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once a week and if there is a steep fall in the white cell count or severe bone-marrow depression the drug should be withdrawn immediately.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.

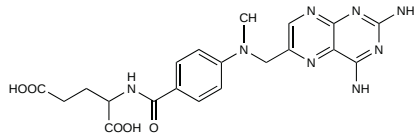
Метотрексат

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