Colchicine

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

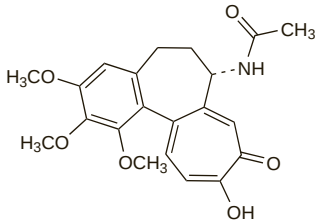
Колхицин

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

CAS — 64-86-8.

ATC — M04AC01.

ATC Vet — QM04AC01.



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. 6.2 (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 31 (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, and alopecia.

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

Symptoms of acute **overdosage** with oral colchicine often do not appear for 2 to 12 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.[1] 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[2] 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.[3] 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.[4]

Rhabdomyolysis has also been reported.[5,6]

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

Effects on the reproductive system. UK licensing information states that colchicine may adversely affect spermatogenesis under certain conditions of therapy. *Animal* data has 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.[1] 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[1] (see also under Pregnancy, below).

1. 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.[1,2]

1. 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)
2. 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 (accessed 21/04/08)

Overdosage. References.

1. McIntyre IM, *et al.* Death following colchicine poisoning. *J Forensic Sci* 1994; **39:** 280–6.
2. Hood RL. Colchicine poisoning. *J Emerg Med* 1994; **12:** 171–7.
3. Baud FJ, *et al.* Brief report: treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Engl J Med* 1995; **332:** 642–5.
4. Critchley JAJH, *et al.* Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol* 1997; **16:** 229–32.
5. Milne ST, Meek PD. Fatal colchicine overdose: report of a case and review of the literature. *Am J Emerg Med* 1998; **16:** 603–8.
6. Kubler PA. Fatal colchicine toxicity. *Med J Aust* 2000; **172:** 498–9.
7. Harris R, *et al.* Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *J Emerg Med* 2000; **18:** 435–40.
8. Mullins ME, *et al.* Fatal cardiovascular collapse following acute colchicine ingestion. *J Toxicol Clin Toxicol* 2000; **38:** 51–4.
9. Arroyo MP, *et al.* Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol* 2004; **150:** 581–8.
10. Ataş B, *et al.* Four children with colchicine poisoning. *Hum Exp Toxicol* 2004; **23:** 353–6.
11. Miller MA, *et al.* Colchicine-related death presenting as an unknown case of multiple organ failure. *J Emerg Med* 2005; **28:** 445–8.
12. 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,[1-3] and some have recommended waiting for 8 hours[2] or 12 hours[3] 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.[4]

1. Milunsky JM, Milunsky A. Breast-feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr* 1991; **119:** 164.
2. Guillonneau M, *et al.* Colchicine is excreted at high concentrations in human breast milk. *Eur J Obstet Gynecol Reprod Biol* 1995; **61:** 177–8.
3. Ben-Chetrit E, *et al.* Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; **39:** 1213–17.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 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.[1]

1. 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

Use of colchicine with clarithromycin, erythromycin, or tolbutamide may cause colchicine toxicity. Thiazide diuretics may increase serum uric acid and interfere with the activity of colchicine. Muscle disorders have been reported when colchicine is used with ciclosporin. Colchicine may impair the absorption of vitamin B_{12}.

Cardiovascular drugs. Acute myopathy has been reported in patients with chronic renal impairment given colchicine with *simvastatin*.[1,2] Similar effects have been seen in patients with renal impairment given colchicine with *fluvastatin*[3], or *pravastatin*.[4] Since many statins are metabolised by the cytochrome P450 isoenzyme CYP3A4, as is colchicine, this has been proposed as one possible mechanism.[3,4] However, fluvastatin and pravastatin are cleared through different isoenzymes. Alternative proposed mechanisms are synergistic myopathy[2,3] or interference with transport mediated by P-glycoprotein.[4] 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.[5]

1. Hsu W-C, *et al.* Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002; **25:** 266–8.
2. Baker SK, *et al.* Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004; **30:** 799–802.
3. Atasoyu EM, *et al.* Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005; **39:** 1368–9.
4. Alaylı G, *et al.* Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005; **39:** 1358–61.
5. 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[1] may be a problem, especially in transplant patients[2] or those with renal impair-

ment.[3] In addition, increased blood-ciclosporin concentrations and nephrotoxicity developed in a renal transplant patient after the introduction of colchicine therapy.[4]

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

Macrolides. Life-threatening colchicine toxicity has been described after use for 2 weeks with *erythromycin* in a patient with hepatic and renal impairment.[1] In a patient with end-stage renal disease, but no hepatic impairment, fatal colchicine toxicity developed after 4 days of *clarithromycin* therapy.[2] A patient with moderate chronic renal impairment developed acute but non-fatal colchicine intoxication on day 4 of a 7-day *Helicobacter pylori* treatment course containing clarithromycin.[3] 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.[4]

1. Caraco Y, *et al.* Acute colchicine intoxication—possible role of erythromycin administration. *J Rheumatol* 1992; **19:** 494–6.
2. 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.
3. Rollot F, *et al.* Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004; **38:** 2074–7.
4. 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 are reached within 2 hours of oral use. Colchicine is partially deacetylated in the liver and the unchanged drug and its metabolites are excreted in the bile and undergo intestinal reabsorption. Colchicine is found in high concentrations in leucocytes, kidneys, the liver, and spleen. Most of the drug is excreted in the faeces but 10 to 20% is excreted in the urine and this proportion rises in patients with liver disorders. Colchicine is distributed into breast milk.

◊ References.

1. 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.
2. 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.552) 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 has also been used in several other conditions including amyloidosis, Behçet's syndrome, familial Mediterranean fever, 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). Although some licensed products allow doses up to a maximum of 10 mg, the *BNF* considers that 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 to 1.2 mg initially; this may be repeated every 2 hours, or 500 or 600 micrograms may be taken every hour (or even every 2 or 3 hours if sufficient), until pain is relieved or gastrointestinal adverse effects occur. The maximum total dose for an acute attack should not exceed 8 mg.

Colchicine has sometimes been 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.

When used for the prophylaxis of gout oral doses are 500 or 600 micrograms once daily; some patients may require doses up to 1.8 mg daily.

Consideration should be given to using reduced dosages in patients with renal impairment, see below.

◊ References.

1. Lange U, *et al.* Current aspects of colchicine therapy: classical indications and new therapeutic uses. *Eur J Med Res* 2001; **6:** 150–60.
2. 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).

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.[1] It has also been suggested that intravenous colchicine, although undoubtedly effective, should not be used because of the risk of severe or fatal adverse effects.[2] For reports of fatalities with intravenous colchicine during unlicensed use, see Inappropriate Administration, above.

1. Morris I, *et al.* Colchicine in acute gout. *BMJ* 2003; **327:** 1275–6.
2. Morris I, *et al.* Colchicine in acute gout. *BMJ* 2004; **328:** 289.

Administration in renal impairment. Some licensed product information in the UK recommends that the dose of colchicine given *orally* should be reduced by up to 50% in patients with mild to moderate renal impairment, and that it should not be used in those with severe impairment. Similar recommendations have been made by various sources in the USA; for example, the *American Hospital Formulary Service* notes that some recommend the prophylactic oral dose should not exceed 600 micrograms daily in patients with a serum creatinine of 1.6 mg per 100 mL or greater, or with a creatinine clearance (CC) of 50 mL/minute or less. Some patients may only need 600 micrograms every alternate day. The *intravenous* dose 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.

Amyloidosis. Colchicine is well known to have a useful role in amyloidosis (p.743) 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,[1] and a later study[2] found no benefit in adding colchicine to the standard therapy. The mechanism of the anti-amyloid effect of colchicine is not clear.

1. 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.
2. 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.1499) 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.[1] The mechanism of action in this condition is believed to be based on the effect on polymorphonuclear leucocytes and other cellular effects.[2] Colchicine has also been used with corticosteroids for acute exacerbations, followed by colchicine maintenance;[3] colchicine with aspirin has also been recommended in acute disease,[4] and colchicine with benzathine benzylpenicillin has been tried.[5]

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

Diffuse parenchymal lung disease. Colchicine is a potential alternative to corticosteroid therapy in patients with cryptogenic fibrosing alveolitis (see Diffuse Parenchymal Lung Disease, p.1502). However the degree of benefit, if any, is unclear although colchicine does appear to be safer and better tolerated than corticosteroid therapy.[1]

1. 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).

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.[1,2] 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.743), which can lead to nephrotic syndrome, renal failure, and death.

Familial Mediterranean fever is managed with colchicine.[1-3] Colchicine cannot stop an established attack, but, given prophylactically in oral adult doses of 1 to 3 mg daily, it reduces the frequency of attacks, prevents amyloidosis and reverses proteinuria. An initial daily dose of 500 micrograms or less has been suggested for children younger than 5 years of age, 1 mg for those aged 5 to 10 years, and 1.5 mg for children aged over 10 years; doses may be increased in a stepwise fashion to a maximum of 2 mg daily if needed.[3] Attacks are usually treated with NSAIDs[2,3] or, in severe cases, opioids.[3] Anecdotal evidence has suggested that prazosin may also be of benefit,[4] but initial reports of improvement with interferon alfa have not been borne out.[2] Anakinra has also been investigated.[5]

1. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet* 1998; **351:** 659–63.
2. Drenth JPH, van der Meer JWM. Hereditary periodic fever. *N Engl J Med* 2001; **345:** 1748–57.
3. 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)
4. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129:** 424–5.
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.1505), refractory to standard therapy, a few patients have had partial or complete response to colchicine[1,2] and further studies have been suggested.[2,3]

1. Strother SV, *et al.* Colchicine therapy for refractory idiopathic thrombocytopenic purpura. *Arch Intern Med* 1984; **144:** 2198–2200.
2. 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.
3. McMillian R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126:** 307–14.

Pericarditis. Mild cases of recurrent pericarditis may be treated with colchicine, as an adjunct to NSAID therapy.[1-3] It may also provide effective prophylaxis, allowing the tapering of corticosteroids, which are usually reserved for the treatment of severe acute attacks.[2,3] The drug has also been used successfully in children.[4] 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.[5] Another open-label study had similar results using adjunctive colchicine for the first episode of acute pericarditis.[6] In patients with two or more relapses of acute pericarditis, colchicine was found to be highly effective in preventing recurrence.[7] 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.

1. Millaire A, *et al.* Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994; **15:** 120–4.
2. Adler Y, *et al.* Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998; **97:** 2183–5.
3. Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000; **84:** 449–54.
4. Yazigi A, *et al.* Colchicine for recurrent pericarditis in children. *Acta Paediatr Scand* 1998; **87:** 603–4.
5. 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.
6. 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.
7. 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.[1] A combination of vitamin E and colchicine has also been suggested as an alternative in early disease.[2]

1. Kadioğlu 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.
2. 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.2408) is a chronic progressive liver disease with no specific treatment, and in general drug therapy has been poor or largely ineffective. Reviewers have noted[1-3] 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.[4] Some consider that combination therapy with colchicine, methotrexate, and ursodeoxycholic acid may be more promising than monotherapy.[2]

1. Heathcote EJ. Evidence-based therapy of primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999; **11:** 607–15.
2. Holtmeier J, Leuschner U. Medical treatment of primary biliary cirrhosis and primary sclerosing cholangitis. *Digestion* 2001; **64:** 137–50.
3. 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).
4. Kaplan MM, *et al.* A prospective trial of colchicine and methotrexate in the treatment of primary biliary cirrhosis. *Gastroenterology* 1999; **117:** 1173–80.

Pyoderma gangrenosum. Pyoderma gangrenosum (p.1583) associated with inflammatory bowel disease has been successfully treated with colchicine in 2 patients.[1,2] Colchicine was also of benefit in 3 patients with pyoderma associated with familial Mediterranean fever.[3] Other isolated reports include the use of low-dose colchicine in idiopathic pyoderma gangrenosum.[4]

1. Paolini O, *et al.* Treatment of pyoderma gangrenosum with colchicine. *Lancet* 1995; **345:** 1057–8.
2. Rampal P, *et al.* Colchicine in pyoderma gangrenosum. *Lancet* 1998; **351:** 1134–5.
3. 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.
4. Kontochristopoulos GJ, *et al.* Treatment of pyoderma gangrenosum with low-dose colchicine. *Dermatology* 2004; **209:** 233–6.

Preparations

BP 2008: Colchicine Tablets;
USP 31: Colchicine Injection; Colchicine Tablets; Probenecid and Colchicine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Xuric; ***Austral.:*** Colgout; Lengout; ***Braz.:*** Cixin; Colchin; Colchis; ***Hong Kong:*** Colcina; Colgout; CP-Colchi; ***Hung.:*** Colchicum-Dispert; ***India:*** Goutnil; ***Indon.:*** Recolfar; ***Malaysia:*** Goutnil†; ***Mex.:*** Colchiquim; Sixol; Ticolcin; ***NZ:*** Colgout; ***Thai.:*** Cochic; Colchily; Colcine; Goutichine; Prochic; Tolchicine; ***Turk.:*** Colchicum-Dispert; Kolsin.

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

Colchicum

Colchico; Colchique.

Безвременник

Profile

Colchicum, the dried ripe seeds or dried corm of the meadow saffron, *Colchicum autumnale*, contains colchicine (p.556) and has been used similarly for the prophylaxis and relief of acute gout.

It is also included in several herbal preparations.

Homoeopathy. Colchicum has been used in homoeopathic 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*.[1-6] 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. Gabrscek 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 Part 3)
Ger.: Colchysat.

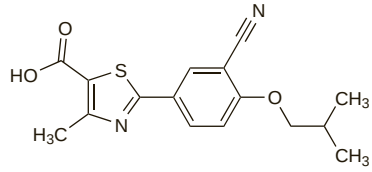
Multi-ingredient: ***Ger.:*** Unguentum lymphaticum; ***Venez.:*** Linfoderm.

Febuxostat *(USAN, rINN)*

Febuxostatum; 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.



Profile

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase, and is under investigation for the treatment of hyperuricaemia in patients with chronic gout.

◊ References.

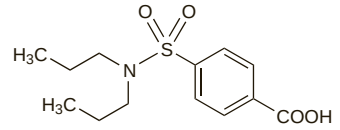
1. Mayer MD, *et al.* Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther* 2005; **12:** 22–34.
2. Schumacher HR. Febuxostat: a non-purine, selective inhibitor of xanthine oxidase for the management of hyperuricaemia in patients with gout. *Expert Opin Invest Drugs* 2005; **14:** 893–903.
3. 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.
4. 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.
5. 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 Pharmacokinet* 2006; **45:** 821–41.
6. Bruce SP. Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. *Ann Pharmacother* 2006; **40:** 2187–94.

Probenecid *(BAN, rINN)* ⊗

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

Пробенецид

$C_{13}H_{19}NO_4S$ = 285.4.
CAS — 57-66-9.
ATC — M04AB01.
ATC Vet — QM04AB01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Probenecid). A white or almost white crystalline powder or small crystals. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone.
USP 31 (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.[1]

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 porphyrinogenicity.

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 sulfonylurea 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.