

# Antigout Drugs

This chapter deals with the treatment of gout and hyperuricaemia and the drugs used mainly for these disorders.

## Gout and hyperuricaemia

Uric acid is the final product of the metabolism of endogenous and exogenous purine in man. An excess of uric acid, measured in the plasma as sodium urate, constitutes **hyperuricaemia**. A patient is usually considered to be hyperuricaemic when plasma-urate concentrations exceed

- 0.42 mmol/litre (7 mg per 100 mL) in men and postmenopausal women
- 0.36 mmol/litre (6 mg per 100 mL) in premenopausal women.

Hyperuricaemia may be caused by an overproduction or underexcretion of urate. It is influenced by genetic and environmental factors and may be classified as primary (mainly idiopathic) or secondary. An increase in urate production may be caused by excessive dietary purine intake, certain cancers or their treatment, or, more rarely, enzyme defects of purine metabolism. Reduced urate excretion may be caused by renal disease, hypertension, or the intake of certain drugs such as thiazide diuretics. Other factors contributing to hyperuricaemia include hyperlipidaemia, obesity, alcohol consumption, and lead exposure.

At hyperuricaemic concentrations there is a risk of crystals of monosodium urate monohydrate being formed and deposited in synovial fluid and various tissues. However, some subjects may have supersaturated plasma-urate concentrations without any crystal deposits, while others may suffer from deposits in the absence of apparent hyperuricaemia.

The presence of urate crystals in the synovial fluid leads to an inflammatory response in the affected joint, commonly at the base of the big toe (podagra). The ensuing exquisite pain, tenderness, erythema, and swelling constitute the clinical manifestations of **acute inflammatory gouty arthritis**. Repeated acute attacks may be associated with a visible or palpable build up of crystal deposits (**tophi**) at various sites including in and around the affected joint. Tophi release urate crystals into the synovial fluid after various stimuli and so cause further acute attacks, leading to **chronic tophaceous gout**. Intra-articular and peri-articular tophi may cause gradual joint erosion, which, without treatment, results in disabling **chronic gouty arthritis**. Rarely, the kidney can be affected by urate deposits producing a gouty nephropathy or by uric acid calculi or stones (uric acid nephrolithiasis or urolithiasis).

**Treatment aims to:**

- alleviate the acute attack
- prevent future attacks
- lower plasma-urate concentration.

Plasma-urate concentrations may be reduced by control of obesity and modification of diet and alcohol intake. Drug treatment can relieve the pain of acute attacks but more prolonged therapy for hyperuricaemia is generally only considered if there are recurrent attacks of gout or there is renal involvement (see under Chronic Gout, below).

**Acute gout.** An attack of acute inflammatory gouty arthritis is best treated as soon as possible with an NSAID. Aspirin or other salicylates are not suitable since they may increase plasma-urate concentrations. Treatment is started with high doses of an NSAID, the doses being reduced as the patient responds. Usually treatment can be withdrawn within 1 to 2 weeks. Colchicine is an effective alternative; it may be used alone, or with an NSAID. Another alternative to NSAIDs or colchicine, for example in those for whom these drugs are contra-indicated, is an oral or intramuscular corticosteroid. Intra-articular corticosteroids are effective in acute monoarticular gout, or when used adjunctively in patients with polyarticular gout; infection of joints should be excluded prior to injection. Intravenous, intramuscular, or subcutaneous corticotropin has also been used, alone or adjunctively. Other therapies for acute gout include adjunctive analgesics and topical ice. Drugs used

for chronic gout (allopurinol or the uricosurics) should not be started during an acute attack since they can exacerbate and prolong it (see below).

**Chronic gout.** If the patient suffers frequent acute attacks or develops tophaceous gout, or has renal complications as a result of urate overproduction, then long-term treatment of hyperuricaemia may be needed. Such **urate-lowering therapy** should not be started during an acute attack, or for 2 to 3 weeks thereafter, as fluctuations in urate concentration may prolong the existing attack or trigger a new one. Treatment involves inhibiting the production of uric acid or enhancing its urinary excretion, in order to maintain a serum urate concentration at or below 0.3 or 0.36 mmol/litre. Hyperuricaemia due to overproduction of urate is treated with allopurinol which inhibits the enzyme xanthine oxidase, involved in purine metabolism. Hyperuricaemia associated with underexcretion of uric acid can be treated with either allopurinol or a uricosuric such as probenecid or sulfinpyrazone. Allopurinol is most commonly given as first-line therapy, but may be combined with or replaced by uricosurics if treatment fails. Allopurinol should also be used for patients with renal urate deposits or with uric acid renal calculi as it reduces urolithiasis. Febuxostat is an alternative xanthine oxidase inhibitor recently introduced.

With either treatment there is mobilisation of urate crystals from established tophi, as the plasma-urate concentration falls, which can trigger further acute attacks of gout. Patients are thus also given **prophylaxis** with an NSAID or colchicine from the start of urate-lowering treatment until at least a month after the plasma-urate has been reduced to an acceptable concentration; up to 6 months of prophylactic cover has been recommended.

Once the hyperuricaemia is corrected, the patient continues to receive therapy with allopurinol or uricosurics indefinitely. If an acute attack occurs during such maintenance therapy, this therapy should be continued to avoid fluctuations in urate concentration, and the acute attack treated in its own right.

Surgery may have to be considered for patients severely affected by chronic tophaceous gout.

References<sup>1-18</sup> to gout and its management are given below.

1. Agudelo CA, Wise CM. Gout: diagnosis, pathogenesis, and clinical manifestations. *Curr Opin Rheumatol* 2001; **13**: 234–9.
2. Schlesinger N, Schumacher HR. Gout: can management be improved? *Curr Opin Rheumatol* 2001; **13**: 240–4.
3. Terkeltaub RA. Gout. *N Engl J Med* 2003; **349**: 1647–55.
4. Rott KT, Agudelo CA. Gout. *JAMA* 2003; **289**: 2857–60.
5. Snaith ML, Adebajo AO. Gout and hyperuricaemia. In: Snaith ML, ed. *ABC of rheumatology*. 3rd ed. London: BMJ Publishing Group, 2004: 39–44.
6. Anonymous. Gout in primary care. *Drug Ther Bull* 2004; **42**: 37–40.
7. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 2004; **64**: 2399–2416.
8. Wortmann RL. Recent advances in the management of gout and hyperuricaemia. *Curr Opin Rheumatol* 2005; **17**: 319–24.
9. Underwood M. Gout. *Clin Evid* 2005; **13**: 1435–44.
10. Suresh E. Diagnosis and management of gout: a rational approach. *Postgrad Med J* 2005; **81**: 572–9.
11. Stamp L, et al. Gout in solid organ transplantation: a challenging clinical problem. *Drugs* 2005; **65**: 2593–2611.
12. Choi HK, et al. Pathogenesis of gout. *Ann Intern Med* 2005; **143**: 499–516.
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14. Teng GG, et al. Pathophysiology, clinical presentation and treatment of gout. *Drugs* 2006; **66**: 1547–63.
15. Underwood M. Diagnosis and management of gout. *BMJ* 2006; **332**: 1315–19.
16. Zhang W, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006; **65**: 1312–24.
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18. Schlesinger N. Overview of the management of acute gout and the role of adrenocorticotropic hormone. *Drugs* 2008; **68**: 407–15.

## Allopurinol (BAN, USAN, rINN)

Allopurinol; Allopurinoli; Allopurinolum; Allopurinolo; Allopurinol; Allopurinolis; BW-56-158; HPP; NSC-1390.

Аллопуринол

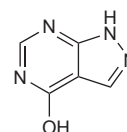
C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>O = 136.1.

CAS — 315-30-0 (allopurinol); 17795-21-0 (allopurinol sodium).

ATC — M04AA01.

ATC Vet — QM04AA01.

UNII — 63CZ7GJN5I.



**Description.** Allopurinol is a tautomeric mixture of 1H-pyrazolo[3,4-d]pyrimidin-4-ol and 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.* and *US*. **Ph. Eur. 6.8** (Allopurinol). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides.

**USP 33** (Allopurinol). A fluffy white to off-white powder having only a slight odour. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of potassium and sodium hydroxides.

**Incompatibility.** Allopurinol sodium as a 3 mg/mL solution in 0.9% sodium chloride was visually incompatible with amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chloramphenicol hydrochloride, chlorpromazine hydrochloride, cimetidine hydrochloride, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin hydrochloride, diphenhydramine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine hydrochloride, idarubicin hydrochloride, imipenem with cilastatin sodium, methylprednisolone sodium succinate, metoclopramide hydrochloride, minocycline hydrochloride, nalbuphine hydrochloride, netilmicin sulfate, ondansetron hydrochloride, pethidine hydrochloride, prochlorperazine edisilate, promethazine hydrochloride, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.<sup>1</sup>

1. Trissel LA, Martinez JF. Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51**: 1792–9.

## Adverse Effects

The most common adverse effect of allopurinol is skin rash. Rashes are generally maculopapular or pruritic, sometimes purpuric, but more serious hypersensitivity reactions may occur and include exfoliative rashes, the Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is therefore recommended that allopurinol be withdrawn immediately if a rash occurs (see Precautions, below). Further symptoms of hypersensitivity include fever and chills, lymphadenopathy, leucopenia or leucocytosis, eosinophilia, arthralgia, and vasculitis leading to renal and hepatic damage and, very rarely, seizures. These hypersensitivity reactions may be severe, even fatal, and patients with hepatic or renal impairment are at special risk.

Hepatotoxicity and signs of altered liver function may also be found in patients who are not hypersensitive. Haematological effects include thrombocytopenia, aplastic anaemia, agranulocytosis, and haemolytic anaemia.

Many other adverse effects have been noted rarely and include paraesthesia, peripheral neuropathy, alopecia, gynaecomastia, hypertension, taste disturbances, nausea, vomiting, abdominal pain, diarrhoea, headache, malaise, drowsiness, vertigo, and visual disturbances.

Patients with gout may have an increase in acute attacks on beginning treatment with allopurinol, although attacks usually subside after several months.

**Incidence of adverse effects.** A Boston Collaborative Drug Surveillance Program involving 29 524 hospitalised patients found that, with the exception of skin reactions, 33 of 1835 patients treated with allopurinol (1.8%) had adverse effects. These effects were dose-related and the most frequent were haematological (11 patients, 0.6%), diarrhoea (5 patients, 0.3%), and drug fever (5 patients, 0.3%). Hepatotoxicity was reported in 3 patients (0.2%). Two patients developed possible hypersensitivity reactions to allopurinol.<sup>1</sup>

A further analysis involving 1748 outpatients indicated no instances of acute blood disorders, skin diseases, or hypersensitivity that warranted hospital treatment. Liver disease, although found, was not considered to be associated with allopurinol. There were only 2 patients in whom renal disease could possibly have been caused by allopurinol.<sup>2</sup>

- McInnes GT, et al. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40**: 245–9.
- Jick H, Perera DR. Reactions to allopurinol. *JAMA* 1984; **252**: 1411.

**Effects on the blood.** In addition to the haematological abnormalities of leucopenia, thrombocytopenia, haemolytic anaemia, and clotting abnormalities noted in the Boston Collaborative Drug Surveillance Program,<sup>1</sup> aplastic anaemia has also been reported, sometimes in patients with renal impairment.<sup>2</sup> Pure red cell aplasia has also been reported.<sup>3,4</sup>

- McInnes GT, et al. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40**: 245–9.
- Anonymous. Allopurinol and aplastic anaemia. *WHO Drug Inf* 1989; **3**: 26.
- Lin Y-W et al. Acute pure red cell aplasia associated with allopurinol therapy. *Am J Hematol* 1999; **61**: 209–11.
- Chao S-C, et al. Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. *Ann Pharmacother* 2005; **39**: 1552–6.

**Effects on the eyes.** Some case reports have suggested an association between allopurinol use and the development of cataracts,<sup>1</sup> but a detailed ophthalmological survey involving 51 patients who had taken allopurinol failed to confirm this.<sup>2</sup> However, a large retrospective case-control study in elderly patients concluded that long-term, or high-dose, allopurinol therapy did increase the risk of cataract extraction.<sup>3</sup>

- Fraunfelder FT, et al. Cataracts associated with allopurinol therapy. *Am J Ophthalmol* 1982; **94**: 137–40.
- Clair WK, et al. Allopurinol use and the risk of cataract formation. *Br J Ophthalmol* 1989; **73**: 173–6.
- Garbe E, et al. Exposure to allopurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 1998; **116**: 1652–6.

**Effects on the skin.** Skin reactions are the most common adverse effects of allopurinol.

One report calculated that of 215 adverse effects noted over a 16-year period 188 (87.4%) were related to the skin or mucous membranes.<sup>1</sup> An analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 6 allergic skin reactions attributed to allopurinol among 784 recipients of the drug.<sup>2</sup> Desensitisation protocols<sup>3</sup> and alternative drugs<sup>4</sup> have been used after cutaneous reactions to allopurinol.

Serious skin reactions to allopurinol may occur as part of a generalised hypersensitivity reaction (see also Hypersensitivity, below). A review of the literature between 1970 and the end of 1990 revealed 101 cases of allopurinol hypersensitivity syndrome, 94 of which involved the skin.<sup>5</sup> Skin reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or a diffuse maculopapular or exfoliative dermatitis; 27 of the 101 patients died. The relative risk of toxic epidermal necrolysis or Stevens-Johnson syndrome occurring with allopurinol was high (calculated to be 5.5) in a case-control study including 13 patients with these cutaneous reactions who had received allopurinol.<sup>6</sup> This risk was not constant over time, being higher during the first 2 months of treatment. During these 2 months the estimated excess risk was 1.5 cases per million users per week. Another case-control study,<sup>7</sup> involving 379 patients with Stevens-Johnson syndrome or toxic epidermal necrolysis, found that allopurinol was the drug most frequently associated with these reactions. The risk again appeared to be restricted to short-term use (less than 8 weeks) and was greater in patients taking 200 mg or more daily.

- Vinciullo C. Allopurinol hypersensitivity. *Med J Aust* 1984; **141**: 449–50.
- Bigby M, et al. Drug-induced cutaneous reactions. *JAMA* 1986; **256**: 3358–63.
- Fam AG, et al. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001; **44**: 231–8.
- Fam AG. Difficult gout and new approaches for control of hyperuricemia in the allopurinol-allergic patient. *Curr Rheumatol Rep* 2001; **3**: 29–35.
- Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; **27**: 337–43.

- Roujeau J-C, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–1607.
- Halevy S, et al. EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008; **58**: 25–32.

**Hypersensitivity.** Skin reactions to allopurinol are common (see Effects on the Skin, above), and may occur as part of a hypersensitivity reaction. A DRESS syndrome (drug rash with eosinophilia and systemic symptoms) characterised by exfoliative dermatitis with eosinophilia, complicated by hepatitis and interstitial nephritis, has been described.<sup>1,2</sup> Syndrome.<sup>2</sup> Pathogenesis of the syndrome is not entirely clear, but may relate to the accumulation of the metabolite oxipurinol. Risk factors include renal impairment and use with thiazide diuretics.<sup>1,2</sup> Patients who developed this syndrome have been successfully treated by immediate withdrawal of allopurinol and use of corticosteroids.<sup>1,2</sup>

- Tausche A-K, et al. The Janus faces of allopurinol—allopurinol hypersensitivity syndrome. *Am J Med* 2008; **121**: e3–e4.
- Markel A. Allopurinol hypersensitivity and DRESS syndrome. *Am J Med* 2008; **121**: e25.

## Precautions

Allopurinol should not be used for the treatment of an acute attack of gout; additionally, allopurinol therapy should not be begun for any purpose during an acute attack. However, allopurinol is continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately.

Treatment should be stopped immediately if any skin reactions or other signs of hypersensitivity develop:

- cautious reintroduction at a low dose may be attempted after resolution of *mild skin reactions* (see Effects on the Skin, above)
- allopurinol should not be reintroduced in those patients who have had *other forms of hypersensitivity reaction*

Dosage should be reduced in renal or hepatic impairment. Care is advised in patients being treated for hypertension or cardiac insufficiency, who may also have renal impairment.

To reduce the risk of renal xanthine deposition an adequate fluid intake (2 to 3 litres daily) is required. In addition, a neutral or slightly alkaline urine may be desirable.

**Breast feeding.** Allopurinol and its metabolite, oxipurinol, are distributed into breast milk, and licensed product information recommends that allopurinol should be used with caution in breast-feeding women. Although oxipurinol was detected in the plasma of a breast-fed infant, no adverse effects were noted in the infant during 6 weeks of maternal treatment with allopurinol.<sup>1</sup> The American Academy of Pediatrics noted that there had been no documented problems with allopurinol and considered its use to be usually compatible with breast feeding.<sup>2</sup>

- Kamilli I, Gresser U. Allopurinol and oxipurinol in human breast milk. *Clin Invest* 1993; **71**: 161–4.
- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 26/05/04)

## Interactions

Drugs that can increase uric acid concentrations may decrease the efficacy of allopurinol. Aspirin and the salicylates possess this activity and should generally be avoided in hyperuricaemia and gout. An increase in hypersensitivity reactions, and possibly also other adverse effects, has been reported in patients taking allopurinol with ACE inhibitors or thiazide diuretics, particularly in patients with renal impairment.

The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and their doses should be markedly reduced when either of them is given with allopurinol to avoid potentially life-threatening toxicity. There have also been reports of allopurinol enhancing the activity of, and possibly increasing the toxicity of, a number of other drugs including some antibacterials, some anticoagulants, some other antineoplastics, ciclosporin, some sulfonylurea antidiabetics, theophylline, and vidarabine.

**ACE inhibitors.** An apparent interaction between allopurinol and *captopril* has been reported in patients with chronic renal failure. Development of fatal Stevens-Johnson syndrome after the introduction of allopurinol in 1 case was thought to be due to potentiation by *captopril*.<sup>1</sup> In another patient hypersensitivity,

characterised by fever, arthralgia, and myalgia, occurred and was believed to be due to *captopril*, or one of its metabolites, potentiated by the addition of allopurinol.<sup>2</sup> Care is advised if allopurinol is used with *captopril*, especially in patients with chronic renal failure.

- Pennell DJ, et al. Fatal Stevens-Johnson syndrome in a patient on *captopril* and allopurinol. *Lancet* 1984; **i**: 463.
- Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on *captopril* and allopurinol. *Lancet* 1984; **i**: 679.

**Antacids.** Allopurinol failed to reduce blood-uric-acid concentrations when given at the same time as *aluminium hydroxide* in 3 patients on chronic haemodialysis. However, if allopurinol was given 3 hours before aluminium hydroxide the expected decrease in uric acid concentration did occur.<sup>1</sup>

- Weissman I, Krivoy N. Interaction of aluminium hydroxide and allopurinol in patients on chronic hemodialysis. *Ann Intern Med* 1987; **107**: 787.

**Antibacterials.** There may be an increased incidence of skin rashes when allopurinol is used with *ampicillin* or *amoxicillin*. For further details, see *Ampicillin*, p.1567.

**Anticoagulants.** For the effect of allopurinol on *dicoumarol*, *phenprocoumon*, or *warfarin*, see *Warfarin*, p.1567.

**Antiepileptics.** For a report of allopurinol possibly inhibiting the metabolism of *phenytoin*, see under *Antigout Drugs*, p.543.

**Antigout drugs.** Uricosuric drugs are likely to increase the renal elimination of oxipurinol (the major active metabolite of allopurinol). For example, *benzbromarone* lowered plasma concentrations of oxipurinol by about 40% when used with allopurinol, although plasma concentrations of allopurinol itself were not affected.<sup>1</sup> The interaction was not of concern, since the combination was more effective than allopurinol alone in lowering serum concentrations of uric acid. Licensed product information recommends reassessing the dosage of allopurinol on an individual basis when a uricosuric drug is added.

*Probenecid* has been reported to decrease the clearance of oral allopurinol riboside.<sup>2</sup> In a pharmacokinetic study in healthy subjects,<sup>3</sup> giving allopurinol and *probenecid* together significantly reduced oxipurinol concentrations; however, this combination had a greater hypouricaemic effect than either drug given alone.

- Müller FO, et al. The effect of benzbromarone on allopurinol/oxipurinol kinetics in patients with gout. *Eur J Clin Pharmacol* 1993; **44**: 69–72.
- Were JBO, Shapiro TA. Effects of *probenecid* on the pharmacokinetics of allopurinol riboside. *Antimicrob Agents Chemother* 1993; **37**: 1193–6.
- Stocker SL, et al. Pharmacokinetic and pharmacodynamic interaction between allopurinol and *probenecid* in healthy subjects. *Clin Pharmacokinet* 2008; **47**: 111–18.

**Antineoplastics.** Allopurinol inhibits the metabolism of *mercaptopurine* and marked dosage reduction of this drug to one-quarter to one-third of the usual dose is required if it is used with allopurinol. There are also reports of interactions between allopurinol and other antineoplastics. Mild chronic allopurinol-induced hepatotoxicity has been reported in a male patient to have been exacerbated by *tamoxifen*.<sup>1</sup> Hypersensitivity vasculitis resulting in the death of a patient receiving allopurinol and *pentostatin* has been described. Although it could not be ascertained whether this effect was due to one of the drugs alone or to an interaction it was believed that this combination should not be used.<sup>2</sup>

For a report of an increased incidence of bone-marrow toxicity in patients given allopurinol with *cyclophosphamide*, see p.769.

- Shah KA, et al. Allopurinol hepatotoxicity potentiated by *tamoxifen*. *N Y State J Med* 1982; **82**: 1745–6.
- Steinmetz JC, et al. Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; **86**: 499.

**Antivirals.** For the effect of allopurinol on *didanosine*, see p.961.

**Immunosuppressants.** Allopurinol inhibits the metabolism of mercaptopurine, the metabolite of *azathioprine*, and marked dosage reduction of azathioprine to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Similar caution is also required with mercaptopurine itself (see Antineoplastics, above). The effects of allopurinol on *ciclosporin* concentrations (a marked increase) are reported on p.1985.

**Xanthines.** For the effect of allopurinol on the pharmacokinetics of *caffeine* and *theophylline*, see p.1230 and p.1259 respectively.

## Pharmacokinetics

Up to 90% of an oral dose of allopurinol is rapidly absorbed from the gastrointestinal tract; its plasma half-life is about 1 to 2 hours. Allopurinol's major metabolite is oxipurinol (alloxanthine), which is also an inhibitor of xanthine oxidase with a plasma half-life of about 15 or more hours in patients with normal renal function, although this is greatly prolonged by renal impairment. Both allopurinol and oxipurinol are conjugated to form their respective ribonucleosides. Allopurinol and oxipurinol are not bound to plasma proteins.

Excretion is mainly through the kidney, but it is slow since oxipurinol undergoes tubular reabsorption. About 70% of a daily dose may be excreted in the urine as oxipurinol and up to 10% as allopurinol; prolonged use may alter these proportions, as allopurinol inhibits its own metabolism. The remainder of the dose is excreted in the faeces. Allopurinol and oxipurinol have also been detected in breast milk.

#### References.

- Murrell GAC, Rapeport WG. Clinical pharmacokinetics of allopurinol. *Clin Pharmacokinet* 1986; **11**: 343–53.
- Turnheim K, et al. Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects. *Br J Clin Pharmacol* 1999; **48**: 501–9.
- Day RO, et al. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxipurinol. *Clin Pharmacokinet* 2007; **46**: 623–44.

### Uses and Administration

Allopurinol is used to treat hyperuricaemia (p.600) associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme disorders, or cancer and its treatment (see Tumour Lysis Syndrome, p.695). It is not used for asymptomatic hyperuricaemia. Allopurinol is also used in the management of renal calculi caused by the deposition of calcium oxalate (in the presence of hyperuricosuria) and of 2,8-dihydroxyadenine (see Renal Calculi, below). It may have the potential to reduce oxidative stress by blocking the production of free radicals and is an ingredient of kidney preservation solutions. In addition allopurinol has antiprotozoal activity and has been used in leishmaniasis and American trypanosomiasis.

Allopurinol is used in **gout and hyperuricaemia** to inhibit the enzyme xanthine oxidase, thus preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. The urinary purine load, normally almost entirely uric acid, is thereby divided between hypoxanthine, xanthine, and uric acid, each with its independent solubility. This results in the reduction of urate and uric acid concentrations in plasma and urine, ideally to such an extent that deposits of monosodium urate monohydrate or uric acid are dissolved or prevented from forming. At low concentrations allopurinol acts as a competitive inhibitor of xanthine oxidase and at higher concentrations as a non-competitive inhibitor. However, most of its activity is due to the metabolite oxipurinol which is a non-competitive inhibitor of xanthine oxidase.

Allopurinol is used in **chronic gout** to correct hyperuricaemia, reduce the likelihood of acute attacks, and prevent the sequelae of chronic gout. Initially, it may increase plasma-concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, so allopurinol should not be started until an acute attack has completely subsided, and treatment should be started with a low dose and increased gradually; an NSAID (but not aspirin or salicylates) or colchicine should also be given for at least 1 month after hyperuricaemia is corrected. It may take several months to deplete the uric acid level sufficiently to control acute attacks.

A suggested oral starting dose of allopurinol is 100 mg daily, gradually increased by 100 mg for example at weekly intervals until the concentration of urate in plasma is reduced to 0.36 mmol/litre (6 mg per 100 mL) or less. A daily dose range of 100 to 300 mg may be adequate for those with mild gout and up to 600 mg for those with moderately severe tophaceous gout. The maximum recommended daily dose is 800 mg in the USA and 900 mg in the UK. Up to 300 mg may be taken as a single daily dose; larger amounts should be taken in divided doses to reduce the risk of gastric irritation. Taking allopurinol after food will also minimise gastric irritation. Patients should maintain an adequate fluid intake to prevent renal xanthine deposition.

Doses of allopurinol should be reduced in patients with renal impairment (see below)

When used for the **prevention of uric acid nephropathy associated with cancer therapy** 600 to 800 mg may be given daily, generally for 2 or 3 days before starting the cancer treatment. A high fluid intake is essential. Maintenance doses of allopurinol in patients with hyperuricaemia secondary to cancer or cancer chemotherapy are similar to those used in gout and are given according to the response.

Allopurinol sodium has been given by intravenous infusion in sodium chloride 0.9% or glucose 5% to patients (usually cancer patients) unable to take allopurinol orally. The recommended dose in adults is the equivalent of allopurinol 200 to 400 mg/m<sup>2</sup> daily up to a maximum of 600 mg daily. Allopurinol sodium 116.2 mg is equivalent to about 100 mg of allopurinol.

The oral dose of allopurinol recommended for the management of recurrent calcium oxalate **renal calculi** in patients with hyperuricosuria is 200 to 300 mg daily, adjusted on the basis of subsequent 24-hour urinary urate excretion.

For doses in children, see Administration in Children, below.

**Administration in children.** The main use of allopurinol in children is for hyperuricaemia associated with cancer or cancer chemotherapy or with enzyme disorders. The dosage used may vary: in the UK an oral dose of 10 to 20 mg/kg daily, up to a maximum of 400 mg daily, is recommended for children under 15 years of age, while in the USA the dose is 150 mg daily for children under 6 years of age and 300 mg daily for those aged 6 to 10 years, adjusted if necessary after 48 hours.

**Administration in hepatic impairment.** UK licensed product information recommends that reduced oral doses of allopurinol be used in patients with hepatic impairment, and that liver function should be periodically monitored in the early stages of therapy.

**Administration in renal impairment.** Excretion of allopurinol and its active metabolite oxipurinol is primarily via the kidneys and therefore the dosage should be reduced in renal impairment according to creatinine clearance (CC).

In the USA the following doses are suggested for oral and intravenous use:

- CC 10 to 20 mL/minute: 200 mg daily
- CC less than 10 mL/minute: no more than 100 mg daily
- CC less than 3 mL/minute: consider also a longer dosage interval

In the UK a maximum initial oral daily dosage of 100 mg is recommended for those with renal impairment, increased only if the response is inadequate. Doses less than 100 mg daily or 100 mg at intervals longer than 1 day are recommended for those with severe renal insufficiency. Because of the imprecision of low creatinine clearance values, it is suggested that, if facilities are available for monitoring, the allopurinol dose should be adjusted to maintain plasma-oxipurinol concentrations below 100 micromoles/litre (15.2 micrograms/mL). A suggested alternative dose for patients requiring dialysis two or three times weekly is 300 to 400 mg allopurinol immediately after dialysis only.

The difficulties of maintaining an appropriate dose in such patients were illustrated by a study<sup>1</sup> in New Zealand involving 227 allopurinol-treated patients. The guidelines used suggested maintenance doses based on CC as follows:

- less than 10 mL/minute: 100 mg every 3 days
- 10 mL/minute: 100 mg every 2 days
- 20 mL/minute: 100 mg daily
- 40 mL/minute: 150 mg daily
- 60 mL/minute: 200 mg daily

The recommended dose or less was used in the majority of cases (183 of 227). However, of 214 patients for whom serum-uric acid concentrations were available, only 48 achieved values of 0.36 mmol/litre or less. The proportion of patients achieving acceptable serum-uric acid concentrations was higher (38%) in patients given higher than recommended doses than in those on doses recommended by the guidelines (19%). Although guidelines might be useful for initial dosing, longer term use could lead to inadequate control of hyperuricaemia.

- Dalbeth N, et al. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; **33**: 1646–50.

**Angina pectoris.** Allopurinol has been investigated for its apparent anti-ischaemic effects in angina (p.1273). A randomised study<sup>1</sup> in 60 subjects with chronic stable angina found that high-dose allopurinol significantly improved exercise tolerance compared with placebo. A proposed mechanism was enhanced myocardial oxygen and ATP balance, possibly supplemented by im-

proved coronary blood flow and reduced left ventricular afterload.

- Noman A, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo-controlled crossover trial. *Lancet* 2010; **375**: 2161–7.

**Bipolar disorder.** A double-blind study was conducted in 141 adults with bipolar disorder (p.402), diagnosed as being acutely manic with or without psychotic features. Patients received lithium and were randomised to either oral allopurinol 600 mg daily, oral dipyrindamole, or placebo. Improvements in mania were significant for those randomised to allopurinol, and were associated with decreasing uric acid concentrations, suggesting a role for purinergic system dysfunction in mania.<sup>1</sup>

- Machado-Vieira R, et al. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyrindamole adjunctive to lithium in acute bipolar mania. *J Clin Psychiatry* 2008; **69**: 1237–45.

**Diagnosis and testing.** Deficiency of the enzyme ornithine carbamoyltransferase can result in severe CNS dysfunction or even in death, and identification of women at risk of being carriers of this genetic enzyme deficiency has been described.<sup>1</sup> The enzyme deficiency causes carbamoyl phosphate to accumulate, which stimulates the synthesis of orotidine. The test relies on giving a single dose of allopurinol, which will, in carriers, greatly increase the urinary excretion of orotidine. However, mutation analysis is now more usually used to establish the diagnosis.

- Hauser ER, et al. Allopurinol-induced orotidinuria. *N Engl J Med* 1990; **322**: 1641–5. Correction. *ibid.* 1997; **336**: 1335.

**Duchenne muscular dystrophy.** Controlled studies of the use of allopurinol in an attempt to increase muscle ATP in Duchenne muscular dystrophy (p.1646) failed to show any benefit from treatment.<sup>1,3</sup>

- Stern LM, et al. The progression of Duchenne muscular dystrophy: clinical trial of allopurinol therapy. *Neurology* 1981; **31**: 422–6.
- Hunter JR, et al. Effects of allopurinol in Duchenne's muscular dystrophy. *Arch Neurol* 1983; **40**: 294–9.
- Bertolini TE, et al. Chronic allopurinol and adenine therapy in Duchenne muscular dystrophy: effects on muscle function, nucleotide degradation, and muscle ATP and ADP content. *Neurology* 1985; **35**: 61–5.

**Epilepsy.** Reduction in the frequency of seizures has been described in some patients with severe or intractable epilepsy (p.507) when allopurinol was added to their existing antiepileptic therapy.<sup>1–4</sup> Although the mode of action was not known it was noted that the patients were not hyperuricaemic and that allopurinol did not affect plasma concentrations of existing antiepileptics.<sup>1</sup> However, others<sup>5</sup> have seen no benefit.

- DeMarco P, Zagnoni P. Allopurinol and severe epilepsy. *Neurology* 1986; **36**: 1538–9.
- Tada H, et al. Clinical effects of allopurinol on intractable epilepsy. *Epilepsia* 1991; **32**: 279–83.
- Zagnoni PG, et al. Allopurinol as an add-on therapy in refractory epilepsy—a double-blind placebo-controlled randomised study. *Epilepsia* 1994; **35**: 107–12.
- Togha M, et al. Allopurinol as adjunctive therapy in intractable epilepsy: a double-blind and placebo-controlled trial. *Arch Med Res* 2007; **38**: 313–16.
- Coppola G, Pascoato A. Double-blind, placebo-controlled, crossover trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* 1996; **18**: 50–2.

**Hypertension.** Hypertension (p.1290) may be associated with hyperuricaemia. Thirty adolescents with mild hypertension and a serum uric acid concentration of 6 mg per 100 mL or more, and not on any antihypertensive therapy, were randomised to oral allopurinol 200 mg twice daily or placebo for 4 weeks in a double-blind, crossover study. Allopurinol treatment was associated with a significant decrease in systolic and diastolic blood pressure.<sup>1</sup>

- Feig DL, et al. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 2008; **300**: 924–32.

**Organ and tissue transplantation.** Allopurinol 25 mg on alternate days has been added to the immunosuppressive treatment for renal transplantation,<sup>1</sup> and is reported to reduce the frequency of acute rejection. One possible explanation for this effect is allopurinol's ability to suppress the production of free radicals (see Oxidative Stress, below). Organ and tissue transplantation, and the more usual drugs used in immunosuppressive regimens are discussed on p.1968. It should be noted that allopurinol interacts with azathioprine (see Immunosuppressants, under Interactions, above) and ciclosporin (p.1985).

- Chocair P, et al. Low-dose allopurinol plus azathioprine/ciclosporin/prednisolone, a novel immunosuppressive regimen. *Lancet* 1993; **342**: 83–4.

**Oxidative stress.** Allopurinol, through its inhibition of xanthine oxidase, can block the development of superoxide free radicals during reperfusion after an ischaemic episode. Consequently, the ability of allopurinol to reduce oxidative stress has been investigated in a number of clinical situations.

In a small study<sup>1</sup> of patients with idiopathic dilated cardiomyopathy, short-term intracoronary allopurinol improved myocardial efficiency by decreasing the oxygen demand of left ventricular contraction.

In patients undergoing coronary artery bypass graft surgery, perioperative allopurinol reduced hospital mortality, the incidence of arrhythmias, the number of ischaemic events, and the need for

inotropic support, although the findings were not consistent in all studies.<sup>2</sup>

Improved endothelial dysfunction has been found in patients with chronic heart failure given allopurinol.<sup>3,4</sup>

A large study<sup>5</sup> in neonates undergoing cardiac surgery found that allopurinol caused a reduction in seizures and cardiac events in those with hypoplastic left heart syndrome. No benefit was found in neonates with less severe forms of congenital heart disease, considered to be at lower risk of adverse surgical outcome or reperfusion injury. Allopurinol also failed to reduce the incidence of periventricular leucomalacia (thought to represent ischaemic infarction of the developing brain) in preterm infants compared with placebo in a large study.<sup>6</sup> Similarly, allopurinol did not reduce the incidence of infarct extension in patients with acute myocardial infarction.<sup>7</sup>

The possibility that allopurinol limits the production of free radicals has also led to allopurinol sodium being included as an ingredient of the University of Wisconsin solution [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)], which is used for the preservation of organs for transplantation.<sup>8</sup>

A pilot study using allopurinol showed a beneficial effect on free radical formation, cerebral blood volume, and electrical brain activity in severely asphyxiated newborns.<sup>9</sup> However, a systematic review<sup>10</sup> of this and 2 other studies in such infants was unable to determine whether allopurinol produced clinically important benefits.

For evidence that allopurinol may be of value in angina pectoris see above.

1. Cappola TP, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 2001; **104**: 2407–11.
2. Weimert NA, et al. Allopurinol as a cardioprotectant during coronary artery bypass graft surgery. *Ann Pharmacother* 2003; **37**: 1708–11.
3. Doehner W, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricaemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; **105**: 2619–24.
4. Farquharson CAJ, et al. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; **106**: 221–6.
5. Clancy RR, et al. Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. *Pediatrics* 2001; **108**: 61–70.
6. Russell GAB, Cooke RWI. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **73**: F27–F31.
7. Parmley LF, et al. Allopurinol therapy of ischemic heart disease with infarct extension. *Can J Cardiol* 1992; **8**: 280–6.
8. Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995; **46**: 235–47.
9. Van Bel F, et al. Effect of allopurinol on postasphyxial free radical formation, cerebral haemodynamics, and electrical brain activity. *Pediatrics* 1998; **101**: 185–93.
10. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 14/07/08).

**Prostatitis.** Although allopurinol has been reported to be of benefit<sup>1</sup> in a small study in patients with chronic prostatitis (p.2382), a systematic review<sup>2</sup> found no other satisfactory evidence of benefit, and considered that the clinical relevance of the original study results was unclear.

1. Persson BE, et al. Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. *J Urol (Baltimore)* 1996; **155**: 961–4.
2. McNaughton Collins M, Wilt T. Allopurinol for chronic prostatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 18/05/06).

**Protozoal infections.** Allopurinol has been widely used as an adjunct to pentavalent antimonials in the treatment<sup>1,2</sup> of Old World visceral leishmaniasis (p.909), particularly where resistance to antimony alone is likely, although the degree of benefit has been called into question.<sup>3</sup> It has also been used with other drugs such as pentamidine<sup>4</sup> or azole antifungals,<sup>5–8</sup> including in transplant patients<sup>7</sup> or those with AIDS,<sup>5</sup> or in whom antimonials were otherwise poorly tolerated.<sup>8</sup> Allopurinol has also been tried alone<sup>9,10</sup> or with other drugs in both Old World<sup>11–13</sup> and New World<sup>14–16</sup> cutaneous or mucocutaneous leishmaniasis; results, particularly in the latter, have been variable. Allopurinol is usually given in oral doses of 15 to 20 mg/kg daily in 3 divided doses for leishmaniasis, and treatment lasts about 30 days.<sup>3,4,11,12</sup>

Beneficial results have been noted in some<sup>17–20</sup> but not all<sup>21</sup> studies using allopurinol in indeterminate and chronic Chagas' disease (*American trypanosomiasis*, p.913). It may be less effective and have more adverse effects than itraconazole. Allopurinol 8.5 mg/kg daily is typically given orally for about 60 days;<sup>17,19,20</sup> higher doses (900 mg daily) were ineffective for chronic disease.<sup>21</sup>

The selective antiparasitic action of allopurinol is believed to be due to its incorporation into the protozoal, but not the mammalian, purine salvage pathway. This leads to the formation of 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analogue of adenosine triphosphate, that is incorporated into ribonucleic acid. This action of allopurinol is shared by allopurinol riboside, one of the minor metabolites in man, but not by oxipurinol, the major human metabolite. Thus, some studies have been conducted with allopurinol riboside, rather than allopurinol,

in an attempt to enhance activity by avoiding host-mediated inactivation.<sup>22</sup>

1. di Martino L, et al. Low dosage combination of meglumine antimoniate plus allopurinol as first choice treatment of infantile visceral leishmaniasis in Italy. *Trans R Soc Trop Med Hyg* 1990; **84**: 534–5.
2. Gradoni L, et al. Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; **73**: 191–7.
3. Singh NKP, et al. Combination therapy in kala-azar. *J Assoc Physicians India* 1995; **43**: 319–20.
4. Das VNR, et al. A randomized clinical trial of low dosage combination of pentamidine and allopurinol in the treatment of antimony unresponsive cases of visceral leishmaniasis. *J Assoc Physicians India* 2001; **49**: 609–13.
5. Raffi F, et al. Use of an itraconazole/allopurinol combination for the treatment of visceral leishmaniasis in a patient with AIDS. *Clin Infect Dis* 1995; **21**: 1338–9.
6. Torrus D, et al. Fluconazole plus allopurinol in treatment of visceral leishmaniasis. *J Antimicrob Chemother* 1996; **37**: 1042–3.
7. Hueso M, et al. The renal transplant patient with visceral leishmaniasis who could not tolerate meglumine antimoniate-cure with ketoconazole and allopurinol. *Nephrol Dial Transplant* 1999; **14**: 2941–3.
8. Kuyucu N, et al. Successful treatment of visceral leishmaniasis with allopurinol plus ketoconazole in an infant who developed pancreatitis caused by meglumine antimoniate. *Pediatr Infect Dis J* 2001; **20**: 455–7.
9. Halbert AR, et al. Allopurinol for Old World cutaneous leishmaniasis. *Pediatr Dermatol* 1995; **12**: 287–8.
10. D'Oliveira A, et al. Evaluating the efficacy of allopurinol for the treatment of cutaneous leishmaniasis. *Int J Dermatol* 1997; **36**: 938–40.
11. Efsandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Gluantime) in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2002; **41**: 521–4.
12. Momeni AZ, Aminjavaheri M. Successful treatment of non-healing cases of cutaneous leishmaniasis, using a combination of meglumine antimoniate plus allopurinol. *Eur J Dermatol* 2003; **13**: 40–3.
13. Efsandiarpour I, Dabiri SH. Treatment of cutaneous leishmaniasis recidivans with a combination of allopurinol and meglumine antimoniate: a clinical and histologic study. *Int J Dermatol* 2007; **46**: 848–52.
14. Velez I, et al. Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Ann Intern Med* 1997; **126**: 232–6.
15. Martinez S, et al. Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis* 1997; **24**: 165–9.
16. Llanos-Cuentas A, et al. Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. *Clin Infect Dis* 1997; **25**: 677–84.
17. Apt W, et al. Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; **59**: 133–8.
18. Amato Neto V. Etiological treatment for infection by *Trypanosoma cruzi*. *Rev Inst Med Trop Sao Paulo* 1999; **41**: 211–3.
19. Apt W, et al. Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; **97**: 23–9.
20. Apt W, et al. Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the results of clinical and parasitological examinations 11 years post-treatment. *Ann Trop Med Parasitol* 2005; **99**: 733–41.
21. Rassi A, et al. Specific treatment for *Trypanosoma cruzi*: lack of efficacy of allopurinol in the human chronic phase of Chagas disease. *Am J Trop Med Hyg* 2007; **76**: 58–61.
22. Shapiro TA, et al. Pharmacokinetics and metabolism of allopurinol riboside. *Clin Pharmacol Ther* 1991; **49**: 506–14.

**Renal calculi.** In conjunction with a reduced dietary purine intake, high fluid intake, and potassium citrate, allopurinol may be used to prevent the recurrence of calcium oxalate renal calculi (p.2383) in patients with hyperuricosuria.<sup>1,2</sup> Allopurinol is also advocated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with deficient activity of the enzyme adenine phosphoribosyltransferase.

1. Ettlinger B, et al. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986; **315**: 1386–9.
2. Sorensen CM, Chandhoke PS. Hyperuricosuric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002; **31**: 915–25.

**Sarcoidosis.** Although corticosteroids remain the mainstay of drug therapy for sarcoidosis (p.1650), and other drugs are very much second line, there are reports<sup>1–3</sup> of benefit in cutaneous disease from the use of allopurinol.

1. Brechtel B, et al. Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol* 1996; **135**: 307–9.
2. Antony F, Layton AM. A case of cutaneous acral sarcoidosis with response to allopurinol. *Br J Dermatol* 2000; **142**: 1052–3.
3. Bregnohej A, Jemec GB. Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. *J Dermatol Treat* 2005; **16**: 125–7.

**Schizophrenia.** Involvement of purinergic neurotransmission has been hypothesised to play some role in schizophrenia (p.1058), and allopurinol has been investigated as a possible adjunctive treatment, with some evidence of benefit, especially in patients with refractory positive symptoms.<sup>1</sup>

1. Buie LW, et al. Allopurinol as adjuvant therapy in poorly responsive or treatment refractory schizophrenia. *Ann Pharmacother* 2006; **40**: 2200–4.

**Skin disorders.** Reactive perforating collagenosis (RPC) is a condition in which altered collagen is eliminated through the epidermis; it may be inherited or acquired. In 3 of 4 patients with RPC refractory to antibacterials and oral and topical corticosteroids, significant improvement was seen with allopurinol, in

terms of reduction of new lesions, improvement of existing lesions, and reduction of pruritus. The fourth patient died from unrelated causes before review.<sup>1</sup>

1. Hoque SR, et al. Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. *Br J Dermatol* 2006; **154**: 759–62.

## Preparations

**BP 2010:** Allopurinol Oral Suspension; Allopurinol Tablets; **USP 33:** Allopurinol Oral Suspension; Allopurinol Tablets.

**Proprietary Preparations (details are given in Volume B)**

**Arg:** Alfidaman; Puntek; **Austral:** Allohexal†; Allogis; Capurate†; Progot; Zylorim; **Austria:** Allostad; Gewapuro; Gichtex; Purinol; Urosin; Zyloric; **Belg:** Alpuric; Docallo†; Zyloric; **Braz:** Labopurinol†; Lopurax; Uricemil†; Zilopor; Zyloric; **Canad:** Allopurinol; Novo-Puro†; Zylorim; **Chile:** Talol; Urogotan A; Zyloric; **Cz:** Apuro†; Milurit; Purinol; **Denm:** Abopur†; Apurinj†; Hexanurat; **Fin:** Allopurinol; **France:** Arturic; Zyloric; **Ger:** Allo; Allo-Efeka†; Allo-Parent†; Allobeta; Bleminol; Cellidrin; dura AL†; Epidrolap; Foligan; Janapurinol†; Milurit†; Remid; Uribenz; Zyloric; **Gr:** Arsol; Gealgica; Petrazyc; Purigan; Soluric; Stradumel; Zylaporic; Zyloric; **Hong Kong:** Allopurinol; Amol; Marinol; Milurit; Progot; Purinol; Synpurinol; Zyloric†; **Hung:** Harpaginj†; Milurit; **India:** Ciploric; Zyloric; **Indon:** Algut†; Aluric; Benoxuric; Hycemia†; Isoric; Licoric; Llanof†; Nilapur; Ponuric; Purinol; Puricemia; Reucid; Rinolic; Sinoric; Tylonic; Unica; Unicol†; Xanturic; Zyloric; **Irl:** Allopurinol; Purinol; Tipuric; **Israel:** Alloril; Zylor†; Zyloric†; **Ital:** Allurit; Zyloric; **Malaysia:** Zyloric; **Mex:** Acyprin; Altoprin; Apo-Tinol†; Atsunil; Biolon; Darzune; Etindrax; Unizuric; Zylorim; **Neth:** Apurin†; Zyloric; **Norw:** Allopurinol; Arturic†; Zyloric; **NZ:** Allohexal†; Aloron; Progot; **Philipp:** AL; Allocor; Allurase; Alpurase; Elavil; Llanol; Lopnic; Lorigid; Priton; Purinase; Purisep; Puristin; Synol; Trianol; Uninol; Xanurace; Zylorim; **Pol:** Allupol; Milurit; Zyloric; **Port:** Allosarf†; Uniprim; Zurin; **Rus:** Purinol (Пуринол); **S.Afr:** Lonol; Puricos; Redurate†; Urinol†; Zylorim; **Singapore:** Progot; Zyloric; **Spain:** Zyloric; **Swed:** Zyloric; **Switz:** allo-basan†; Allopurinol; Cellidrin; Mephanol; Sigapurol N†; Uricomone; Zyloric; **Thai:** Alinol; Allo; Aloron; Allopin; Alloric; Apinol; Apuro†; Chimol; Medoric†; Puricinj†; Puridic; Uricad; Valeric†; Xandase; Xanol; Zylic; Zyloric; **Turk:** Allo-Unik Allogut; Unkoliz; UKC; Capelan; Cosuric; Rimapurinol; Zyloric; **Ukr:** Allohexal (Аллохексал); **USA:** Allopurinol; Zyloric; **Venez:** Aluprol†; Aluron; Zyloric.

**Multi-ingredient:** **Arg:** Artrex; Calpuril; Xuric-A; **Austria:** Allobenz; Duovitan†; Gichtex plus; **Belg:** Comburic†; **Ger:** Allocomp; Harpaginj†; **Ital:** Uricodue†; **Philipp:** Allomaron; **S.Afr:** Allomaron†; **Thai:** Allomaron†.

## Benzbromarone (BAN, USAN, rINN)

Benzbromarone; Bentsbromaroni; Benzbromaron; Benzbromarona; Benzbromaronas; Benzbromaronum; L-2214; MJ-10061. 3,5-Dibromo-4-hydroxyphenyl 2-ethylbenzofuran-3-yl ketone.

Бензбромарон

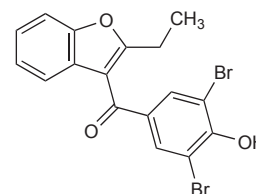
C<sub>17</sub>H<sub>12</sub>Br<sub>2</sub>O<sub>3</sub> = 424.1.

CAS — 3562-84-3.

ATC — M04AB03.

ATC Vet — QM04AB03.

UNII — 4POG0RL690.



**Pharmacopoeias.** In *Eur*: (see p.vii) and *Jpm*.

**Ph. Eur. 6.8** (Benzbromarone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Product from light.

## Adverse Effects

Benzbromarone may cause gastrointestinal adverse effects, especially diarrhoea. It may precipitate an acute attack of gout and cause uric acid renal calculi and renal colic. Hepatotoxicity, sometimes fatal, has been reported and monitoring of liver function has been recommended.

**Effects on the liver.** Benzbromarone-induced liver damage, sometimes fatal, has been reported.<sup>1,4</sup>

1. Van Der Klauw MM, et al. Hepatic injury caused by benzbromarone. *J Hepatol* 1994; **20**: 376–9.
2. Anonymous. Benzbromarone and hepatitis. *WHO Drug Inf* 2000; **14**: 29.
3. Wagayama H, et al. Fatal fulminant hepatic failure associated with benzbromarone. *J Hepatol* 2000; **32**: 874.
4. Arai M, et al. Fulminant hepatic failure associated with benzbromarone treatment: a case report. *J Gastroenterol Hepatol* 2002; **17**: 625–6.

**Effects on the lungs.** Benzbromarone has been associated with the development of drug-induced eosinophilic pneumonia and pulmonary alveolar haemorrhage.<sup>1</sup> Symptoms resolved on stopping the drug and treatment with corticosteroids.

1. Hara A, et al. Drug-induced eosinophilic pneumonia with pulmonary alveolar haemorrhage caused by benzbromarone. *Intern Med* 2010; **49**: 435–8.

## Precautions

Benzbromarone should be avoided in patients with moderate or severe renal impairment, in those with uric acid renal calculi, and in those with urinary uric acid excretion rates of greater than

700 mg per 24 hours. Like other uricosurics, treatment with benzbromarone should not be started during an acute attack of gout. Similarly, an adequate fluid intake should be maintained to reduce the risk of uric acid renal calculi; additionally, alkalisation of the urine may be considered.

**Porphyria.** Benzbromarone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

#### Interactions

Aspirin and other salicylates antagonise the effect of benzbromarone. Benzbromarone may increase the anticoagulant activity of coumarin oral anticoagulants (see under Interactions of Warfarin, p.1567).

**Antigout drugs.** For mention of the effects of benzbromarone on the clearance of oxipurinol, the major active metabolite of *allopurinol*, and the view that this was not clinically significant, see under Interactions of Allopurinol, p.601.

#### Pharmacokinetics

Benzbromarone is only partially absorbed from the gastrointestinal tract, reaching peak plasma concentrations about 2 to 4 hours after an oral dose. Benzbromarone is extensively bound to plasma proteins. It is metabolised in the liver, and is excreted mainly in the faeces; a small amount appears in the urine.

#### References

- Maurer H, Wollenberg P. Urinary metabolites of benzbromarone in man. *Arzneimittelforschung* 1990; **40**: 460–2.
- Walter-Sack I, et al. Variation of benzbromarone elimination in man—a population study. *Eur J Clin Pharmacol* 1990; **39**: 173–6.

#### Uses and Administration

Benzbromarone is a uricosuric drug that reduces plasma concentrations of uric acid by blocking renal tubular reabsorption. It has been suggested that benzbromarone may also increase the intestinal elimination of uric acid. It has been used to treat hyperuricaemia including that associated with chronic gout (p.600) although it has been withdrawn in many countries due to reports of hepatotoxicity.

Benzbromarone is not used to treat acute attacks of gout and may exacerbate and prolong them if given during an attack; treatment should not start therefore until an acute attack has subsided.

The usual oral dose has been 50 to 200 mg daily. An NSAID or colchicine should be given initially to reduce the risk of precipitating acute gout. An adequate fluid intake should be maintained. Lower doses of benzbromarone (20 mg) have also been used in the form of a combination product with allopurinol.

#### References

- Hanvivadhanakul P, et al. Efficacy of benzbromarone compared to allopurinol in lowering serum uric acid level in hyperuricemic patients. *J Med Assoc Thai* 2002; **85** (suppl 1): S40–S47.
- Kumar S, et al. Benzbromarone therapy in management of refractory gout. *N Z Med J* 2005; **118**: U1528.
- Lee M-HH, et al. A benefit-risk assessment of benzbromarone in the treatment of gout. Was it withdrawn from the market in the best interest of patients? *Drug Safety* 2008; **31**: 643–65.
- Reinders MK, et al. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis* 2009; **68**: 51–6.

#### Preparations

**Proprietary Preparations** (details are given in Volume B)

**Austria:** Uricovac†; **Braz.:** Narcarcina†; **Hung.:** Harpagin†; **Jpn.:** Urinorm; **Neth.:** Desuric; **Spain:** Urinorm; **Thai.:** Benarone; Narcarcin†.

**Multi-ingredient:** **Austria:** Allobenz Duovitan†; Gichtex plus; **Belg.:** Combun†; **Ger.:** Allocomp; Harpagin†; **Philipp.:** Allomaron; **S.Afr.:** Allomaron†; **Thai.:** Allomaron†.

#### Benziodarone (BAN, rINN)

Benziodarona; Bentsiodaroni; Benziodaron; Benziodaronum; L-2329. 2-Ethylbenzofuran-3-yl 4-hydroxy-3,5-di-iodophenyl ketone.

Бензйодарон

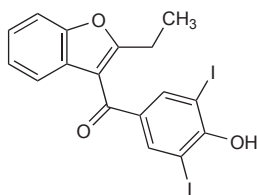
$C_{17}H_{12}O_3 = 518.1$ .

CAS — 68-90-6.

ATC — C01DX04.

ATC Vet — QC01DX04.

UNII — 75CL65GTYR.



#### Profile

Benziodarone is a uricosuric drug structurally related to benzbromarone (see above) that has been given orally to reduce hyperuricaemia in chronic gout.

All cross-references refer to entries in Volume A

Benziodarone has been associated with jaundice and thyroid disorders.

#### Preparations

**Proprietary Preparations** (details are given in Volume B)

**Multi-ingredient:** **Ital.:** Uricodue†.

## Colchicine

Colchicina; Colchicinum; Kolchicin; Kolchicinas; Kolkicin; Kolkisiini; Kolşisin. (S)-N-(5,6,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[ $\alpha$ ]heptalen-7-yl)acetamide.

КОЛХИЦИН

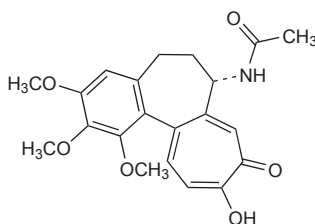
$C_{22}H_{25}NO_6 = 399.4$ .

CAS — 64-86-8.

ATC — M04AC01.

ATC Vet — QM04AC01.

UNII — SML2Y3J35T.



**Description.** Colchicine is an alkaloid obtained from various *Colchicum* spp.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.* and *US*. *Chin.* also has a monograph for colchicine amide.

**Ph. Eur. 6.8** (Colchicine). A yellowish-white amorphous or crystalline powder. Very soluble in water, rapidly recrystallising from concentrated solutions as the sesquihydrate; freely soluble in alcohol and in chloroform. Protect from light.

**USP 33** (Colchicine). An alkaloid obtained from various *Colchicum* spp. and other genera. Pale yellow to pale greenish-yellow amorphous scales, or powder or crystalline powder. Is odourless or nearly so, and darkens on exposure to light. Soluble 1 in 25 of water and 1 in 220 of ether; freely soluble in alcohol and in chloroform. Store in airtight containers. Protect from light.

#### Adverse Effects and Treatment

The most frequent adverse effects of oral colchicine are those involving the gastrointestinal tract and may be associated with its antimitotic action. Diarrhoea, nausea, vomiting, and abdominal pain are often the first signs of toxicity and are usually an indication that colchicine therapy should be stopped or the dose reduced. Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, skin rashes, and renal and hepatic damage.

Rarely, bone marrow depression with agranulocytosis, thrombocytopenia, and aplastic anaemia have occurred on prolonged treatment as have peripheral neuropathy, myopathy, rashes, disseminated intravascular coagulation, and alopecia. Fatal pancytopenia has been reported.

Adverse effects after intravenous use include cardiac arrhythmias and local reactions such as thrombophlebitis and neuritis. Extravasation may cause tissue necrosis.

Symptoms of acute **overdose** with oral colchicine often do not appear for up to 6 hours. The first signs of toxicity are nausea, vomiting, and diarrhoea; a burning sensation of the throat, stomach, and skin may also occur. The diarrhoea may be severe and haemorrhagic and, coupled with vascular damage or paralytic ileus can lead to dehydration, hypotension, and shock. Multiple organ failure may occur, manifest as CNS toxicity (confusion, delirium, sometimes coma), bone marrow depression, hepatocellular damage, muscle damage, neuropathy, respiratory distress, myocardial depression, and renal damage. A toxic epidermal necrolysis-like reaction has also been reported. Death may be due to respiratory depression, cardiovascular collapse, or sepsis after pancytopenia. In surviving patients, alopecia, rebound leucocytosis, and stomatitis may occur about 10 days after the acute overdose. The lethal dose

varies: 7 mg of colchicine has caused death, yet recovery has occurred after much larger doses.

When treating colchicine overdosage or acute poisoning patients should be carefully monitored for some time to take account of the delayed onset of symptoms. The stomach may be emptied by lavage in adults within 1 hour of acute poisoning; multiple dose activated charcoal should be given to adults and children who have ingested more than 300 micrograms/kg of colchicine provided vomiting has not started. Treatment is primarily symptomatic and supportive with attention being given to the control of respiration, maintenance of blood pressure and the circulation, and correction of fluid and electrolyte imbalance.

**Effects on the neuromuscular system.** Colchicine-induced myoneuropathy may be a common but unrecognised condition in patients with *reduced* renal function who receive usual doses of colchicine.<sup>1</sup> Although both skeletal muscles and peripheral nerves are affected, myopathy is most prominent and associated axonal neuropathy is mild. The condition usually presents with proximal muscle weakness and is always accompanied by elevations in serum creatine kinase concentrations. Withdrawal of colchicine leads to spontaneous remission of these symptoms within a few weeks but resolution of the polyneuropathy is slow. Examination of proximal muscles shows marked abnormal spontaneous activity and, because of the features of the condition, it is often initially misdiagnosed as probable polymyositis or uraemic myopathy. A literature review<sup>2</sup> identified renal impairment as the primary risk factor for the development of colchicine-induced myopathy; dosage adjustment is advised in these patients.

There have been reports suggesting colchicine-induced myopathy may develop in patients who have *normal* renal function.

A patient with normal renal function but chronic alcohol-induced liver disease developed an unusual form of myoneuropathy after receiving only a short course of colchicine. This patient was also taking tolbutamide, the microsomal enzyme-inhibiting activity of which may have exacerbated the toxicity of colchicine.<sup>3</sup> A teenager with familial Mediterranean fever who had normal renal and hepatic function developed toxic myopathy due to colchicine use. Myopathy improved after colchicine was stopped and recurred when it was restarted at a lower dose.<sup>4</sup>

Rhabdomyolysis has also been reported.<sup>5,6</sup>

- Kunel RW, et al. Colchicine myopathy and neuropathy. *N Engl J Med* 1987; **316**: 1562–8.
- Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy* 2004; **24**: 1784–92.
- Besana C, et al. Colchicine myoneuropathy. *Lancet* 1987; **ii**: 1271–2.
- Savarioglu M, et al. Colchicine-induced myopathy in a teenager with familial Mediterranean fever. *Ann Pharmacother* 2003; **37**: 1821–4.
- Chattopadhyay I, et al. Colchicine induced rhabdomyolysis. *Postgrad Med J* 2001; **77**: 191–2.
- Boomershine KH. Colchicine induced rhabdomyolysis. *Ann Pharmacother* 2002; **36**: 824–6.

**Effects on the reproductive system.** UK licensed product information states that colchicine may adversely affect spermatogenesis under certain conditions of therapy. *Animal* data have shown that colchicine in high doses may arrest spermatogenesis and lead to azoospermia. However, in clinical practice male infertility does not seem to be common in patients given colchicine, and may be related in some cases to the underlying disease rather than the drug.<sup>1</sup> Similarly, although colchicine is not recommended in the first trimester of pregnancy, it may improve fertility in women with familial Mediterranean fever, and results in women who have been taking colchicine at conception and during pregnancy have been relatively reassuring<sup>1</sup> (see also under Pregnancy, below).

- Mijatovic V, et al. Familial Mediterranean fever and its implications for fertility and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2003; **108**: 171–6.

**Inappropriate administration.** Intravenous use of colchicine is associated with a risk of severe or fatal adverse effects (see Administration, below). Although unlicensed either orally or parenterally for use in back pain, intravenous colchicine has apparently been used in alternative medicine for this indication. As of February 2008, the FDA had received reports of 50 adverse events, including 23 deaths, associated with the unapproved use of intravenous colchicine. Three of the reported deaths were associated with compounded colchicine that, due to preparation errors, was 8 times more potent than the amount stated on the label. Potentially fatal effects include neutropenia, thrombocytopenia, pancytopenia, acute renal failure, and congestive heart failure.<sup>1,2</sup>

- FDA. FDA takes action to stop the marketing of unapproved injectable drugs containing colchicine (issued 6th February 2008). Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01791.html> (accessed 21/04/08)
- FDA. Questions and answers about FDA's enforcement action against unapproved injectable colchicine products (issued 6th February 2008). Available at: [http://www.fda.gov/cder/drug/unapproved\\_drugs/colchicine\\_qa.htm](http://www.fda.gov/cder/drug/unapproved_drugs/colchicine_qa.htm) (accessed 21/04/08)

**Overdosage.** References.

- McIntyre IM, et al. Death following colchicine poisoning. *J Forensic Sci* 1994; **39**: 280–6.
- Hood RL. Colchicine poisoning. *J Emerg Med* 1994; **12**: 171–7.
- Baud FJ, et al. Brief report: treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Engl J Med* 1995; **332**: 642–5.
- Critchley JAJH, et al. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol* 1997; **16**: 229–32.
- Milne ST, Meek PD. Fatal colchicine overdose: report of a case and review of the literature. *Am J Emerg Med* 1998; **16**: 603–8.
- Kubler PA. Fatal colchicine toxicity. *Med J Aust* 2000; **172**: 498–9.
- Harris R, et al. Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *J Emerg Med* 2000; **18**: 435–40.
- Mullins ME, et al. Fatal cardiovascular collapse following acute colchicine ingestion. *J Toxicol Clin Toxicol* 2000; **38**: 51–4.
- Arroyo MP, et al. Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol* 2004; **150**: 581–8.
- Atas B, et al. Four children with colchicine poisoning. *Hum Exp Toxicol* 2004; **23**: 353–6.
- Miller MA, et al. Colchicine-related death presenting as an unknown case of multiple organ failure. *J Emerg Med* 2005; **28**: 445–8.
- Borras-Blasco J, et al. Acute renal failure associated with an accidental overdose of colchicine. *Int J Clin Pharmacol Ther* 2005; **43**: 480–4.

**Precautions**

Colchicine should be given with great care to elderly or debilitated patients who may be particularly susceptible to cumulative toxicity. It should also be used with caution in patients with cardiac, hepatic, renal, or gastrointestinal disease. Colchicine should be avoided in patients with blood disorders. It should also generally be avoided in pregnancy since it is known to be teratogenic in animals and there have also been some suggestions of a risk of fetal chromosome damage in humans.

Colchicine should not be given by subcutaneous or intramuscular injection as it causes severe local irritation.

**Breast feeding.** Colchicine is distributed into breast milk,<sup>1,3</sup> and some have recommended waiting for 8 hours<sup>2</sup> or 12 hours<sup>3</sup> after a dose before breast feeding to minimise exposure of the infant. However, since no adverse effects on the infant have been noted in these reports, the American Academy of Pediatrics considered its use to be usually compatible with breast feeding.<sup>4</sup>

- Milunsky JM, Milunsky A. Breast-feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr* 1991; **119**: 164.
- Guillonnet M, et al. Colchicine is excreted at high concentrations in human breast milk. *Eur J Obstet Gynecol Reprod Biol* 1995; **61**: 177–8.
- Ben-Chetrit E, et al. Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; **39**: 1213–17.
- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 26/05/04)

**Pregnancy.** Colchicine is contra-indicated in pregnancy because of animal teratogenicity. However, it has been used during pregnancy in women with familial Mediterranean fever (see under Uses, below). There was no increase in abnormality rate of the newborns and no problems were detected in 130 offspring.<sup>1</sup>

- Rabinovitch O, et al. Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. *Am J Reprod Immunol* 1992; **28**: 245–6.

**Interactions**

Colchicine is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these may increase colchicine blood concentrations and the potential for toxicity; life-threatening or fatal drug interactions have been reported when colchicine was given with clarithromycin, erythromycin, ciclosporin, or calcium channel antagonists such as verapamil and diltiazem. If treatment with a P-glycoprotein inhibitor or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the colchicine dose may need to be adjusted (see Uses and Administration, below). Such combinations should be avoided in patients with renal or hepatic impairment.

Cases of myopathy and rhabdomyolysis have been reported in patients taking colchicine with statins, fibrates, ciclosporin, or digoxin.

Thiazide diuretics may increase serum uric acid and interfere with the activity of colchicine. Colchicine may impair the absorption of vitamin B<sub>12</sub>.

**Cardiovascular drugs.** Muscle toxicity is a known adverse effect of both colchicine and statins, and there may be an increased risk if they are given together, particularly if renal function is impaired. Acute myopathy has been reported in patients with chronic renal impairment given colchicine with fluvastatin,<sup>1</sup> pravastatin,<sup>2</sup> or simvastatin,<sup>3,4</sup> while a patient<sup>5</sup> with nephrotic syndrome but normal renal function developed rhabdomyolysis when atorvastatin was added to long-standing colchicine therapy. Another patient with normal renal function developed myopathy when lovastatin was added to colchicine.<sup>6</sup> Since many statins are metabolised by the cytochrome P450 isoenzyme CYP3A4, as is colchicine, this has been proposed as one possible mechanism.<sup>1,2,6</sup> However, fluvastatin and pravastatin are cleared through different isoenzymes. Alternative proposed mechanisms are synergistic myopathy<sup>1,4</sup> or interference with transport mediated by P-glycoprotein.<sup>2,5</sup>

Tetraparesis developed in a patient who took colchicine with verapamil; this was considered to be due to a pharmacokinetic interaction which increased serum and CSF concentrations of colchicine.<sup>7</sup>

- Atasoy EM, et al. Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005; **39**: 1368–9.
- Alayli G, et al. Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005; **39**: 1358–61.
- Hsu W-C, et al. Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002; **25**: 266–8.
- Baker SK, et al. Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004; **30**: 799–802.
- Tufan A, et al. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. *Ann Pharmacother* 2006; **40**: 1466–9.
- Torgovnick J, et al. Colchicine and HMG Co-A reductase inhibitors induced myopathy—a case report. *Neurotoxicology* 2006; **27**: 1126–7.
- Tröger U, et al. Tetraparesis associated with colchicine is probably due to inhibition by verapamil of the P-glycoprotein efflux pump in the blood-brain barrier. *BMJ* 2005; **331**: 613. Correction. *ibid.* 2006; **332**: 882.

**Ciclosporin.** There is a need for caution if colchicine is used with ciclosporin. Myopathies or rhabdomyolysis<sup>1</sup> may be a problem, especially in transplant patients<sup>2</sup> or those with renal impairment.<sup>3</sup> In addition, increased blood-ciclosporin concentrations and nephrotoxicity developed in a renal transplant patient after the introduction of colchicine therapy.<sup>4</sup>

- Arellano F, Krupp P. Muscular disorders associated with ciclosporin. *Lancet* 1991; **337**: 915.
- Simkin PA, Gardner GC. Colchicine use in ciclosporin treated transplant recipients: how little is too much? *J Rheumatol* 2000; **27**: 1334–7.
- Rumpf KW, Henning HV. Is myopathy in renal transplant patients induced by ciclosporin or colchicine? *Lancet* 1990; **335**: 800–1.
- Menta R, et al. Reversible acute ciclosporin nephrotoxicity induced by colchicine administration. *Nephrol Dial Transplant* 1987; **2**: 380–1.

**Grapefruit juice.** Near-fatal colchicine toxicity occurred in an 8-year-old girl with familial Mediterranean fever who was also drinking large quantities of grapefruit juice daily.<sup>1</sup>

- Goldbart A, et al. Near fatal acute colchicine intoxication in a child: a case report. *Eur J Pediatr* 2000; **159**: 895–7.

**Macrolides.** Life-threatening or fatal colchicine toxicity has been reported with use of colchicine and clarithromycin<sup>1,2</sup> or erythromycin.<sup>3</sup> A FDA analysis of safety data found that about half of the reported deaths associated with therapeutic oral doses of colchicine involved patients who were also taking clarithromycin.<sup>4</sup> A retrospective study in 116 patients given both drugs concluded that clarithromycin increased the risk of colchicine toxicity, especially in those patients with renal impairment, and that the two drugs should not be used together.<sup>5</sup>

- Dogukan A, et al. Acute fatal colchicine intoxication in a patient on continuous ambulatory peritoneal dialysis (CAPD): possible role of clarithromycin administration. *Clin Nephrol* 2001; **55**: 181–2.
- Rollot F, et al. Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004; **38**: 2074–7.
- Caraco Y, et al. Acute colchicine intoxication—possible role of erythromycin administration. *J Rheumatol* 1992; **19**: 494–6.
- FDA. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys) (issued 30th July, 2009). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm> (accessed 10/09/09)
- Hung IFN, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005; **41**: 291–300.

**Tolbutamide.** For a suggestion that tolbutamide may have exacerbated the toxicity of colchicine in a patient with liver disease, see under Effects on the Neuromuscular System, above.

**Pharmacokinetics**

Peak plasma concentrations of colchicine occur within 2 hours of oral use. Absolute bioavailability is reported to be about 45%. The absorption of colchicine from the gastrointestinal tract is thought to be limited by its expulsion by P-glycoprotein, for which colchicine is a substrate. Absorbed colchicine is found in high concentrations in the kidney, liver, and spleen. It is demethylated in the liver via the cytochrome P450

isoenzyme CYP3A4 to 2 primary metabolites, 2-*O*-demethylcolchicine and 3-*O*-demethylcolchicine (2-DMC and 3-DMC, respectively), and 1 minor metabolite, 10-*O*-demethylcolchicine (also known as colchicine). Plasma concentrations of metabolites are minimal. Enterohepatic recycling occurs. The main route of elimination is hepatobiliary excretion through the stool. Renal excretion accounts for 10 to 20% of colchicine elimination in patients with normal renal function. The mean elimination half-life is about 28 hours. Colchicine crosses the placenta and is distributed into breast milk.

## ◇ References.

- Rochdi M, et al. Pharmacokinetics and absolute bioavailability of colchicine after iv and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol* 1994; **46**: 351–4.
- Ferron GM, et al. Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol* 1996; **36**: 874–83.

**Uses and Administration**

Colchicine is used for the relief of acute gout (p.600) and for the prophylaxis of acute attacks, particularly during the first few months of treatment with allopurinol or uricosurics. Colchicine produces a dramatic response in acute gout, probably by reducing the inflammatory reaction to urate crystals; this effect might be due to several actions including decreased leucocyte mobility. It is not an analgesic and has no effect on blood concentrations of uric acid, or on the excretion of uric acid. Colchicine also has an antimitotic action.

Colchicine is used for the treatment of familial Mediterranean fever and has also been used in several other conditions including amyloidosis, Behçet's syndrome, idiopathic thrombocytopenic purpura, pericarditis, primary biliary cirrhosis, and pyoderma gangrenosum.

If colchicine is used for acute attacks of gout, then treatment should be started as soon as possible and an effect may be expected within 12 hours. The recommended oral dose in the UK is 1 mg initially, then 500 micrograms every 2 to 3 hours until pain relief is obtained or gastrointestinal adverse effects occur (but see also Administration, below). The total dose should not exceed 6 mg. At least 3 days should elapse before another course is given. In the USA the oral dose is 1.2 mg initially followed by 600 micrograms one hour later. The maximum total dose for an acute attack is 1.8 mg over 1 hour.

When colchicine is given with strong inhibitors of the cytochrome P450 isoenzyme CYP3A4, or if these drugs have been taken within 14 days of colchicine treatment, a reduced oral dose of colchicine 600 micrograms followed by 300 micrograms one hour later, is recommended in the USA. When moderate CYP3A4 inhibitors are used, a single oral dose of colchicine 1.2 mg is recommended, and when a P-glycoprotein inhibitor is given, a single oral dose of colchicine 600 micrograms is recommended. Treatment courses should not be repeated within 3 days.

Although no longer licensed in many countries, colchicine was formerly given intravenously in a dose of 1 or 2 mg over 2 to 5 minutes with additional doses of 0.5 or 1 mg every 6 hours as required to a total dose of not more than 4 mg in 24 hours; once this amount of colchicine has been given further doses should not then be given by any route for at least 7 days. For the view that the intravenous route should be avoided, see Administration, below.

In the UK, colchicine is also used for the prophylaxis of gout; oral doses are 500 micrograms two or three times daily.

For familial Mediterranean fever, US licensed product information for colchicine recommends an oral dose of 1.2 to 2.4 mg daily (which can be given in 2 divided doses); adjustments can be made as needed within this range in increments of 300 micrograms daily.

When colchicine is given with strong inhibitors of the cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein inhibitors, or if these drugs have been taken within

14 days of colchicine treatment, a reduced maximum daily dose of oral colchicine 600 micrograms is recommended, which can be given in 2 divided doses. When moderate CYP3A4 inhibitors are used, a maximum daily dose of oral colchicine 1.2 mg is recommended, which can also be given in 2 divided doses.

Although colchicine is not licensed in the UK for familial Mediterranean fever, the *BNF 59* suggests an oral dose of 0.5 to 2 mg once daily as prophylaxis.

For dose recommendations in children or patients with hepatic or renal impairment, see below.

#### References

- Lange U, *et al.* Current aspects of colchicine therapy: classical indications and new therapeutic uses. *Eur J Med Res* 2001; **6**: 150–60.
- Schlesinger N, *et al.* Colchicine for acute gout. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/04/08).
- Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. *Curr Rheumatol Rep* 2008; **10**: 218–27.

**Administration.** Although colchicine 1 mg orally, followed by 500 micrograms every 2 to 3 hours, is recommended in the UK for the treatment of acute gout, many rheumatologists consider this excessive; a low-dose regimen of 500 micrograms no more than 3 times daily has been advocated in preference.<sup>1</sup> In the USA, a total oral dose of 1.8 mg is recommended, as studies found low-dose (1.2 mg followed by a single dose of 600 micrograms) and high-dose (1.2 mg followed by 600 micrograms every hour for 6 hours) colchicine regimens to have similar efficacy, but considerably fewer adverse effects were seen with the low-dose schedule.<sup>2</sup>

The safety of intravenous colchicine has been questioned, and it has been suggested that, although undoubtedly effective, it should not be used because of the risk of severe or fatal adverse effects.<sup>3,4</sup> For reports of fatalities with intravenous colchicine during unlicensed use, see Inappropriate Administration, above.

- Morris I, *et al.* Colchicine in acute gout. *BMJ* 2003; **327**: 1275–6.
- FDA. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys) (issued 30th July, 2009). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm> (accessed 10/09/09)
- Morris I, *et al.* Colchicine in acute gout. *BMJ* 2004; **328**: 289.
- Schlesinger N. Reassessing the safety of intravenous and compounded injectable colchicine in acute gout treatment. *Expert Opin Drug Safety* 2007; **6**: 625–9.

**Administration in children.** In the USA, colchicine is licensed for use in children for the treatment of familial Mediterranean fever. It is given orally in the following daily doses according to age:

- 4 to 6 years: 300 micrograms to 1.8 mg
- 6 to 12 years: 900 micrograms to 1.8 mg
- over 12 years: adult doses are given, see above

**Administration in hepatic impairment.** Although the clearance of colchicine may be significantly reduced in chronic hepatic impairment, long-term therapy with oral colchicine 600 micrograms twice daily has been well tolerated in patients with cirrhosis.

When colchicine is used for acute gout, licensed product information in the USA considers dose reduction is not necessary for patients with hepatic impairment, but suggests that they should be monitored closely for adverse effects. Treatment courses should not be repeated more often than once every 2 weeks in patients with severe impairment, and alternative therapy considered.

In familial Mediterranean fever, US licensed product information suggests that patients with mild to moderate hepatic impairment are monitored closely for adverse effects. Dose reduction may be considered for patients with severe hepatic impairment. Colchicine should not be used in patients with hepatic impairment who are taking P-glycoprotein inhibitors or strong cytochrome P450 isoenzyme CYP3A4 inhibitors.

**Administration in renal impairment.** When colchicine is used for acute gout, licensed product information in the UK suggests a dose reduction or an increased interval between doses in patients with a creatinine clearance (CC) of 10 to 50 mL/min, and contra-indicates its use in patients with severe renal impairment (CC less than 10 mL/min), or those on dialysis. In the USA, no dose reduction is considered necessary in patients with mild to moderate renal impairment (CC 30 to 80 mL/min); patients with severe renal impairment (CC less than 30 mL/min) also do not require a dose reduction, but treatment courses should not be repeated more than once every 2 weeks. In dialysis patients, the total recommended dose for acute gout should be reduced to a single oral dose of 600 micrograms, not repeated more than once every 2 weeks. It was formerly advised that intravenous doses should be reduced by 50% in patients with a CC of between 10 and 50 mL/minute, and it is contra-indicated in those patients with a CC less than 10 mL/minute but such products are no longer licensed in many countries.

In familial Mediterranean fever, US licensed product information suggests that patients with mild to moderate renal impairment (30 to 80 mL/min) should be monitored closely; a reduction in colchicine dose may be necessary. For patients with severe renal impairment (CC less than 30 mL/min) or dialysis patients, an initial oral dose of colchicine 300 micrograms is recommended, with close monitoring after any dose increases.

Colchicine should not be used in patients with renal impairment who are taking P-glycoprotein inhibitors or strong cytochrome P450 isoenzyme CYP3A4 inhibitors.

**Amyloidosis.** Colchicine is well known to have a useful role in amyloidosis (p.815) secondary to familial Mediterranean fever, where results have suggested the possibility of reversing nephropathic changes due to renal amyloid deposition (see below). However, combination therapy with melphalan and prednisone was found to be more effective than colchicine alone in primary amyloidosis,<sup>1</sup> and a later study<sup>2</sup> found no benefit in adding colchicine to the standard therapy. The mechanism of the anti-amyloid effect of colchicine is not clear.

- Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomised trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100**: 290–8.
- 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.

**Behçet's syndrome.** Behçet's syndrome (p.1637) has been treated with numerous drugs. Where possible, topical treatment of local lesions should be tried before starting systemic therapy. Corticosteroids are favoured for systemic treatment in many countries, but colchicine has also been widely used. Beneficial responses have been described for most of the symptoms including the arthritic, ocular, and cutaneous manifestations, although a systematic review has questioned colchicine's efficacy.<sup>1</sup> The mechanism of action in this condition is believed to be based on the effect on polymorphonuclear leucocytes and other cellular effects.<sup>2</sup> Colchicine has also been used with corticosteroids for acute exacerbations, followed by colchicine maintenance;<sup>3</sup> colchicine with aspirin has also been recommended in acute disease,<sup>4</sup> and colchicine with benzathine benzylpenicillin has been tried.<sup>5</sup>

- Saenz A, *et al.* Pharmacotherapy for Behçet's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 27/04/05).
- Schattner A. Colchicine—expanding horizons. *Postgrad Med J* 1991; **67**: 223–6.
- Rakover Y, *et al.* Behçet disease: long-term follow-up of three children and review of the literature. *Pediatrics* 1989; **83**: 986–92.
- Wechsler B, Piette JC. Behçet's disease. *BMJ* 1992; **304**: 1199–1200.
- Çalgüneri M, *et al.* Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. *Dermatology* 1996; **192**: 125–8.

**Familial Mediterranean fever.** Familial Mediterranean fever (recurrent or paroxysmal polyserositis; periodic disease) is an inherited disorder that primarily affects Sephardic Jews or persons of Arab, Armenian, or Turkish ancestry.<sup>1,2</sup> It is characterised by attacks of acute abdominal pain, fever, and signs of peritonitis, which resolve spontaneously, usually in 24 to 48 hours. Pleuritic chest pain, arthritis, skin rash, pericarditis, and headache may occur. The most dangerous complication, however, is type AA amyloidosis (see also p.815), which can lead to nephrotic syndrome, renal failure, and death.

Familial Mediterranean fever is managed with colchicine.<sup>1–3</sup> Colchicine cannot stop an established attack, but, given prophylactically, it reduces the frequency of attacks, prevents amyloidosis and reverses proteinuria. Attacks are usually treated with NSAIDs,<sup>2,3</sup> or, in severe cases, opioids.<sup>3</sup> Anecdotal evidence has suggested that prazosin may also be of benefit,<sup>4</sup> but initial reports of improvement with interferon alfa have not been borne out.<sup>2</sup> Anakinra has also been investigated.<sup>5</sup>

- Ben-Cherit E, Levy M. Familial Mediterranean fever. *Lancet* 1998; **351**: 659–63.
- Drenth JPH, van der Meer JWM. Hereditary periodic fever. *N Engl J Med* 2001; **345**: 1748–57.
- Kallinich T, *et al.* Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; **119**: e474–e483. Also available at: <http://pediatrics.aappublications.org/cgi/reprint/119/2/e474> (accessed 21/04/08)
- Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129**: 424–5.
- Roldan R, *et al.* Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine* 2008; **75**: 504–5.

**Idiopathic thrombocytopenic purpura.** In idiopathic thrombocytopenic purpura (p.1643), refractory to standard therapy, a few patients have had partial or complete response to colchicine<sup>1,2</sup> and further studies have been suggested.<sup>2,3</sup>

- Strother SV, *et al.* Colchicine therapy for refractory idiopathic thrombocytopenic purpura. *Arch Intern Med* 1984; **144**: 2198–2200.
- Bonnotte B, *et al.* Efficacy of colchicine alone or in combination with vinca alkaloids in severe corticoid-resistant thrombocytopenic purpura: six cases. *Am J Med* 1999; **107**: 645–6.
- McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126**: 307–14.

**Interstitial lung disease.** Colchicine is a potential alternative to corticosteroid therapy in patients with idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p.1644). However the degree of benefit, if any, is unclear although colchicine does appear to be safer and better tolerated than corticosteroid therapy.<sup>1</sup>

- Davies HR, *et al.* Immunomodulatory agents for idiopathic pulmonary fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 27/04/05).

**Pericarditis.** Mild cases of recurrent pericarditis may be treated with colchicine, as an adjunct to NSAID therapy.<sup>1–3</sup> It may also provide effective prophylaxis, allowing the tapering of corticosteroids, which are usually reserved for the treatment of severe acute attacks.<sup>2,3</sup> The drug has also been used successfully in children.<sup>4</sup> In an open-label study, colchicine added to conventional therapy with aspirin or prednisone significantly decreased the recurrence rate in patients with a first episode of recurrent pericarditis, compared with conventional therapy alone.<sup>5</sup> Another open-label study had similar results using adjunctive colchicine for the first episode of acute pericarditis.<sup>6</sup> In patients with two or more relapses of acute pericarditis, colchicine was found to be highly effective in preventing recurrence.<sup>7</sup> The proportion of patients with relapses during or after colchicine therapy was significantly higher, and the duration of colchicine therapy significantly longer, in those who had pre-treatment with corticosteroids.

- Millaire A, *et al.* Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994; **15**: 120–4.
- Adler Y, *et al.* Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998; **97**: 2183–5.
- Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000; **84**: 449–54.
- Yazigi A, *et al.* Colchicine for recurrent pericarditis in children. *Acta Paediatr Scand* 1998; **87**: 603–4.
- Imazio M, *et al.* Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005; **165**: 1987–91.
- Imazio M, *et al.* Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PERicarditis (COPE) trial. *Circulation* 2005; **112**: 2012–16.
- Artom G, *et al.* Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-centre all-case analysis. *Eur Heart J* 2005; **26**: 723–7.

**Peyronie's disease.** Beneficial effects have been reported with colchicine in men with Peyronie's disease. Small studies show colchicine to be most effective in reducing pain during penile erection.<sup>1</sup> A combination of vitamin E and colchicine has also been suggested as an alternative in early disease.<sup>2</sup>

- Kadioglu A, *et al.* Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res* 2000; **12**: 169–75.
- Prieto Castro RM, *et al.* Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int* 2003; **91**: 522–4.

**Primary biliary cirrhosis.** Primary biliary cirrhosis (p.2646) is a chronic progressive liver disease with no specific treatment, and in general drug therapy has been poor or largely ineffective. Reviewers have noted<sup>1–3</sup> that several studies have been conducted with colchicine, and, although biochemical parameters were improved, a beneficial effect on clinical symptoms or liver histology was not found. A comparative study of colchicine and methotrexate showed that while both drugs improved biochemical test results and symptoms, the response to methotrexate was greater.<sup>4</sup> Some consider that combination therapy with colchicine, methotrexate, and ursodeoxycholic acid may be more promising than monotherapy.<sup>2</sup>

- Heathcote EJ. Evidence-based therapy of primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999; **11**: 607–15.
- Holtmeier J, Leuschner U. Medical treatment of primary biliary cirrhosis and primary sclerosing cholangitis. *Digestion* 2001; **64**: 137–50.
- Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 27/04/05).
- Kaplan MM, *et al.* A prospective trial of colchicine and methotrexate in the treatment of primary biliary cirrhosis. *Gastroenterology* 1999; **117**: 1173–80.

**Poderma gangrenosum.** Pyoderma gangrenosum (p.1724) associated with inflammatory bowel disease has been successfully treated with colchicine in 2 patients.<sup>1,2</sup> Colchicine was also of benefit in 3 patients with pyoderma associated with familial Mediterranean fever.<sup>3</sup> Other isolated reports include the use of low-dose colchicine in idiopathic pyoderma gangrenosum.<sup>4</sup>

- Paolini O, *et al.* Treatment of pyoderma gangrenosum with colchicine. *Lancet* 1995; **345**: 1057–8.
- Rampal P, *et al.* Colchicine in pyoderma gangrenosum. *Lancet* 1998; **351**: 1134–5.
- Lugassy G, Ronnen M. Severe pyoderma associated with familial Mediterranean fever: favourable response to colchicine in three patients. *Am J Med Sci* 1992; **304**: 29–31.
- Kontochristopoulos GJ, *et al.* Treatment of pyoderma gangrenosum with low-dose colchicine. *Dermatology* 2004; **209**: 233–6.

#### Preparations

**BP 2010:** Colchicine Tablets;  
**USP 33:** Colchicine Injection; Colchicine Tablets; Probenedic and Colchicine Tablets.

**Proprietary Preparations** (details are given in Volume B)

**Arg:** Xuric; **Austral:** Colgout; Lengout; **Braz:** Cixin; **Colchin;** Colchis; **Colchitr;** **Hong Kong:** Colcinat; **Colgout;** **CP:** Colchi; **Hung:** Colchicum-Dispers; **India:** Goutnil; **Indon:** Recolfin; **Malaysia:** Goutnil; **Mex:** Colchiquim; **Sixol;** **Ticolin;** **NZ:** Colgout; **Philipp:** Goutnil; **Thai:** Colchic;

Colchily; Colcine; Colcitem; Goutichine; Koji; Prochic; Tolchicine; Zoric; **Turk:** Colchicum-Disperit; Kolsin; **USA:** Colcrys.

**Multi-ingredient:** **Arg:** Artrex; Colchimax; Colpuril; Xuric-A; **Fr:** Colchimax; **Mex:** Butayonacol; **Spain:** Colchimax; **USA:** ColBenemid.

**Homeopathic:** **Ger:** Agnesin†; Anore rheumatic N; Arthribosan B 3†; Cefarheumin S.

## Colchicum

Colchico; Colchique.

Безвременник

UNII — 75UW9D360K.

### Profile

Colchicum, the dried ripe seeds or dried corm of the meadow saffron, *Colchicum autumnale*, contains colchicine (p.604) and has been used similarly for the prophylaxis and relief of acute gout.

It is also included in several herbal preparations.

**Homeopathy.** Colchicum has been used in homeopathic medicines under the following names: Colchicinum; Colchicum autumnale; Colchicum, tuber; Colch. at.

**Poisoning.** *Colchicum autumnale* is quite similar to a species of garlic *Allium ursinum*, especially in leaf appearance, and both plants grow in the same areas at the same time of year. There are reports of colchicine poisoning, some of them fatal, after accidental ingestion of *C. autumnale*.<sup>1-6</sup> Colchicine poisoning should be considered in patients with gastroenterocolitis after a wild plant meal.

1. Brnčić N, et al. Accidental plant poisoning with Colchicum autumnale: report of two cases. *Croat Med J* 2001; **42**: 673-5.
2. Sannohe S, et al. Colchicine poisoning resulting from accidental ingestion of meadow saffron (*Colchicum autumnale*). *J Forensic Sci* 2002; **47**: 1391-6.
3. Gabrsek L, et al. Accidental poisoning with autumn crocus. *J Toxicol Clin Toxicol* 2004; **42**: 85-8.
4. Brvar M, et al. Case report: fatal poisoning with Colchicum autumnale. *Crit Care* 2004; **8**: R56-R59.
5. Brvar M, et al. Acute poisoning with autumn crocus (*Colchicum autumnale* L.). *Wien Klin Wochenschr* 2004; **116**: 205-8.
6. Sundov Z, et al. Fatal colchicine poisoning by accidental ingestion of meadow saffron-case report. *Forensic Sci Int* 2005; **149**: 253-6.

### Preparations

**Proprietary Preparations** (details are given in Volume B)

**Ger:** Colchysat.

**Multi-ingredient:** **Chile:** Uroknop; **Ger:** Unguentum lymphaticum; **Venez:** Linfodem.

**Homeopathic:** **Austria:** Colchicum Med Complex†; Daram†; Pulsatilla Med Complex†; Rheu†; **Canada:** Arnica-Heel Comp; Backache; Ledum†; Homeo-Form AR; Hyalgesic LBP; Indigestion†; Renelix; **Chile:** Arnica Compuesta; Artroplex; **Fr:** Basilicum Complexe No 96; Berberis Complexe No 83; L 8; Ledum Complexe No 81; Momordica Complexe No 109; Rhus Toxicodendron Complexe No 80; Urarhthone; **Ger:** Alho-Arthrosan N; Arthridif S†; Arthrorrell; Berberis N Oligoplex; Colchicum comp†; Colchicum Complex Doloject; GI-Injektos; Girha "Schuh†"; Girheult HM; Girheult HOM; Harnsauretrophen F; Hewerheum N; Lymphdiaral; Poly-Arthrisan M; Restructa SN†; Rheucostan R; rheuma-loges; Rheuma-Pasc; Rheumodoron 2; Salkort-R†; Sanguisorbis N†.

## Febuxostat

Febuxostatium; TMX-67. 2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.

Фебуксостат

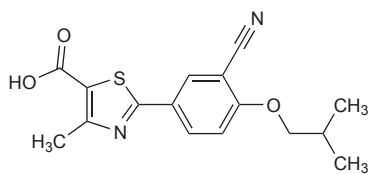
$C_{16}H_{16}N_2O_3S = 316.4$ .

CAS — 144060-53-7.

ATC — M04AA03.

ATC Vet — QM04AA03.

UNII — 101V0R1N2E.



### Adverse Effects

The most common adverse effects of febuxostat are liver function abnormalities, diarrhoea, headache, nausea, and rashes. Liver function should be monitored periodically; hepatitis and gallstones have also been reported. Less commonly reported effects include gastrointestinal adverse effects such as abdominal pain and constipation, fatigue, oedema, thirst, hemiparesis, Guillain-Barré syndrome, agitation, depression, flushing, dizziness, paraesthesia, somnolence, insomnia, altered taste, tinnitus, vertigo, hearing loss, blurred vision, hypersensitivity, herpes zoster infection, electrolyte disturbances, hyperglycaemia, hyperlipidaemia, diabetes mellitus, renal failure, nephrolithiasis, haematuria, urinary frequency, dermatitis, urticaria, pruritus, altered skin pigmentation, photosensitivity, and musculoskeletal effects such as arthralgia and myalgia. Blood disorders include anaemia, leucopenia, and thrombocytopenia. Abnormal coagulation tests have

occurred. Thromboembolic events such as myocardial infarction and stroke have been reported, as have arrhythmias, angina, hypertension, hypertension, and palpitations. Respiratory adverse effects include cough, bronchitis, dyspnoea, and upper respiratory-tract infections. Erectile dysfunction, breast pain, and gynaecomastia have occurred. Alterations in hair colour and growth pattern have been reported, as has alopecia.

### Precautions

Febuxostat therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Febuxostat is not recommended for the control of hyperuricaemia secondary to malignant disease or cancer chemotherapy. Treatment in patients with ischaemic heart disease or congestive heart failure is not recommended.

### Interactions

Inhibition of xanthine oxidase is known to increase concentrations of mercaptopurine or azathioprine, so use of febuxostat with these drugs is not recommended. Similarly, caution is advised when febuxostat is given with theophylline, and theophylline concentrations should be monitored.

Febuxostat is metabolised via the uridine diphosphate glucuronosyltransferase enzyme system, and inhibitors or inducers of this system might affect exposure to febuxostat. Serum uric acid should be monitored 1 to 2 weeks after starting treatment with a potent inducer of glucuronidation.

### Pharmacokinetics

Febuxostat is rapidly and well absorbed after oral doses. Although dosage with a high-fat meal decreases peak plasma concentration and exposure, this is not thought clinically significant, and febuxostat may be taken with or without food. Plasma protein binding is about 99%. Febuxostat is extensively metabolised by conjugation via the uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system, and by oxidation via the cytochrome P450 isoenzyme system; active metabolites are formed mainly by UGT1A1, UGT1A8, UGT1A9, and by CYP1A1, CYP1A2, CYP2C8, or CYP2C9. Febuxostat has a mean terminal half-life of about 5 to 8 hours. About half of a dose is excreted via the urine, and the other half via the faeces.

### Uses and Administration

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase. It is used for the treatment of hyperuricaemia in patients with chronic gout. In the EU, the recommended oral dose is 80 mg once daily. If the serum uric acid is above 6 mg per 100 mL after 2 to 4 weeks, the dose may be increased to 120 mg once daily. In the USA, febuxostat 40 mg once daily is given initially; if the serum uric acid is 6 mg per 100 mL or above after 2 weeks, the dose may be increased to 80 mg once daily.

Initially, febuxostat may increase plasma concentrations of urate and uric acid, and treatment should not be started until an acute attack of gout has completely subsided; an NSAID or colchicine should be given for at least 6 months after starting febuxostat.

For dosage recommendations in hepatic and renal impairment, see below.

### References

1. Schumacher HR. Febuxostat: a non-purine, selective inhibitor of xanthine oxidase for the management of hyperuricaemia in patients with gout. *Expert Opin Invest Drugs* 2005; **14**: 893-903.
2. Becker MA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005; **353**: 2450-61. Correction. *ibid.* 2006; **354**: 1533.
3. Khosravan R, et al. Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin Pharmacol Ther* 2006; **45**: 821-41.
4. Bruce SP. Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. *Ann Pharmacother* 2006; **40**: 2187-94.
5. Khosravan R, et al. The effect of age and gender on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2008; **48**: 1014-24.
6. Schumacher HR, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008; **59**: 1540-8.
7. Hair PJ, et al. Febuxostat. *Drugs* 2008; **68**: 1865-74.
8. NICE. Febuxostat for the management of hyperuricaemia in people with gout (TA164, issued December 2008). Available at: <http://www.nice.org.uk/nicemedia/pdf/TA164Guidance.pdf> (accessed 07/01/09).
9. Wardlaw NJ. Febuxostat: a new treatment for hyperuricaemia in gout. *Rheumatology (Oxford)* 2009; **48** (suppl 2): ii15-ii19.
10. Ernst ME, Fravel MA. Febuxostat: a selective xanthine-oxidase/xanthine-dehydrogenase inhibitor for the management of hyperuricemia in adults with gout. *Clin Ther* 2009; **31**: 2503-18.
11. Becker MA, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010; **12**: R63.
12. Schlesinger N. New agents for the treatment of gout and hyperuricemia: febuxostat, puricase, and beyond. *Curr Rheumatol Rep* 2010; **12**: 130-4.

**Administration in hepatic impairment.** Exposure to febuxostat did not change significantly in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment compared with subjects with normal hepatic function.<sup>1</sup> EU licensed product information states that the recommended oral dose of febuxostat in patients with mild hepatic im-

pairment is 80 mg daily. No dose recommendations are given for moderate impairment; efficacy and safety of febuxostat has not been studied in those with severe (Child-Pugh class C) hepatic impairment. In the USA, no dosage adjustment is considered necessary for mild or moderate hepatic impairment; caution is advised in severe impairment due to a lack of data.

1. Khosravan R, et al. The effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2006; **46**: 88-102.

**Administration in renal impairment.** In patients with mild, moderate, or severe renal impairment, peak plasma concentrations of febuxostat did not alter, relative to those with normal renal function; however, the mean area under the concentration-time curve was increased in those with severe renal impairment. EU and US licensed product information state that no dosage adjustments are considered necessary in those with mild or moderate renal impairment, but that efficacy and safety have not been evaluated in those with severe renal impairment (creatinine clearance of less than 30 mL/min).

A study<sup>1</sup> found that although exposure to febuxostat and its metabolites was generally higher in subjects with increasing degrees of renal impairment, decreases in uric acid were comparable regardless of renal function.

1. Mayer MD, et al. Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther* 2005; **12**: 22-34.

### Preparations

**Proprietary Preparations** (details are given in Volume B)

**Cz:** Adenuric; **Fr:** Adenuric; **Ir:** Adenuric; **Jpn:** Uloric; **Port:** Adenuric; **UK:** Adenuric; **USA:** Uloric.

## Probenecid

Probenecidas; Probenécide; Probenecidum; Probenesid; Probenesidi. 4-(Dipropylsulphamoyl)benzoic acid.

Пробенецид

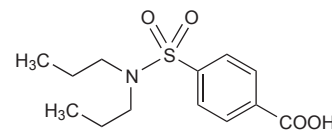
$C_{13}H_{19}NO_4S = 285.4$ .

CAS — 57-66-9.

ATC — M04B01.

ATC Vet — QM04B01.

UNII — P0572Z7917.



**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.* and *US*. **Ph. Eur.** 6.8 (Probenecid). A white or almost white crystalline powder or small crystals. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone.

**USP 33** (Probenecid). A white or practically white, fine, practically odourless, crystalline powder. Practically insoluble in water and in dilute acids; soluble in alcohol, in acetone, in chloroform, and in dilute alkali.

### Adverse Effects and Treatment

Probenecid may cause nausea, vomiting, anorexia, headache, sore gums, flushing, alopecia, dizziness, anaemia, and urinary frequency. Hypersensitivity reactions, with fever, dermatitis, pruritus, urticaria, and, rarely, anaphylaxis, and Stevens-Johnson syndrome have occurred. There have been reports of leucopenia, hepatic necrosis, nephrotic syndrome, and aplastic anaemia. Haemolytic anaemia has also occurred, and may be associated with G6PD deficiency.

When used in chronic gout, and particularly during the first few months of therapy, probenecid may precipitate acute attacks. Uric acid renal calculi, with or without haematuria, costovertebral pain and renal colic may occur.

In massive overdosage probenecid causes stimulation of the CNS, with convulsions and death from respiratory failure. Severe overdosage should be managed by lavage and symptomatic treatment.

### Precautions

Probenecid therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Probenecid is also unsuitable for the control of

hyperuricaemia secondary to cancer or cancer chemotherapy. Probenecid should not be given to patients with a history of uric acid renal calculi or blood disorders. It should be used with caution in patients with a history of peptic ulceration. Probenecid should not be used as an antibacterial adjunct in patients with known renal impairment, and it is ineffective in gout in patients with severe renal impairment.

To reduce the risk of uric acid renal calculi in patients with gout an adequate fluid intake (2 to 3 litres daily) is required, and, if necessary, especially during the first few months of treatment, sodium bicarbonate or potassium citrate may be given to render the urine alkaline. A reducing substance has been found in the urine of some patients taking probenecid, and may give false positive results with some tests for glucose in the urine. Probenecid reduces the excretion of some iodinated contrast media and may interfere with laboratory tests by decreasing the excretion of aminohippuric acid, phenolsulfonphthalein, and sulfobromophthalein.

**Abuse.** It has been alleged that some athletes using banned anabolic steroids have taken probenecid in an attempt to inhibit the urinary excretion of steroid metabolites in order to avoid detection by urine screening tests.<sup>1</sup> The World Anti-Doping Agency includes probenecid among substances prohibited for use by athletes in and out of competition.

1. Anonymous. Does probenecid mask steroid use? *Pharm J* 1987; 239: 299.

**Porphyria.** Probenecid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrogenicity.

### Interactions

The dose of probenecid may need to be increased if patients are also given drugs, such as diuretics or pyrazinamide, that increase the blood concentration of uric acid. Salicylates, including aspirin, and probenecid are mutually antagonistic and should not be given together. Probenecid may also affect many other drugs. By inhibiting renal tubular secretion, it has the potential to increase the toxicity and/or to enhance the therapeutic efficacy of drugs excreted by that route. In some instances a reduction in dose is essential to counteract an increase in toxicity, as is the case with methotrexate. Some combinations, such as that with ketorolac, should be avoided. Conversely, probenecid may be given with some antibacterials such as the penicillins and cephalosporins to increase their effects.

Altered excretion may also increase serum concentrations of other antibacterials (aminosalicylic acid, conjugated sulfonamides, dapsone, meropenem, some quinolones, rifampicin), some antivirals (aciclovir, ganciclovir, zalcitabine, zidovudine, and possibly famciclovir), some benzodiazepines (adinazolam, lorazepam, and nitrazepam), some ACE inhibitors (captopril and enalapril), some NSAIDs (diflunisal, indometacin, ketoprofen, meclofenamate, naproxen), paracetamol, and sulfonyleurea hypoglycaemic drugs. The clinical significance of such interactions is not entirely clear although the possibility of the need for a reduction in dosage of these drugs should be borne in mind.

It has been reported that patients receiving probenecid require lower doses of thiopental for induction of anaesthesia. Probenecid may increase the speed of induction of anaesthesia with midazolam.

Reducing the urinary concentration of some drugs could diminish their activity in certain diseases as might happen with nitrofurantoin or some quinolones in urinary-tract infections and penicillamine in cystinuria.

**Allopurinol.** Probenecid may increase the clearance of allopurinol despite an increased hypouricaemic effect when these 2 drugs are given together (see Antigout Drugs, under Allopurinol, p.601).

### Pharmacokinetics

Probenecid is completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after a dose. It is extensively bound to plasma

proteins (85 to 95%). The plasma half-life is dose-dependent and ranges from less than 5 to more than 8 hours. Probenecid crosses the placenta. It is metabolised by the liver, and excreted in the urine mainly as metabolites. Excretion of unchanged probenecid is increased in alkaline urine.

### Uses and Administration

Probenecid is a uricosuric drug used to treat hyperuricaemia (p.600) associated with chronic gout; it has also been used to treat hyperuricaemia caused by diuretic therapy. It is also used as an adjunct to some antibacterials to reduce their renal tubular excretion and is given with the antiviral cidofovir to reduce nephrotoxicity.

Probenecid is used in **chronic gout and hyperuricaemia** to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. Probenecid is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production, and is not used for hyperuricaemia associated with cancer or cancer therapy.

Probenecid has no analgesic or anti-inflammatory action and is of no value in acute gout. Initially it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence probenecid should not be started until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

It is usual to start treatment for gout with oral doses of 250 mg twice daily increased after a week to 500 mg twice daily and later, if the therapeutic effects are inadequate, by increments of 500 mg every 4 weeks, up to 2 g daily. Probenecid may not be effective in chronic renal impairment particularly when the glomerular filtration rate is less than 30 mL/minute. An adequate fluid intake is required to reduce the risk of uric acid renal calculi.

When the patient has been free from acute attacks for at least 6 months, and provided that the plasma-urate concentration is within acceptable limits, the daily dose may be gradually reduced, by 500 mg every 6 months, to the lowest effective maintenance dose which is then given indefinitely.

Probenecid may also be used as an **adjunct to antibacterial therapy** particularly when treating severe or resistant infections. It reduces the tubular excretion of penicillins and most cephalosporins and may increase their plasma concentrations up to fourfold. The usual dosage for reducing tubular excretion of penicillins and cephalosporins is 500 mg four times daily, or less in elderly patients with suspected renal impairment. When renal impairment is sufficient to retard the excretion of antibacterials, probenecid should not be given.

For doses in children, see Administration in Children, below.

Single oral doses of probenecid 1 g are given with a suitable oral antibacterial, or at least 30 minutes before an injected antibacterial, in the single-dose treatment of gonorrhoea (p.206).

Doses of probenecid to be used with cidofovir are given on p.958.

**Administration in children.** For children aged 2 years of age or older and weighing 50 kg or less, the recommended oral dose of probenecid is 25 mg/kg (or 700 mg/m<sup>2</sup>) initially, followed by 40 mg/kg (or 1.2 g/m<sup>2</sup>) daily, given in 4 divided doses. For children weighing more than 50 kg, the usual adult dose is recommended (see Uses and Administration, above).

### Preparations

**BP 2010:** Probenecid Tablets;

**USP 33:** Ampicillin and Probenecid for Oral Suspension; Probenecid and Colchicine Tablets; Probenecid Tablets.

**Proprietary Preparations** (details are given in Volume B)

**Austral.:** Pro-Cid, **Canad.:** Benuryl, **Fr.:** Benemide, **Gr.:** Benemid, **India:** Bencid, **Mex.:** Bencid, **Norw.:** Probecid, **S.Afr.:** Proben, **Swed.:** Probecid, **Switz.:** Santuril, **Thai.:** Benacid, Bencid, **USA:** Benemid<sup>†</sup>.

**Multi-ingredient:** **USA:** ColBenemid.

Used as an adjunct in: **Braz.:** Eemiclin; Gonol; **Spain:** Blenox<sup>†</sup>.

### Sulfinpyrazone (BAN, rINN)

G-28315; Sulfinpirazona; Sulfinpirazonas; Sulfinpyratsoni; Sulfinpyrazon; Sulfinpyrazonum; Sulphinpyrazone; Sulphoxyphenylpyrazolidine; Szulfipirazon. 1,2-Diphenyl-4-(2-phenylsulphonyl-ethyl)pyrazolidine-3,5-dione.

Сульфинпиразон

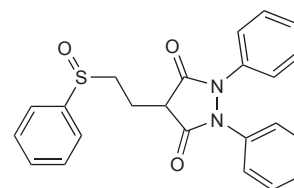
C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S = 404.5.

CAS — 57-96-5.

ATC — M04AB02.

ATC Vet — QM04AB02.

UNII — V6OFU47K3W.



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

**Ph. Eur. 6.8** (Sulfinpyrazone). A white or almost white powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

**USP 33** (Sulfinpyrazone). A white to off-white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol and in acetone; sparingly soluble in dilute alkali.

### Adverse Effects and Treatment

The most frequent adverse effects of sulfinpyrazone involve the gastrointestinal tract, and include nausea, vomiting, diarrhoea and abdominal pain. It may cause gastric bleeding or aggravate existing peptic ulcers. Skin rashes have been reported, and may be associated with a hypersensitivity reaction. Aplastic anaemia, agranulocytosis, leucopenia, and thrombocytopenia have been reported rarely as have raised liver enzyme values, jaundice, and hepatitis, renal impairment, salt and water retention, and acute renal failure.

When used in chronic gout, particularly during the first few months of treatment, sulfinpyrazone may precipitate acute attacks and there is a risk of uric acid renal calculi developing.

Symptoms of overdose include hypotension, acute renal failure, arrhythmias, respiratory disorders, convulsions, and coma, as well as gastrointestinal effects. Treatment of overdose may involve activated charcoal if a substantial amount has been ingested within 1 hour of presentation, followed by symptomatic and supportive therapy.

**Effects on the kidneys.** Although renal failure has been reported occasionally in patients receiving sulfinpyrazone for gout<sup>1</sup> many of the cases have occurred in those given the drug for myocardial infarction.<sup>2,3</sup> Acute renal failure may also occur after overdose or in patients with intravascular volume depletion.<sup>4,5</sup>

1. Durham DS, Ibels LS. Sulfinpyrazone-induced acute renal failure. *BMJ* 1981; 282: 609.
2. Boelaert J, et al. Sulfinpyrazone-induced decrease in renal function: a review of reports with discussion of pathogenesis. *Acta Clin Belg* 1982; 37: 368-75.
3. Lijnen P, et al. Decrease in renal function due to sulfinpyrazone treatment early after myocardial infarction. *Clin Nephrol* 1983; 19: 143-6.
4. Florkowski CM, et al. Acute non-oliguric renal failure secondary to sulfinpyrazone overdose. *J Clin Pharm Ther* 1992; 17: 71.
5. Walls M, et al. Acute renal failure due to sulfinpyrazone. *Am J Med Sci* 1998; 315: 319-21.

### Precautions

Sulfinpyrazone should not be started during an acute attack of gout; however, treatment is usually continued when acute attacks occur in patients already receiving

the drug, and the acute attack is treated separately. Sulfinpyrazone is not suitable for the control of hyperuricaemia associated with cancer or cancer chemotherapy.

Sulfinpyrazone should be given with care to patients with renal impairment or heart failure and is contra-indicated in those with severe renal or hepatic impairment. It is also contra-indicated in patients with blood dyscrasias or blood coagulation disorders, and in patients with uric acid renal calculi or peptic ulcer disease or a history of such disorders.

Sulfinpyrazone should not be given to patients hypersensitive to it or to other pyrazole derivatives such as phenylbutazone; nor should it be given to patients in whom hypersensitivity reactions (including bronchospastic reactions in asthmatics) have been provoked by aspirin or by other drugs with prostaglandin-synthetase inhibiting activity.

To reduce the risk of uric acid renal calculi an adequate fluid intake (2 to 3 litres daily) is required; alkalinising the urine with sodium bicarbonate or potassium citrate may also be considered. It is recommended that patients have periodic full blood counts to detect any haematological abnormalities.

Renal-function tests involving aminohippuric acid or phenolsulphonphthalein may be invalidated.

**Porphyria.** Sulfinpyrazone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

### Interactions

Doses of sulfinpyrazone may need to be increased if it is given with other drugs, such as diuretics or pyrazinamide, that increase uric acid concentrations. Sulfinpyrazone and salicylates including aspirin are mutually antagonistic and should not be used together. There may also be an increased risk of bleeding when sulfinpyrazone is used with other drugs such as aspirin that inhibit platelet function.

Sulfinpyrazone's renal tubular secretion is inhibited by probenecid although with little clinical effect. Since sulfinpyrazone, like probenecid, inhibits the tubular secretion of weak organic acids, interactions can be expected with penicillins although the effect is not considered to be clinically useful.

Sulfinpyrazone can potentiate the action of some drugs. The most significant interaction of this type involves warfarin, acenocoumarol, and possibly other coumarin anticoagulants (p.1567). Patients receiving sulfinpyrazone and such an anticoagulant should have their prothrombin times monitored and the anticoagulant dosage reduced as appropriate. Similarly, sulfinpyrazone may potentiate the effects of phenytoin (see Antiepileptics, p.543), and possibly some sulfonamides and sulfonylureas.

In contrast, sulfinpyrazone may increase the metabolism of theophylline (p.1259) and diminish its activity.

### Pharmacokinetics

Sulfinpyrazone is readily absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins and has a plasma half-life of about 2 to 4 hours. Sulfinpyrazone is partly metabolised in the liver and some of the metabolites are active. On long-term therapy, sulfinpyrazone induces its own metabolism. Unchanged drug and metabolites are mainly excreted in the urine.

#### References

- Bradbrook ID, et al. Pharmacokinetics of single doses of sulfinpyrazone and its major metabolites in plasma and urine. *Br J Clin Pharmacol* 1982; **13**: 177-85.
- Schlicht F, et al. Pharmacokinetics of sulfinpyrazone and its major metabolites after a single dose and during chronic treatment. *Eur J Clin Pharmacol* 1985; **28**: 97-103.

### Uses and Administration

Sulfinpyrazone is a uricosuric drug used to treat hyperuricaemia associated with chronic gout (p.600). It also has some antiplatelet activity.

The symbol † denotes a preparation no longer actively marketed

Sulfinpyrazone is used in chronic gout to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. It is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production and is not used for hyperuricaemia associated with cancer or cancer therapy.

Sulfinpyrazone has little analgesic or anti-inflammatory action and is of no value in acute gout. Initially, it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence sulfinpyrazone should not be given until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

The initial oral dose of sulfinpyrazone in the UK has been 100 to 200 mg daily (although no longer available there, the USA formerly allowed up to 200 mg twice daily), taken with meals or milk. This may be gradually increased over 1 to 3 weeks until a daily dosage of 600 mg is reached; up to 800 mg daily may be given if necessary. After the plasma-urate concentration has been controlled, the daily maintenance dose may be reduced to as low as 200 mg. An adequate fluid intake is required to prevent formation of uric acid renal calculi.

**Antiplatelet therapy.** Sulfinpyrazone inhibits platelet function, thereby inhibiting thrombosis. A meta-analysis of studies, conducted by the Antiplatelet Trialists' Collaboration, has shown that it reduces the risk of myocardial infarction, stroke, or vascular death in patients at high risk of occlusive vascular disease<sup>1</sup> and also reduces the risk of occlusion in patients undergoing arterial reperfusion and revascularisation procedures.<sup>2</sup> However, aspirin is the most widely used antiplatelet therapy, as discussed under Cardiovascular Risk Reduction, on p.1281.

- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**: 81-106.
- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994; **308**: 159-68.

### Preparations

**BP 2010:** Sulfinpyrazone Tablets;  
**USP 33:** Sulfinpyrazone Capsules; Sulfinpyrazone Tablets.

**Proprietary Preparations** (details are given in Volume B)

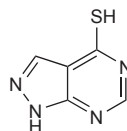
**Gr.:** Eryfrace; **Ital.:** Enturen; **Port.:** Sullifona†; **Thai.:** Sullin; **UK:** Anturan†; **USA:** Anturan†.

### Tisopurine (rINN)

MPP; Thioallopurinol; Thiopurinol; Tisopurina; Tisopurinum. 1H-Pyrazolo[3,4-d]pyrimidine-4-thiol.

Тизопурин

C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>S = 152.2.  
CAS — 5334-23-6.  
ATC — M04AA02.  
ATC Vet — QM04AA02.  
UNII — 79F912R16M.



### Profile

Tisopurine, an analogue of allopurinol, is an inhibitor of uric acid synthesis. It is used orally in the treatment of disorders associated with hyperuricaemia (p.600), including gout, in doses of 100 to 400 mg daily.

### Preparations

**Proprietary Preparations** (details are given in Volume B)

**Austria:** Exuracid.

### Urate Oxidase

CB-8129; Urato oxidasa; Uricasa; Uricase.

Уратоксидаза

CAS — 9002-12-4.  
ATC — M04AX01.  
ATC Vet — QM04AX01.

### Pegloticase (USAN, rINN)

Pegloticasa; Pégloticase; Pegloticasum.

Пэглотиказа

CAS — 885051-90-1.  
ATC — M04AX02.  
ATC Vet — QM04AX02.

### Rasburicase (BAN, USAN, rINN)

Rasburicasa; Rasburicasum; Rasburikaasi; Rasburikas; Rasburikaz; SR-29142.

Разбуриказа

CAS — 134774-45-1.  
ATC — V03AF07.  
ATC Vet — QV03AF07.  
UNII — 08GY9K1EUO.

**Description.** Rasburicase is a recombinant form of the enzyme urate oxidase.

### Adverse Effects

The most serious adverse effects of rasburicase involve hypersensitivity reactions, including anaphylaxis, rashes, bronchospasm, rhinitis, urticaria, hypotension, dyspnoea, and chest pain and tightness. Haemolysis and methaemoglobinemia have also been reported. Other adverse effects are nausea, vomiting, abdominal pain, constipation, diarrhoea, headache, fever, respiratory distress, sepsis, neutropenia, and mucositis.

### Precautions

Treatment with rasburicase should be immediately and permanently stopped if hypersensitivity reactions, methaemoglobinemia, or haemolysis develop. Rasburicase is contra-indicated in patients with G6PD deficiency or other cellular metabolic disorders known to cause haemolytic anaemia; hydrogen peroxide, which is produced during oxidation of uric acid to allantoin, can induce haemolytic anaemia in these patients. Patients at higher risk of having G6PD deficiency should be screened before receiving rasburicase.

### Uses and Administration

Rasburicase is a recombinant form of the enzyme urate oxidase, which oxidises uric acid to allantoin. It is used in the treatment and prophylaxis of severe hyperuricaemia (p.600) associated with the treatment of malignancy. Rasburicase is diluted to a final volume of 50 mL with sodium chloride 0.9%, and given by intravenous infusion over 30 minutes. The recommended dose is 200 micrograms/kg as a single daily dose. Duration of treatment may vary from 5 to 7 days.

For doses in children, see Administration in Children, below.

Pegloticase is a recombinant, pegylated form of the enzyme urate oxidase. It is under investigation for the management of hyperuricaemia associated with chronic gout that is refractory to conventional urate-lowering therapy. The native form of urate oxidase has also been used.

**Administration in children.** Rasburicase is used in children for the treatment and prophylaxis of severe hyperuricaemia associated with treatment of malignancy in the same dose as for adults (see Uses and Administration, above). For further discussion of its use in children with tumour lysis syndrome, see below.

**Gout.** Rasburicase has been used successfully to treat gout in patients allergic to allopurinol.<sup>1,2</sup> Pegloticase has also successfully reduced plasma-urate concentrations in patients with treatment-resistant disease,<sup>3</sup> although more evidence is needed to assess its risks and benefits.<sup>4</sup>

- Vogt B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol Dial Transplant* 2005; **20**: 431-3.

- Richette P, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol* 2006; **2**: 338-42.

- Sundy JS, et al. Pegloticase Phase 2 Study Investigators. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. *Arthritis Rheum* 2008; **58**: 2882-91.

- Anderson A, Singh JA. Pegloticase for chronic gout. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2010 (accessed 10/05/10).

**Tumour lysis syndrome.** The tumour lysis syndrome (p.695) represents a biochemical disturbance after massive release of cellular breakdown products from tumour cells sensitive to therapy; hyperuricaemia is a cardinal feature. Rasburicase was effective in the prophylaxis or treatment of hyperuricaemia in children and

young adults with leukaemia or lymphoma who either presented with abnormally high plasma concentrations of uric acid or had large tumour cell burdens.<sup>1</sup> Treatment was mostly well tolerated; one patient developed nausea and vomiting and one experienced bronchospasm and hypoxaemia 3 hours after infusion. Antibodies to rasburicase were seen in 17 of 121 assessable patients. Safety and efficacy were confirmed in further studies of children<sup>2</sup> and adults<sup>2,3</sup> considered to be at particularly high risk of tumour lysis syndrome. In children<sup>4</sup> with haematologic malignancies at high risk for tumour lysis, rasburicase given intravenously achieved more rapid control and lower levels of plasma uric acid than oral allopurinol. No antibodies to rasburicase were detected at day 14. In 3 children with acute lymphoblastic leukaemia, hyperuricaemia was reportedly controlled with oral allopurinol and a single dose of rasburicase, although subclinical tumour lysis was apparent.<sup>5</sup> Rasburicase has also been used for tumour lysis syndrome in neonates. One infant was given a single dose of rasburicase after 2 days of induction chemotherapy for neuroblastoma, started on day 21 of life; serum urate normalised and chemotherapy was completed without further incident. A second infant, with acute lymphoblastic leukaemia and renal

dysfunction, presented with tumour lysis syndrome, and had 6 doses of intravenous rasburicase plus aggressive supportive therapy, but died of complications on day 7 of life.<sup>6</sup> Reviews<sup>7,8</sup> have concluded that rasburicase is highly effective at decreasing uric acid concentrations rapidly and thoroughly; there is some suggestion that shorter durations of treatment (between 1 and 3 days as opposed to 5 days) may be sufficient even in high-risk patients.

1. Pui C-H, *et al.* Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukaemia or lymphoma. *J Clin Oncol* 2001; **19**: 697–704.
2. Pui C-H, *et al.* Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia* 2001; **15**: 1505–9.
3. Coiffier B, *et al.* Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003; **21**: 4402–6.
4. Goldman SC, *et al.* A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001; **97**: 2998–3003.

5. Lee ACW, *et al.* Treatment of impending tumor lysis with single-dose rasburicase. *Ann Pharmacother* 2003; **37**: 1614–17.
6. McNutt DM, *et al.* Rasburicase for the management of tumor lysis syndrome in neonates. *Ann Pharmacother* 2006; **40**: 1445–50.
7. Bessmertny O, *et al.* Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. *Curr Pharm Des* 2005; **11**: 4177–85.
8. Oldfield V, Perry CM. Rasburicase: a review of its use in the management of anticancer therapy-induced hyperuricaemia. *Drugs* 2006; **66**: 529–45.

## Preparations

**Proprietary Preparations** (details are given in Volume B)

**Austral.:** Fasturtec; **Austria:** Fasturtec; **Belg.:** Fasturtec; **Braz.:** Fasturtec; **Canad.:** Fasturtec; **Cz.:** Fasturtec; **Denm.:** Fasturtec; **Fin.:** Fasturtec; **Fr.:** Fasturtec; **Ger.:** Fasturtec; **Gr.:** Fasturtec; **Hong Kong:** Fasturtec; **Hung.:** Fasturtec; **Irl.:** Fasturtec; **Ital.:** Fasturtec; **Neth.:** Fasturtec; **Norw.:** Fasturtec; **NZ:** Fasturtec; **Pol.:** Fasturtec; **Port.:** Fasturtec; **Singapore:** Fasturtec; **Spain:** Fasturtec; **Swed.:** Fasturtec; **Switz.:** Fasturtec; **Turk.:** Fasturtec; **UK:** Fasturtec; **USA:** Elitek; **Venez.:** Fasturtec.