nol 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.[18]


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. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2002; **41:** 521–4.
12. Velez I, *et al.* Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 232–6.
13. Martinez S, *et al.* Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis* 1997; **24:** 165–9.
14. 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.
15. Apt W, *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; **59:** 133–8.
16. Amato Neto V. Etiological treatment for infection by Trypanosoma cruzi. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 211–3.
17. 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.
18. 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.2181) in patients with hyperuricosuria.[1,2] The recommended oral dose of allopurinol is 200 to 300 mg daily adjusted on the basis of subsequent 24-hour urinary urate excretion. 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. Ettinger 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.1512), and other drugs are very much second line, there are reports[1-3] 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. Bregnhoej 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.955), and allopurinol has been investigated as a possible adjunctive treatment, with some evidence of benefit, especially in patients with refractory positive symptoms.[1]


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.[1]


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 2008:*** Allopurinol Tablets;
***USP 31:*** Allopurinol Oral Suspension; Allopurinol Tablets.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Alfadiman; Alloboxal†; Gotir†; Puritenk; ***Austral.:*** Allohexal; Allorin†; Allosig; Capurate†; Progout; Zyloprim; ***Austria:*** Allostad; Allotyrol†; Apurin†; Gewapurol; Gichtex; Purinol; Urosin; Zyloric; ***Belg.:*** Alpuric; Docallopu; Zyloric; ***Braz.:*** Labopurinol†; Lopurax; Uricemil†; Zilopur; Zyloric; ***Canad.:*** Novo-Purol; Zyloprim; ***Chile:*** Talol; Urogotan A; Zyloric; ***Cz.:*** Apurol†; Milurit; Purinol; ***Denm.:*** Abopur; Apurin; Hexanurat; ***Fin.:*** Allonol; Apurin; Arturic; Zyloric; ***Fr.:*** Zyloric; ***Ger.:*** Allo; Allo-Efeka; Allo-Puren†; Allobeta; Bleminol; Cellidrin; dura AL; Epidropal; Foligan; Jenapurinol; Milurit; Pureduct†; Remid; Uribenz; Uripurinol†; Zyloric; ***Gr.:*** Soluric; Zylapour; Zyloric; ***Hong Kong:*** Allnol†; Marinol; Mephanol†; Milurit; Progout; Zyloric; ***Hung.:*** Harpagin†; Milurit; ***India:*** Ciploric; Zyloric; ***Indon.:*** Algut; Benoxuric; Hycemia; Isoric; Licoric; Llanol; Nilapur; Pritanol; Puricemia; Reucid; Rinolic; Sinoric; Tylonic; Urica; Uricnol; Xanturic; Zyloric; ***Irl.:*** Purinol; Tipuric; Zyloric; ***Israel:*** Alloril; Zylol; Zyloric†; ***Ital.:*** Allurit; Uricemil†; Zyloric; ***Malaysia:*** Harpagin†; Uritab†; Zyloric; ***Mex.:*** Acyprin; Apo-Tinole†; Atisuril; Aurigen†; Bionol; Darzune; Etindrax; Unizuric; Zyloprim; ***Neth.:*** Apurin; Zyloric; ***Norw.:*** Allopur; Arturic; Zyloric; ***NZ:*** Allohexal; Allorin; Progout; ***Philipp.:*** Allurase; Alpurase; Elavil; Llanol; Lopric; Loricid; Purinase; Purispec; Puristen; Synol; Trianol; Xanurace; Zyloprim; ***Pol.:*** Allupol; Milurit; Zyloric; ***Port.:*** Alosfar; Uriprim; Zurim; Zyloric; ***Rus.:*** Purinol (Пуринол); ***S.Afr.:*** Lonol; Puricos; Redurate; Urinol; Zyloprim; ***Singapore:*** Erloric†; Progout; Valeric†; Zyloric; ***Spain:*** Zyloric; ***Swed.:*** Zyloric; ***Switz.:*** allo-basan†; Allopur; Cellidrine; Mephanol; Sigapurol N†; Uriconorme; Zyloric; ***Thai.:*** Alinol; Allopin; Apnol; Apurol; Loporic†; Medoric; Puricin†; Puride; Uricad; Valeric†; Xanol; Zyloric; ***Turk.:*** Allo-Urik; Allogut; Urikoliz; ***UK:*** Caplenal; Cosuric; Rimapurinol; Xanthomax†; Zyloric; ***USA:*** Aloprim; Zyloprim; ***Venez.:*** Aluprol†; Aluron; Zyloric.

**Multi-ingredient:** ***Arg.:*** Artrex; Colpuril; Xuric-A; ***Austria:*** Allobenz; Duovitan; Gichtex plus; ***Belg.:*** Comburic; ***Ger.:*** Allo.comp.; Allomaron†; Harpagin; ***Ital.:*** Uricodue; ***Philipp.:*** Allomaron; ***Port.:*** Acifugan†; ***S.Afr.:*** Allomaron†; ***Spain:*** Acifugan†; Facilit†; ***Thai.:*** Allomaron.

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## Benzbromarone *(BAN, USAN, rINN)*

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

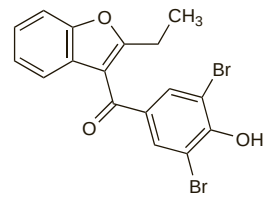
Бензбромарон

$C_{17}H_{12}Br_2O_3$ = 424.1.

*CAS — 3562-84-3.*

*ATC — M04AB03.*

*ATC Vet — QM04AB03.*



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

**Ph. Eur. 6.2** (Benzbromarone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect 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 has occurred and monitoring of liver function has been recommended.

**Effects on the liver.** Benzbromarone-induced liver damage has been reported.[1-4]


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.


### 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, alkalinisation 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.1429).

**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.553.

### 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.


1. Maurer H, Wollenberg P. Urinary metabolites of benzbromarone in man. *Arzneimittelforschung* 1990; **40:** 460–2.
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.552) 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.


1. 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.
2. Kumar S, *et al.* Benzbromarone therapy in management of refractory gout. *N Z Med J* 2005; **118:** U1528.


### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Max Uric†; ***Austria:*** Uricovac; ***Belg.:*** Desuric†; ***Braz.:*** Narcaricina†; ***Ger.:*** Narcaricin†; ***Hung.:*** Harpagin†; ***Jpn:*** Urinorm; ***Malaysia:*** Harpagin†; ***Mex.:*** Desuric†; ***Neth.:*** Desuric; ***S.Afr.:*** Minuric†; ***Singapore:*** Narcaricin†; ***Spain:*** Urinorm; ***Switz.:*** Desuric†; Obaron†; ***Thai.:*** Narcaricin†.

**Multi-ingredient:** ***Austria:*** Allobenz; Duovitan; Gichtex plus; ***Belg.:*** Comburic; ***Ger.:*** Allo.comp.; Allomaron†; Harpagin; ***Philipp.:*** Allomaron; ***Port.:*** Acifugan†; ***S.Afr.:*** Allomaron†; ***Spain:*** Acifugan†; Facilit†; ***Thai.:*** Allomaron.

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## Benziodarone *(BAN, rINN)*

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

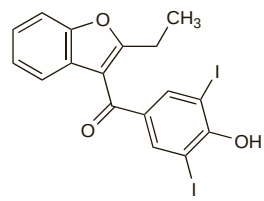
Бензйодарон

$C_{17}H_{12}I_2O_3$ = 518.1.

*CAS — 68-90-6.*

*ATC — C01DX04.*

*ATC Vet — QC01DX04.*



### Profile

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

Benziodarone has been associated with jaundice and thyroid disorders.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Spain:*** Dilafurane†.

**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[α]heptalen-7-yl)acetamide.

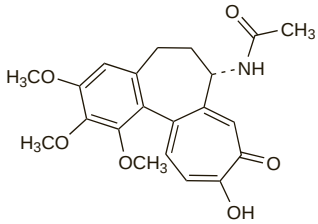
Колхицин

$C_{22}H_{25}NO_6$ = 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-