Pharmacokinetics

Peak plasma-dihydroergotamine concentrations have been attained within about 1 to 2 hours after oral doses, about 30 minutes after intramuscular injection, about 15 to 45 minutes after subcutaneous injection, and about 45 to 55 minutes after intranasal doses. However, the bioavailability of dihydroergotamine after oral doses is very low; values ranging from less than 0.1 to 1.5% have been reported. Although dihydroergotamine is incompletely absorbed from the gastrointestinal tract, the low bioavailability is considered to be determined primarily by extensive first-pass hepatic metabolism. Bioavailability after intranasal doses is 43%. Dihydroergotamine is 90 to 95% bound to plasma proteins.

Dihydroergotamine undergoes extensive metabolism, the major metabolite, 8′-β-hydroxydihydroergotamine, being active. Plasma concentrations of this metabolite are greater than those of dihydroergotamine. A further oxidation step produces 8′,10′-dihydroxydihydroergotamine, which is also active. Other metabolites are also formed. Most of a dose is excreted as metabolites, mainly in the bile; 5 to 10% is excreted in the urine of which only trace amounts are of unchanged drug. The elimination of dihydroergotamine is biphasic; half-lives of about 1 to 2 hours and 22 to 32 hours have been reported for the 2 phases, respectively.

◊ References.

1. Little PJ, *et al.* Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol* 1982; **13:** 785–90.
2. Müller-Schweinitzer E. Pharmacological actions of the main metabolites of dihydroergotamine. *Eur J Clin Pharmacol* 1984; **26:** 699–705.
3. de Marées H, *et al.* Relationship between the venoconstrictor activity of dihydroergotamine and its pharmacokinetics during acute and chronic oral dosing. *Eur J Clin Pharmacol* 1986; **30:** 685–9.
4. Humbert H, *et al.* Human pharmacokinetics of dihydroergotamine administered by nasal spray. *Clin Pharmacol Ther* 1996; **60:** 265–75.

Uses and Administration

Dihydroergotamine is a semisynthetic ergot alkaloid that has weaker oxytocic and vasoconstrictor effects than ergotamine (p.621). Its activity as a 5-HT_1 agonist is believed to contribute to its antimigraine action. It is used in the treatment of migraine and cluster headache, and in the treatment of orthostatic hypotension. It has also been used for the prophylaxis of venous thromboembolism (see below).

Dihydroergotamine is commonly used as the mesilate by subcutaneous, intramuscular, or intravenous injection, although it may also be given as a nasal spray or orally.

For the treatment of migraine and to terminate an acute attack of cluster headache, dihydroergotamine mesilate is usually given by subcutaneous or intramuscular injection in doses of 1 mg repeated, if necessary, after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg up to a maximum daily dose of 2 mg. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 500 micrograms sprayed into each nostril as a 0.4% solution followed after 15 minutes by an additional 500 micrograms in each nostril. A total intranasal dose of 2 mg per attack should not be exceeded. In the USA, the maximum dose in 24 hours is 3 mg and in a 7-day period is 4 mg, while maximum daily doses of up to 4 mg with a maximum dose of 12 mg in a 7-day period have been given in other countries. In some countries it is given orally; up to 10 mg daily has been given orally for the treatment of acute attacks of migraine. Lower oral doses have been given in some countries for migraine prophylaxis.

Dihydroergotamine mesilate has also been used alone or with etilefrine hydrochloride (p.1284) in the treatment of orthostatic hypotension, in usual oral doses of up to 10 mg daily in divided doses. Doses of up to 40 to 60 mg have been used in some patients.

Dihydroergotamine tartrate has been used for indications similar to those of the mesilate.

Medication-overuse headache. Dihydroergotamine may be used in the treatment of medication-overuse headache (p.616), including symptoms of ergotamine withdrawal.

Migraine and cluster headache. Although sumatriptan is often the treatment of choice to abort acute attacks of migraine (p.616) that do not respond to simple analgesic preparations, parenteral dihydroergotamine, especially with an antiemetic, is an alternative for patients who develop severe or refractory migraine.[1-3] Preparations for intranasal[4,5] use are also available; in some countries, it is given orally. In a comparative study, relief of migraine was slower after subcutaneous dihydroergotamine than after subcutaneous sumatriptan, but headache recurred less often.[6] In other studies, intranasal dihydroergotamine was not as effective as subcutaneous[5] or intranasal[7] sumatriptan.

Dihydroergotamine is also used in the treatment of cluster headache (p.616), usually in emergency settings, where it is given to abort individual headache attacks.

1. Scott AK. Dihydroergotamine: a review of its use in the treatment of migraine and other headaches. *Clin Neuropharmacol* 1992; **15:** 289–96.
2. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45:** 577–84.
3. Colman I, *et al.* Parenteral dihydroergotamine for acute migraine headache: a systematic review of the literature. *Ann Emerg Med* 2005; **45:** 393–401.
4. Ziegler D, *et al.* Dihydroergotamine nasal spray for the acute treatment of migraine. *Neurology* 1994; **44:** 447–53.
5. Touchon J, *et al.* A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology* 1996; **47:** 361–5.
6. Winner P, *et al.* A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996; **53:** 180–4.
7. Boureau F, *et al.* A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *Int J Clin Pract* 2000; **54:** 281–6.

Orthostatic hypotension. Dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p.1530). It is sometimes used in preparations with sympathomimetics such as etilefrine. After parenteral dihydroergotamine, standing blood pressure is increased, but total peripheral resistance and supine blood pressure are also increased.[1] It does not prevent postprandial hypotension, presumably because it does not constrict the splanchnic veins, although use with caffeine may overcome this problem. The main disadvantage of dihydroergotamine, however, is that it is ineffective, or at best weakly effective, when given by mouth, although there has been some evidence that oral ergotamine tartrate may be of value.

Dihydroergotamine has been suggested for use in the prevention of hypotension associated with epidural[2] or spinal anaesthesia,[3] the usual management of which is discussed in Treatment of Adverse Effects of Local Anaesthetics, p.1851. It has also been tried in the management of hypotension associated with haemodialysis.[4]

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Mattila M, *et al.* Dihydroergotamine in the prevention of hypotension associated with extradural anaesthesia. *Br J Anaesth* 1985; **57:** 976–82.
3. Critchley LAH, Woodward DK. Haemodynamic effects of three doses of dihydroergotamine during spinal anaesthesia. *Br J Anaesth* 2001; **87:** 499–501.
4. Milutinovic S. Dihydroergotamin in der Behandlung von Patienten mit symptomatischer Hypotonie während Dauerhämodialyse. *Arzneimittelforschung* 1987; **37:** 554–6.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism is usually with heparin or low-molecular-weight heparin (p.1189). Dihydroergotamine can reduce venous stasis by vasoconstriction of capacitance vessels and has enhanced postoperative prophylaxis when used with heparin.[1] Doses of dihydroergotamine mesilate 500 micrograms with heparin 5000 units, both given subcutaneously 2 hours before surgery, have been used. This regimen has then been given every 8 to 12 hours for 5 to 14 days depending on the risk of thrombosis. The use of dihydroergotamine with low-molecular-weight heparin has been shown to be of similar efficacy to dihydroergotamine with heparin[2,3] but might offer a more convenient dosing schedule. However, although dihydroergotamine might enhance the effect of heparin, a US National Institutes of Health consensus conference warned of the potential risk associated with its vasoconstrictive effects, and the contraindications to its use.[4] In 1989 the Swedish Adverse Drug Reactions Advisory Committee recommended that dihydroergotamine with heparin should not be given for more than 7 days (see Effects on the Cardiovascular System, under Adverse Effects, above).

1. Lindblad B. Prophylaxis of postoperative thromboembolism with low dose heparin alone or in combination with dihydroergotamine: a review. *Acta Chir Scand* 1988; (suppl 543): 31–42.
2. Sasahara AA, *et al.* Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *Br J Surg* 1986; **73:** 697–700.
3. Haas S, *et al.* Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. *Arzneimittelforschung* 1987; **37:** 839–43.
4. NIH Consensus Development. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986; **256:** 744–9.

Preparations

USP 31: Dihydroergotamine Mesylate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Dihydergot; ***Austria:*** Detemes; DHE; Dihydergot; Divegal; Ergont; Ergovasan; Migranal; ***Belg.:*** Diergo; Dihydergot; Dystonal; ***Braz.:*** Dihydergot†; ***Canad.:*** Migranal; ***Cz.:*** Clavigrenin†; Dihydergot; ***Fin.:*** Orstanorm; ***Fr.:*** Ikaran; Seglor; Tamik; ***Ger.:*** Agit; Angionorm; Clavigrenin†; DET MS; DET MS spezial†; DHE; Dihydergot†; Dihytamin; Erganton†; Ergomimet†; Ergont†; ergotam; Verladyn; ***Gr.:*** Dihydergot; Pervone†; Verteblan†; ***Hong Kong:*** Tamik†; ***India:*** Dihydergot†; Migranil; ***Indon.:*** Dihydergot; ***Ital.:*** Diidergot; Ikaran; Migranal†; Seglor; ***Mex.:*** Dihydergot; ***Port.:*** Dihydergot†; Seglor; ***Spain:*** Dihydergot; ***Swed.:*** Migranal†; Orstanorm; ***Switz.:*** Dihydergot; Ergotonine; Ikaran†; ***Thai.:*** Poligot†; ***USA:*** DHE; Migranal; ***Venez.:*** Dihydergot.

Multi-ingredient: ***Arg.:*** Parsel†; Polper Vascular; ***Austria:*** Agilan; Defluina; Dihydergot; Effortil comp; Hypodyn; Tonopan; Troparin compositum; Venotop; ***Braz.:*** Cefalium; Cefaliv; Enxak; Migraliv; Parcel; Tonopan; ***Chile:*** Emagrip; Migratapsin; Migrax; Parsel†; ***Fr.:*** Diergospray; ***Ger.:*** Agit plus†; Dihydergot plus; Effortil plus; Embolex NM†; Ergo-Lonarid PD†; Ergolefrin; Ergomimet plus†; Optalidon special NOC†; ***Mex.:*** Parsel; Tonopan; ***Spain:*** Tonopan; ***Switz.:*** Dihydergot; Dihydergot plus; Effortil plus; Tonopan†; ***Venez.:*** Brudol; Difen; Dol; Ivagan; Letydol; Parsel; Tainol†.

Eletriptan Hydrobromide

(BANM, USAN, rINNM)

Eletriptaanihydrobromidi; Élétriptan, Bromhydrate d'; Eletriptan-hydrobromid; Eletriptani Hydrobromidum; Hidrobromuro de eletriptán; UK-116044-04. 3-{[(*R*)-1-Methyl-2-pyrrolidinyl]methyl}-5-[2-(phenylsulfonyl)ethyl]indole hydrobromide.

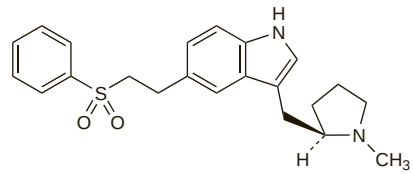
Элетриптана Гидробромид

$C_{22}H_{26}N_2O_2S,HBr$ = 463.4.

CAS — 143322-58-1 (eletriptan); 177834-92-3 (eletriptan hydrobromide).

ATC — N02CC06.

ATC Vet — QN02CC06.



(eletriptan)

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Eletriptan should not be used in patients with severe hepatic or severe renal impairment. Blood pressure effects of eletriptan are increased in renal impairment and therefore the dose should be reduced in patients with mild to moderate renal impairment. No dosage adjustment is needed in mild or moderate hepatic impairment.

Breast feeding. Eletriptan is distributed into breast milk and the manufacturer has suggested that infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

Interactions

As for Sumatriptan, p.626.

Eletriptan should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as erythromycin and ketoconazole; increased plasma levels of eletriptan have been noted after such combinations. It is recommended that eletriptan should not be taken within at least 72 hours of treatment with such drugs.

Pharmacokinetics

After oral doses eletriptan is rapidly and well absorbed (at least 81%) and has a bioavailability of about 50%. Peak plasma concentrations are attained within 1.5 hours. Eletriptan is about 85% protein bound. It is primarily metabolised by the hepatic cytochrome P450

isoenzyme CYP3A4. Non-renal clearance accounts for about 90% of the elimination of eletriptan and the plasma elimination half-life is about 4 hours. A small amount is distributed into breast milk.

◊ References.

1. Shah AK, *et al.* Pharmacokinetics and safety of oral eletriptan during different phases of the menstrual cycle in healthy volunteers. *J Clin Pharmacol* 2001; **41:** 1339–44.
2. Shah AK, *et al.* The pharmacokinetics and safety of single escalating oral doses of eletriptan. *J Clin Pharmacol* 2002; **42:** 520–7.
3. Milton KA, *et al.* Pharmacokinetics, pharmacodynamics, and safety of the 5-HT agonist eletriptan following intravenous and oral administration. *J Clin Pharmacol* 2002; **42:** 528–39.

Uses and Administration

Eletriptan hydrobromide is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Eletriptan is given orally as the hydrobromide, but doses are expressed in terms of the base; eletriptan hydrobromide 24.2 mg is equivalent to about 20 mg of eletriptan.

The usual dose is 40 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. Doses of 80 mg may be used in subsequent attacks, but should not be repeated within a 24-hour period. For doses in renal impairment, see below.

Administration in renal impairment. In the UK, a dose of 20 mg of eletriptan is recommended in patients with mild to moderate renal impairment. The maximum daily dose should not exceed 40 mg. Eletriptan should not be used in severe impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Mathew NT, *et al.* Tolerability and safety of eletriptan in the treatment of migraine: a comprehensive review. *Headache* 2003; **43:** 962–74.
2. Takiya L, *et al.* Safety and efficacy of eletriptan in the treatment of acute migraine. *Pharmacotherapy* 2006; **26:** 115–28.
3. McCormack PL, Keating GM. Eletriptan: a review of its use in the acute treatment of migraine. *Drugs* 2006; **66:** 1129–49.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Relpax; ***Belg.:*** Relert; ***Canad.:*** Relpax; ***Chile:*** Relpax; ***Cz.:*** Relpax; ***Denm.:*** Relpax; ***Fin.:*** Relert; ***Fr.:*** Relpax; ***Ger.:*** Relpax; ***Gr.:*** Relpax; ***Hung.:*** Relpax; ***Israel:*** Relert; ***Ital.:*** Relpax; ***Mex.:*** Relpax; ***Neth.:*** Relpax; ***Norw.:*** Relpax; ***Pol.:*** Relpax; ***Port.:*** Relert; ***Rus.:*** Relpax (Релпакс); ***S.Afr.:*** Relpax; ***Singapore:*** Relpax; ***Spain:*** Relert; Relpax; ***Swed.:*** Relpax; ***Switz.:*** Relpax; ***Turk.:*** Relpax; ***UK:*** Relpax; ***USA:*** Relpax.

Ergotamine Tartrate *(BANM, rINNM)*

Ergotamiinitartraatti; Ergotamin Tartarat; Ergotamin Tartrat; Ergotamine, tartrate d'; Ergotamini tartras; Ergotamino tartratas; Ergotamin-tartarát; Ergotamintartrat; Ergotaminy winian; Tartrato de ergotamina. (5′*S*)-12′-Hydroxy-2′-methyl-5′-benzylergotaman-3′,6′,18-trione tartrate; (5′*S*)-12′-Hydroxy-2′-methyl-3′,6′,18-trioxo-5-benzylergotaman (+)-tartrate.

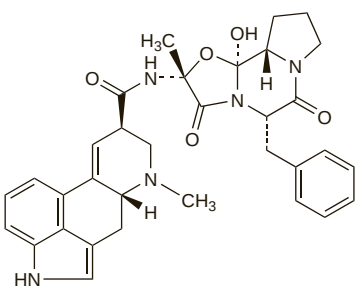
Эрготамина Тартрат

$(C_{33}H_{35}N_5O_5)_2,C_4H_6O_6$ = 1313.4.

CAS — 113-15-5 (ergotamine); 379-79-3 (ergotamine tartrate).

ATC — N02CA02.

ATC Vet — QN02CA02.



(ergotamine)

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

Ph. Eur. 6.2 (Ergotamine Tartrate). Slightly hygroscopic, colourless crystals or a white or almost white crystalline powder. It may contain 2 molecules of methanol of crystallisation. Slightly soluble in alcohol. Aqueous solutions slowly become cloudy owing to hydrolysis; this may be prevented by the addition of tartaric acid. A 0.25% suspension in water has a pH of 4.0 to 5.5. Store in airtight glass containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Ergotamine Tartrate). Colourless odourless crystals or a white or yellowish-white crystalline powder. Soluble 1 in about 3200 of water, but soluble 1 in about 500 of water in the presence of a slight excess of tartaric acid; soluble 1 in 500 of alcohol. Store at a temperature not exceeding 8°. Protect from light.

Stability in solution. References.

1. Kreilgård B, Kisbye J. Stability of ergotamine tartrate in aqueous solution. *Arch Pharm Chemi (Sci)* 1974; **2:** 1–13 and 38–49.

Adverse Effects

The adverse effects of ergotamine may be attributed either to its effects on the CNS, or to vasoconstriction of blood vessels and possible thrombus formation.

After therapeutic doses nausea and vomiting commonly occur as a result of the direct emetogenic effect of ergotamine; some patients may also experience abdominal pain. Weakness and muscle pains in the extremities and numbness and tingling of the fingers and toes may occur. There may occasionally be localised oedema and itching in hypersensitive patients. Treatment should be stopped if symptoms of vasoconstriction develop. Susceptible patients, especially those with sepsis, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine.

Symptoms of acute overdosage include nausea, vomiting, diarrhoea, extreme thirst, coldness, tingling, and itching of the skin, a rapid and weak pulse, hypertension or hypotension, shock, confusion, convulsions, and unconsciousness; fatalities have been reported. Further symptoms of peripheral vasoconstriction or of cardiovascular disturbances, as seen in chronic ergotamine poisoning, may also occur but may be delayed.

In chronic poisoning or ergotism, resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, severe circulatory disturbances may develop. The extremities, especially the feet and legs, become numb, cold, tingling, and pale or cyanotic, with muscle pain; there may be no pulse in the affected limb. Eventually gangrene develops in the toes and sometimes the fingers. Anginal pain, tachycardia or bradycardia, and hypertension or hypotension have been reported. Myocardial infarction has occurred rarely. Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Chronic, intractable headache (rebound headache) may occur and is also a major withdrawal symptom following the development of ergotamine dependence (see under Precautions, below). Other adverse effects include confusion and convulsions. On rare occasions symptoms of vasoconstriction of blood vessels in the brain, eye, intestines, and kidneys occur. Anorectal ulceration, sometimes leading to rectal necrosis and stenosis or rectovaginal fistula, has been reported after excessive use of suppositories containing ergotamine.

Effects on the cardiovascular system. Reports[1-9] of adverse cardiovascular effects associated with ergotamine, including mention of fatalities.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.
2. Corrocher R, *et al.* Multiple arterial stenoses in chronic ergot toxicity. *N Engl J Med* 1984; **310:** 261.
3. Fisher PE, *et al.* Ergotamine abuse and extra-hepatic portal hypertension. *Postgrad Med J* 1985; **61:** 461–3.
4. Deviere J, *et al.* Ischemic pancreatitis and hepatitis secondary to ergotamine poisoning. *J Clin Gastroenterol* 1987; **9:** 350–2.
5. Galer BS, *et al.* Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache* 1991; **31:** 446–50.
6. Redfield MM, *et al.* Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* 1992; **117:** 50–2.
7. Lazarides MK, *et al.* Severe facial ischaemia caused by ergotism. *J Cardiovasc Surg* 1992; **33:** 383–5.
8. Hillis W, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341:** 1564–5. Correction. *ibid.*; **342:** 1310.
9. Zavaleta EG, *et al.* St. Anthony's fire (ergotamine induced leg ischemia)—a case report and review of the literature. *Angiology* 2001; **52:** 349–56.

Fibrosis. For reference to fibrosis associated with the use of ergotamine tartrate, see Methysergide Maleate, p.623.

Treatment of Adverse Effects

Treatment of acute poisoning with ergotamine is symptomatic. Although the benefit of gastric decontamination is uncertain, activated charcoal may be given to patients who present within 1 hour of ingesting a toxic dose (more than 125 micrograms/kg in adults) or any amount in a child or adult with peripheral vascular disease, ischaemic heart disease, severe infection, or hepatic or renal impairment. Alternatively, gastric lavage may be considered in adults within 1 hour of ingesting a potentially life-threatening overdose. In chronic poisoning, withdrawal of ergotamine may be all that is required in some patients.

In both acute and chronic poisoning, attempts must be made to maintain an adequate circulation to the affected parts of the body in order to prevent the onset of gangrene. In severe arterial vasospasm vasodilators such as sodium nitroprusside by intravenous infusion have been given; heparin and dextran 40 have also been advocated to minimise the risk of thrombosis. Analgesics may be required for severe ischaemic pain.

Cardiovascular effects. Sodium nitroprusside has been used in severe ergotamine poisoning for its vasodilating and hypotensive actions; it should, however, be used with care if hypotension is a symptom of poisoning. It is usually given by intravenous infusion[1-4] although there have also been reports of intra-arterial infusion for ergotamine-induced ischaemia;[5,6] for details of precautions to be observed, see p.1397.

Many other drugs have been used in the treatment of circulatory disturbances induced by ergotamine. These include captopril by mouth,[7] alprostadil by intra-arterial infusion,[8,9] and glyceryl trinitrate by intravenous infusion.[10,11]

1. Carliner NH, *et al.* Sodium nitroprusside treatment of ergotamine-induced peripheral ischemia. *JAMA* 1974; **277:** 308–9.
2. Andersen PK, *et al.* Sodium nitroprusside and epidural blockade in the treatment of ergotism. *N Engl J Med* 1977; **296:** 1271–3.
3. Eurin B, *et al.* Ergot and sodium nitroprusside. *N Engl J Med* 1978; **298:** 632–3.
4. Carr P. Self-induced myocardial infarction. *Postgrad Med J* 1981; **57:** 654–5.
5. O'Dell CW, *et al.* Sodium nitroprusside in the treatment of ergotism. *Radiology* 1977; **124:** 73–4.
6. Whitsett TL, *et al.* Nitroprusside reversal of ergotamine-induced ischemia. *Am Heart J* 1978; **96:** 700.
7. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288:** 364.
8. Levy JM, *et al.* Prostaglandin E for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Intervent Radiol* 1984; **7:** 28–30.
9. Horstmann R, *et al.* Kritische Extremitätenischämie durch Ergotismus: Behandlung mit intraarterieller Prostaglandin-E -Infusion. *Dtsch Med Wochenschr* 1993; **118:** 1067–71.
10. Husum B, *et al.* Nitroglycerin infusion for ergotism. *Lancet* 1979; **ii:** 794–5.
11. Tfelt-Hansen P, *et al.* Nitroglycerin for ergotism: experimental studies in vitro and in migraine patients and treatment of an overt case. *Eur J Clin Pharmacol* 1982; **22:** 105–9.

Precautions

Ergotamine tartrate is contra-indicated in patients with severe or uncontrolled hypertension, shock, severe or persistent sepsis, peripheral vascular disease, ischaemic heart disease, temporal arteritis, hyperthyroidism, or hepatic or renal impairment. It is also contra-indicated in those with basilar or hemiplegic migraine. Ergotamine tartrate should be used with care in patients with anaemia. It is contra-indicated in pregnancy because of its oxytocic effect (see also below).

Patients should be warned to keep within the recommended dosage. Some symptoms of overdosage may mimic those of migraine. Numbness or tingling of the extremities generally indicates that ergotamine should be stopped. Although ergotamine is used for limited periods in the prevention of episodic cluster headache, it should not be given prophylactically in other circumstances, as prolonged use may give rise to gangrene. Dependence has occurred with regular use of ergotamine tartrate even if dosage recommendations are adhered to (see below).

Dizziness and feelings of anxiety have been reported; if affected, patients should avoid driving or operating machinery.