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.

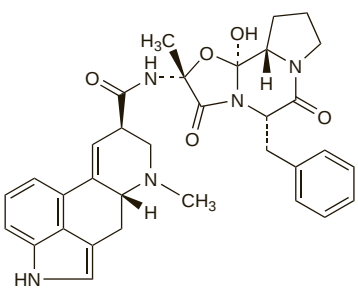
Эрготамина Тартрат

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

Breast feeding. Although the American Academy of Pediatrics includes ergotamine among those drugs that may be given with caution to breast-feeding mothers,[1] it notes that maternal use in doses equivalent to those given for the treatment of migraine has been associated with vomiting, diarrhoea, and convulsions in nursing infants. UK licensed product information recommends that ergotamine tartrate should be avoided during breast feeding; the distribution of unchanged drug and metabolites into breast milk presents a risk of ergotism in the infant and repeated doses of ergotamine may impair lactation.

1. 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 01/06/04)

Cardiovascular disorders. In the USA, dihydroergotamine is contra-indicated in patients with ischaemic heart disease and other cardiovascular disorders such as hypertension, peripheral arterial disease, or coronary artery vasospasm and it is also recommended that it should not be given to those with a family history of ischaemic heart disease, to postmenopausal women or men aged over 40, or to those with other ischaemic risk factors such as hypertension, hypercholesterolaemia, smoking, diabetes, or obesity, unless cardiovascular evaluation to exclude such disease has been carried out. Similar precautions and contra-indications, which resemble those that apply to serotonin (5-HT_1) agonists such as sumatriptan (p.626), may be applicable to other ergot derivatives used in migraine such as ergotamine.

In other countries, warnings concerning the use of ergot derivatives in patients with risk factors for myocardial ischaemia appear to be less stringent, although caution is clearly advisable.

Dependence. Dependence can develop insidiously when ergotamine tartrate is used for more than 2 days each week, even if total daily or weekly dosage recommendations are observed.[1] Individual reports indicate a state of addiction characterised by a predictable and irresistible pattern of drug usage, the development of tolerance to adverse effects, and a syndrome of withdrawal on stopping the drug. Ergotamine-dependent patients suffer from daily, or almost daily, migraine headaches, often referred to as medication-overuse headaches or 'rebound headaches', which are only alleviated by ergotamine. Intensifying headache with autonomic disturbances occurs within 24 to 48 hours of withdrawal of ergotamine and may continue for 72 hours or longer. As with other medication-overuse headaches (p.616), supportive and symptomatic measures should be taken to treat the withdrawal syndrome.

1. Saper JR. Ergotamine dependency—a review. *Headache* 1987; **27:** 435–8.

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

Pregnancy. Ergotamine is contra-indicated in pregnancy because of its oxytocic effect. Accidental dosage of ergotamine in the form of a *Cafergot* suppository (ergotamine tartrate 2 mg and caffeine 100 mg) to a patient at 39 weeks of pregnancy caused uterine contractions and fetal tachycardia.[1] An emergency caesarean section was undertaken because of suspected placental abruption but no clear signs of retroplacental haemorrhage were found. The neonate recovered quickly after delivery and had developed normally during the next 10 years.

Jejunal atresia has been reported[2] in an infant born prematurely to a woman who had taken ergotamine tartrate 6 to 8 mg daily, as *Cafergot* tablets, throughout her pregnancy. Two cases of Möbius syndrome (a condition characterised by facial paralysis as a result of hypoplasia of cranial nerve nuclei) have been associated with exposure to ergotamine during the first trimester of pregnancy.[3,4] In the first report[3] the mother had inadvertently been given three *Cafergot* suppositories within a period of 1 to 2 hours and at the time had experienced uterine cramping and a bloody vaginal discharge. The second mother[4] had used 2-mg ergotamine suppositories on a regular basis during the first 8 weeks of pregnancy.

1. de Groot ANJA, *et al.* Ergotamine-induced fetal stress: review of side effects of ergot alkaloids during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **51:** 73–7.
2. Graham JM, *et al.* Jejunal atresia associated with Cafergot ingestion during pregnancy. *Clin Pediatr (Phila)* 1983; **22:** 226–8.
3. Graf WD, Shepard TH. Uterine contraction in the development of Möbius syndrome. *J Child Neurol* 1997; **12:** 225–7.
4. Smets K, *et al.* Ergotamine as a possible cause of Möbius sequence: additional clinical observation. *J Child Neurol* 2004; **19:** 398.

Interactions

The vasoconstrictor effects of ergotamine are enhanced by sympathomimetics such as adrenaline. There is also an increased risk of peripheral vasoconstriction during use of ergotamine with beta blockers.

Ergotamine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and consequently it should not be given with potent inhibitors of this isoenzyme; elevated ergotamine concentrations sufficient to cause ergotism may occur with azole antifungals, macrolide antibacterials such as erythromycin and clarithromycin, and HIV-protease inhibitors including indinavir and ritonavir. Use of tetracycline with ergotamine may also increase the risk of ergotism and should be avoided.

Ergotamine should not be used with or given until several hours after stopping a serotonin (5-HT_1) agonist, since there is an additional risk of prolonged vasospastic reactions; at least 6 hours is advised for almotriptan, rizatriptan, sumatriptan, and zolmitriptan, and at least 24 hours for eletriptan and frovatriptan. Conversely, a delay is advised before starting a serotonin agonist in patients who have been receiving ergotamine: almotriptan, eletriptan, frovatriptan, rizatriptan, sumatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of preparations containing ergotamine.

Antibacterials. Acute reactions ranging from minor ergotism[1] to severe vasospasm[2] have been reported in patients given *erythromycin* in addition to ergotamine. There are also reports of acute ergotism in patients receiving ergotamine tartrate and *clarithromycin*[3,4] or *troleandomycin*.[5] The theoretical possibility exists that there may be a similar interaction with *azithromycin*. Ergotism has also been reported in patients receiving erythromycin[6] or troleandomycin[7] with dihydroergotamine.

1. Lagier G, *et al.* Un cas d'ergotisme mineur semblant en rapport avec une potentialisation de l'ergotamine par l'éthylsuccinate d'érythromycine. *Therapie* 1979; **34:** 515–21.
2. Ghali R, *et al.* Erythromycin-associated ergotamine intoxication: arteriographic and electrophysiologic analysis of a rare cause of severe ischemia of the lower extremities and associated ischemic neuropathy. *Ann Vasc Surg* 1993; **7:** 291–6.
3. Horowitz RS, *et al.* Clinical ergotism with lingual ischemia induced by clarithromycin-ergotamine interaction. *Arch Intern Med* 1996; **156:** 456–8.
4. Ausband SC, Goodman PE. An unusual case of clarithromycin associated ergotism. *J Emerg Med* 2001; **21:** 411–13.
5. Matthews NT, Havill JH. Ergotism with therapeutic doses of ergotamine tartrate. *N Z Med J* 1979; **89:** 476–7.
6. Leroy F, *et al.* Dihydroergotamine-erythromycin-induced ergotism. *Ann Intern Med* 1988; **109:** 249.
7. Franco A, *et al.* Ergotisme aigu par association dihydroergotamine-triacétyloléandomycine. *Nouv Presse Med* 1978; **7:** 205.

Antidepressants. There have been isolated case reports[1] of the serotonin syndrome (p.416) in patients receiving dihydroergotamine with *amitriptyline*, *imipramine*, *paroxetine*, or *sertraline*.

1. Mathew NT, *et al.* Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* 1996; **16:** 323–7.

Antimigraine drugs. Arterial occlusion has been reported[1] in 2 patients given *methysergide* with a high parenteral dosage of ergotamine for cluster headache; the combination should be avoided. Use of ergotamine as supplementary antimigraine medication in patients receiving *dihydroergotamine* is not recommended.

For reports of arterial vasoconstriction in patients taking *beta blockers* and antimigraine drugs, see below. See also Interactions, above for a comment on the risk of vasospastic reactions with serotonin (5-HT_1) agonists such as *sumatriptan*.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.

Antivirals. There have been reports of ergotism in patients who received ergotamine and combination antiviral treatment for HIV infection. It was suggested that the ergotism might have been caused by inhibition of ergotamine metabolism by *ritonavir* in 4 cases,[1-4] *indinavir* in one,[5] and *nelfinavir*[6] in another. One of the patients receiving ritonavir,[4] who had taken three 1-mg tablets of ergotamine tartrate over the 4 days before presentation, also developed signs of cerebrovascular involvement and eventually went into an irreversible coma.

The metabolism of ergot alkaloids may be inhibited by *delavirdine* or *efavirenz*.

1. Caballero-Granado FJ, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and ritonavir in an AIDS patient. *Antimicrob Agents Chemother* 1997; **41:** 1207.
2. Montero A, *et al.* Leg ischemia in a patient receiving ritonavir and ergotamine. *Ann Intern Med* 1999; **130:** 329–30.
3. Liaudet L, *et al.* Severe ergotism associated with interaction between ritonavir and ergotamine. *BMJ* 1999; **318:** 771.
4. Pardo Rey C, *et al.* Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* 2003; **37:** e72–e73.
5. Rosenthal E, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and indinavir. *JAMA* 1999; **281:** 987.
6. Mortier E, *et al.* Ergotism related to interaction between nelfinavir and ergotamine. *Am J Med* 2001; **110:** 594.

Beta blockers. Peripheral vasoconstriction was reported in a patient with migraine after addition of *propranolol* to regular use of *Cafergot* (ergotamine and caffeine) suppositories twice daily.[1] This combination has been used without complication by others, who suggested that excessive dosage of ergotamine tartrate, rather than an interaction between ergotamine and propranolol, was responsible.[2] However, arterial vasoconstriction has been reported after use of methysergide with propranolol and *oxprenolol* with ergotamine.[3] Such combinations should therefore be used with caution.

1. Baumrucker JF. Drug interaction—propranolol and Cafergot. *N Engl J Med* 1973; **288:** 916–17.
2. Diamond S. Propranolol and ergotamine tartrate. *N Engl J Med* 1973; **289:** 159.
3. Venter CP, *et al.* Severe peripheral ischaemia during concomitant use of beta blockers and ergot alkaloids. *BMJ* 1984; **289:** 288–9.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to increase the oral bioavailability and plasma concentrations of dihydroergotamine in patients with orthostatic hypotension.[1]

1. Bobik A, *et al.* Low oral bioavailability of dihydroergotamine and first-pass extraction in patients with orthostatic hypotension. *Clin Pharmacol Ther* 1981; **30:** 673–9.

Tacrolimus. Ergotamine may inhibit the metabolism of tacrolimus by cytochrome P450 isoenzymes (see p.1845).

Pharmacokinetics

Absorption of ergotamine from the gastrointestinal tract is poor and may be further decreased by the occurrence of gastric stasis during migraine attacks. Bioavailability is also diminished by a high first-pass hepatic metabolism. Ergotamine has been given rectally or by inhalation in an attempt to overcome these effects, with some improvement in absorption, but bioavailability is still about 5% or less. Absorption of sublingual ergotamine is very poor. There is considerable interindividual variation in the bioavailability of ergotamine, regardless of the route. Caffeine is sometimes included in oral and rectal preparations of ergotamine to improve the latter's absorption, although whether it does so is not clear. Drugs such as metoclopramide are sometimes given with the aim of alleviating gastric stasis and thus improve the absorption of ergotamine.

Plasma protein binding is about 93 to 98%. Ergotamine is metabolised extensively in the liver via the cytochrome P450 isoenzyme CYP3A4; the majority of metabolites are excreted in the bile. About 4% of a dose is excreted in the urine. Some of the metabolites are pharmacologically active. The elimination of ergotamine is biphasic; half-lives of about 2 and 21 hours have been reported for the 2 phases, respectively. Ergotamine or its metabolites have been detected in breast milk.

◊ References.

1. Schmidt R, Fanchamps A. Effect of caffeine on intestinal absorption of ergotamine in man. *Eur J Clin Pharmacol* 1974; **7:** 213–16.
2. Eadie MJ. Ergotamine pharmacokinetics in man: an editorial. *Cephalalgia* 1983; **3:** 135–8.
3. Perrin VL. Clinical pharmacokinetics of ergotamine in migraine and cluster headache. *Clin Pharmacokinet* 1985; **10:** 334–52.

Uses and Administration

Ergotamine is an alkaloid derived from ergot (p.2010). It has marked vasoconstrictor effects, and a partial agonist action at serotonin (5-HT) receptors; it also has a powerful oxytocic action on the uterus, although less so than ergometrine (p.2009). It is used in migraine and cluster headache, and has been tried in orthostatic hypotension.

Ergotamine is commonly used as the tartrate. It is usually given orally, but has also been given sublingually, rectally, and by oral inhalation. It was formerly given by subcutaneous or intramuscular injection. Caffeine is sometimes given with ergotamine tartrate with the intention of improving the latter's absorption, although whether it does so is not clear. Antiemetics such as cyclizine hydrochloride are sometimes included in combination preparations with ergotamine tartrate.

Ergotamine is used in migraine unresponsive to non-opioid analgesics. However, its adverse effects limit its use and prevent use for prophylaxis. It is most effective when given as early as possible in a migraine attack, preferably during the prodromal phase.

The usual oral dose is 1 to 2 mg of ergotamine tartrate, repeated, if necessary, half an hour later. Usually not more than 6 mg should be given in 24 hours, although some manufacturers recommend not more than 4 mg in 24 hours and others not more than 8 mg per attack. The recommended minimum interval between successive 24-hour courses is 4 days, and the total weekly

dose is limited to a maximum of 12 mg, although again some manufacturers recommend a lower weekly limit of 8 mg. It is also recommended that patients should receive no more than 2 courses per month. Similar doses may be given sublingually.

Ergotamine tartrate may also be given rectally as suppositories, especially if the oral route is not effective or not practicable. The rectal dose of ergotamine tartrate is 2 mg repeated, if necessary, one hour later. Usually, not more than 4 mg should be given in 24 hours and not more than 8 mg in one week with an interval of at least 4 days between successive 24-hour courses.

A more rapid onset of action may be achieved by oral inhalation. One dose containing 360 micrograms of ergotamine tartrate has been inhaled at the onset of the attack and repeated, if necessary, at 5-minute intervals. Not more than 6 inhalation doses should be taken in 24 hours and not more than 12 in one week, with an interval of at least 4 days between successive 24-hour courses.

Ergotamine is used in patients with cluster headache to treat individual attacks of headache but since such attacks are short-lived oral inhalation may be preferable to oral, sublingual, or rectal routes. Doses used are similar to those given to treat migraine. It has also been used to prevent headache attacks during cluster periods, when it is usually given daily in low doses for up to 2 weeks, either orally or rectally (see below).

Migraine and cluster headache. Ergotamine was formerly one of the main drugs used to treat acute attacks of migraine (p.616) unresponsive to non-opioid analgesics, but triptan serotonin (5-HT_1) agonists such as sumatriptan are now preferred. Since ergotamine may exacerbate the nausea and vomiting that commonly develops as a migraine attack progresses it is often necessary to give an antiemetic as well. Poor oral bioavailability may be reduced further during a migraine attack and ergotamine has sometimes been given sublingually, rectally, or by inhalation. Adverse effects limit the dose that can be used for an individual attack and prevent the long-term use that would be required for migraine prophylaxis.

Ergotamine may be used similarly in cluster headache (p.616) to treat individual headaches during a cluster period. Ergotamine is also used in low doses given by mouth or rectally for limited periods of up to 2 weeks in the prophylaxis of headache attacks during a cluster period. Regimens that have been tried for such prophylaxis include 1 to 2 mg of ergotamine tartrate given 1 to 2 hours before an expected attack or 1 to 2 hours before bedtime for nocturnal attacks. The total maximum dose of ergotamine tartrate that may be given weekly for the prevention of cluster headache is less well established than for the treatment of migraine. Ergotamine is often given for only 5 to 6 days in each week, which allows the patient to assess whether the cluster period has ended.

References.

1. 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.
2. Tfelt-Hansen P, *et al*. Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 2000; **123:** 9–18.

Orthostatic hypotension. Ergotamine and dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p.1530). Ergotamine is believed[1] to be less selective than dihydroergotamine (p.619) in its actions and affects both venous capacitance and peripheral resistance.[2,3] However, the oral bioavailability of ergotamine is greater[2] than that of dihydroergotamine and there have also been some reports of successful treatment with inhaled[3,4] or rectal[5] ergotamine.

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39:** 74–85.
3. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153:** 474–85.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51:** 648–60.
5. Toh V, *et al*. Ergotamine use in severe diabetic autonomic neuropathy. *Diabet Med* 2006; **23:** 574–6.

Preparations

BP 2008: Ergotamine Sublingual Tablets;
USP 31: Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Ergotamine Tartrate Inhalation Aerosol; Ergotamine Tartrate Injection; Ergotamine Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Ergodryl Mono†; ***Austria:*** Ergokapton; ***Chile:*** Jaquedryl; ***Ger.:*** ergo sanol spezial N; Ergo-Kranit Migrane; Migrexa†; ***Hung.:*** Ergam; ***Ital.:*** Ergotan; ***Philipp.:*** Avamigran; ***Thai.:*** Ergosia; Gynaemine; ***USA:*** Ergomar.

Multi-ingredient: ***Arg.:*** Cafergot; Cefalex; Ibu-Tetralgin; Ibumar Migra†; Ibupirac Migra; Integrobe Plus; Jaquedryl†; Migra Dioxadol; Migra Donixina; Migral; Migral Compositum; Migral II; Mikesan; Solacil; Tetralgin; Tetralgin Novo; Zilactin-E†; ***Austral.:*** Cafergot; Ergodryl†; ***Austria:*** Avamigran; Cafergot; Migril; Secokapton; Synkapton; ***Belg.:*** Cafergot; ***Braz.:*** Migrane; Neogrein; Ormigrein; ***Canad.:*** Bellergal; Cafergot; Cafergot-PB†; Ergodryl; Gravergol†; ***Chile:*** Bellergal Retardado†; Cafergot-PB†; Cefalmin; Cinabel; Clonalgin Compuesto; Ergobelan; Ergonef; Fredol; Migra-Nefersil; Migragesic; Migranol; Migratam; Ultrimin; ***Cz.:*** Bellaspon†; ***Denm.:*** Ergokoffin; Gynergen Comp; ***Fin.:*** Anervan; ***Fr.:*** Gynergene Cafeine; ***Ger.:*** Avamigran N†; Cafergot N†; Ergo-Kranit†; Ergoffin†; Migratan S†; RubieNex spezial†; ***Gr.:*** Cafergot; ***Hong Kong:*** Cafergot; Gravergol†; Migril†; ***Hung.:*** Kefalgin; ***India:*** Migranil; ***Indon.:*** Bellapheen; Cafergot; Ericaf; ***Irl.:*** Migranat; Migril†; ***Israel:*** Cafergot; Temigran; ***Ital.:*** Cafergot; Virdex; ***Malaysia:*** Cafergot; ***Mex.:*** Cafergot; Caftar; Ergocaf; Optium; Sydolil; Trinergot; ***Neth.:*** Cafergot; Ercycof†; ***Norw.:*** Anervan; ***NZ:*** Cafergot; ***Pol.:*** Bellergot; Coffecom; ***Port.:*** Avamigran†; Migretil; ***S.Afr.:*** Cafergot; Cafergot-PB†; Migril; ***Singapore:*** Cafergot; ***Spain:*** Cafergot; Cafergot-PB†; Hemicraneal; ***Swed.:*** Anervan; Cafergot; ***Switz.:*** Bellagotin†; Cafergot; Cafergot-PB; ***Thai.:*** Avamigran; Bellergal†; Benera; Cafergot; Degran; Neuramizone; Poligot-CF; Polygot; Tofago; ***Turk.:*** Avmigran; Bellergal; Cafergot; Ergafein; ***UK:*** Cafergot; Migril; ***USA:*** Bel-Phen-Ergot S; Bellamine; Bellergal-S; Cafatine; Cafatine-PB; Cafergot; Ercaf; Folergot-DF; Phenerbel-S; Wigraine†; ***Venez.:*** Cafergot†; Ervostal; Migradorixina; Traveget.

Feverfew

Camomille, grande; Matricaria; Mattram; Nat' kopretiny řimbaby; Őszi margitvirág; Reunuspäivänkakkara; Tanaceti parthenii herba; Vaistinių skaistenių žolė.

Pharmacopoeias. In *Eur.* (see p.vii) and in *US*. US also describes Powdered Feverfew.
Ph. Eur. 6.2 (Feverfew). The dried, whole or fragmented aerial parts of *Tanacetum parthenium*. It contains not less than 0.2% of parthenolide ($C_{15}H_{20}O_3$ = 248.3), calculated with reference to the dried drug. It has a camphoraceous odour. Protect from light.
USP 31 (Feverfew). It consists of the dried leaves of *Tanacetum parthenium* (Asteraceae), collected when the plant is in flower. Store in a dry place. Protect from light.

Adverse Effects and Precautions

Mouth ulceration and soreness have been reported following ingestion of feverfew, and may be due to sensitisation; if they occur feverfew should be withdrawn. Contact dermatitis has been reported. Feverfew is reputed to have abortifacient properties and it is suggested that preparations should not be used in pregnancy.

Effects on the blood. There have been suggestions that feverfew may increase the risk of bleeding during surgery or in patients taking anticoagulants. However, although inhibition of platelet aggregation has been reported *in vitro* or in *animals* a review[1] of clinical studies noted that feverfew did not appear to affect haematological safety parameters.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Interactions

It has been suggested that feverfew may enhance the effects of anticoagulants (but see Effects on the Blood, above).

Uses and Administration

Feverfew consists of the dried leaves of the plant *Tanacetum parthenium* (Asteraceae). It is a traditional herbal remedy used in the prophylaxis of migraine. Its effects have been attributed to the plant's content of sesquiterpene lactones, notably parthenolide. A preparation of the dried leaf powder, which has been standardised to provide a minimum of 0.2% parthenolide, is available in some countries. A suggested oral dose is 250 mg daily; a lower dose of 100 mg daily has also been given..

Migraine. Feverfew is a traditional herbal remedy used in the prophylaxis of migraine (p.616). Studies of standardised preparations of the freeze-dried powdered leaf have produced variable results in preventing or ameliorating migraine attacks, and systematic reviews[1,2] suggest that its effectiveness in preventing migraine remains to be established.

1. Vogler BK, *et al*. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998; **18:** 704–8.
2. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Rheumatoid arthritis. Feverfew has been used as a herbal medicine for the treatment of arthritis but although it has anti-inflammatory activity *in vitro*, a clinical trial[1] found it to be ineffective in rheumatoid arthritis.

1. Pattrick M, *et al*. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis* 1989; **48:** 547–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Herbal Headache Relief†; ***Braz.:*** Tanaceto; Tenliv; ***Canad.:*** Tanacet; ***UK:*** Migraherb; Tanacet.

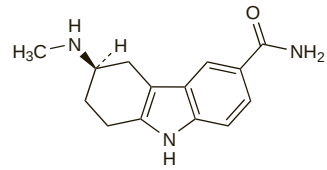
Multi-ingredient: ***Austral.:*** Albizia Complex; Extralife Arthri-Care; Extralife Migrai-Care; Guaiacum Complex†; ***Ital.:*** Neuralta Migren.

Frovatriptan *(BAN, rINN)*

Frovatriptaani; Frovatriptán; Frovatriptanum; SB-209509AX (frovatriptan or frovatriptan succinate); VML-251 (frovatriptan or frovatriptan succinate). (6*R*)-5,6,7,8-Tetrahydro-6-methylaminocarbazole-3-carboxamide.

Фроватриптан

$C_{14}H_{17}N_3O$ = 243.3.
CAS — 158747-02-5.
ATC — N02CC07.
ATC Vet — QN02CC07.



Frovatriptan Succinate *(BANM, USAN, rINNM)*

Frovatriptan, Succinate de; Frovatriptani Succinas; SB-209509AX (frovatriptan or frovatriptan succinate); Succinato de frovatriptán; VML-251 (frovatriptan or frovatriptan succinate).

Фроватриптана Суксинат

$C_{14}H_{17}N_3O,C_4H_6O_4,H_2O$ = 379.4.
CAS — 158930-17-7.
ATC — N02CC07.
ATC Vet — QN02CC07.

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Frovatriptan should not be used in patients with severe hepatic impairment. No dosage adjustment is needed in mild or moderate hepatic impairment.

Interactions

As for Sumatriptan, p.626.

Fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2 and has been shown to increase the blood levels of frovatriptan by 27 to 49%.

Pharmacokinetics

After oral doses, peak plasma-frovatriptan concentrations are attained in 2 to 4 hours, and bioavailability is about 20% in men and 30% in women. Food may delay the time to peak plasma concentrations by about 1 hour. Frovatriptan is 15% protein bound. It is primarily metabolised by the hepatic cytochrome P450 isoenzyme CYP1A2. About 32% of an oral dose is excreted in the urine and 62% in faeces. The plasma elimination half-life of frovatriptan is about 26 hours.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Buchan P, *et al*. Clinical pharmacokinetics of frovatriptan. *Headache* 2002; **42** (suppl 2): S54–S62.
2. Elkind AH, *et al*. Pharmacokinetics of frovatriptan in adolescent migraineurs. *J Clin Pharmacol* 2004; **44:** 1158–65.

Uses and Administration

Frovatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Frovatriptan is given orally as the succinate although doses are expressed in terms of the base; frovatriptan succinate 3.9 mg is equivalent to about 2.5 mg of frovatriptan.

The recommended dose is 2.5 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of at least 2 hours. The maximum dose of frovatriptan in 24 hours is 5 mg in the UK although, in the USA, a maximum daily dose of 7.5 mg is allowed.

◊ References.

1. Goldstein J. Frovatriptan: a review. *Expert Opin Pharmacother* 2003; **4:** 83–93.