NAME OF THE MEDICINE

Active ingredient  Ergotamine tartrate  Caffeine
CAS number  379-79-3  58-08-2
Molecular weight  1313  194.2
Molecular formula  (C_{33}H_{35}N_{5}O_{5})_{2},C_{4}H_{6}O_{6}  C_{8}H_{10}N_{4}O_{2}

DESCRIPTION

Ergotamine tartrate is a slightly hygroscopic colourless, odourless crystal or white or yellowish-white crystalline powder. It is soluble in water, slightly soluble in ethanol and chloroform and practically insoluble in ether.

Caffeine is an odourless, silky white crystal, or white crystalline powder which sublimes readily. It is sparingly soluble in water and is slightly soluble in alcohol and ether.

Tablets
Cafergot® tablets contain ergotamine tartrate 1 mg and caffeine 100 mg. Cafergot tablets are white, round sugar coated, tablets with no markings.

Suppositories
Cafergot® S suppositories contain ergotamine tartrate 2 mg and caffeine 100 mg. Cafergot S suppositories are whitish or with a tinge of grey/pink, approximately 30 mm in length and approximately 10 mm thick.
**PHARMACOLOGY**

Pharmacotherapeutic group: antimigraine preparations
ATC code: NO2C A52

**Mechanism of action**

The mode of action of ergotamine in aborting attacks of migraine and other vascular headaches may be due to its direct vasoconstrictive action on the dilated extracranial arteries. Caffeine accelerates and increases the enteral absorption of ergotamine.

**Pharmacokinetics**

**Ergotamine**

**Absorption**

There is limited information on the kinetics of ergotamine; it appears that there is great inter-individual variation in the absorption of ergotamine with the oral absorption being described as 62% in a study of elderly subjects. However, there appears to be extensive first pass metabolism. A study using rectal suppositories revealed low and variable plasma levels of ergotamine. Bioavailability is ≤ 5% from both oral and rectal formulations. It has been suggested that the therapeutic effects of the drug are partially due to active metabolites.

**Distribution**

There is very little information on distribution and protein binding.

**Metabolism**

Metabolism occurs in the liver.

**Elimination**

The main mode of ergotamine excretion is via the bile. Information on plasma half life is based on a study of six elderly subjects which revealed that elimination of ergotamine was biphasic with half- lives of 2.7 and 21 hours in the alpha and beta phase respectively.

**Caffeine**

**Absorption**

Caffeine is rapidly and totally absorbed and is completely bioavailable.

**Distribution**

The volume of distribution of caffeine is 0.5 to 0.8 L/kg with a tendency to have higher values in females than males. It is 35-40% protein bound.

**Biotransformation/Metabolism**

Caffeine is metabolised mainly in the liver.
Elimination
Caffeine is excreted predominantly in the urine. The half life varies in individuals from 2.5 to 10 hours.

Ergotamine tartrate and caffeine
No formal pharmacokinetic data are available on the fixed combination of ergotamine tartrate and caffeine.

INDICATIONS
Acute attacks of migraine, migraine variants and related types of vascular headaches.

CONTRAINDICATIONS
- Peripheral vascular disorders
- Obliterative vascular disease
- Coronary artery disease
- Severe and/or inadequately controlled hypertension
- Hepatic or renal impairment
- Concomitant treatment with CYP3A4 inhibitors, including antifungals (ketoconazole, itraconazole), HIV-protease inhibitors or reverse transcriptase inhibitors (ritonavir, nelfinavir, indinavir, delavirdine) and macrolide antibiotics (erythromycin, clarithromycin) [see “PRECAUTIONS”]
- Concomitant treatment with vasoconstrictor agents (including ergot alkaloids, sumatriptan and other 5HT1 receptor agonists) [see “INTERACTIONS WITH OTHER MEDICINES”]
- Pregnancy and lactation (see “PRECAUTIONS”)
- Septic conditions, shock
- Temporal arteritis, hemiplegic or basilar migraine
- Hypersensitivity to any component of the drug.

PRECAUTIONS
CYP3A4 inhibitors
There have been rare reports of serious adverse events in connection with the co-administration of ergot alkaloids and potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischaemia and/or ischaemia of the extremities. Examples of some of the more potent CYP3A4 inhibitors include the antifungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir and indinavir, and the macrolide antibiotics erythromycin and clarithromycin. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetene,
fluvoxamine and clotrimazole. The use of CYP3A4 inhibitors with Cafergot should be avoided (see “CONTRAINDICATIONS”). These lists are not exhaustive and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with Cafergot.

**Fibrotic complications**
There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of ergot alkaloids. Rarely, prolonged use of ergot alkaloids has also been associated with cardiac valvular fibrosis (see “ADVERSE REACTIONS”).

Although signs and symptoms of vasospasm are rarely reported even after long term intermittent use of Cafergot, care should be taken to remain within the limits of the recommended dosage to avoid ergotism. Ergotism is manifested by symptoms and signs of peripheral vascular ischaemia due to vasoconstriction by direct action on the vascular smooth muscle. Headache, intermittent claudication, muscle pain, numbness, coldness and pallor of the digits may occur with chronic intoxication which, if allowed to progress, may result in gangrene.

Patients who are being treated with Cafergot should be informed of the maximum doses allowed and of the first symptoms of overdosage: hypoaesthesia, paresthesia (e.g. numbness, tingling) in the fingers and toes, non-migraine-related nausea and vomiting, and symptoms of myocardial ischaemia (e.g. precordial pain). If symptoms of peripheral vascular disturbance appear, such as tingling in fingers or toes, weakness in legs, muscle pain etc., treatment should be discontinued at once and the physician consulted.

**Hepatic impairment**
Patients with mild to moderate hepatic impairment, especially cholestatic patients should be appropriately monitored.

**Cardivascular**
Owing to its vasoconstrictor properties, ergotamine may cause myocardial ischaemia or, in rare cases, infarction, even in patients with no known history of coronary heart disease. If chest pain occurs, the treatment should be withdrawn.

**Dependence**
Ergotamine has caused dependence when used on a regular basis for migraine prophylaxis. Caffeine dependence could also occur with withdrawal causing headache, tiredness, runny nose and muscle pain.

**Drug-induced headaches**
The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot. Withdrawal after long indiscriminate use has, in rare instances, led to patients developing withdrawal headaches.
Rare cases of a solitary rectal or anal ulcer have occurred from abuse of ergotamine-containing suppositories, usually at higher than recommended doses or with continuous use at the recommended dose for many years.

Like all drugs, Cafergot should be kept out of reach of children.

**Prolonged or excessive use**

Continued daily use of Cafergot in excess of the recommended doses must be avoided since this may cause vasospasm.

**Visual disturbances**

Cases with sudden and transient loss of vision have been reported in post-marketing use. This adverse event may be related to vasospasm and ischaemic episode. Patients should stop using Cafergot immediately if they experience visual disturbances and seek medical help in a timely manner.

**Mutagenicity**

No mutagenicity study was performed with ergotamine/caffeine combinations.

**Carcinogenicity**

No study is available which evaluated the carcinogenic potential of ergotamine or ergotamine and caffeine combinations.

**Paediatrics**

Safety and efficacy has not been established in paediatric patients.

**Geriatrics**

No studies have been performed in elderly patients (65 years age and above).

**Use in Pregnancy (Category C)**

Women planning to become pregnant should not take Cafergot. When pregnancy is confirmed in women taking Cafergot, the treatment should be discontinued immediately (see “CONTRAINDICATIONS”).

Ergotamine and ergot derivatives induce uterine contraction and may therefore cause premature parturition or hypertonic labour. Products containing ergotamine or ergot derivatives should therefore be avoided during pregnancy.

**Use in Lactation**

Ergotamine is excreted in breast milk and may cause symptoms of vomiting, diarrhoea, weak pulse and unstable blood pressure in infants. Thus, Cafergot is contraindicated in nursing mothers (see “CONTRAINDICATIONS”).
Effects on Ability to Drive or Operate Machinery:
Patients experiencing visual disturbance, dizziness, or other central nervous system disturbances should not drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES
CYP3A4 inhibitors (e.g. macrolide antibiotics and protease inhibitors):
Pharmacokinetic interactions have been reported in patients treated orally with ergot alkaloids (e.g. increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of CYP3A4 metabolism of the alkaloids by troleandomycin. Ergot alkaloids have also been shown to be both inhibitors and substrates of CYP3A4 catalysed reactions and rare reports of ergotism have been obtained from patients treated with ergot alkaloids and macrolide antibiotics (e.g. troleandomycin, clarithromycin, erythromycin). Patients treated with ergot alkaloids and protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine), presumably due to inhibition of CYP3A4 metabolism of ergotamine (see “CONTRAINDICATIONS” and “PRECAUTIONS-CYP3A4 inhibitors”). No pharmacokinetic interactions involving other CYP450 isoenzymes are known.

Vasoconstrictors:
Ergotamine tartrate and caffeine should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker propranolol has been reported to potentiate the vasoconstrictive action of ergotamine tartrate and caffeine by blocking the vasodilating property of epinephrine. Nicotine (e.g. smoking) and sympathomimetics may provoke vasoconstriction in some patients, predisposing to a greater ischaemic response to ergot therapy. Concurrent use of ergotamine and caffeine with other ergot alkaloids, sumatriptan and other 5-HT1 (5-hydroxtryptamine) receptor agonists must also be avoided since this may result in enhanced vasoconstriction (see “CONTRAINDICATIONS”).

Any possible increase in plasma concentration of caffeine due to interaction with other drug(s) may translate to increase in absorption of ergotamine.

Caffeine undergoes extensive metabolism by CYP1A2 and the drugs that enhance or reduce the enzyme activity can modulate the metabolic clearance of caffeine.

Fluoroquinolones, mexiletine, fluvoxamine, and oral contraceptives can increase the plasma exposure of caffeine. Interactions of caffeine with sympathomimetics can lead to increased blood pressure.

Beta-blockers
A few cases of vasospastic reactions have been reported among patients treated concomitantly with ergotamine-containing preparations and propranolol.
Moderate/weak CYP3A4 inhibitors
Moderate to weak CYP3A4 inhibitors such as cimetidine, clotrimazole, fluconazole, grapefruit juice, quinupristin/dalfopristin and zileuton can also increase the exposure to ergotamine and caution is required for their concomitant use.

Serotonin reuptake inhibitors
Concurrent use of ergotamine with Serotonin reuptake inhibitors (e.g. amitriptyline) including selective agents (e.g. sertraline) can lead to serotonin syndrome and need to be used with caution.

CYP3A4 inducers
Drugs (e.g. nevirapine, rifampicin) inducing CYP3A4 can lead to decrease in pharmacological action of ergotamine.

ADVERSE EFFECTS
The most common adverse effects are nausea and vomiting. Depending on the dose of ergotamine, signs and symptoms of vasoconstriction may occur.

The following adverse drug effects (Table 1) have been derived from clinical trials and post-marketing experience with Cafergot via spontaneous case reports and literature cases. Because these post-marketing reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse effects are listed according to system organ classes in MedDRA. Within each system organ class, adverse effects are presented in order of decreasing seriousness.

Adverse effects are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports.

Table 1

Immune system disorders
Rare: Hypersensitivity reactions

Nervous system disorders
Common: Dizziness
Uncommon: Paraesthesia (e.g. tingling), hypoaesthesia (e.g. numbness)
Rare: Drowsiness
Not known: Somnolence, drug-induced headaches

Eye disorders:
Not known: Visual impairment

Ear and labyrinth disorders
Rare: Vertigo

Cardiac disorders
Uncommon: Cyanosis
Rare: Bradycardia, tachycardia
Very rare: Myocardial ischaemia, myocardial infarction
Not known: Endocardial fibrosis
**Vascular disorders**
- Uncommon: Peripheral vasoconstriction
- Rare: Increase in blood pressure
- Very rare: Gangrene

**Respiratory, thoracic and mediastinal disorders**
- Rare: Dyspnoea
- Not known: Pleural fibrosis

**Gastrointestinal disorders**
- Common: Nausea and vomiting (not migraine related), abdominal pain
- Uncommon: Diarrhoea
- Not known: Retroperitoneal fibrosis*, Rectal ulcer***, Anal ulcer***

**Skin and subcutaneous tissue disorders**
- Rare: Rash, face oedema, urticaria

**Musculoskeletal and connective tissue disorders**
- Uncommon: Pain in extremities
- Rare: Myalgia

**General disorders and administration site conditions**
- Uncommon: Weakness in extremities

**Investigations**
- Rare: Absence of pulse

**Injury, poisoning and procedural complications**
- Rare: Ergotism

1 Hypersensitivity reactions such as skin rash, face oedema, urticaria and dyspnoea.

2 Ergotism is defined as an intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia of the extremities and other tissues (such as renal or cerebral vasospasm).

* If ergotamine-containing drugs are used excessively over years, they may induce fibrotic changes, in particular of the pleura and the retroperitoneum. There have also been rare reports of fibrotic changes of the cardiac valves (see “PRECAUTIONS”).

** Dependence has been reported, with withdrawal headaches. The occurrence of drug-induced headaches has been reported during prolonged and uninterrupted treatment with Cafergot (see “PRECAUTIONS”).

*** Rectal and anal ulcers may occur after long term use or use at doses higher than the recommended dose of ergotamine-containing suppositories (see “PRECAUTIONS”).

**DOSAGE AND ADMINISTRATION**

Cafergot is specifically designed for the treatment of the acute migraine attack; it should be administered upon the first symptom of the attack.

**Adults**

An initial dose of two Cafergot tablets or one Cafergot S suppository is recommended. This dose is usually sufficient although some patients may require higher dosages, but the maximum daily dose indicated below should not be exceeded.

**Maximum dose per attack or per day:** 6 mg ergotamine tartrate - six tablets or three suppositories.
**Maximum weekly dose:** 10 mg ergotamine tartrate - ten tablets or five suppositories.
**Children**

Cafergot S suppositories and Cafergot tablets are not recommended for use in children under 12 years.

The following restriction must be observed: If supplementary antimigraine medication is required, the use of any ergotamine-containing preparations, intranasal or parenteral dihydroergotamine, sumatriptan or other 5HT₁-receptor agonist must be avoided [see “CONTRAINDICATIONS”].

**OVERDOSAGE**

**Symptoms**

Symptoms of acute poisoning include nausea, vomiting, diarrhoea, thirst, coldness of the skin, pain, numbness or tingling in the extremities, weak or absent pulses, tachycardia, hypertension or hypotension, drowsiness, somnolence, dizziness, confusion, convulsions, respiratory distress coma, shock, symptoms and complications of ergotism.

Ergotism is defined as an intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia of the extremities such as numbness, tingling and pain in the extremities, cyanosis, absence of pulse and if the condition is allowed to progress untreated, gangrene may result. Furthermore ergotism can also involve signs and symptoms of vascular ischemia of other tissues such as renal or cerebral vasospasm. Most cases of ergotism are associated with chronic intoxication and/ or overdosage.

**Treatment**

Treatment is symptomatic. Administration of activated charcoal is advised. Adequate pulmonary ventilation needs to be ensured, and hypotension corrected.

Arterial spasm could be treated with warmth and protection of the ischaemic limbs; vasodilators may be administered if required.

Nausea and vomiting may be relieved by metoclopramide. Anticoagulants and antibiotics may be given if necessary.

**PRESENTATION AND STORAGE CONDITIONS**

**Presentation**

White, round sugar coated tablets with no markings containing 1 mg ergotamine tartrate and 100 mg caffeine. Bottles of 20*.

Suppositories, whitish or with a tinge of grey/pink containing 2 mg ergotamine tartrate and 100 mg caffeine. Strips of 5*. 
* Not all presentations may be available.

**Storage Condition**
Store below 25°C.

**POISON SCHEDULE**

Schedule S4 – Prescription Medicine.

**DATE OF FIRST INCLUSION IN AUSTRALIAN REGISTER OF THERAPEUTIC GOODS**

24 November 1997 - Cafergot Tablets, AUST R 62251
21 August 1991 - Cafergot S Suppositories, AUST R 13339

**SPONSOR**

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13 April 2012