lent to about 1 mg of melphalan. Frequent blood counts are essential and dosage should be adjusted according to haematological response. Therapy should be interrupted if the platelet or white cell count fall below acceptable levels (see also Bone-marrow Depression, p.639). It should be given with great caution if the neutrophil count has recently been depressed by chemotherapy or radiotherapy.

Numerous conventional-dose regimens have been tried for the treatment of multiple myeloma and there is still uncertainty as to the best schedule. Licensed **oral** dosage regimens include:

- 150 micrograms/kg daily in divided doses for 4 to 7 days
- 250 micrograms/kg daily for 4 days
- 6 mg daily for 2 to 3 weeks

Melphalan is usually combined with corticosteroids. Courses are followed by a rest period of up to 6 weeks to allow recovery of haematological function and are then repeated, or maintenance therapy may be instituted, usually with a daily dose of 1 to 3 mg, or up to 50 micrograms/kg. For optimum effect, therapy is usually adjusted to produce a moderate leucopenia, with white cell counts in the range 3000 to 3500 cells/mm^3.

In the treatment of breast cancer, licensed doses are 150 micrograms/kg daily or 6 mg/m^2 daily for 5 days, repeated every 6 weeks. Doses of 200 micrograms/kg daily for 5 days every 4 to 8 weeks have been given to patients with ovarian carcinoma.

In patients with polycythaemia vera, doses of 6 to 10 mg daily for 5 to 7 days, and then 2 to 4 mg daily, have been used for remission induction; a dose of 2 to 6 mg weekly has been used for maintenance.

Melphalan is also given **intravenously**; a single dose of 1 mg/kg, repeated in 4 weeks if the platelet and neutrophil counts permit, has been licensed in ovarian adenocarcinoma. It may be infused in sodium chloride 0.9% or injected into the tubing of a fast-running drip; when given by infusion the time from reconstitution of the solution to completion of infusion should not exceed 1.5 hours and prolonged infusions should be carried out with several batches of solution, each freshly prepared. In multiple myeloma, the licensed dose for use as a single agent is an intravenous dose of 400 micrograms/kg or 16 mg/m^2, infused over 15 to 20 minutes; the first 4 doses may be given at 2-week intervals, but further doses should be given at 4-week intervals depending on toxicity.

High-dose melphalan has been given intravenously in some malignancies: doses of 100 to 240 mg/m^2 have been licensed in neuroblastoma, and 100 to 200 mg/m^2 in multiple myeloma, generally followed by autologous stem cell rescue, which becomes essential where doses exceed 140 mg/m^2. High doses should be given through a central venous catheter.

Melphalan may be given by **local arterial perfusion** in the management of melanoma and soft-tissue sarcomas. A typical dosage range for upper extremity perfusions is 0.6 to 1 mg/kg, whereas for lower extremity perfusions doses of 0.8 to 1.5 mg/kg (in melanoma) or 1 to 1.4 mg/kg (in sarcoma) are typically used.

The dose of melphalan should be reduced in patients with **renal impairment** (see below).

Administration in renal impairment. The initial dose of intravenous melphalan should be reduced by about 50% in patients with renal impairment and dosage reduction should be considered when giving it by mouth. High-dose regimens are not recommended in patients with moderate to severe renal impairment.

Amyloidosis. Amyloidosis refers to a group of conditions characterised by accumulation of a waxy proteinaceous infiltrate within body tissues. Various forms are known,[1-3] including:

- primary or AL amyloidosis, in which the amyloid is derived from immunoglobulin light chains
- ATTR amyloidosis (a familial form), in which amyloid is derived from transthyretin
- AA amyloidosis, which is most often secondary to chronic inflammation, such as that associated with rheumatoid arthritis, tuberculosis, or familial Mediterranean fever (p.557)

Symptoms vary, depending on where the amyloid is deposited. The organs most commonly affected are the heart and kidneys. Renal amyloidosis can present as proteinuria, leading to nephrotic syndrome and renal failure. While renal disease is common in the AA and AL forms, it is less prevalent in ATTR amyloidosis, which commonly presents with neuropathy. Cardiac involvement, rare in AA amyloidosis, is variable in the ATTR form, and common in the AL form; it manifests as restrictive cardiomyopathy, leading to congestive heart failure. Painful peripheral sensory neuropathy and carpal tunnel syndrome also occur frequently. Amyloid deposition in the gastrointestinal tract can lead to malabsorption. Hepatomegaly is common. Macroglossia, due to deposition of amyloid in the tongue, occurs only in the AL form.[1,2]

Management depends to some extent upon the type of amyloidosis involved, and the site, but no drug or combination of drugs is unequivocally effective. Treatment for AA amyloidosis secondary to chronic inflammation is aimed at the underlying disease; immunosuppressants such as chlorambucil, cyclophosphamide, and methotrexate have been used, as well as inhibitors of tumour necrosis factor and interleukin-1 receptor antagonists.[4] Colchicine is effective in the treatment of AA amyloidosis complicating familial Mediterranean fever, but is not considered to be of benefit in other forms of amyloidosis.[1,5] Melphalan plus prednisone or prednisolone has been shown to increase median survival in primary amyloidosis patients.[6] It is considered the treatment of choice in AL amyloidosis for patients in whom more intensive chemotherapy is not appropriate; evidence of benefit from the addition of a corticosteroid has not been evaluated and in some patients, it may be reasonable not to include a corticosteroid.[5] Melphalan, prednisone, and colchicine was found to be more effective than colchicine alone in the treatment of AL amyloidosis,[7] but a later trial[8] found no benefit in adding colchicine to the standard therapy. Addition of multiple alkylating agents such as vincristine, carmustine, and cyclophosphamide to the standard therapy[9] did not improve survival or response. Evidence to support the use of alkylating-based combination chemotherapy for primary amyloidosis is lacking.[5] Alternatively, cycles of vincristine, doxorubicin, and dexamethasone (VAD) may be effective, but patients with cardiac amyloidosis may be at increased risk of anthracycline toxicity.[10] In the UK, VAD is considered as first-line therapy in patients under the age of 70 years who do not have cardiac failure, autonomic neuropathy, or peripheral neuropathy.[5] High-dose intravenous melphalan with autologous haematopoietic stem cell transplantation (HSCT) has been used;[11] it may result in complete remission of primary amyloidosis,[12-14] and some[1] consider it the treatment of choice. While this may improve renal disease,[12] the therapy remains very toxic, and patient selection on the basis of limited organ disease and no significant cardiac involvement, may reduce morbidity and mortality.[5,13] The outcome of treatment with high-dose intravenous melphalan with autologous HSCT was not superior to standard-dose oral melphalan plus oral dexamethasone in patients with newly diagnosed AL amyloidosis.[15] High-dose dexamethasone or thalidomide may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those refractory to chemotherapy;[5] good results have been reported in patients with AL amyloidosis given a regimen combining cyclophosphamide with dexamethasone and thalidomide.[16] Local application or oral dosage of dimethyl sulfoxide, and 4′-iodo-4′-deoxydoxorubicin has been investigated.[1,10]

Symptomatic management is also important. Care must be taken to avoid digitalis toxicity when cardiac amyloid is present, as well as to avoid salt and water depletion through injudicious use of diuretics. Calcium-channel blockers and beta blockers should be avoided.[1] Renal transplantation may be considered in end-stage renal failure due to amyloidosis, but unless amyloid production has been stopped disease is likely to recur in the new kidney. Cardiac transplantation, and subsequent chemotherapy with epirubicin, carmustine, and cyclophosphamide to suppress the underlying disease and control amyloid deposition in the graft has also been described.[17] Liver transplantation is the definitive therapy for patients with ATTR amyloidosis.[1,18] Because amyloid deposits contain a plasma glycoprotein serum amyloid P component (SAP) that contributes to the stability of the deposits, and thus contributes to the pathogenesis of amyloidosis, future therapeutic approaches include the targeting of SAP to deplete it from the tissues and clear it from the plasma. Ro-63-8695 (CPHPC) is being investigated.[3,19] Eprodisate disodium is under investigation for AA amyloidosis.[20]

1. Khan MF, Falk RH. Amyloidosis. *Postgrad Med J* 2001; **77:** 686–93.
2. Falk RH, Skinner M. The systemic amyloidoses: an overview. *Adv Intern Med* 2000; **45:** 107–37.
3. Gillmore JD, Hawkins PN. Drug Insight: emerging therapies for amyloidosis. *Nat Clin Pract Nephrol* 2006; **2:** 263–70.
4. Lachmann HJ, *et al.* Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356:** 2361–71.
5. British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. *Br J Haematol* 2004; **125:** 681–700. Also available at: http://www.bcshguidelines.com/pdf/ALamyloidosis_210604.pdf (accessed 07/03/06)
6. Gertz MA, Rajkumar SV. Primary systemic amyloidosis. *Curr Treat Options Oncol* 2002; **3:** 261–71.
7. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100:** 290–8.
8. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; **336:** 1202–7.
9. Gertz MA, *et al.* Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis. *J Clin Oncol* 1999; **17:** 262–7.
10. Sezer O, *et al.* New therapeutic approaches in primary systemic AL amyloidosis. *Ann Hematol* 2000; **79:** 1–6.
11. Sanchorawala V, Seldin DC. An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. *Amyloid* 2007; **14:** 261–9.
12. Dember LM, *et al.* Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. *Ann Intern Med* 2001; **134:** 746–53.
13. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002; **99:** 4276–82.
14. Skinner M, *et al.* High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004; **140:** 85–93.
15. Jaccard A, *et al.* Myélome Autogreffe (MAG) and Intergroupe Francophone du Myélome (IFM) Intergroup. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; **357:** 1083–93.
16. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109:** 457–64.
17. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309:** 1135–7.
18. Suhr OB, *et al.* Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; **6:** 263–76.
19. Pepys MB, *et al.* Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* 2002; **417:** 254–9.
20. Dember LM, *et al.* Eprodisate for AA Amyloidosis Trial Group. Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; **356:** 2349–60.

Bone disorders, non-malignant. Fibrogenesis imperfecta ossium is a rare progressive bone disease in which disorders of bone collagen and mineralisation, and subsequent abnormal bone structure, result in bone pain and fractures. A patient responded to treatment with melphalan 10 mg and prednisolone 20 or 30 mg daily, in 7-day courses every 2 months.[1,2] Another showed some improvement with intermittent 5-day courses of melphalan 10 mg daily and prednisolone 40 mg daily.[3] However, melphalan alone was reported to be ineffective in 2 other patients; both experienced bone-marrow depression.[3,4]

1. Stamp TCB, *et al.* Fibrogenesis imperfecta ossium: remission with melphalan. *Lancet* 1985; **i:** 582–3.
2. Ralphs JR, *et al.* Ultrastructural features of the osteoid of patients with fibrogenesis imperfecta ossium. *Bone* 1989; **10:** 243–9.
3. Carr AJ, *et al.* Fibrogenesis imperfecta ossium. *J Bone Joint Surg Br* 1995; **77:** 820–9.
4. Lafage-Proust M-H, *et al.* Fibrogenesis imperfecta ossium: ineffectiveness of melphalan. *Calcif Tissue Int* 1996; **59:** 240–4.

Malignant neoplasms. The important role played by melphalan in the management of multiple myeloma is discussed on p.658. Melphalan is also used as part of salvage regimens for relapsed Hodgkin's disease (see p.655), in ovarian cancer (p.670), and for local perfusion of melanoma (p.673).

Preparations

BP 2008: Melphalan Injection; Melphalan Tablets;
USP 31: Melphalan Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alkerana; ***Austral.:*** Alkeran; ***Austria:*** Alkeran; ***Belg.:*** Alkeran; ***Braz.:*** Alkeran; ***Canad.:*** Alkeran; ***Chile:*** Alkeran; ***Cz.:*** Alkeran; ***Denm.:*** Alkeran; ***Fin.:*** Alkeran; ***Fr.:*** Alkeran; ***Ger.:*** Alkeran; ***Gr.:*** Alkeran; ***Hong Kong:*** Alkeran; ***India:*** Alkeran; ***Irl.:*** Alkeran; ***Israel:*** Alkeran; ***Ital.:*** Alkeran; ***Malaysia:*** Alkeran; ***Mex.:*** Alkeran; ***Neth.:*** Alkeran; ***Norw.:*** Alkeran; ***NZ:*** Alkeran; ***Philipp.:*** Alkeran; ***Pol.:*** Alkeran; ***Port.:*** Alkeran; ***Rus.:*** Alkeran (Алкеран); ***S.Afr.:*** Alkeran; ***Singapore:*** Alkeran; ***Swed.:*** Alkeran; ***Switz.:*** Alkeran; ***Thai.:*** Alkeran; ***Turk.:*** Alkeran; ***UK:*** Alkeran; ***USA:*** Alkeran.

Mepolizumab *(USAN, rINN)*

Mépolizumab; Mepolizumabum; SB-240563. Immunoglobulin G1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563 γ1-chain), disulfide with human-mouse monoclonal SB-240563 κ-chain, dimer.

Меполизумаб

CAS — 196078-29-2.

Profile

Mepolizumab is an anti-interleukin-5 monoclonal antibody. It is under investigation in the treatment of hypereosinophilic syndrome (chronic eosinophilic leukaemia), as well as eosinophilic oesophagitis, and asthma.

◊ References.

1. Leckie MJ, *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; **356:** 2144–8.
2. Plötz S-G, *et al.* Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003; **349:** 2334–9.
3. Braun-Falco M, *et al.* Angiolymphoid hyperplasia with eosinophilia treated with anti-interleukin-5 antibody (mepolizumab). *Br J Dermatol* 2004; **151:** 1103–4.

4. Garrett JK, *et al.* Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004; **113:** 115–19.
5. Rothenberg ME, *et al.* Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358:** 1215–28.

Mercaptopurine *(BAN, rINN)*

Mercaptopurina; Mercaptopurinum; Mercaptopurinum Monohydricum; Merkaptopuriini; Merkaptopürin; Merkaptopurin; Merkaptopurin monohydrát; Merkaptopurinas; Merkaptopurына; NSC-755; 6MP; Purinethiol; WR-2785. 6-Mercaptopurine monohydrate; Purine-6-thiol monohydrate; 1,7-Dihydro-6*H*-purine-6-thione monohydrate.

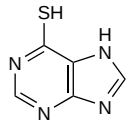
Меркаптопурин

$C_5H_4N_4S,H_2O$ = 170.2.

CAS — 50-44-2 (anhydrous mercaptopurine); 6112-76-1 (mercaptopurine monohydrate).

ATC — L01BB02.

ATC Vet — QL01BB02.



NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine and mercaptamine (formerly cysteamine, p.2340) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

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

Ph. Eur. 6.2 (Mercaptopurine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Mercaptopurine). A yellow, odourless or practically odourless, crystalline powder. Insoluble in water, in acetone, and in ether; soluble in hot alcohol and in dilute alkali solutions; slightly soluble in 2N sulfuric acid.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression with mercaptopurine, manifesting as leucopenia, thrombocytopenia, and anaemia, may be delayed; hypoplasia may occur. Mercaptopurine is less toxic to the gastrointestinal tract than the folic acid antagonists or fluorouracil but gastrointestinal disturbances may occur. Hepatotoxicity has been reported, with cholestatic jaundice and necrosis, sometimes fatal. Gastrointestinal and hepatic toxicity are reported to be more frequent in adults than in children, and are more likely at higher doses. Crystalluria with haematuria has been observed rarely as have skin disorders including hyperpigmentation. Fever may occur.

Mercaptopurine is potentially carcinogenic and mutagenic; an increased incidence of abortion has occurred in women given mercaptopurine during the first trimester of pregnancy.

Mercaptopurine should be used with care in patients with impaired hepatic or renal function. Hepatic function should be monitored periodically.

Effects on the blood. Measurement of the activity of thiopurine methyltransferase (TPMT) or the concentration of its substrate, tioguanine nucleotide, has been suggested as a way of predicting those individuals likely to have severe myelotoxicity with mercaptopurine and related drugs (see Azathioprine, p.1819). Patients with an inherited deficiency of the TPMT enzyme may be at increased risk of myelosuppression from mercaptopurine. US licensed product information suggests TPMT testing in patients with evidence of toxicity, and state that reductions in the dose of mercaptopurine may be necessary in those with TPMT deficiency, although optimal initial doses have not been established for these patients. The UK licensed information states that tests for TPMT deficiency have not been shown to identify all patients at risk of severe toxicity, and that close monitoring of blood counts should still be performed.

Effects on the pancreas. Pancreatitis occurred in 13 of 396 patients given mercaptopurine for inflammatory bowel disease.[1] Symptoms resolved on withdrawal but recurred in 7 who were re-challenged with mercaptopurine or azathioprine. Acute pancreatitis has also been reported in 2 children given mercaptopurine during maintenance chemotherapy for acute lymphoblastic leukaemia.[2] They had also suffered pancreatitis from asparaginase during earlier therapy, and the authors suggested that subclinical damage to the pancreas by asparaginase may have been exacerbated by mercaptopurine, but also noted that most patients who develop asparaginase-induced pancreatitis receive mercaptopurine without developing this complication.

1. Present DH, *et al.* 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111:** 641–9.
2. Willert JR, *et al.* Recurrent mercaptopurine-induced acute pancreatitis: a rare complication of chemotherapy for acute lymphoblastic leukemia in children. *Med Pediatr Oncol* 2002; **38:** 73–4.

Handling and disposal. A method for the destruction of mercaptopurine or tioguanine in *wastes* by oxidation with potassium permanganate in sulfuric acid.[1] Residues produced by this method had no mutagenic activity. *Urine and faeces* produced for up to 48 hours and 5 days, respectively after a dose of mercaptopurine 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.

Overdosage. Despite substantial overdose, no acute renal or hepatic toxicity occurred in 2 children. In one case, in which no specific detoxification measures were implemented, neutrophils reached a nadir on day 11 followed by a gradual recovery to normal by day 46. In the other case, gastric lavage was performed and activated charcoal was given; no evidence of neutropenia was seen. The authors recommended that management of acute accidental ingestion should include gastric lavage if the patient presents within 1 hour or if the amount ingested is large. Haemodialysis may be considered if the patient presents within 3 hours of ingestion. Liver function should be monitored. Severe myelosuppression may be managed with granulocyte colony-stimulating factor and a bone-marrow harvest may be of benefit if performed within several hours of the overdose.[1]

1. Chow LML, *et al.* Toxic ingestion of 6-mercaptopurine by young siblings of pediatric oncology patients. *J Pediatr* 2004; **144:** 669–71.

Porphyria. Mercaptopurine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Mercaptopurine should be given with particular caution with other hepatotoxic drugs. Its effects are enhanced by allopurinol and the dose of mercaptopurine should be reduced to one-third to one-quarter of the usual dose when allopurinol is also given.

Allopurinol. Mercaptopurine plasma concentrations were markedly increased by allopurinol when mercaptopurine was given by mouth but not when it was given intravenously.[1] The results appear to indicate that allopurinol inhibits the first-pass metabolism of mercaptopurine.

1. Zimm S, *et al.* Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. *Clin Pharmacol Ther* 1983; **34:** 810–17.

Anticoagulants. For reference to mercaptopurine diminishing the activity of *warfarin*, see p.1429.

Antineoplastics. For a suggestion that *doxorubicin* might enhance the hepatotoxicity of mercaptopurine, see under Daunorubicin Hydrochloride, p.709.

Giving mercaptopurine with low-dose oral *methotrexate* increased mean peak plasma concentrations of mercaptopurine by 26% compared with the same dose of mercaptopurine alone in a study in 14 patients with acute lymphoblastic leukaemia.[1] The effect was probably due to inhibition of the first-pass metabolism of mercaptopurine by methotrexate, which is a potent inhibitor of xanthine oxidase. In another study[2] of 10 children with acute lymphoblastic leukaemia, high-dose intravenous methotrexate (2 or 5 g/m^2) increased the peak plasma concentrations of mercaptopurine by 108 and 121% respectively. However, the clinical effect of this pharmacokinetic interaction is probably only minor because of the low, and highly variable, mercaptopurine bioavailability and the lack of correlation between mercaptopurine plasma concentrations and effect.[3] Mercaptopurine and methotrexate have been widely used in combination chemotherapy regimens for acute lymphoblastic leukaemia for their synergistic pharmacodynamic interaction.

1. Balis FM, *et al.* The effect of methotrexate on the bioavailability of oral 6-mercaptopurine. *Clin Pharmacol Ther* 1987; **41:** 384–7.
2. Innocenti F, *et al.* Clinical and experimental pharmacokinetic interaction between 6-mercaptopurine and methotrexate. *Cancer Chemother Pharmacol* 1996; **37:** 409–14.
3. Giverhaug T, *et al.* The interaction of 6-mercaptopurine (6-MP) and methotrexate (MTX). *Gen Pharmacol* 1999; **33:** 341–6.

Azathioprine. For a report of a fatality when a patient was prescribed mercaptopurine and azathioprine by separate practitioners, see Interactions, under Azathioprine, p.1819.

Gastrointestinal drugs. The enzyme thiopurine methyltransferase is inhibited *in vitro* by *sulfasalazine* and *mesalazine*, raising the possibility of an interaction in patients treated simultaneously with an aminosalicylate and a thiopurine such as mercaptopurine or azathioprine.[1] Myelotoxicity has been reported in a patient receiving mercaptopurine and *olsalazine*.[2] Similarly, severe pancytopenia has occurred in a 13-year-old boy when azathioprine was added to mesalazine therapy.[3] In a study[4] of 34 patients with Crohn's disease in which *balsalazide*, mesalazine, or sulfasalazine was added to established azathioprine or mercaptopurine therapy, mild leucopenia was common in patients given mesalazine or sulfasalazine, and whole blood concentrations of tioguanine nucleotide were found to be increased, probably due to thiopurine methyltransferase inhibition. These effects were not statistically significant in patients given balsalazide.

1. Szumlanski C, Weinshilboum RM. Sulfasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; **39:** 456–9.
2. Lewis LD, *et al.* Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. *Clin Pharmacol Ther* 1997; **62:** 464–75.
3. Chouragui JP, *et al.* Azathioprine toxicity in a child with ulcerative colitis: interaction with mesalazine. *Gastroenterology* 1996; **110** (suppl): A883.
4. Lowry PW, *et al.* Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. *Gut* 2001; **49:** 656–64.

Pharmacokinetics

Mercaptopurine is variably and incompletely absorbed from the gastrointestinal tract; about 50% of an oral dose has been reported to be absorbed, but the absolute bioavailability is somewhat lower, probably due to gastrointestinal or first-pass metabolism, and is also subject to wide interindividual variation. Once absorbed it is widely distributed throughout body water and tissues. Plasma half-lives ranging from about 20 to 90 minutes have been reported after intravenous injection and the drug is not found in plasma after about 8 hours but this is of limited significance since mercaptopurine is activated intracellularly by conversion to nucleotide derivatives which persist for much longer. It is rapidly and extensively metabolised in the liver, by methylation and oxidation as well as by the formation of inorganic sulfates. Thiol methylation is catalysed by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. Patients with little or no detectable enzyme activity may accumulate excessive cellular concentrations of active tioguanine nucleotides, predisposing them to mercaptopurine toxicity. Considerable amounts of mercaptopurine are also oxidised to thiouric acid by the enzyme xanthine oxidase. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Mercaptopurine crosses the blood-brain barrier to some extent and is found in the CSF, but only in subtherapeutic concentrations.

Therapeutic drug monitoring. For a discussion of therapeutic drug monitoring for mercaptopurine, see under Azathioprine, p.1819.

Uses and Administration

Mercaptopurine is an antineoplastic that acts as an antimetabolite. It is an analogue of the natural purines hypoxanthine and adenine. After the intracellular conversion of mercaptopurine to active nucleotides, including thioinosinic acid, it appears to exhibit a variety of actions including interfering with nucleic acid synthesis. It also has immunosuppressant properties. Its actions are specific for cells in S phase.

Mercaptopurine is used, usually with other agents, in the treatment of leukaemia. It induces remissions in acute lymphoblastic and myeloid leukaemias (p.651 and p.652, respectively) but other agents are generally preferred and mercaptopurine is chiefly employed in maintenance programmes, commonly with methotrexate. It may also be effective in chronic myeloid leukaemia (p.653). There is cross-resistance between mercaptopurine and tioguanine (p.779).