Medicines Adverse Reactions Committee

Meeting date	**14 March 2019**	Agenda item	3.2.5
Title	**Ergotamine containing medicines and pancreatitis**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituents Ergotamine tartrate 1 mg Caffeine 100 mg	**Medicines** Cafergot tablet	**Sponsors** AFT Pharmaceuticals Ltd	
Funding	Cafergot is funded. There is also a tablet Cafergot S29 which is funded.		
Previous MARC meetings	This topic has not been discussed previously.		
Prescriber Update	Risk of fibrosis with medicines containing ergot derivatives, *Prescriber Update 35(2) 6 June 2014*		
Schedule	Prescription medicine		
Usage data	2013 number of dispensings: 7812 (for 2388 patients) 2017 number of dispensings: 6459 (for 1869 patients) Source: MoH Data Pharm, extracted 18 January 2019.		
Advice sought	**The Committee is asked to advise whether:** – The safety section of the data sheets for ergotamine products should be updated with the risk of pancreatitis. – If any further regulatory action is required. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.		

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1.0 PURPOSE

The safety of Cafergot was recently highlighted by a report made to CARM of a patient who developed acute pancreatitis. This patient had taken a number of medicines including Cafergot.

Cafergot is indicated for the management of migraine. However it is not a first line treatment and it is not available in many countries. Considering the circumstances of the case report, Medsafe considered that the case and the safety of Cafergot should be reviewed by the MARC.

2.0 BACKGROUND

The case triggering this review described a 13 year old male who was hospitalised with acute pancreatitis. The patient had been prescribed ergotamine + caffeine (Cafergot), codeine, prochlorperazine, paracetamol and ibuprofen for acute migraine the day before. The reaction was suspected to be medicine induced. For further details of the case, see section 3.4.

2.1 Ergotamine

2.1.1 Pharmacodynamics and usage

Ergotamine is an alkaloid derived from ergot. Ergot (or ergot fungi) refers to a group of fungus which grow on rye and related plants and produces alkaloids that can cause ergotism (see section 2.1.3). Ergotamine has marked vasoconstrictor effects, and a partial agonist action at serotonin (5-HT) receptors; it also has a powerful oxytocic action on the uterus (1). The data sheet indication for Cafergot is treatment of acute attacks of migraine with or without aura in adults (2).

Ergotamine aborts attacks of migraine with or without aura by its specific vasotonic action on distended extracranial arteries. Ergotamine can cause vasoconstriction by stimulating alpha-adrenergic and 5-HT receptors. It displays moderate to high affinity for various serotonin receptor subtypes however its beneficial effect in migraine are primarily linked to agonist properties at 5-HT1B and 5-HT1D (2).

Caffeine is sometimes given with ergotamine tartrate with the intention of improving the latter's absorption, although whether it does so is not clear (1). However, most placebo-controlled trials of oral ergotamine alone have failed to show efficacy in the relief of migraine (3).

Ergotamine is used in migraine unresponsive to non-opioid analgesics or triptans. It is not used for prevention of migraine attacks. It is most effective when given as early as possible in a migraine attack, preferably during the prodromal phase. The usual oral dose is 2 mg of ergotamine tartrate (1).

If relief is not obtained within half an hour, a further tablet should be administered; this may be repeated at half-hourly intervals, but the maximum daily dose of 6 tablets should not be exceeded. Taking Cafergot repeatedly over extended periods must be avoided (2).

Comment: The vasoconstriction effect of ergotamine provides a biologically plausible mechanism of action to cause pancreatitis.

2.1.2 Pharmacokinetics

Absorption of ergotamine from the gastrointestinal tract is poor and variable, and may be further decreased by the occurrence of gastric stasis during migraine attacks. Plasma protein binding is about 93 to 98%. Ergotamine is metabolised extensively in the liver via the cytochrome P450 isoenzyme CYP3A4. It has been suggested that the therapeutic effects of the drug are partially due to

active metabolites (2). Parent drug and metabolites are mainly excreted in the bile. Their elimination from plasma is biphasic, with half-lives of 2.7 and 21 hours, respectively.

Tight receptor binding produces a longer duration of action. In one study after intramuscular injection, the effect on peripheral arteries, measured as a decrease in toe-arm systolic gradients, developed slowly and was well sustained after 29 hours (4).

2.1.3 Adverse effects

The adverse effects of ergotamine may be attributed either to its effects on the central nervous system, 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 have 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 (1).

Symptoms of ergotamine overdose are nausea, vomiting, drowsiness, confusion, tachycardia, dizziness, respiratory depression, hypotension, convulsion, shock, coma, 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, and 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 overdose (2).

Chronic, intractable headache (rebound headache) may occur after an overdose and is also a major withdrawal symptom following the development of ergotamine dependence.

Ergotamine should not be taken in those patients suffering with heart disease, uncontrolled glaucoma or hypertension, liver or kidney disease, or circulation problems because of the risk of vasospasm.

2.1.4 Interactions

Several interactions may occur if ergotamine are used together with other medicines.

Concomitant treatment with cytochrome P450 3A4 (CYP3A4) inhibitors such as macrolide antibiotics (all except spiramycin), HIV protease or reverse transcriptase inhibitors and azole antifungals (for example ketoconazole) is contraindicated.

Moderate to weak CYP3A4 inhibitors such as cimetidine, fluconazole, quinupristin/ dalfopristin, zileuton and grapefruit juice can also increase exposure to ergotamine and caution is required for concomitant use.

Concomitant treatment with vasoconstrictor agents including ergot alkaloids, sumatriptan, other 5HT1 receptor agonists, nicotine (e.g. heavy smoking) and sympathomimetics are contraindicated since this may result in enhanced vasoconstriction. Allow 24 hours between the discontinuation of triptans and the use of the alkaloid.

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

A few cases of vasospastic reactions have been reported among patients treated concomitantly with ergotamine-containing preparations and propranolol.

Some antidepressants such as fluoxetine, fluvoxamine or nefazodone may increase the levels of the ergot derivatives. Concurrent use of ergotamine with serotonin reuptake inhibitors (e.g. amitriptyline) including selective agents (e.g. sertraline) can lead to serotonin syndrome. Caution is required for concurrent use.

Concomitant treatment with fluoroquinolones, mexiletine, fluvoxamine, and oral contraceptives is contraindicated. These medicines can modulate the metabolic clearance of caffeine which consequently may translate to increase in absorption of ergotamine (2).

2.1.5 Pregnancy and breastfeeding

Cafergot is contraindicated during pregnancy and breastfeeding.

Comment: The difficulties in absorption of ergotamine as well as its interactions and safety profile, particularly nausea, vomiting, abdominal pain, and muscular cramps, limits the value of ergotamine in the treatment of migraine.

2.2 Caffeine

2.2.1 Pharmacodynamics

Caffeine accelerates and increases the enteral absorption of ergotamine. Caffeine also exerts analgesic activity through blockade of peripheral actions of adenosine and the activation of central noradrenergic pathways that constitute an endogenous pain suppressing system.

2.2.2 Pharmacokinetics

Caffeine is rapidly and almost completely absorbed after oral administration. Plasma protein binding is 35%. Caffeine is distributed relatively uniformly throughout all body tissues. Caffeine is metabolized to a large extent and eliminated mainly by the urine. Plasma elimination half-life is about 3.5 hours (2).

2.3 Migraine and its treatment

Migraine is characterised by recurrent attacks of headache that typically last 4 to 72 hours. The headache is usually a unilateral pulsating pain that is aggravated by movement and is usually of sufficient severity to disturb or prevent daily activities. It is frequently accompanied by nausea, vomiting, or other gastrointestinal disturbances and the patient may experience photophobia and phonophobia.

Migraine with aura (classic migraine) is characterised by an aura consisting of visual or sensory symptoms that lasts less than an hour. The headache usually follows the aura directly, or within 1 hour, but may begin simultaneously with the aura. In addition, aura can occur without headache. Migraine without aura (common migraine) is the more common form.

Migraine is described as a neurovascular headache. Traditionally, intracranial vasoconstriction was considered responsible for the aura and extracranial vasodilatation for the headache. However, it appears that vascular events may be secondary to neuropathic changes and the liberation of vasoactive substances including serotonin (5-HT), catecholamines, histamine, kinins, neuropeptides such as calcitonin gene-related peptide (CGRP), and prostaglandins.

There are several factors that may precipitate migraine attacks, including anxiety, physical and emotional stress and change in sleep pattern (1).

The NZ webpage Health Navigator describes how migraine is treated with medicines, last reviewed in November 2017 and last updated in December 2018 (5):

Medications for the treatment of migraines fall into a few categories:

- Pain-relieving medicines (paracetamol, NSAID, triptans), which are taken during the migraine attack.
- Medicines against nausea or vomiting (metoclopramide, domperidone or prochlorperazine).
- Prevention medicines (propranolol, atenolol, nadolol, metoprolol, timolol, amitriptyline, nortriptyline, topiramate, sodium valproate, gabapentin).

Regarding Cafergot the Health Navigator states that ergotamine:

- is only for people who have recurring migraines that cannot be managed by other medications
- has many side effects including nausea, vomiting, abdominal pain and muscle cramps
- should not be used more than twice per month.

Health Navigator refers to the NICE Clinical Guidelines for management of migraine with or without aura from 2014 (6). For acute treatment the NICE guidelines recommends:

Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For people aged 12–17 years consider a nasal triptan in preference to an oral triptan.

For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events.

Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting.

Do not offer ergots or opioids for the acute treatment of migraine.

For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:

- offer a non-oral preparation of metoclopramide or prochlorperazine **and**
- consider adding a non-oral NSAID or triptan if these have not been tried.

In Martindale, ergot derivatives are described as a group of medicines that is rarely needed nowadays in the treatment of migraine.

Comment: Ergotamine is not recommended as a first line treatment in New Zealand and NICE states it should not be used. Note also that codeine is not recommended in the guidelines.

2.4 Pancreatitis

Pancreatitis is inflammation in the pancreas, an organ lying behind the lower part of the stomach. Pancreatitis can occur as acute pancreatitis — meaning it appears suddenly and lasts for days. Chronic pancreatitis is a similar, but more low-grade, ongoing process over many years, characterised by recurrent symptoms of abdominal pain and with progressive damage to the pancreas (7).

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas that may extend to local and distant extra-pancreatic tissues. Signs and symptoms include upper abdominal pain, abdominal pain that radiates to the back and feels worse after eating, fever, nausea and vomiting (7).

AP can occur if there is damage to the acinar cells and/or injury to the pancreatic duct that leads to inappropriate accumulation and activation of proenzymes within the pancreas. The activated pancreatic enzymes digest the cell membranes of the pancreas and activate an inflammatory response, which increases the vascular permeability of the pancreas. Hemorrhage, edema, ischemia, and necrosis can result (8).

Conditions that can lead to pancreatitis include alcoholism, gallstones, abdominal surgery, family history, certain medicines, infection or injury. Gallstones lead to an obstruction in the pancreatic duct which activates the process. Athough gallstones and alcohol are responsible for more than 90% of all cases in adults, medicines have been recognized as a potential cause of AP, for example enalapril, simvastatin and codeine (8).

2.5 Data sheets and product information

2.5.1 New Zealand

Cafergot is not recommended for use in children under the age of 18 years or adults over the age of 65 years. Safety and efficacy have not been established in these age groups.

Pancreatitis is not included as an adverse effect in the data sheet for Cafergot.

The data sheet lists the following adverse effects, ranked in every MeDRA system organ class according to frequency:

Immune system disorders Rare: Hypersensitivity reactions ***Eye Disorders*** Not known: Visual impairment ***Cardiac disorders*** Uncommon: Cyanosis Rare: Bradycardia, tachycardia Very rare: Myocardial ischaemia, myocardial infarction Not known: Endocardial fibrosis ***Respiratory, thoracic and mediastinal disorders*** Rare: Dyspnoea Not known: Pleural fibrosis ***Skin and subcutaneous tissue disorders*** Rare: Rash, face oedema, urticarial ***Investigations*** Rare: Pulse absent ***Injury, poisoning and procedural complications*** Rare: Ergot poisoning	***Nervous system disorders*** Common: Dizziness Uncommon: Paraesthesia in fingers and toes, numbness Rare: Drowsiness Not known: Somnolence, drug-induced headache ***Ear and labyrinth disorders*** Rare: Vertigo ***Vascular disorders*** Uncommon: Peripheral vasoconstriction Rare: Hypertension Very rare: Gangrene ***Gastrointestinal disorders*** Common: Nausea and vomiting (not migraine related), abdominal pain Uncommon: Diarrhoea Not known: Retroperitoneal fibrosis ***Musculoskeletal and connective tissue disorders*** Uncommon: Pain in extremity, weakness in extremity

One contraindication to Cafergot is patients with severe hepatic impairment. Patients with mild to moderate hepatic impairment, especially cholestatic patients (when substances normally excreted in the bile are retained due to a decrease in bile flow), should be appropriately monitored (2).

2.5.2 UK

Cafergot is not registered in the UK but instead another ergotamine product is available, called Migril. Migril contains 2 mg ergotamine tartrate, 100 mg caffeine hydrate and 50 mg cyclizine hydrochloride (the desired effect of cyclizine being treatment and prevention of nausea, vomiting and dizziness).

See the table below for a comparison of Cafergot and Migril:

Medicine	Ergotamine tartrate	Caffeine	Cyclizine hydrochloride
Cafergot	1 mg	100 mg	-
Migril	2 mg	100 mg	50 mg

Pancreatitis is not included as an adverse effect in the product information (PI) for Migril (9).

2.5.3 US

Pancreatitis is not included as an adverse effect in the data sheet for Cafergot in the US (10).

2.5.4 Australia

Cafergot or ergotamine medicines are not available in Australia.

2.5.5 Europe

In most countries in the EU, Cafergot or ergotamine medicines are not available (11). For example, Cafergot was deregistered in Sweden in 2006 and no other ergotamine products are available.

2.5.6 Canada

In Canada, a nasal spray and a parenteral product containing dihydroergotamine are marketed. Dihydroergotamine is more potent than ergotamine with respect to its adrenergic blocking actions and less potent with respect to its capacity to produce arterial vasoconstriction. There is no published product information for the parenteral product. In the product information for the nasal spray it is stated that patients with mild to moderate hepatic impairment, especially cholestatic patients, should be appropriately monitored. Pancreatitis is not included as an adverse effect in the product information (12).

Comment: Cafergot/ergotamine is not available in many countries. In some countries Cafergot was previously available but has been deregistered.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search on Pub Med revealed only one article, presented below.

3.1.1 Deviere et al 1987

This is a case report about a 29 year old male with a history of depression and migraine headaches who had been treated with ergotamine tartrate for about one year (1 or 2 mg about once a week) (13). He did not take any other medicines. He was admitted to the ICU after a suicide attempt when he ingested 40 tablets of Cafergot. His ergotamine intoxication was complicated by peripheral ischemia, pancreatitis and hepatitis.

The patient did not take any other medications, was not alcoholic and had no history of hepatic or pancreatic disease. He was intubated and ventilated and treatment with sodium nitroprusside was initiated. Peripheral vasoconstriction and unconsciousness resolved after 36 h of treatment. On the second day increases in amylase, lipase and the lever enzymes SGOT and SGPT (transaminases) were observed as well as in lactic dehydrogenase and alkaline phosphatase. An abdominal computed tomographic (CT) scan on the third day showed focal necrosis of the pancreas tail. The enzyme levels returned to normal after 14 days and the patient was discharged without complications.

The authors discuss that the localisation of the pancreatic lesions is in agreement with an ischemic origin since the tail is the terminal vascular bed of the principal and inferior pancreatic arteries and ergotamine is known to act distally in the arteriolar smooth muscle and cause infarction of the distal organ.

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[redacted]

3.4 CARM data

The case report which is the background to this review is the only case reported to CARM. The patient was a male, aged 13. [redacted]

3.5 The other medicines used

This patient was also prescribed other medicines at the time when he got Cafergot: codeine, proclorperazine, ibuprofen and paracetamol.

The data sheet for codeine includes biliary spasm but not pancreatitis

A search on PubMed for codeine and pancreatitis resulted in some case reports and a retrospective study. There are also review articles on drug-induced pancreatitis, listing codeine as one medicine where a possible or probable causality had been considered after a spontaneous report (14).

Prochlorperazine has antidopamine action. Antidopaminergic medicines have been associated with pancreatitis in case reports. However, pancreatitis is not listed in the data sheet.

Comment: One well-known adverse effect of codeine is cramps in the biliary tract. This is included in the NZ data sheet for codeine as biliary spasm. A suggested mechanism for acute pancreatitis caused by codeine has been due to a spasm of the sphincter of Oddi, especially if the patient had a prior cholecystomy. Pancreatitis is not included as an adverse reaction in the data sheets either for codeine or prochlorperazine.

4.0 DISCUSSION AND CONCLUSIONS

Acute pancreatitis is a serious event that may occur for many reasons, one of them medicine use. The case report describes a 13 year old patient who developed acute pancreatitis [redacted]. Medsafe notes that this is off-label use in a child and possibly inappropriate use as no history of trial of other medicines was provided. Guidelines state that Cafergot should only be used when other treatments are ineffective.

The reaction was suspected to be medicine induced, but it was unclear as to which medicine was the cause. One of the suspect medicines was Cafergot.

Difficulties in absorption of ergotamine as well as its interactions and safety profile, particularly nausea, vomiting, abdominal pain, and muscular cramps limits the value of ergotamine in the treatment of migraine.

When searching for pancreatitis as a potential adverse effect of Cafergot, the only publication found describes a patient who took an overdose of Cafergot. No other cases have been reported to CARM. [redacted]

[redacted]

Therefore, there seems to be little evidence linking Cafergot with pancreatitis, at the intended dose it may be associated with overdose. Cafergot is an old medicine which appears not to be used any longer in many countries and it is also associated with other serious side effects such as fibrosis. This case appears to represent a lack of awareness of these facts.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The safety section of the data sheets for ergotamine products should be updated with the risk of pancreatitis.
- If any further regulatory action is required.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. [redacted]

7.0 REFERENCES

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