by methotrexate on the right (slide 2), the red cell precursors are larger, tend to appear immature, and have a characteristically abnormal appearance of the nucleus.





Pictures provided by Dr Frank Firkin, St Vincent's Hospital, Melbourne

- advise the patient not to take a catch up dose if one dose is missed; the flare-up of disease is unlikely
- make a carer responsible for giving the drug if the patient appears to have cognitive or severe sensory difficulties

Most of these principles are relevant when advocating unusual or atypical regimens. The consequences of incorrect dosage can be fatal but are often preventable.[3]

REFERENCES

1. Methotrexate misadventures – a need for care and counselling. Aust Adv Drug React Bull 1999;18:14.
2. Methotrexate – name the day. Aust Adv Drug React Bull 1998;17:7.
3. Low dose methotrexate therapy – toxic if not taken correctly. Adverse Drug Reactions Advisory Committee. Med J Aust 1994;161:152.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Board is prepared to do this. Before new drugs are prescribed, the Board believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Anagrelide

Agrylin (Orphan)

0.5 mg capsules

Approved indication: essential thrombocythaemia

Australian Medicines Handbook Section 7

Essential thrombocythaemia is an uncommon abnormality of the bone marrow. This clonal stem cell disorder results in the production of abnormal platelets and an increased platelet count. Patients are not only at risk of thrombosis, but also bleeding.[1]

Patients require treatment if they develop complications or if their platelet count exceeds 1000 x 10^9/L. While some patients require plateletpheresis, many patients are treated with hydroxyurea. This drug can have serious adverse effects so anagrelide will offer an alternative treatment.

Anagrelide was originally developed as an inhibitor of platelet aggregation, but was found to cause thrombocytopenia. It is thought to impair the maturation of megakaryocytes.

A clinical trial investigated anagrelide in 577 patients with conditions such as polycythaemia vera and chronic granulocytic leukaemia. The trial included 335 patients with essential thrombocythaemia, but only 262 were evaluable. After completing at least four weeks of treatment, 247 had a platelet count which had reduced by half or fallen below 600 x 10^9/L.[2]

Patients begin treatment with 0.5 mg four times a day or 1 mg twice a day for at least a week. The dose is adjusted to the lowest dose able to keep the platelet count under control. The platelet count should be measured every two days in the first week, then weekly until the maintenance dose is found. In clinical studies the mean duration of treatment was 65 weeks, but more than 20% of patients took anagrelide for two years.

The drug is rapidly absorbed. Although food reduces bioavailability the effect is not significant. Anagrelide has a half-life of 1.3 hours and is extensively metabolised. Most of the metabolites are excreted in the urine. Patients with liver or kidney disease must be monitored carefully as anagrelide may alter liver function and possibly cause renal failure.

Anagrelide causes vasodilatation. Patients may develop hypotension, palpitations, tachycardia and heart failure. These symptoms led to the withdrawal of some patients from the clinical trials. In total 15% of the patients withdrew. Other reasons for withdrawal included headache, diarrhoea and abdominal pain which are common adverse reactions to anagrelide.

Anaemia is common and thrombocytopenia can develop. In addition to full blood counts, renal and liver function should also be checked during treatment.

REFERENCES

1. Bentley MA, Taylor KM, Wright SJ. Essential thrombocythaemia. Med J Aust 1999;171:210-3.
2. Anagrelide Study Group. Anagrelide, a therapy for thrombocythemic states: experience in 577 patients. Am J Med 1992;92:69-76.

Varicella vaccine

Varilix (SmithKline Beecham)

vials containing a powder pellet for reconstitution

Approved indication: immunisation

Australian Medicines Handbook Section 20.1

Chickenpox is usually a mild childhood infection. It can, however, be fatal in immunocompromised patients. In the USA the cost of managing chickenpox is estimated to be US$400 million.[1] Universal vaccination is now recommended for all American children.

The vaccine which has been approved for use in Australia is a live attenuated strain of the varicella-zoster virus. A single dose is recommended for children more than nine months old. Older children and adults have two doses at least six weeks apart. The deltoid area is the preferred site for the subcutaneous injection.

In children a single dose of vaccine has an efficacy of 88%. Children who catch chickenpox despite vaccination appear to develop an attenuated infection.

Injection site reactions occur in 27% of cases. Some vaccinees develop a mild varicella-like disease within a month.

Although varicella vaccines have been available overseas for