interleukin 1 alpha protects mice from lethal bacterial infection. *J Exp Med* 1989;169:2021-7.
24 Froidevaux C, Roger T, Martin C, Glauser MP, Calandra T. Macrophage migration inhibitory factor and innate immune responses to bacterial infections. *Crit Care Med* 2001;29:S13-5.
25 Roger T, David J, Glauser MP, Calandra T. MIF regulates innate immune responses through modulation of Toll-like receptor 4. *Nature* 2001;414:920-4.
26 Calandra T, Echtenacher B, Roy DL, Pugin J, Metz CN, Hultner L, et al. Protection from septic shock by neutralization of macrophage migration inhibitory factor. *Nat Med* 2000;6:164-70.
27 Bernhagen J, Calandra T, Mitchell RA, Martin SB, Tracey KJ, Voelter W, et al. MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. *Nature* 1993;365:756-9.
28 Bozza M, Satoskar AR, Lin G, Lu B, Humbles AA, Gerard C, et al. Targeted disruption of migration inhibitory factor gene reveals its critical role in sepsis. *J Exp Med* 1999;189:341-6.
29 Wang H, Yang H, Czura CJ, Sama AE, Tracey KJ. HMGB1 as a late mediator of lethal systemic inflammation. *Am J Respir Crit Care Med* 2001;164:1768-73.
30 Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, et al. HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 1999;285:248-51.

Lesson of the week

Low dose methotrexate and bone marrow suppression

Michael Sosin, Sunil Handa

Department of Haematology, Sandwell General Hospital, West Bromwich, West Midlands, B71 4HJ
Michael Sosin *senior house officer*
Sunil Handa *consultant haematologist*

Correspondence to: Sunil Handa sunil.handa@swellhot.wmids.nhs.uk

BMJ 2003;326:266–7

Methotrexate is an antimetabolite that, apart from its use in malignant disorders, is taken orally in low doses for the control of conditions such as rheumatoid arthritis and psoriasis. When used in chemotherapy it causes profound suppression of bone marrow. However, even at a low dose it may be associated with bone marrow suppression—particularly in the presence of renal insufficiency or when other drugs are taken concomitantly (box 1). Its unusual weekly dosing regimen can result in dose error by patients or clinicians. We present three cases of bone marrow suppression in patients taking low dose methotrexate who presented at a district general hospital during a period of four years (table).

Case reports

Case 1

A 78 year old woman with rheumatoid arthritis had been taking a weekly dose of 17.5 mg of methotrexate for two months. Before this the dose had been gradually built up over several years. She was admitted with breathlessness and found to be pancytopenic (haemoglobin concentration 100 g/l, white cell count 3.0 × 10^9/l, neutrophils 2.5 × 10^9/l, platelets 13 × 10^9/l). A month earlier her full blood count had been normal.

Methotrexate treatment was discontinued. She was treated with intravenous folinic acid and antibiotics and was given transfusions of blood products. Her blood count showed recovery (haemoglobin concentration 137 g/l, white cell count 11.0 × 10^9/l, neutrophils 8.1 × 10^9/l, platelets 178 × 10^9/l). After a prolonged admission of about four weeks she was discharged home well.

Case 2

A 67 year old man with rheumatoid arthritis had been taking methotrexate for six months. He was admitted with diarrhoea and vomiting. Both he and his family were unclear about the dose of methotrexate he had taken recently, but it seemed likely that he had been taking methotrexate daily instead of weekly. He was pancytopenic (haemoglobin concentration 102 g/l, white cell count 1.2 × 10^9/l, neutrophils 0.3 × 10^9/l, platelets 66 × 10^9/l). A month previously his blood count showed a neutrophilia (haemoglobin concentration 111 g/l, white cell count 15.5 × 10^9/l, neutrophils 13.7 × 10^9/l, platelets 393 × 10^9/l). His weekly dose of methotrexate had been increased from 5 mg to 7.5 mg at that time, and this may have resulted in the presumed dose error.

Methotrexate was discontinued, and he was treated with blood transfusion and with intravenous antibiotics and folinic acid. His blood count recovered (haemoglobin concentration 117 g/l, white cell count 15.6 × 10^9/l, neutrophils 8.5 × 10^9/l, platelets 153 × 10^9/l), and he was discharged home well.

Case 3

A 74 year old woman, who had been taking methotrexate (5 mg weekly) for 10 years, was admitted with abdominal pain and pancytopenia (haemoglobin concentration 78 g/l, white cell count 0.5 × 10^9/l, neutrophils 0.4 × 10^9/l, platelets 14 × 10^9/l). She had received a course of trimethoprim for a presumed urinary tract infection one week before admission. Three weeks earlier her blood count had been normal.

Methotrexate was discontinued. She was treated with intravenous antibiotics and folinic acid and transfusion of blood products. She did not improve and was started on treatment with granulocyte colony stimulating factor. Her white cell count rose rapidly, and her last blood count showed a neutrophilia (haemoglobin concentration 132 g/l, white cell count 52.0 × 10^9/l, neutrophils 48.4 × 10^9/l, platelets 190 × 10^9/l). After

Details of patients with bone marrow suppression after taking methotrexate

Patient	Age, sex	Weekly dose of methotrexate (duration of treatment)	Indication	Symptoms at presentation to hospital	Precipitating factor	Outcome
1	78, female	17.5 mg (2 months)	Rheumatoid arthritis	Shortness of breath	Unknown	Recovered
2	67, male	5 mg (6 months)	Rheumatoid arthritis	Diarrhoea and vomiting	Dose error	Recovered
3	74, female	5 mg (10 years)	Rheumatoid arthritis	Abdominal pain	Concomitant trimethoprim	Died
4*	40, male	10 mg (7 months)	Psoriasis	Fever and rigors	Unprescribed self treatment	Recovered

*Not described in the text.

initial improvement she developed pneumonia and died 17 days after admission.

Discussion

Methotrexate is often used to treat psoriasis and rheumatoid arthritis. For these conditions it is usually given orally in a low dose, once weekly (up to 30 mg a week). Overall it is very well tolerated, with a low incidence of bone marrow suppression.[1 2] In a study of 2170 patients with rheumatoid arthritis, Grove et al found methotrexate to be the best tolerated of the disease modifying antirheumatic drugs.[3] A recent prospective study found that methotrexate may improve survival in patients with rheumatoid arthritis, largely by reducing cardiovascular mortality.[4] However, the unusual dosing regimen can cause errors, sometimes resulting in death.[5–7] Deaths associated with low dose methotrexate and concomitant use of interacting drugs or renal insufficiency, without dose error, have also been reported previously.[6–9] In our case 1 there was no evidence of use of interacting drugs or dose error. All the patients had normal renal function. Bone marrow suppression can therefore occur in patients taking low dose methotrexate, in the absence of other risk factors. Methotrexate is sometimes given in conjunction with low dose, oral folic acid (5 mg daily). This may reduce the incidence of bone marrow suppression and has not been shown to reduce the efficacy of methotrexate.[2 8 10] None of our patients was taking folic acid before admission.

Each of the patients described here suffered considerable morbidity, requiring prolonged admission and intensive treatment—including transfusion of blood products, intravenous antibiotics, and, in one case, treatment with growth factor. One patient did not survive. A further case (table), occurring in a patient who had been treating his psoriasis with methotrexate obtained from a relative, has not been fully described. Two other cases occurred at the hospital during this period, both fatal, but we could not contact relatives and so cannot present case details. Two of these patients had normal full blood count results within one month before admission, showing that bone marrow suppression can have a rapid onset.

Although regular monitoring of blood counts, as recommended by the national guidelines of the British Society of Rheumatology (box 3),[11] is helpful in picking up some cases of early toxicity, it may not prevent all episodes of bone marrow suppression. Because of the rapid onset of bone marrow suppression, more frequent monitoring is unlikely to reduce its occurrence. Oral folic acid may reduce the incidence of this complication. More importantly, however, patients and health professionals must be aware of the importance of avoiding interacting drugs and taking the wrong dose.

Box 1: Drugs that may cause bone marrow suppression when combined with methotrexate

Chloramphenicol
Ciclosporin
Cisplatin
Corticosteroids
Kanamycin
Nitrous oxide
Non-steroidal anti-inflammatory drugs
Omeprazole
Penicillins
Phenytoin
Probenecid
Retinoids
Tetracycline
Triamterene
Trimethoprim or co-trimoxazole

Box 2: Treatment of neutropenia induced by methotrexate

Stop methotrexate treatment
Give folinic acid, up to 120 mg in divided doses per 24 hours
Follow local guidelines for treatment of the neutropenic patient
Give granulocyte colony stimulating factor if the neutrophil count fails to recover or if the patient is severely ill with infection

Box 3: British Society for Rheumatology's guidelines for the monitoring of methotrexate treatment (July 2000)

Dose regimen: 7.5 mg weekly, increasing by 2.5 mg every six weeks to a maximum of 25 mg

Pretreatment assessment:
- Full blood count
- Urea and electrolytes
- Creatinine
- Liver function tests
- Chest radiography

Monitoring:
- Full blood count and liver function tests fortnightly until six weeks after last increase in dose, then monthly
- Urea and electrolytes every 6-12 months

Contributors: SH was involved in management of the patients, conceived the paper, and will act as guarantor. MS was involved in management of the patients and researched and wrote the paper.

Funding: None.

Competing interests: None declared.

1 Hirshberg B, Muszkat M, Schlesinger O, Rubinow A. Safety of low dose methotrexate in elderly patients with rheumatoid arthritis. *Postgrad Med J* 2000;76:787-9.
2 O'Dell JR. Methotrexate use in rheumatoid arthritis. *Rheum Dis Clin North Am* 1997;23:779-96.
3 Grove ML, Hassell AB, Hay EM, Shadforth MF. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. *Q J Med* 2001;94:309-19.
4 Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173-7.
5 Lomaestro BM, Lesar TS, Hager TP. Errors in prescribing methotrexate. *JAMA* 1992;268:2031-2.
6 Adverse drug reactions advisory committee. Low dose methotrexate therapy—toxic if not taken correctly. *Med J Aust* 1994;161:152.
7 McArthur G, Cole-Sinclair MF, van der Weyden M. Haemopoetic toxicity and low dose methotrexate. *Med J Aust* 1992;156:296.
8 Stockley IH, ed. *Drug interactions*. 5th ed. London: Pharmaceutical Press, 1999.
9 Omdal R, Goransson L, Bergrem H. Fatal outcome of low-dose methotrexate therapy in rheumatoid arthritis. *Clin Rheumatol* 1993;12:283-4.
10 Griffith SM, Fisher J, Clarke S, Montgomery B, Jones PW, Saklatvala J, et al. Do patients with rheumatoid arthritis established on methotrexate and folic acid 5 mg daily need to continue on folic acid supplements long term? *Rheumatology* 2000;39:1102-9.
11 British Society for Rheumatology. *National guidelines for the monitoring of second line drugs*. https://www.msecportal.org/portal/editorial/PublicPages/bsr/536883013/3.doc (accessed 24 September 2002).

(Accepted 28 June 2002)