Mercaptopurine has been used for its immunosuppressant properties in the treatment of auto-immune disorders such as inflammatory bowel disease but has been largely replaced by azathioprine.

Mercaptopurine is given orally. The usual initial antineoplastic dose for children and adults is 2.5 mg/kg or 50 to 75 mg/m^2 daily but dosage varies according to individual response and tolerance. If there is no clinical improvement and no evidence of white-cell depression after 4 weeks, the dose may be cautiously increased up to 5 mg/kg daily. In maintenance schedules the dose may vary from 1.5 to 2.5 mg/kg daily. Blood counts should be taken at least once a week and if there is a steep fall in the white cell count or severe bone-marrow depression the drug should be withdrawn immediately. Therapy may be resumed carefully if the white cell count remains constant for 2 or 3 days or rises.

It has been used intravenously as mercaptopurine sodium. Thioinosine (mercaptopurine riboside) has also been used.

Administration. There is evidence[1] that the maintenance dosage of mercaptopurine should be tailored individually to achieve an appropriate systemic exposure in children with acute lymphoblastic leukaemia (although this would involve determining mercaptopurine pharmacokinetics in each child). Improvements in survival since 1980 may be associated with changes in the prescribing of mercaptopurine which have resulted in greater cumulative doses being given;[2] some children may have been undertreated in the past because of variations in the pharmacokinetics of mercaptopurine (particularly boys, who tolerate mercaptopurine better than girls,[3] but who have a poorer prognosis).[2] The concentration of tioguanine nucleotide metabolites in the erythrocytes has been shown to be directly related to the risk of relapse in children with acute lymphoblastic leukaemia.[4] Thiopurine methyltransferase (TPMT) activity (which results in methylation and inactivation of mercaptopurine rather than the formation of active nucleotides) may play a substantial role in this variation,[5] but titration of the dose of mercaptopurine until myelotoxicity occurs may prevent the problem:[2] despite gaps in therapy caused by more frequent drug withdrawal, it appears to result in greater accumulation of tioguanine nucleotides in the cells.[6]

1. Koren G, *et al.* Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *N Engl J Med* 1990; **323:** 17–21.
2. Hale JP, Lilleyman JS. Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. *Arch Dis Child* 1991; **66:** 462–6.
3. Lilleyman JS, *et al.* Childhood lymphoblastic leukaemia: sex difference in 6-mercaptopurine utilization. *Br J Cancer* 1984; **49:** 703–7.
4. Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet* 1994; **343:** 1188–90.
5. Lennard L, *et al.* Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet* 1990; **336:** 225–9.
6. Lennard L, *et al.* Mercaptopurine in childhood leukaemia: the effects of dose escalation on thioguanine nucleotide metabolites. *Br J Clin Pharmacol* 1996; **42:** 525–7.

Inflammatory bowel disease. Mercaptopurine has been reported to be of benefit in ulcerative colitis[1,2] and Crohn's disease,[3-5] although azathioprine has generally been preferred (see p.1820). The *BNF* considers that in resistant or frequently relapsing cases mercaptopurine 1 to 1.5 mg/kg given daily may be of use.

1. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; **85:** 717–22.
2. George J, *et al.* The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; **91:** 1711–14.
3. Present DH, *et al.* Treatment of Crohn's disease with 6-mercaptopurine: a long-term randomized, double-blind study. *N Engl J Med* 1980; **302:** 981–7.
4. Sandborn W, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 16/05/08).
5. Markowitz J, *et al.* A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119:** 895–902.

Polymyositis. Mercaptopurine has been tried in a few patients with polymyositis but has not been formally assessed.

Preparations

BP 2008: Mercaptopurine Oral Suspension; Mercaptopurine Tablets; ***USP 31:*** Mercaptopurine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Puri-Nethol; Varimer; ***Austral.:*** Puri-Nethol; ***Austria:*** Puri-Nethol; ***Belg.:*** Puri-Nethol; ***Braz.:*** Puri-Nethol; ***Canad.:*** Purinethol; ***Chile:*** Puri-Nethol; ***Cz.:*** Puri-Nethol; ***Fr.:*** Puri-Nethol; ***Ger.:*** Puri-Nethol; ***Gr.:*** Puri-Nethol; ***Hong Kong:*** Puri-Nethol; ***India:*** Puri-Nethol; ***Irl.:*** Puri-Nethol; ***Israel:*** Puri-Nethol; ***Ital.:*** Puri-Nethol; ***Mex.:*** Puri-Nethol; ***Neth.:*** Puri-Nethol; ***Norw.:*** Puri-Nethol; ***NZ:*** Puri-Nethol; ***Philipp.:*** Capmerin; Empurine; Puri-Nethol; ***Rus.:*** Puri-Nethol (Пури-нетол); ***S.Afr.:*** Puri-Nethol; ***Singapore:*** Puri-Nethol; ***Swed.:*** Puri-Nethol; ***Switz.:*** Puri-Nethol; ***Thai.:*** Empurine; Puri-Nethol; ***Turk.:*** Puri-Nethol; ***UK:*** Puri-Nethol; ***USA:*** Purinethol.

Methotrexate *(BAN, USAN, rINN)*

Amethopterin; 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid; 4-Amino-10-methylfolic Acid; CL-14377; α-Methopterin; Methotrexát; Méthotrexate; Methotrexatum; Metotreksaatti; Metotreksatas; Metotrexát; Metotrexat; Metotrexato; MTX; NSC-740; WR-19039. *N*-{4-[(2,4-Diamino-6-pteridinylmethyl)methylamino]benzoyl}-L-glutamic acid.

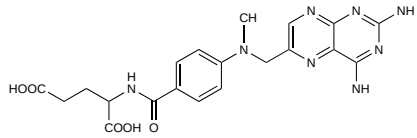
Метотрексат

$C_{20}H_{22}N_8O_5$ = 454.4.

CAS — 59-05-2.

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Methotrexate). A yellow or orange, hygroscopic, crystalline powder. It contains not more than 13% of water. Practically insoluble in water, in alcohol, and in dichloromethane; dissolves in dilute solutions of mineral acids and of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

USP 31 (Methotrexate). It is a mixture of 4-amino-10-methylfolic acid and closely related substances; it contains not less than 98% and not more than 102% of $C_{20}H_{22}N_8O_5$, calculated on the anhydrous basis. A yellow or orange-brown crystalline powder. It contains not more than 12% of water. Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. Store in airtight containers. Protect from light.

Methotrexate Sodium *(BANM, rINNM)*

Méthotrexate de Sodium; Methotrexate Disodium; Metotreksat Sodyum; Metotrexate sodium; Natrii Methotrexatum.

Натрий Метотрексат

$C_{20}H_{20}N_8Na_2O_5$ = 498.4.

CAS — 7413-34-5 (methotrexate disodium); 15475-56-6 (methotrexate sodium, xNa).

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

Incompatibility. Methotrexate sodium has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate;[1] however, another study suggests it is compatible with fluorouracil.[2] Furthermore a mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°, although precipitation did occur on storage for several days.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Stability to light. Methotrexate undergoes photodegradation when stored in the light in diluted solutions, although undiluted commercial preparations are reported to show negligible photodegradation.[1] The bicarbonate ion catalyses this reaction and such admixtures should be avoided if possible, although they may be stable in light for 12 hours. Storage of solutions diluted in sodium chloride 0.9% injection in PVC bags was reported to protect against photodegradation although the length of the study was only 4 hours.[2] Photodegradation can take place under normal lighting, but is more rapid in direct sunlight, with about 11% drug loss from a 1 mg/mL solution after 7 hours; storage under normal lighting resulted in little change in drug concentration over 24 hours with a decrease of up to 12% by 48 hours.[3] Loss was greatest from unprotected polybutadiene tubing, with almost 80% drug loss in 48 hours.

1. Chatterji DC, Gallelli JF. Thermal and photolytic decomposition of methotrexate in aqueous solutions. *J Pharm Sci* 1978; **67:** 526–31.
2. Dyvik O, *et al.* Methotrexate in infusion solutions—a stability test for the hospital pharmacy. *J Clin Hosp Pharm* 1986; **11:** 343–8.
3. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Adverse Effects

For general discussions see Antineoplastics, p.635.

The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may exhibit an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death.

Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given. Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors it is teratogenic, and it has been associated with fetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned (see Carcinogenicity, below).

Carcinogenicity. There are reports of lymphomas associated with low-dose methotrexate therapy for rheumatic disorders,[1-4] which in some cases have been associated with concomitant Epstein-Barr virus infection.[2] Transitional cell bladder cancer has also been associated with such therapy.[5] However, a retrospective analysis involving 16 263 patients with rheumatoid arthritis found no evidence of a relationship between the use of methotrexate as an antirheumatic and the development of haematological malignancy.[6] Nonetheless, the spontaneous remission of lymphoma after withdrawal of methotrexate in some patients seems to support an association[7] A later prospective study[8] of all new cases of lymphoma, detected over 3 years in patients treated with methotrexate for rheumatoid arthritis, also found a higher incidence of Hodgkin's disease compared with the general population. The carcinogenic risk with antimetabolites such as methotrexate has generally been considered less than with alkylating agents (p.635).

1. Zimmer-Galler I, Lie JT. Choroidal infiltrates as the initial manifestation of lymphoma in rheumatoid arthritis after treatment with low-dose methotrexate. *Mayo Clin Proc* 1994; **69:** 258–61.
2. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; **328:** 1317–21.
3. Viraben R, *et al.* Reversible cutaneous lymphoma occurring during methotrexate therapy. *Br J Dermatol* 1996; **135:** 116–18.
4. Ebeo CT, *et al.* Methotrexate-induced pulmonary lymphoma. *Chest* 2003; **123:** 2150–3.
5. Millard RJ, McCredie S. Bladder cancer in patients on low-dose methotrexate and corticosteroids. *Lancet* 1994; **343:** 1222–3.
6. Moder KG, *et al.* Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: a retrospective study. *Am J Med* 1995; **99:** 276–81.
7. Georgescu L, Paget SA. Lymphoma in patients with rheumatoid arthritis: what is the evidence of a link with methotrexate? *Drug Safety* 1999; **20:** 475–87.
8. Mariette X, *et al.* Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002; **99:** 3909–15.

Effects on the blood. Although serious and sometimes fatal blood dyscrasias are a well-known consequence of high-dose methotrexate therapy the UK CSM[1] stated in September 1997 that it was also aware of 83 reports of blood dyscrasias associated with low-dose methotrexate used to treat psoriasis or rheumatoid arthritis; there were 36 fatalities. Many of the cases had contributing factors such as advanced age, renal impairment, or use with interacting drugs.

1. Committee on Safety Medicines/Medicines Control Agency. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

MEGALOBLASTIC ANAEMIA. Megaloblastic anaemia, usually with marked macrocytosis, has been reported in mainly elderly patients given long-term weekly methotrexate therapy.[1-3] It has been suggested that therapy should be withdrawn if the mean corpuscular volume exceeds 106 femtolitres.[1] Symptoms appear to be associated with folate depletion by methotrexate,[2,4,5] probably due to increased excretion,[6] and in one case megaloblastic anaemia developed after starting a weight-reducing diet poor in folate.[4] Folate supplementation, conversely, may permit continuation of methotrexate therapy with resolution of the anaemia.[5]

1. Dodd HJ, *et al.* Megaloblastic anaemia in psoriatic patients treated with methotrexate. *Br J Dermatol* 1985; **112:** 630.
2. Dahl MGC. Folate depletion in psoriatics on methotrexate. *Br J Dermatol* 1984; **111** (suppl 26): 18.
3. Casserly CM, *et al.* Severe megaloblastic anemia in a patient receiving low-dose methotrexate for psoriasis. *J Am Acad Dermatol* 1993; **29:** 477–80.
4. Fulton RA. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; **114:** 267–8.
5. Oxholm A, Thomsen K. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; **114:** 268–9.
6. Duhra P, *et al.* Intestinal folate absorption in methotrexate treated psoriatic patients. *Br J Dermatol* 1988; **119:** 327–32.

Effects on the gastrointestinal tract. Although gastrointestinal toxicity is well recognised as an effect of high-dose regimens, oral ulceration has also been reported after low-dose (weekly) methotrexate use.[1,2] In some instances it was related to overdosage; symptoms resolved upon correction of the dose and with folate supplementation.[1] Folate deficiency may increase the oral toxicity of methotrexate, and folate supplementation may also avoid the need to stop low-dose methotrexate.[2]

1. Deeming GMJ, *et al.* Methotrexate and oral ulceration. *Br Dent J* 2005; **198:** 83–5.
2. Kalantzis A, *et al.* Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100:** 52–62.

Effects on the kidneys. High-dose methotrexate therapy can result in supersaturation of the urine with methotrexate and its metabolites leading to crystal formation.[1] These crystals can cause intrarenal obstruction and are a factor in the development of acute renal failure. Risk factors for crystal formation are acid urine, volume depletion, and renal impairment. Adequate hydration, and urinary alkalinisation with sodium bicarbonate or acetazolamide play an important role in minimising nephrotoxicity in high-dose methotrexate regimens. A study found that the incidence of severe toxicity was reduced in patients given greater hydration and alkalinisation. However, this more intensive hydration regimen also significantly lowered methotrexate plasma concentrations.[2] More recently glucarpidase (p.1447), a recombinant glutamate carboxypeptidase, has been developed and may be useful in the management of methotrexate-induced renal dysfunction when methotrexate concentrations are very high.[3]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; **106:** 459–65.
2. Christensen ML, *et al.* Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. *J Clin Oncol* 1988; **6:** 797–801.
3. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist* 2006; **11:** 694–703.

Effects on the liver. Methotrexate is well established as a cause of hepatotoxicity, including periportal fibrosis, when given in relatively high doses as an antineoplastic, and it has become clear that its long-term use in lower doses for disorders such as psoriasis and rheumatoid arthritis can also be associated with liver toxicity.[1] There has been some difficulty in these patients in distinguishing the effects of the drug from the effects of the disease, but there is good evidence that the risk is increased in patients given doses on a daily rather than a weekly regimen, and in those with a high alcohol intake.[1] Pre-existing liver disease, obesity (especially if associated with diabetes mellitus), renal impairment, and increasing total cumulative dose may also increase the risk of hepatotoxicity.[1] A lower incidence of hepatotoxicity in patients with rheumatoid arthritis (compared with older studies in patients with psoriasis) may be due to improved dosage regimens and greater awareness of the risks.[1]

In order to minimise the risks of serious liver damage various guidelines and recommendations have been issued for the use of methotrexate in psoriasis and rheumatoid arthritis, and the appropriate monitoring.

- For patients with *psoriasis*, US guidelines[2] recommend a liver biopsy at the beginning of treatment and after each cumulative dose of 1 to 1.5 g, together with monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, and albumin. The need to repeat routine liver biopsies has been questioned.[3] Some[4] recommend omitting the baseline biopsy in patients with no risk factors. Practice in the UK has been similar but monitoring of the aminoterminal peptide of type III procollagen (PIIINP), a serological marker of hepatic fibrosis,[5] is now recommended by the British Association of Dermatologists[6] as a safer alternative to liver biopsy. PIIINP values should be determined before starting methotrexate and then every 2 to 3 months during treatment. A liver biopsy may then be considered in those with persistently abnormal values. However, some[5] have said that larger studies of the value of PIIINP assays should be undertaken before definitive recommendations can be made.
- In patients with *rheumatoid arthritis* US guidelines[7] suggest an initial biopsy only in patients with a history of excessive alcohol consumption, persistently abnormal AST values or chronic hepatitis B or C infection. All patients should undergo monitoring of liver enzyme values (AST and ALT) and albumin every 4 to 8 weeks, and a biopsy should be performed if 5 of 9 or 6 of 12 measurements of AST are elevated in a 12-month interval; if liver changes are moderate to severe, methotrexate should be discontinued. However, some rheumatologists[8,9] consider that less stringent monitoring may be warranted, especially in those with no risk factors for hepatotoxicity. Similarly, although these guidelines have been widely adopted for use in children with juvenile idiopathic arthritis, some[10] consider that routine blood tests every 4 to 8 weeks are unnecessarily frequent.

The UK CSM advised in 1997 that liver-function tests (together with blood count and renal-function testing) should be performed before beginning long-term low-dose methotrexate therapy and repeated weekly until therapy was stabilised, and thereafter every 2 to 3 months.[11]

1. West SG, *et al.* Methotrexate hepatotoxicity. *Rheum Dis Clin North Am* 1997; **23:** 883–915.
2. Roenigk HH, *et al.* American Academy of Dermatology. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; **19:** 145–6.
3. Boffa MJ, *et al.* Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; **133:** 774–8.
4. Roenigk HH, *et al.* Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998; **38:** 478–85.
5. Maurice PDL, *et al.* Monitoring patients on methotrexate: hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. *Br J Dermatol* 2005; **152:** 451–8.
6. British Association of Dermatologists. Psoriasis Guideline 2006. Available at: http://www.bad.org.uk/healthcare/guidelines/psoriasis_guideline_(Final_update)_280906.pdf (accessed 31/07/08)
7. Kremer JM, *et al.* American College of Rheumatology. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; **37:** 316–28.
8. Yazici Y, *et al.* Monitoring by rheumatologists for methotrexate-, etanercept-, infliximab-, and anakinra-associated adverse events. *Arthritis Rheum* 2003; **48:** 2769–72.
9. Yazici Y, *et al.* Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities. *Clin Exp Rheumatol* 2005; **23:** 517–20.
10. Ortiz-Alvarez O,*et al.* Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol* 2004; **31:** 2501–6.
11. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

Effects on the lungs. Pulmonary toxicity due to methotrexate has been well described.[1,2] A review[1] of over 120 reports of methotrexate pneumonitis found that onset usually occurred during treatment, presenting as dyspnoea, cough, and fever. Examination often found tachypnoea and crackles, eosinophilia, reduced pulmonary function, interstitial and alveolar infiltrates on chest radiography, and interstitial inflammation and fibrosis. The majority of cases were managed with cessation of methotrexate with or without corticosteroid therapy; most patients improved, but there were 16 deaths caused by respiratory disease. Methotrexate was restarted in 16 patients, and pneumonitis recurred in 4 of these.

Up to 25 April 2003, the UK CSM had received 90 reports of parenchymal lung disorders, including 52 reports of pneumonitis, 21 of pulmonary fibrosis, 5 of interstitial lung disease, and 3 of interstitial pneumonitis. The CSM has suggested that patients should seek medical attention if symptoms such as dyspnoea, dry, nonproductive cough, or fever develop; methotrexate should be stopped and corticosteroids given in the event of suspected pneumonitis.[3]

A multicentre case-control study[4] which examined 29 cases of methotrexate-induced lung injury among rheumatoid arthritis patients reported a number of risk factors. These included age over 60 years, pleuropulmonary disease (or to a lesser extent other extra-articular disease), previous use of other disease-modifying antirheumatic drugs, and low serum-albumin; an association with smoking, nonsedentary occupations, and diabetes mellitus was also noted.

1. Imokawa S, *et al.* Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000; **15:** 373–81.
2. Lateef O, *et al.* Methotrexate pulmonary toxicity. *Expert Opin Drug Saf* 2005; **4:** 723–30.
3. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Methotrexate and pneumonitis. *Current Problems* 2003; **29:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
4. Alarcón GS, *et al.* Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis: a multicenter, case-control study. *Ann Intern Med* 1997; **127:** 356–64.

Effects on mental function. Children who had received intrathecal methotrexate with cranial irradiation for the prophylaxis of CNS leukaemia, had a significant intellectual deficit compared with their siblings.[1] There was no corresponding significant reduction in IQ in a group of children who had received systemic chemotherapy and radiotherapy when compared with their sibling controls. The results suggest that intrathecal methotrexate and cranial irradiation cause intellectual problems, particularly on the higher, more complex and integrated intellectual functions, and that the repercussions are greater in younger children. Subsequent results in these patients indicated that although the lowering of IQ had persisted, it had not progressed since the original study.[2] A further study confirmed the adverse neurological effects of leukaemia treatment, and its effects on IQ, and did not find a reduced radiation dose to be any less toxic.[3] Neurotoxicity appeared to be greater when systemic therapy with intramuscular rather than oral methotrexate was given with CNS prophylaxis. A study[4] of children who underwent surgery, chemotherapy, and craniospinal radiotherapy for medulloblastoma also found that those patients who received intrathecal methotrexate had significantly worse cognitive deficits than those who did not, and all patients performed worse than a control group of cousins and siblings.

In a small study[5] of children treated for leukaemia with chemotherapy that included intrathecal methotrexate, but without irradiation, there were lower cognitive scores in some measures compared with a group of healthy controls, but overall no major cognitive impairment was found.

A study in 20 patients receiving intermittent oral methotrexate for psoriasis found no evidence of psychological impairment.[6]

1. Twaddle V, *et al.* Intellectual function after treatment for leukaemia or solid tumours. *Arch Dis Child* 1983; **58:** 949–52.
2. Twaddle V, *et al.* Intellect after malignancy. *Arch Dis Child* 1986; **61:** 700–2.
3. Chessells JM, *et al.* Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation. *Arch Dis Child* 1990; **65:** 416–22.
4. Riva D, *et al.* Intrathecal methotrexate affects cognitive function in children with medulloblastoma. *Neurology* 2002; **59:** 48–53.
5. Kingma A, *et al.* No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. *J Pediatr Hematol Oncol* 2002; **24:** 106–14.
6. Duller P, van de Kerkhof PCM. The impact of methotrexate on psycho-organic functioning. *Br J Dermatol* 1985; **113:** 503–4.

Effects on the nervous system. Methotrexate has a cumulative toxic effect on the nervous system, and generalised and focal neurotoxic reactions are associated with intrathecal and high-dose intravenous use.[1] An immediate, usually transient, effect occurring within a day of high intravenous doses can cause nausea and vomiting, headache, somnolence, lethargy, confusion, disorientation, seizures, and increased intracranial pressure. Reversible acute meningitis can follow intrathecal use, with similar results.[1] Aseptic meningitis has also been reported after intramuscular methotrexate.[2] Spinal cord myelopathy resulting in transient or permanent paraplegia has also followed intrathecal methotrexate use, especially if other neurotoxic treatments have also been used. A subacute form of toxic reaction can occur up to several weeks after treatment. It is usually transient and characterised by seizures, varying degrees of paresis, aphasia, anaesthesia, blurred vision, and pseudobulbar palsy. A more delayed syndrome occurs weeks to months after treatment and is of variable severity, but can progress to lethargy, seizures, spasticity, paresis, drooling, and dementia. This condition is characterised by leukoencephalopathy and chronic calcification of brain tissue. It is dose-related, and more severe if the patient has also received radiotherapy.[1]

See also Effects on Mental Function, above.

1. Shuper A, *et al.* Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *J Child Neurol* 2000; **15:** 573–80.
2. Hawboldt J, Bader M. Intramuscular methotrexate-induced aseptic meningitis. *Ann Pharmacother* 2007; **41:** 1906–11.

Effects on the skin. There are rare reports[1,2] of painful erythema of the hands and feet, particularly the fingertips, with progression to blistering and desquamation (palmar-plantar erythrodysesthesia syndrome, p.639) after the use of high-dose intravenous methotrexate. Purpuric skin lesions due to vasculitis have occurred after both high-dose[3] and low-dose[4,5] methotrexate. Accelerated rheumatoid nodulosis has been reported[6,7] after the use of methotrexate in patients with rheumatoid arthritis. Erosion of psoriatic plaques, accompanied by pain and erythema, has been seen[8,9] after low-dose methotrexate therapy; blistering and necrosis consistent with toxic epidermal necrolysis has occurred.[8] Possible exacerbation of a photosensitivity reaction to ciprofloxacin has been described,[10] and reactivation of sunburn

has also been reported[11] in a number of cases where methotrexate was given within 2 to 5 days after the initial sunburn.

1. Doyle LA, *et al.* Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983; **98:** 611–12.
2. Millot F, *et al.* Acral erythema in children receiving high-dose methotrexate. *Pediatr Dermatol* 1999; **16:** 398–400.
3. Navarro M, *et al.* Leukocytoclastic vasculitis after high-dose methotrexate. *Ann Intern Med* 1986; **105:** 471–2.
4. Marks CR, *et al.* Small-vessel vasculitis and methotrexate. *Ann Intern Med* 1984; **100:** 916.
5. Torner O, *et al.* Methotrexate related cutaneous vasculitis. *Clin Rheumatol* 1997; **16:** 108–9.
6. Williams FM, *et al.* Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. *J Am Acad Dermatol* 1998; **39:** 359–62.
7. Filosa G, *et al.* Accelerated nodulosis during methotrexate therapy for refractory rheumatoid arthritis: a case report. *Adv Exp Med Biol* 1999; **455:** 521–4.
8. Reed KM, Sober AJ. Methotrexate-induced necrolysis. *J Am Acad Dermatol* 1983; **8:** 677–9.
9. Pearce HP, Wilson BB. Erosion of psoriatic plaques: an early sign of methotrexate toxicity. *J Am Acad Dermatol* 1996; **35:** 835–8.
10. Nedorost ST, *et al.* Drug-induced photosensitivity reaction. *Arch Dermatol* 1989; **125:** 433–4.
11. Khan AJ, *et al.* Methotrexate and the photodermatitis reactivation reaction: a case report and review of the literature. *Cutis* 2000; **66:** 379–82.

Hypersensitivity. There are rare reports of anaphylactic reactions in patients given methotrexate. Reactions have usually occurred in patients who had previous exposure to methotrexate, but there are also reports of reaction during initial exposure to high-dose intravenous therapy.[1] Serious reactions have also been described after low-dose intravenous[2] and intrathecal[3] use.

1. Alkins SA, *et al.* Anaphylactoid reactions to methotrexate. *Cancer* 1996; **77:** 2123–6.
2. Cohn JR, *et al.* Systemic anaphylaxis from low dose methotrexate. *Ann Allergy* 1993; **70:** 384–5.
3. Devecioğlu Ö, *et al.* Systemic near-fatal anaphylactic reaction after intrathecal methotrexate administration. *Med Pediatr Oncol* 2000; **34:** 151–2.

Treatment of Adverse Effects

For general guidelines, see p.639.

Folinic acid neutralises the immediate toxic effects of methotrexate on the bone marrow. It is given as sodium or calcium folinate orally, intramuscularly, by intravenous bolus injection, or by infusion. When overdosage is suspected the dose of folinate should be at least as high as that of methotrexate and should be given as soon as possible; further doses are given as required preferably based on serum-methotrexate concentrations. Folinate should be continued until serum-methotrexate concentrations fall below 0.05 to 0.1 micromol/litre, which may necessitate prolonged treatment in patients with delayed elimination. Other dosage regimens, given intramuscularly or orally, may be appropriate for more modest toxicity associated with conventional doses of methotrexate. For details, see under Folinic Acid, p.1944. After intrathecal overdose, the drainage of 30 mL of CSF within 15 minutes removes about 95% of methotrexate; but methotrexate rapidly enters the systemic circulation and folinic acid treatment should be based on serum-methotrexate concentrations.

Folinic acid is usually given with high-dose methotrexate regimens to prevent damage to normal tissue ('folinic acid rescue') and this is discussed in Uses and Administration, below.

An adequate flow of alkaline urine should be maintained after high doses of methotrexate to prevent precipitation of methotrexate or its metabolites in the renal tubules; in addition to adequate hydration, the use of acetazolamide or sodium bicarbonate is recommended.

The recombinant glutamate carboxypeptidase glucarpidase (p.1447) rapidly hydrolyses methotrexate to inactive metabolites, and is under investigation in the management of methotrexate toxicity.

Folate supplementation. A discussion of the selection of the appropriate route for folinic acid rescue with *high-dose methotrexate* regimens.[1] The general objective is to give folinic acid (as folinate) at doses that maintain plasma concentrations of reduced folates at a level equivalent to or greater than the plasma-methotrexate concentration. In any clinical situation suggesting impaired gastrointestinal function calcium folinate should be given by injection. Although absorption of intramuscular doses is relatively complete and rapid the intravenous route is usually preferable for other reasons, such as a reduced risk of bleeding at injection sites. In the absence of impaired gastrointestinal function, and where there are no concomitant risk factors for methotrexate toxicity, the oral route may be used provided that methotrexate concentrations are expected to be less than 1 micromol/litre. For very high dose methotrexate regimens it is generally appropriate to begin folinic acid rescue intravenously to ensure adequate initial therapy, but the majority of the dosage regimen can generally be given orally.

There is no consensus on the use of folate supplementation in patients taking *low-dose methotrexate*,[2] although reviews have concluded that supplementation with either folic or folinic acid reduces adverse effects related to the liver function tests, gastrointestinal tract and oral mucosa.[2,3] However, a study found that while folate supplementation reduced the incidence of methotrexate-related liver enzyme elevations, it had no effect on incidence, severity, or duration of other adverse effects.[4] Effects of folate supplementation on the efficacy of methotrexate have been inconclusive;[3] some consider the effect to be small.[4,5] There is some suggestion that folinic acid, but not folic acid, may reduce the efficacy of methotrexate.[2] However, an analysis[6] of two studies found a reduction in efficacy with folic acid supplementation. The issue of supplementation remains controversial, with some recommending routine folic acid,[2,5,7] and others suggesting that folate only be added when demand for folate increases, such as during infection or with antibacterial use.[8]

1. Rodman JH, Crom WR. Selecting an administration route for leucovorin rescue. *Clin Pharm* 1989; **8:** 617, 621.
2. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004; **43:** 267–71.
3. Ortiz Z, *et al.* Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 08/02/06).
4. van Ede AE, *et al.* Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; **44:** 1515–24.
5. Griffith SM, *et al.* Do patients with rheumatoid arthritis established on methotrexate and folic acid 5 mg daily need to continue folic acid supplements long term? *Rheumatology (Oxford)* 2000; **39:** 1102–9.
6. Khanna D, *et al.* Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. *Arthritis Rheum* 2005; **52:** 3030–8.
7. Hornung N, *et al.* Folate, homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. *J Rheumatol* 2004; **31:** 2374–81.
8. Manna R, *et al.* Folic acid supplementation during methotrexate treatment: nonsense? *Rheumatology (Oxford)* 2005; **44:** 563–4.

Other drugs. Pretreatment with fluorouracil is reported to reduce the toxicity of methotrexate sufficiently to permit high-dose methotrexate without the need for folinic acid rescue.[1] Methotrexate has also been given before fluorouracil to modulate its activity (see Administration, in Fluorouracil, p.724).

The acute neurotoxic effects of methotrexate have been reported to be relieved by intravenous aminophylline or oral theophylline in some children.[2]

For reference to the ineffectiveness of diltiazem in preventing the nephrotoxicity due to high-dose methotrexate, see Kidney Disorders, under Diltiazem p.1267.

For evidence that colestyramine might decrease serum-methotrexate concentrations, see Interactions, below. For reference to the use of glucarpidase to manage methotrexate-induced renal toxicity see Effects on the Kidneys, above.

1. White RM. 5-Fluorouracil modulates the toxicity of high dose methotrexate. *J Clin Pharmacol* 1995; **35:** 1156–65.
2. Bernini JC, *et al.* Aminophylline for methotrexate-induced neurotoxicity. *Lancet* 1995; **345:** 544–7.

Precautions

For general discussions see p.641.

Methotrexate should be used with great care in patients with bone-marrow, hepatic, or renal impairment. It should also be used cautiously in ulcerative disorders of the gastrointestinal tract, and in the elderly and the very young. Pleural or ascitic effusions may act as a depot for methotrexate and produce enhanced toxicity, and should be drained before treatment.

Regular monitoring of haematological, renal, and hepatic function, and gastrointestinal toxicity is advisable. Treatment should be interrupted if myelosuppression, diarrhoea, or stomatitis occur. Dyspnoea or cough may be a sign of pulmonary toxicity and patients should be advised to contact their doctor if they develop these symptoms. Treatment should be withdrawn and the patient investigated to exclude infection. If methotrexate-induced lung disease is suspected corticosteroid therapy may be started and further treatment with methotrexate should not be given. Patients or their carers should report any symptoms or signs suggestive of infection, especially sore throat.

In patients receiving **low-dose methotrexate for psoriasis or rheumatoid arthritis** full blood counts and renal and liver function tests should be performed before starting treatment and repeated regularly thereafter (for discussion of guidelines for monitoring in these patients see Effects on the Liver, above). Treatment should be interrupted if myelosuppression, stomatitis, or any abnormality of liver function is detected. Methotrexate should not be used to treat rheumatoid arthritis or psoriasis in patients with alcoholism, liver disease or persistent abnormal liver function tests, or in those with significant renal impairment, immunodeficiency, or blood disorders. A test dose has been recommended. Severe or fatal toxicity has resulted from overdosage when doses intended for a low-dose weekly regimen were mistakenly taken daily, and particular care should be taken to avoid confusion about dosage frequency.

With **high-dose regimens**, serum concentrations of methotrexate should be monitored. Maintenance of an adequate flow of alkaline urine is essential (see Treatment of Adverse Effects, above).

Methotrexate is a potent teratogen and should be avoided in **pregnancy**. Some manufacturers advise that conception should be avoided for at least 6 months after therapy but others consider 3 months adequate.

Blood products. Enhanced toxicity was seen in 2 of 14 patients receiving methotrexate by 24-hour infusion when packed red cells were transfused immediately after the methotrexate infusion.[1] Erythrocytes act as reservoirs for methotrexate and probably resulted in the prolonged high serum-methotrexate concentrations seen in these patients. Great care should be exercised whenever packed red blood cells and methotrexate are given concurrently.

1. Yap AKL, *et al.* Methotrexate toxicity coincident with packed red cell transfusions. *Lancet* 1986; **ii:** 641.

Breast feeding. Methotrexate has been detected in breast milk in low concentrations.[1] The American Academy of Pediatrics considers[2] that methotrexate may interfere with cellular metabolism, causing neutropenia and possibly immune suppression in the nursing infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Johns DG, *et al.* Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972; **112:** 978–80.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/04)

Handling and disposal. Care should be taken to avoid inhalation of methotrexate or contact with skin and mucous membranes. It may cause irritation of the eyes.

Methods have been published for the oxidative destruction of methotrexate *wastes* using potassium permanganate and sulfuric acid, aqueous alkaline potassium permanganate, or sodium hypochlorite.[1] The first method may also be used for dichloromethotrexate. Residues produced by the degradation of methotrexate by these methods showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 72 hours and 7 days respectively after a dose of methotrexate should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.* eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hepatitis. Reactivation of hepatitis B infection, with the development of hepatocellular necrosis and fulminant hepatic failure requiring liver transplantation, developed on stopping low-dose methotrexate therapy in a patient with rheumatoid arthritis who was also an asymptomatic chronic hepatitis B carrier.[1] It was suggested that all patients being considered for low-dose methotrexate therapy should be screened for the presence of serum HBsAg before beginning therapy.

1. Flowers MA, *et al.* Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; **112:** 381–2.

Porphyria. Methotrexate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

PUVA. Of a total of 94 patients with psoriasis and 38 with mycosis fungoides treated with PUVA therapy (methoxsalen and ultraviolet light) 2 of the former also given methotrexate developed skin cancers.[1] It was suggested that the combination of methotrexate and PUVA may be synergistic in inducing cutaneous malignancy. However, in a cohort study[2] of patients with severe psoriasis, exposure to methotrexate for at least 4 years was associated with an increase in risk of squamous cell carcinoma but

not basal cell carcinoma, and no interaction was found between methotrexate and PUVA.

1. Fitzsimons CP, *et al.* Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet* 1983; **i:** 235–6.
2. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73:** 2759–64.

Radiation. Analysis of neutrophil counts for 18 months in children with acute lymphoblastic leukaemia showed that methotrexate-induced neutropenia was significantly greater in patients given CNS irradiation and was considered to have contributed to 3 of 5 deaths during remission.[1]

For the effect of cranial irradiation and intrathecal methotrexate on intellectual development, see Effects on Mental Function, above.

1. Report to the Medical Research Council of the Working Party on Leukaemia in Childhood. Analysis of treatment in childhood leukaemia: I—predisposition to methotrexate-induced neutropenia after craniospinal irradiation. *BMJ* 1975; **3:** 563–6.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. The effects of methotrexate may be enhanced by drugs that decrease its renal excretion, such as NSAIDs and salicylates, probenecid, and some penicillins. Fatal toxicity has occurred in patients given NSAIDs with methotrexate (see below). Severe toxicity has occurred rarely when co-trimoxazole or trimethoprim was given with methotrexate. Use with other myelotoxic, hepatotoxic, or nephrotoxic agents may increase the risk of toxicity. Folic acid and its derivatives may decrease the effectiveness of methotrexate, although they are often used together to reduce methotrexate toxicity (see Treatment of Adverse Effects, above).

Animal studies suggested methotrexate toxicity may be increased by chloramphenicol, para-aminobenzoic acid, and hypoglycaemics, but there does not appear to be any evidence of this clinically.

Antibacterials. The oral *aminoglycosides* neomycin[1] and paromomycin[2] have been reported to reduce the gastrointestinal absorption of methotrexate. Various *penicillins* have been reported to markedly decrease the clearance of methotrexate given intravenously for treatment of neoplasms,[3-6] although *ceftazidime* may not.[4] There have also been a few reports of penicillins possibly exacerbating the toxicity of low-dose methotrexate in patients being treated for psoriasis or rheumatoid arthritis, but a small study found that although flucloxacillin decreased methotrexate clearance slightly, this was not clinically significant.[7] Methotrexate toxicity has been reported in a patient receiving low-dose methotrexate after a course of *tetracycline*.[8] In a patient receiving high-dose methotrexate, giving *doxycycline* before the eleventh cycle was believed to be responsible for an exacerbation of methotrexate toxicity, with raised plasma concentrations and reduced clearance of methotrexate.[9] *Sulfonamides* such as sulfafurazole and sulfamethoxazole may displace methotrexate from binding sites[10] and reduce renal clearance.[11] Megaloblastic pancytopenia has been reported on a number of occasions when methotrexate was given with *co-trimoxazole*[12-14] or *trimethoprim*;[13,15,16] possible mechanisms involved include an additive antifolate effect, in addition to the effect of the sulfamethoxazole component in the case of co-trimoxazole.

1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; **3:** 1–13.
2. Cohen MH, *et al.* Effect of oral prophylactic broad spectrum nonabsorbable antibiotics on the gastrointestinal absorption of nutrients and methotrexate in small cell bronchogenic carcinoma patients. *Cancer* 1976; **38:** 1556.
3. Bloom EJ, *et al.* Delayed clearance (CL) of methotrexate (MTX) associated with antibiotics and antiinflammatory agents. *Clin Res* 1986; **34:** 560A.
4. Yamamoto K, *et al.* Delayed elimination of methotrexate associated with piperacillin administration. *Ann Pharmacother* 1997; **31:** 1261–2.
5. Dean R, *et al.* Possible methotrexate-mezlocillin interaction. *Am J Pediatr Hematol Oncol* 1992; **14:** 88–9.
6. Ronchera CL, *et al.* Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. *Ther Drug Monit* 1993; **15:** 375–9.
7. Herrick AL, *et al.* Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1996; **41:** 223–7.
8. Turck M. Successful psoriasis treatment then sudden 'cytotoxicity'. *Hosp Pract* 1984; **19:** 175–6.
9. Tortajada-Ituren JJ, *et al.* High-dose methotrexate—doxycycline interaction. *Ann Pharmacother* 1999; **33:** 804–8.
10. Liegler DG, *et al.* The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* 1969; **10:** 849–57.
11. Ferrazzini G, *et al.* Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* 1990; **117:** 823–6.
12. Liddle BJ, Marsden JR. Drug interactions with methotrexate. *Br J Dermatol* 1989; **120:** 582–3.
13. Jeurissen ME, *et al.* Pancytopenia and methotrexate with trimethoprim-sulfamethoxazole. *Ann Intern Med* 1989; **111:** 261.
14. Groenendal H, Rampen FHJ. Methotrexate and trimethoprim–sulphamethoxazole—a potentially hazardous combination. *Clin Exp Dermatol* 1990; **15:** 358–60.
15. Steuer A, Gumpel JM. Methotrexate and trimethoprim: a fatal interaction. *Br J Rheumatol* 1998; **37:** 105–6.
16. Govert JA, *et al.* Pancytopenia from using trimethoprim and methotrexate. *Ann Intern Med* 1992; **117:** 877–8.

Antiepileptics. For mention of the reduction in serum-*valproate* concentration produced by methotrexate see p.511.

Antineoplastics. Enhanced methotrexate toxicity might be expected with nephrotoxic agents (such as *cisplatin*) that can reduce methotrexate excretion by impairing renal function. Sequential use of methotrexate and *fluorouracil* may result in synergistic enhancement of effect (see Administration, in Fluorouracil, p.724), and equally, fluorouracil before methotrexate may reduce its toxicity (see Other Drugs, under Treatment of Adverse Effects, above), but if *asparaginase* (p.682) is given before methotrexate the cytotoxic effect of methotrexate may be reduced.

Methotrexate may increase the bioavailability of *mercaptopurine*, probably by interference with first-pass metabolism (see p.744).

Colestyramine. Serum-methotrexate concentrations were markedly reduced in 3 patients given colestyramine to treat methotrexate toxicity.[1,2] Colestyramine appears to bind methotrexate and reduce its enterohepatic recirculation.

1. Erttmann R, Landbeck G. Effect of oral cholestyramine on the elimination of high-dose methotrexate. *J Cancer Res Clin Oncol* 1985; **110:** 48–50.
2. Shinozaki T, *et al.* Successful rescue by oral cholestyramine of a patient with methotrexate nephrotoxicity: nonrenal excretion of serum methotrexate. *Med Pediatr Oncol* 2000; **34:** 226–8.

Dantrolene. Dantrolene was considered to have caused methotrexate toxicity in a patient given high-dose methotrexate.[1]

1. André N, *et al.* Can dantrolene contribute to methotrexate toxicity? *Ann Pharmacother* 2006; **40:** 1695–6.

Gastrointestinal drugs. Elevated serum concentrations of methotrexate were reported when it was given to 2 patients also receiving *omeprazole*.[1,2] The effect was not seen with subsequent cycles of methotrexate therapy once omeprazole had been stopped. In another case[3] however, raised methotrexate concentrations were thought to be due to an interaction with omeprazole, but were identical during a second cycle after omeprazole had been withdrawn. Severe generalised myalgia and bone pain were reported in a patient who received methotrexate and *pantoprazole*.[4] The same reaction occurred on rechallenge with the combination, but not with methotrexate alone. Although methotrexate concentrations were unchanged, concentrations of the metabolite 7-hydroxymethotrexate were raised suggesting an interaction with its renal elimination. *Lansoprazole* has been reported not to affect the pharmacokinetics of methotrexate.[5]

1. Reid T, *et al.* Impact of omeprazole on the plasma clearance of methotrexate. *Cancer Chemother Pharmacol* 1993; **33:** 82–4.
2. Beorlegui B, *et al.* Potential interaction between methotrexate and omeprazole. *Ann Pharmacother* 2000; **34:** 1024–7.
3. Whelan J, *et al.* Omeprazole does not alter plasma methotrexate clearance. *Cancer Chemother Pharmacol* 1999; **44:** 88–9.
4. Tröger U, *et al.* Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. *BMJ* 2002; **324:** 1497.
5. Vakily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 1179–86.

Immunosuppressants. For reports of enhanced toxicity with *ciclosporin* in patients who have received methotrexate see p.1826.

Leflunomide. For a report of the effect of methotrexate in patients receiving leflunomide, see p.76.

Nitrous oxide. Severe unpredictable myelosuppression and stomatitis have been attributed to the use of nitrous oxide anaesthesia in patients receiving methotrexate, potentiating the effects of methotrexate on folate metabolism.[1] The effect could be reduced by the use of folinic acid rescue.

1. Goldhirsch A, *et al.* Methotrexate/nitrous-oxide toxic interaction in perioperative chemotherapy for early breast cancer. *Lancet* 1987; **ii:** 151.

NSAIDs. Severe, and in some cases fatal, aggravation of methotrexate toxicity has been reported when it was given with various NSAIDs including *aspirin* and other *salicylates*,[1,2] *azapropazone*,[3] *diclofenac*,[4] *indometacin*,[4,5] and *ketoprofen*.[6] The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an effect of NSAIDs on the kidney resulting in reduced methotrexate excretion.[6,7] *Naproxen* has been reported not to affect the pharmacokinetics of methotrexate,[8,9] but a fatal interaction has nonetheless been reported.[10] Despite the risks, some commentators have pointed out that methotrexate and NSAIDs are frequently used together in the treatment of rheumatoid arthritis,[11,12] and that provided this is done with caution, in low doses, and patients are appropriately monitored and cautioned to avoid additional 'over-the-counter' analgesics, such combinations need not be contra-indicated. A study in patients receiving low-dose methotrexate for rheumatoid arthritis suggested that *flurbiprofen*, *ketoprofen*, or *piroxicam* did not influence methotrexate clearance.[13] A case of methotrexate toxicity has nevertheless been described[14] in an elderly woman when flurbiprofen was added to low-dose methotrexate therapy.

Manufacturers of methotrexate generally contra-indicate the use of NSAIDs with high-dose methotrexate.

1. Baker H. Intermittent high dose oral methotrexate therapy in psoriasis. *Br J Dermatol* 1970; **82:** 65–9.
2. Zuik M, Mandel MA. Methotrexate-salicylate interaction: a clinical and experimental study. *Surg Forum* 1975; **26:** 567–9.
3. Daly HM, *et al.* Methotrexate toxicity precipitated by azapropazone. *Br J Dermatol* 1986; **114:** 733–5.
4. Gabrielli A, *et al.* Methotrexate and nonsteroidal anti-inflammatory drugs. *BMJ* 1987; **294:** 776.
5. Maiche AG. Acute renal failure due to concomitant action of methotrexate and indomethacin. *Lancet* 1986; **i:** 1390.
6. Thyss A, *et al.* Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. *Lancet* 1986; **i:** 256–8.
7. Furst DE, *et al.* Effect of aspirin and sulindac on methotrexate clearance. *J Pharm Sci* 1990; **79:** 782–6.
8. Stewart CF, *et al.* Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. *Clin Pharmacol Ther* 1990; **47:** 540–6.
9. Vakily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 1179–86.
10. Singh RR, *et al.* Fatal interaction between methotrexate and naproxen. *Lancet* 1986; **i:** 1390.
11. Tully M. NSAIDs. *Pharm J* 1991; **247:** 746.
12. Zachariae H. Methotrexate and nonsteroidal anti-inflammatory drugs. *Br J Dermatol* 1992; **126:** 95.
13. Tracy TS, *et al.* Methotrexate disposition following concomitant administration of ketoprofen, piroxicam and flurbiprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1994; **37:** 453–6.
14. Frenia ML, Long KS. Methotrexate and nonsteroidal antiinflammatory drug interactions. *Ann Pharmacother* 1992; **26:** 234–7.

Probenecid. Probenecid can produce two- to fourfold increases in serum-methotrexate concentrations,[1-3] presumably by inhibiting renal excretion of methotrexate. Although probenecid has been shown to reduce protein binding of methotrexate,[4] usual doses of probenecid are unlikely to significantly affect methotrexate elimination by this mechanism. A woman receiving low-dose weekly methotrexate for rheumatoid arthritis developed severe pancytopenia when probenecid was given for asymptomatic hyperuricaemia.[5]

1. Aherne GW, *et al.* Prolongation and enhancement of serum methotrexate concentrations by probenecid. *BMJ* 1978; **1:** 1097–9.
2. Howell SB, *et al.* Effect of probenecid on cerebrospinal fluid methotrexate kinetics. *Clin Pharmacol Ther* 1979; **26:** 641–6.
3. Lilly MB, Omura GA. Clinical pharmacology of oral intermediate-dose methotrexate with or without probenecid. *Cancer Chemother Pharmacol* 1985; **15:** 220–2.
4. Paxton JW. Interaction of probenecid with the protein binding of methotrexate. *Pharmacology* 1984; **28:** 86–9.
5. Basin KS, *et al.* Severe pancytopenia in a patient taking low dose methotrexate and probenecid. *J Rheumatol* 1991; **18:** 609–10.

Retinoids. An increased risk of hepatotoxicity has been reported when methotrexate and *etretinate* are given together,[1] possibly due to increased plasma concentrations of methotrexate.[2,3]

1. Zachariae H. Dangers of methotrexate/etretinate combination therapy. *Lancet* 1988; **i:** 422.
2. Harrison PV, *et al.* Methotrexate and retinoids in combination for psoriasis. *Lancet* 1987; **ii:** 512.
3. Larsen FG, *et al.* Interaction of etretinate with methotrexate pharmacokinetics in psoriatic patients. *J Clin Pharmacol* 1990; **30:** 802–7.

Xanthines. For mention of the effect of methotrexate on the clearance of theophylline, see Antineoplastics, under Interactions of Theophylline, p.1144.

Pharmacokinetics

When given in low doses, methotrexate is rapidly absorbed from the gastrointestinal tract, but higher doses are less well absorbed. It is also rapidly and completely absorbed after intramuscular doses. Peak serum concentrations are achieved in 1 to 2 hours after an oral dose, and 30 to 60 minutes after an intramuscular one.

Methotrexate is distributed to tissues and extracellular fluid with a steady-state volume of distribution of 0.4 to 0.8 litres/kg; it penetrates ascitic fluid and effusions, which may act as a depot and thus enhance toxicity. Clearance from plasma is reported to be triphasic, with a terminal elimination half-life of between 3 and 10 hours after doses less than 30 mg/m^2 or 8 to 15 hours after high-dose parenteral therapy. It is about 50% bound to plasma protein. Methotrexate enters the cells in part by an active transport mechanism and is bound as polyglutamate conjugates: bound drug may remain in the body for several months, particularly in the liver.

Only small or insignificant amounts cross the blood-brain barrier and enter the CSF after oral or parenteral doses although this may be increased by giving higher doses; however, after intrathecal doses there is significant passage into the systemic circulation.

Methotrexate has been detected in very small amounts in saliva and breast milk. It crosses the placenta.

Methotrexate does not appear to undergo significant metabolism at low doses; after high-dose therapy the 7-hydroxy metabolite has been detected. Methotrexate may be partly metabolised by the intestinal flora after oral doses. It is excreted primarily in the urine, by glomerular filtration and active tubular secretion. Small amounts are excreted in bile and found in faeces; there is some evidence for enterohepatic recirculation.

Considerable interindividual variation exists in the pharmacokinetics of methotrexate: those patients in whom clearance is delayed are at increased risk of toxicity.

◊ References.
1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; **3:** 1–13.
2. Balis FM, *et al.* Clinical pharmacokinetics of commonly used anticancer drugs. *Clin Pharmacokinet* 1983; **8:** 202–32.
3. Wang Y-M, Fujimoto T. Clinical pharmacokinetics of methotrexate in children. *Clin Pharmacokinet* 1984; **9:** 335–48.
4. Witter FR. Clinical pharmacokinetics in the treatment of rheumatoid arthritis in pregnancy. *Clin Pharmacokinet* 1993; **25:** 444–9.
5. Bannwarth B, *et al.* Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis. *Clin Pharmacokinet* 1996; **30:** 194–210.
6. Chládek J, *et al.* Pharmacokinetics and pharmacodynamics of low-dose methotrexate in the treatment of psoriasis. *Br J Clin Pharmacol* 2002; **54:** 147–56.
7. Grim J, *et al.* Pharmacokinetics and pharmacodynamics of methotrexate in non-neoplastic diseases. *Clin Pharmacokinet* 2003; **42:** 139–51.
8. Aumente D, *et al.* Population pharmacokinetics of high-dose methotrexate in children with acute lymphoblastic leukaemia. *Clin Pharmacokinet* 2006; **45:** 1227–38.
9. Thompson PA, *et al.* Methotrexate pharmacokinetics in infants with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 2007; **59:** 847–53.

Uses and Administration

Methotrexate is an antineoplastic that acts as an antimetabolite of folic acid. It also has immunosuppressant properties. Within the cell, folic acid is reduced to dihydrofolic and then tetrahydrofolic acid. Methotrexate competitively inhibits the enzyme dihydrofolate reductase and prevents the formation of tetrahydrofolate which is necessary for purine and pyrimidine synthesis and consequently the formation of DNA and RNA. It is most active against cells in the S phase of the cell cycle. Folinic acid (the 5-formyl derivative of tetrahydrofolic acid) has been given after high doses to bypass the block in tetrahydrofolate production in normal cells and prevent the adverse effects of methotrexate. A suggested schedule for *folinic acid rescue* is described under Folinic Acid, p.1944. (See also Treatment of Adverse Effects, above). Methotrexate, in very high doses, followed by folinic acid rescue, is used in treating some malignant diseases.

Methotrexate is used in the management of acute lymphoblastic leukaemia. It is seldom used for the induction of remission but is employed in maintenance programmes and in the prophylaxis and treatment of meningeal leukaemia. It may be used for Burkitt's and other non-Hodgkin's lymphomas. In the solid neoplasms it is an important part of curative regimens for choriocarcinoma and other gestational trophoblastic tumours, and for the adjuvant therapy of osteosarcoma and breast cancer. It may also be used in malignant neoplasms of the bladder and head and neck, and some other neoplasms, as indicated by the cross references given below.

Methotrexate is of value in the treatment of psoriasis but because of the risks associated with this use, it should only be given when the disease is severe and has not responded to other forms of treatment. It is widely used as a disease-modifying antirheumatic drug in rheumatoid arthritis. Methotrexate may be used to prevent graft-versus-host disease after bone marrow transplantation and may be used as a cytotoxic immunosuppressant and corticosteroid-sparing agent in non-malignant diseases.

Methotrexate has a role in the management of ectopic pregnancy and in the termination of early pregnancy (see below).

Methotrexate may be given orally as the base or the sodium salt, or by injection as the sodium salt. Doses are calculated in terms of methotrexate. Methotrexate sodium 16.5 mg is equivalent to about 15 mg of methotrexate. The doses and regimens used vary enormously, and may need to be adjusted according to bone marrow or other toxicity (see also under Bone-marrow Depression, p.639). Doses larger than 100 mg are usually given partly or wholly by intravenous infusion over not more than 24 hours.

A common dose for maintenance therapy of acute lymphoblastic **leukaemia** is 15 mg/m^2 once or twice weekly, orally or intramuscularly, with other agents such as mercaptopurine; 20 to 30 mg/m^2 twice weekly has also been given. Alternatively, 2.5 mg/kg may be given intravenously every 14 days. Meningeal leukaemia may be treated by the intrathecal injection of 12 mg/m^2 (maximum 15 mg) once weekly for 2 to 3 weeks, then once monthly; an alternative is 200 to 500 micrograms/kg at intervals of 2 to 5 days until the cell count of the CSF returns to normal. Another regimen has been recommended for children based on age, with children under the age of 1 year receiving 6 mg, 8 mg for those 1 year of age, 10 mg in 2-year-olds, and 12 mg in those 3 years of age or older. Intrathecal doses have also sometimes been given prophylactically to patients with lymphoblastic leukaemia in association with intrathecal cytarabine and hydrocortisone. Methotrexate in intravenous doses of about 500 mg/m^2, followed by folinic acid rescue, may also produce effective concentrations in the CSF and has been used for meningeal leukaemia.

Choriocarcinoma has been treated with doses of 15 to 30 mg daily orally or intramuscularly for 5 days repeated after an interval of 1 week or more, for 3 to 5 courses. Alternatively 0.25 to 1 mg/kg up to a maximum of 60 mg has been given intramuscularly every 48 hours for 4 doses, followed by folinic acid rescue, and repeated at intervals of 7 days for 4 or more courses. Combination chemotherapy may be necessary in patients with metastases.

Doses of 10 to 60 mg/m^2 are given intravenously in the treatment of **breast cancer**, often with cyclophosphamide and fluorouracil.

In advanced **lymphosarcoma** doses of 0.625 to 2.5 mg/kg daily have been suggested with other antineoplastics. Alternatively, higher doses of up to 30 mg/kg have been given intravenously, followed by folinic acid rescue. For Burkitt's lymphoma 10 to 25 mg of oral methotrexate has been given daily for 4 to 8 days, repeated after an interval of 7 to 10 days, while patients with mycosis fungoides may be given an oral dose of 2.5 to 10 mg daily to induce remission; alternatively 50 mg may be given weekly as a single dose or two divided doses, by intramuscular injection.

Very high doses, in the range 12 to 15 g/m^2 have been given by intravenous infusion, followed by folinic acid, as part of combined adjuvant therapy in patients with **osteosarcoma**. High-dose regimens have been tried in other malignancies, including carcinoma of the lung and of the head and neck.

Single weekly doses of 10 to 25 mg may be given orally or by intramuscular or intravenous injection in the treatment of **psoriasis** and adjusted by response. Other, more frequent, regimens have been used but a weekly dosage regimen appears to be less hepatotoxic than a daily one. In the treatment of **rheumatoid arthritis** doses of 7.5 mg orally once weekly are used, adjusted by response and not exceeding 20 mg/week.

It is essential that blood counts and tests of renal and liver function should be made before, during, and after each course of treatment with methotrexate (see Precautions, above).

Asthma. Various immunosuppressants, including methotrexate, have been tried for their anti-inflammatory and corticosteroid-sparing properties in chronic asthma (p.1108), but because of fears about toxicity are largely reserved for certain patients dependent upon systemic corticosteroids. Results of individual studies with methotrexate have been conflicting, but it appears that some patients may benefit from the corticosteroid-sparing effects of methotrexate.[1,2] However, other reviewers considered that the reduction in corticosteroid dose was insufficient to offset the adverse effects of methotrexate.[3] Methotrexate therapy must be given for at least 3 months for an adequate assessment of efficacy.

1. Shulimzon TR, Shiner RJ. A risk-benefit assessment of methotrexate in corticosteroid-dependent asthma. *Drug Safety* 1996; **15:** 283–90.
2. Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997; **112:** 29–33.
3. Davies H, *et al.* Methotrexate as a steroid sparing agent for asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 12/05/05).

Connective tissue and muscular disorders. Reports in a limited number of patients indicate that methotrexate given once weekly in low to moderate doses may be of benefit in patients with SLE (p.1513), with benefit reported particularly for joint and mucocutaneous symptoms.[1] In a retrospective analysis of patients with cutaneous lupus erythematosus, low doses of methotrexate significantly decreased disease activity.[2]

Methotrexate therapy has been investigated for its potential corticosteroid-sparing properties in polymyalgia rheumatica (p.1510). Different regimens have been tried and although one study[3] reported benefit, others[4,5] found no evidence of clinical efficacy or a corticosteroid-sparing effect.

Methotrexate is widely used in rheumatoid arthritis (see below) and in polymyositis (p.1510), and has been tried in Cogan's syndrome (p.1502).

1. Sato EI. Methotrexate therapy in systemic lupus erythematosus. *Lupus* 2001; **10:** 162–4.
2. Wenzel J, *et al.* Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol* 2005; **153:** 157–62.
3. Ferraccioli G, *et al.* Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol* 1996; **23:** 624–8.
4. Feinberg HL, *et al.* The use of methotrexate in polymyalgia rheumatica. *J Rheumatol* 1996; **23:** 1550–2.
5. van der Veen MJ, *et al.* Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis* 1996; **55:** 218–23.

Ectopic pregnancy. Ectopic pregnancy occurs when the fertilised ovum implants outside the uterus, usually in the fallopian tube itself (tubal pregnancy). Earlier detection has become possible due to improved diagnostic techniques. In many countries, there has been a rise in the rate of ectopic pregnancies followed by a decline; this may be partly due to increasing rates of infection with *Chlamydia*, followed by the effect of prevention, and changes in the popularity of intra-uterine devices.[1] Although ectopic pregnancies may spontaneously abort early, without clinical sequelae, the potential adverse effects are serious, ranging from pelvic pain and bleeding at 5 to 6 weeks of gestation (indistinguishable from spontaneous abortion), to potentially fatal intra-abdominal haemorrhage later in the course of an otherwise asymptomatic pregnancy.

Laparoscopic surgery remains the standard treatment.[1-3] In some countries non-surgical methods are increasing in popularity because of earlier diagnosis.[1,4] Perhaps the most experience of the latter has been with methotrexate. Management with intramuscular methotrexate may be appropriate for selected women with small unruptured tubal pregnancies who are haemodynamically stable, have low serum-chorionic gonadotrophin concentrations, and lack contra-indications to methotrexate use.[2-6] Surgery is preferred where there is cardiac activity in the conceptus, since a living embryo increases resistance to methotrexate.[5,6] Two regimens of intramuscular methotrexate have been described. A multiple-dose regimen of 1 mg/kg on 4 alternate days, with folinic acid rescue,[1] has similar efficacy to surgery.[3] A single dose of 50 mg/m^2 can be used instead[1,4] but systematic reviews have indicated that it has a higher failure rate than surgery[3,7] and about 20% of patients will require more than one cycle of treatment.[4] The addition of an oral dose of mifepristone to single-dose methotrexate has been investigated[1,8,9] and may reduce treatment failure rates.

Methotrexate has been given by local injection directly into the ectopic (salpingocentesis). Doses of 1 mg/kg or 50 mg have been used[10] but this technique is significantly less successful than surgery.[3] Systemic methotrexate (with folinic acid rescue) has also been reported to be effective in resolving persistent ectopic pregnancy unsuccessfully treated with surgery.

The role of other agents in the management of ectopic pregnancy is less well established. Local instillation of glucose 50% by salpingocentesis has also been used in the treatment of ectopic pregnancy,[10,11] but one study was stopped because of a higher failure rate with glucose treatment compared with local methotrexate.[12]

Methotrexate may also be used in the termination of early uterine pregnancy (see below).

1. Farquhar CM. Ectopic pregnancy. *Lancet* 2005; **366:** 583–91.
2. Tay JI, *et al.* Ectopic pregnancy. *BMJ* 2000; **320:** 916–9. Correction. *ibid.*; **321:** 424.
3. Hajenius PJ, *et al.* Interventions for tubal ectopic pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 19/05/08).
4. Lipscomb GH, *et al.* Nonsurgical treatment of ectopic pregnancy. *N Engl J Med* 2000; **343:** 1325–9.

5. Lipscomb GH, *et al.* Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999; **341:** 1974–8.
6. American College of Obstetricians and Gynecologists. ACOG practice bulletin: medical management of tubal pregnancy. Number 3, December 1998. *Int J Gynecol Obstet* 1999; **65:** 97–103.
7. Parker J, *et al.* A systematic review of single-dose intramuscular methotrexate for the treatment of ectopic pregnancy. *Aust N Z J Obstet Gynaecol* 1998; **38:** 145–50.
8. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; **13:** 1987–90.
9. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; **179:** 640–3.
10. Natofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; **42:** 39–47.
11. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; **76:** 797–800.
12. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; **265:** 82–4.

Inflammatory bowel disease. Methotrexate (given intramuscularly once weekly in a dose of 25 mg) was reported to improve symptoms and reduce corticosteroid requirements in a large controlled study in patients with chronic active Crohn's disease.[1] Those patients who were in remission after 16 weeks of methotrexate treatment were entered into a further placebo-controlled trial[2] of methotrexate 15 mg weekly by intramuscular injection. During 40 weeks of follow-up, a higher proportion of patients receiving methotrexate remained in remission, and had fewer relapses. Smaller studies have also reported modest benefit for oral methotrexate 12.5 to 22.5 mg/week in chronic active disease.[3,4] Subcutaneous methotrexate has also been used.[5] A review[6] concluded that low-dose methotrexate could be recommended for induction of remission and for its corticosteroid-sparing effect in refractory and corticosteroid-dependent Crohn's disease, although the precise indications, dose, and route for its use were still unclear. The value of methotrexate in ulcerative colitis is doubtful: although benefits have been seen in some patients,[5,7] a study in active ulcerative colitis found no significant differences between oral methotrexate 12.5 mg/week and placebo.[8] For a discussion of inflammatory bowel disease, see p.1697.

1. Feagan BG, *et al.* Methotrexate for the treatment of Crohn's disease. *N Engl J Med* 1995; **332:** 292–7.
2. Feagan BG, *et al.* A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *N Engl J Med* 2000; **342:** 1627–32.
3. Oren R, *et al.* Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; **92:** 2203–9.
4. Arora S, *et al.* Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46:** 1724–9.
5. Egan LJ, *et al.* A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 1999; **13:** 1597–1604.
6. Egan LJ, Sandborn WJ. Methotrexate for inflammatory bowel disease: pharmacology and preliminary results. *Mayo Clin Proc* 1996; **71:** 69–80.
7. Kozarek RA. Methotrexate for refractory Crohn's disease: preliminary answers to definitive questions. *Mayo Clin Proc* 1996; **71:** 104–5.
8. Oren R, *et al.* Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; **110:** 1416–21.

Malignant neoplasms. Methotrexate is extensively used in the management of malignant disease. In acute lymphoblastic leukaemia it is used for maintenance therapy, and intrathecally for prophylaxis of CNS relapse, as discussed on p.651, while it also forms part of a number of regimens used for Burkitt's and other aggressive, intermediate- to high-grade non-Hodgkin's lymphomas (see p.657 and p.656), including mycosis fungoides (p.657) and those associated with AIDS (p.657). In the solid neoplasms it is an important part of curative regimens for gestational trophoblastic tumours (p.650), the adjuvant therapy of osteosarcoma (p.675) and is used in regimens for tumours of the bladder (p.659), brain (p.660), breast (p.661), stomach (p.664), and head and neck (p.666).

Multiple sclerosis. Results suggest that methotrexate 7.5 mg by mouth weekly may be of benefit[1] in slowing the progression of multiple sclerosis (p.892). Although the results of studies of immunosuppressant therapy in this condition have tended to be disappointing, it has been pointed out that benefit was assessed differently in the methotrexate study,[2] which may have a bearing on its more favourable conclusions.

1. Goodkin DE, *et al.* Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol* 1995; **37:** 30–40.
2. Whitaker JN, *et al.* Clinical outcomes and documentation of partial beneficial effects of immunotherapy for multiple sclerosis. *Ann Neurol* 1995; **37:** 5–6.

Myasthenia gravis. Methotrexate has been tried in the management of myasthenia gravis (p.629) in patients who require immunosuppression but are intolerant of or unresponsive to corticosteroids and azathioprine.

Organ and tissue transplantation. For reference to the use of methotrexate (usually with ciclosporin) in bone marrow transplantation, see Haematopoietic Stem Cell Transplantation, p.1811.

Primary biliary cirrhosis. Like other drugs used for primary biliary cirrhosis (p.2408) methotrexate has been associated with biochemical improvement but evidence of clinical and in particular histological improvement is harder to demonstrate, and the toxicity of immunosuppressants such as methotrexate is problematic. A randomised study comparing methotrexate with colchicine found a slightly lower survival with methotrexate after 10 years of treatment;[1] a systematic review[2] concluded that methotrexate increased mortality in patients with primary biliary cirrhosis and that its use could not be recommended.

1. Kaplan MM, *et al.* A randomized controlled trial of colchicine plus ursodiol versus methotrexate plus ursodiol in primary biliary cirrhosis: ten-year results. *Hepatology* 2004; **39:** 915–23.
2. Gong Y, Gluud C. Methotrexate for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 08/02/06).

Psoriatic arthritis. Methotrexate may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p.13) when the arthritis is not controlled by physical therapy and NSAIDs, although toxicity may limit long-term use in some patients.

Rheumatoid arthritis. Therapy of rheumatoid arthritis (p.11) is conventionally begun with an analgesic and an NSAID for symptomatic relief, to which a disease-modifying antirheumatic drug (DMARD) is subsequently added in an attempt to retard the disease process. It is now clear that irreversible joint damage commonly occurs in early disease and rheumatologists now generally add the DMARD shortly after rheumatoid arthritis has been diagnosed. Methotrexate is widely used,[1] and is the DMARD of first choice in many patients. Systematic review has confirmed that methotrexate has significant benefit in the short-term treatment of the disease.[2] Methotrexate has also been tried with ciclosporin, hydroxychloroquine and sulfasalazine, leflunomide, etanercept, and infliximab. Studies have shown improved responses to these combinations compared with methotrexate alone, but long-term efficacy and safety has not been studied.[3]

Methotrexate may be of benefit in juvenile idiopathic arthritis (p.10).[4-6]

Methotrexate may also be of value in the management of associated uveitis (see below).

1. Anonymous. Modifying disease in rheumatoid arthritis. *Drug Ther Bull* 1998; **36:** 3–6.
2. Suarez-Almazor ME, *et al.* Methotrexate for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 12/05/05).
3. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001; **134:** 695–706.
4. Ravelli A, *et al.* Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. *J Pediatr* 1998; **133:** 262–5.
5. Takken T, *et al.* Methotrexate for treating juvenile idiopathic arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 12/05/05).
6. Ramanan AV, *et al.* Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; **88:** 197–200.

Sarcoidosis. Where therapy is required for sarcoidosis (p.1512) corticosteroids are the first choice of drug; methotrexate is one of the preferred second-line immunosuppressants.

References.

1. Webster GF, *et al.* Methotrexate therapy in cutaneous sarcoidosis. *Ann Intern Med* 1989; **111:** 538–9.
2. Soriano FG, *et al.* Neurosarcoidosis: therapeutic success with methotrexate. *Postgrad Med J* 1990; **66:** 142–3.
3. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; **155:** 846–51.
4. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999; **54:** 742–6.

Scleroderma. There is some evidence of benefit with methotrexate in patients with scleroderma (p.1817), particularly for cutaneous symptoms, although not all studies have shown clear value.

References.

1. van den Hoogen FH, *et al.* Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996; **35:** 364–72.
2. Seyger MMB, *et al.* Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol* 1998; **39:** 220–5.
3. Uziel Y, *et al.* Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; **136:** 91–5.
4. Pope JE, *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; **44:** 1351–8.
5. Weibel L, *et al.* Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol* 2006; **155:** 1013–20.

Skin disorders, non-malignant. Methotrexate is widely used in the treatment of severe refractory psoriasis. As discussed on p.1583 the aim of such therapy is to bring the disease under control, enabling a return to other therapy. For use in psoriatic arthritis see above. Methotrexate is also used with corticosteroids in the management of pemphigus and pemphigoid (p.1582).

Termination of pregnancy. Methotrexate has been investigated as an alternative to mifepristone for use with misoprostol for the termination of early pregnancy (p.2004). Intramuscular methotrexate followed 3 days later by intravaginal misoprostol was more effective than misoprostol alone for termination at 56 days or less;[1] the combination was reported to be less successful after 57 to 63 days of gestation.[2] Later studies[3,4] however found the combination to be safe and effective in terminating pregnancies up to 63 days of gestation; in these the misoprostol was given up to 7 days after the methotrexate. Oral methotrexate is also effective.[5-7] However, the efficacy of methotrexate followed by misoprostol does appear to diminish with increasing gestational age,[8] and the time to complete abortion generally takes longer with regimens using methotrexate compared with mifepristone.[9] The American College of Obstetricians and Gynecologists[10] recommends that methotrexate with misoprostol may be used in pregnancies of up to 49 days of gestation, the usual regimen being methotrexate, either 50 mg/m^2 intramuscularly or 50 mg orally, followed 3 to 7 days later by misoprostol 800 micrograms vaginally. The College also advises that it may take up to 4 weeks for complete abortion to occur in about 15 to 25% of women given such regimens.

For the role of methotrexate in the management of ectopic pregnancy, see above.

1. Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion: a randomized controlled trial. *JAMA* 1994; **272:** 1190–5.
2. Creinin MD. Methotrexate and misoprostol for abortion at 57-63 days gestation. *Contraception* 1994; **50:** 511–15.
3. Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. *N Engl J Med* 1995; **333:** 537–40.
4. Creinin MD, *et al.* A randomized trial comparing misoprostol three and seven days after methotrexate for early abortion. *Am J Obstet Gynecol* 1995; **173:** 1578–84.
5. Creinin MD. Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1996; **54:** 15–18.
6. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90:** 611–16.
7. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; **57:** 83–8.
8. Creinin MD, *et al.* Methotrexate and misoprostol for early abortion: a multicenter trial. *Contraception* 1996; **53:** 321–7.
9. Wiebe E, *et al.* Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002; **99:** 813–19.
10. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, October 2005). *Obstet Gynecol* 2005; **106:** 871–82.

Uveitis. Methotrexate has been reported to be safe and effective[1-3] when used to treat uveitis (p.1515) in small numbers of patients.

1. Samson CM, *et al.* Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. *Ophthalmology* 2001; **108:** 1134–9.
2. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005; **32:** 362–5.
3. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol* 2005; **89:** 806–8.

Vasculitic syndromes. In giant cell arteritis (p.1503), improved clinical response and a corticosteroid-sparing effect have been reported with the addition of methotrexate to corticosteroid therapy,[1] but other studies using different designs and dosages[2,3] have failed to find any benefit. For the use of methotrexate in Takayasu's arteritis and Wegener's granulomatosis see p.1514 and p.1515, respectively.

1. Jover JA, *et al.* Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; **134:** 106–14.
2. Spiera RF, *et al.* A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; **19:** 495–501.
3. Hoffman GS, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; **46:** 1309–18.

Preparations

BP 2008: Methotrexate Injection; Methotrexate Tablets;
USP 31: Methotrexate for Injection; Methotrexate Injection; Methotrexate Tablets.

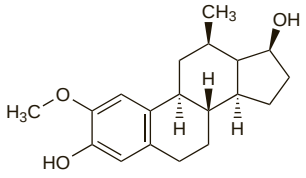
Proprietary Preparations (details are given in Part 3)
Arg.: Artrait; Ervemin; Trixate; Xantromid; ***Austral.:*** Ledertrexate; Methoblastin; ***Austria:*** Ebetrexat; Emthexate; ***Belg.:*** Emthexate; Ledertrexate; ***Braz.:*** Biometrox; Emthexate; Metrexato; Miantrex; Reutrexato; Tecnomet; Trexeron†; Unitrexate†; ***Chile:*** Trixilem; ***Cz.:*** Metoject; ***Denm.:*** Emthexate†; Metoject; ***Fin.:*** Emthexat†; Metoject; Trexan; ***Fr.:*** Ledertrexate†; Novatrex; ***Ger.:*** Farmitrexat†; Lantarel; Metex; MTX; O-trexat; ***Gr.:*** Emthexate; Methobion; Metoject; ***Hung.:*** Metoject; Trexan; ***India:*** Biotrexate; Caditrex; Imutrex; Methocip; Neotrexate; ***Indon.:*** Emthexate; ***Israel:*** Abitrexate; ***Jpn:*** Metolate; ***Malaysia:*** Emthexate; ***Mex.:*** Atrexel; Ifamet; Ledertrexate; Leulin†; Medsatrexate; Methoblastin†; Otaxem; Texate; Trixilem; ***Neth.:*** Emthexate; Ledertrexate†; Metoject; ***Norw.:*** Emthexat; Metoject; ***NZ:*** Emthexate; Ledertrexate†; Methoblastin; ***Philipp.:*** Emthexate; Hextrate; Methobax; Pterin; Zexate; ***Pol.:*** Trexan; ***Port.:*** Fauldexato; Metoject; ***Rus.:*** Trixilem (Трикслем)†; ***S.Afr.:*** Abitrexate; Emthexate; ***Spain:*** Emthexate; Metoject; ***Swed.:*** Emthexat†; Metoject; ***Thai.:*** Abitrexate; Emthexate; Trixilem; Zexate; ***Turk.:*** Emthexate; Trexan; ***UK:*** Maxtrex; Metoject; ***USA:*** Rheumatrex; Trexall; ***Venez.:*** Zexate.

2-Methoxyoestradiol

2-ME2; 2-Methoxyestradiol; NSC-659853. (17β)-2-Methoxyestra-1,3,5(10)-triene-3,17-diol.

$C_{19}H_{26}O_3$ = 302.4.

CAS — 362-07-2.



Profile

2-Methoxyoestradiol is a metabolite of oestradiol (p.2097). It does not exhibit direct oestrogenic activity, but works through multiple cellular pathways to produce antineoplastic effects, including inhibition of angiogenesis and induction of apoptosis. 2-Methoxyoestradiol is under investigation in the treatment of various diseases, including glioblastoma, multiple myeloma, carcinoid tumours, as well as ovarian, prostate, breast, and renal cell cancers. It is also under investigation for pulmonary arterial hypertension.

Mifamurtide *(rINN)*

Mifamurtida; Mifamurtidum; MTP-PE; Muramyl Tripeptide Phosphatidyl Ethanolamine; Muramyl Tripeptide Phosphatidyl Monoethanolamine. 2-[(*N*-{(2*R*)-[(2-Acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate.

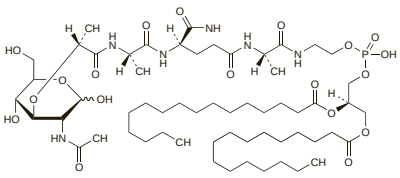
Мифамуртид

$C_{59}H_{109}N_6O_{19}P$ = 1237.5.

CAS — 83461-56-7.

ATC — L03AX15.

ATC Vet — QL03AX15.



NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Mifamurtide Sodium *(rINNM)*

CGP-19835A; L-MTP-PE (liposomal mifamurtide sodium); Mifamurtida sódica; Mifamurtide *(USAN)*; Mifamurtide Sodique; Mifamurtidum Natricum. 2-[(*N*-{(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(Acetylamino)-2,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yloxy]propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexanoyloxy)propyl sodium phosphate hydrate.

Мифамуртид Натрий

$C_{59}H_{108}N_6NaO_{19}P.xH_2O$.

CAS — 838853-48-8.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Profile

Mifamurtide is an immunomodulator that activates macrophages to increase their capacity to destroy cancer cells. It is under investigation for the treatment of osteosarcoma.

Miltefosine *(BAN, rINN)*

D-18506; HDPC; Hexadecylphosphocholine; Miltefosiini; Miltefosin; Miltefosina; Miltéfosine; Miltefosinum. [2-(Trimethylammonio)ethyl][hexadecyloxyphosphonate].

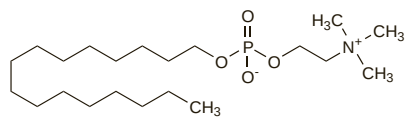
Мильтефозин

$C_{21}H_{46}NO_4P$ = 407.6.

CAS — 58066-85-6.

ATC — L01XX09.

ATC Vet — QL01XX09.



Profile

Miltefosine is a phospholipid derivative which is structurally related to the phospholipid components of the cell membrane and is thought to exert its antineoplastic actions by disruption of cell-membrane function. A 6% solution is applied once or twice daily as a topical antineoplastic agent for skin metastases of breast cancer. Miltefosine has also been tried orally for various malignant neoplasms. It is used for the treatment of visceral and cutaneous leishmaniasis in an oral dose of 1.5 to 2.5 mg/kg daily (maximum daily dose 150 mg) for 28 days.

Leishmaniasis. Miltefosine, given orally in doses of 50 to 150 mg daily, or about 2.5 mg/kg daily, for 28 days, appears to be of benefit[1-7] in the treatment of visceral leishmaniasis (p.824), and has been licensed for this purpose in India and Germany. Benefit has also been reported in patients given similar doses for New World cutaneous leishmaniasis,[8] and it has also been licensed in some South American countries, but success may depend on the infecting *Leishmania* species.[9] The use of longer courses of miltefosine in the treatment of patients with both leishmaniasis and HIV infection has been reported.[10]

1. Sundar S, *et al.* Trial of oral miltefosine for visceral leishmaniasis. *Lancet* 1998; **352:** 1821–3.
2. Jha TK, *et al.* Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; **341:** 1795–1800.
3. Thakur CP, *et al.* Miltefosine in a case of visceral leishmaniasis with HIV co-infection; and rising incidence of this disease in India. *Trans R Soc Trop Med Hyg* 2000; **94:** 696–7.
4. Sundar S, *et al.* Short-course of oral miltefosine for treatment of visceral leishmaniasis. *Clin Infect Dis* 2000; **31:** 1110–13.
5. Sundar S, *et al.* Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med* 2002; **347:** 1739–46.
6. Bhattacharya SK, *et al.* Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clin Infect Dis* 2004; **38:** 217–21.
7. Ritmeijer K, *et al.* A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis* 2006; **43:** 357–64.
8. Soto J, *et al.* Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis* 2001; **33:** e57–e61. Available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/322689 (accessed 01/08/08)
9. Soto J, *et al.* Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 2004; **38:** 1266–72.
10. Sindermann H, *et al.* Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis* 2004; **39:** 1520–3.

Malignant neoplasms. References to the use of topical miltefosine in breast cancer.

1. Terwogt JM, *et al.* Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast cancer. *Br J Cancer* 1999; **79:** 1158–61.
2. Smorenburg CH, *et al.* Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients. *Anticancer Drugs* 2000; **11:** 825–8.
3. Leonard R, *et al.* Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol* 2001; **19:** 4150–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Mitex†; ***Austria:*** Miltex; ***Braz.:*** Miltex; ***Chile:*** Miltex†; ***Cz.:*** Miltex†; ***Fin.:*** Miltex†; ***Fr.:*** Miltex; ***Ger.:*** Impavido; Miltex; ***Hung.:*** Miltex; ***Israel:*** Miltex; ***Ital.:*** Miltex; ***Malaysia:*** Miltex†; ***Philipp.:*** Miltex; ***Singapore:*** Miltex; ***Spain:*** Miltex; ***Swed.:*** Miltex; ***UK:*** Miltex.

Mitobronitol *(BAN, rINN)*

DBM; Dibromomannitol; Mitobronitolum; NSC-94100; R-54; WR-220057. 1,6-Dibromo-1,6-dideoxy-D-mannitol.

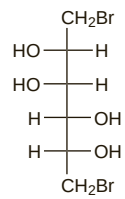
Митобронитол

$C_6H_{12}Br_2O_4$ = 308.0.

CAS — 488-41-5.

ATC — L01AX01.

ATC Vet — QL01AX01.



Pharmacopoeias. In *Br.*

BP 2008 (Mitobronitol). A white or almost white crystalline solid. Slightly soluble in water, in alcohol, and in acetone; practically insoluble in chloroform. Protect from light.

Profile

Mitobronitol is an antineoplastic which appears to act as an alkylating agent, perhaps by epoxide formation. It has been used in the management of thrombocythaemia, both primary, and secondary to chronic myeloid leukaemia or polycythaemia vera.

The usual oral dose is 250 mg daily until the platelet count falls to acceptable levels. Intermittent dosage has been given for maintenance therapy, adjusted according to the blood count. Frequent examination of the blood should be performed during treatment.

Mitobronitol is well absorbed from the gastrointestinal tract and is excreted through the liver into the bile, with reabsorption from the small intestine. It is eliminated as unchanged drug and some bromine-containing metabolites in the urine over several days.

Carcinogenicity. Long-term follow-up of a cooperative study[1] involving 350 patients with polycythaemia vera and treated with mitobronitol was thought to indicate that mitobronitol was less likely than phosphorus-32 or busulfan to induce acute myeloid leukaemia.

For a discussion of the usual management of polycythaemia vera, see p.654.

1. Kelemen E, *et al.* Decreasing risk of leukaemia during prolonged follow-up after mitobronitol therapy for polycythaemia vera. *Lancet* 1987; **ii:** 625.

Preparations

BP 2008: Mitobronitol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Myelobromol; ***UK:*** Myelobromol.

Mitoguazone Dihydrochloride *(rINNM)*

Dihidrocloruro de mitoguazona; Methyl-GAG; Methylglyoxal Bisguanylhydrazone (mitoguazone); MGBG; Mitoguazone, Dichlorhydrate de; Mitoguazoni Dihydrochloridum; NSC-32946. 1,1′-[(Methylethanediylidene)dinitrilo]diguanidine dihydrochloride.

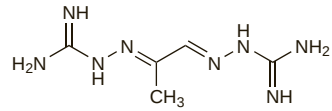
Митогуазона Дигидрохлорид

$C_5H_{12}N_8.2HCl$ = 257.1.

CAS — 459-86-9 (mitoguazone); 7059-23-6 (mitoguazone dihydrochloride).

ATC — L01XX16.

ATC Vet — QL01XX16.



(mitoguazone)

Profile

Mitoguazone is an antineoplastic that may exert its cytotoxic effects by its ability to inhibit polyamine biosynthesis. It has been tried as the dihydrochloride monohydrate or the acetate, in the treatment of leukaemias, lymphomas, and some solid tumours.

Mitoguazone may produce hypoglycaemia and should be given dissolved in glucose-containing infusion fluids; sugar may be taken orally if hypoglycaemia develops during infusion. Granulocytopenia and thrombocytopenia are generally mild and reversible on stopping treatment. Gastrointestinal effects frequently occur.

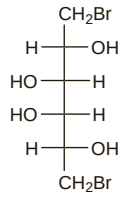
Mitolactol *(rINN)*

DBD; Dibromodulcitol; Mitolactolum; NSC-104800; WR-138743. 1,6-Dibromo-1,6-dideoxy-D-galactitol.

Митолактол

$C_6H_{12}Br_2O_4$ = 308.0.

CAS — 10318-26-0.



Profile

Mitolactol is an antineoplastic that may act by alkylation, probably as epoxide metabolites including dianhydrogalactitol. It has been given orally in the treatment of metastatic breast and cervi-