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

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-HT₁) 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 mi graine: 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 believed1 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 greater2 than that of dihydroergotamine and there have also been some reports of successful treatment with inhaled3,4 or rectal5 ergotamine.

- 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†; ligra; Integrobe Plus; Jaquedryl†; Migra Dioxadol; Migra Dorixina; Migral; Migral Compositum; Migral II; Mikesan; Solacit, Tetralgin; Tetralgin; Novo; Zilactin-E‡; Austral.: Cafergot; Ergodryl†; Austral: Avamigran; Cafergot, Migril; Secokapton; Synkapton; Belg: Cafergot; Braz: Migrane; Neogrein; Ormigrein; Canad.: Bellergal; Cafergot; Cafergot; PB†; Ergodryt; Caravergot]; Chile: Bellergal; Edgrapd; Cafergot; PB†; Celalmin; Cinabel; Clonalgin Compuesto; Ergobelan; Ergonef; Fredot; Migra-Nefersik Migrages; Migranot; Migratam; Ultrimin; Cz.: Bellaspon†; Denm.: Ergokoffin; Gynergen Comp; Fin.: Anervan; Fr.: Gynergene Cafeine; Gen: Avamigran N†; Cafergot; Nhigratam; Ultrimin; Cz.: Bellaspon†; Hung: Kefalgin; India: Migranii; Indon.: Bellaphen; Cafergot; Ericaf; Inl.: Migranat; Migril; Israel: Cafergot; Fergot; Fergot;

Feverfew

Camomille, grande; Matricaria; Mattram; Nat' kopretiny řimbaby; Őszi margitvirág; Reunuspäivänkakkara; Tanaceti parthénii herbá; 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 review¹ 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).

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.

- Vogler BK, et al. Feverfew as a preventive treatment for mi-graine: 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 antiinflammatory activity in vitro, a clinical trial 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, HNN)

Frovatriptaani; Frovatriptán; Frovatriptanum; SB-209509AX (frovatriptan or frovatriptan succinate); VML-251 (frovatriptan or frovatriptan succinate). (6R)-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-HT₁) 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

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

Further references.

- 1. Rapoport A, et al. Dose range-finding studies with frovatriptan in the acute treatment of migraine. Headache 2002; 42 (suppl 2):
- S/4–S83.
 Ryan R, et al. Clinical efficacy of frovatriptan: placebo-controlled studies. Headache 2002; 42 (suppl 2): S84–S92.
 Poolsup N, et al. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. J Clin Pharm Ther 2005; 30: 521–32.

Preparations

Proprietary Preparations (details are given in Part 3) Austria: Eumitan; Cz.: Fromen; Recur; Fin.: Migard; Fr.: Tigreat; Ger.: Allegro; Gr.: Migard; Migralin; Irl.: Frovex; Ital.: Auradol; Rilamig; Neth.: Fromirex; Migard; Port.: Dorlise; Migard; Spain: Forvey; Perlic; Switz.: Menamig; UK: Migard; USA: Frova.

Iprazochrome (rINN)

Ipratsokromi; Iprazochromum; Iprazocromo; Iprazokrom. 3-Hydroxy-I-isopropyl-5,6-indolinedione 5-semicarbazone.

Ипразохром

 $C_{12}H_{16}N_4O_3 = 264.3.$ CAS - 7248-21-7. ATC - N02CX03.

ATC Vet - QN02CX03.

$$\begin{array}{c} O \\ II \\ C \\ N \end{array}$$

Profile

Iprazochrome is a serotonin antagonist used in the prophylaxis of migraine (p.616) and in the management of diabetic retinopathy. It has been given in usual oral doses of 2.5 to 5 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3) Ger.: Divascan†; Hung.: Divascan; Pol.: Divascan

Methysergide (BAN, USAN, rINN)

I-Methyl-D-lysergic Acid Butanolamide; Méthysergide; Methysergidum; Metisergida; Metysergidi. Metysergidi. N-[I-(Hydroxymethyl)propyl]-I-methyl-D-lysergamide; 9,10-Didehydro- $N-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8\beta-carboxa-$

Метизергид

 $C_{21}H_{27}N_3O_2 = 353.5.$ CAS - 361-37-5. ATC - N02CA04.ATC Vet - QN02CA04.

Methysergide Maleate (BANM, rINNM)

Maleato de metisergida; Méthysergide, Maléate de; Methysergidi Maleas.

Метизергида Малеат $C_{21}H_{27}N_3O_2, C_4H_4O_4 = 469.5.$ CAS - 129-49-7. ATC - N02CA04.ATC Vet — QN02CA04.

Pharmacopoeias. In Br. and US.

BP 2008 (Methysergide Maleate). A white or almost white crystalline powder which may have a yellow or pink tinge; odourless or almost odourless. Slightly soluble in water and in methyl alcohol; practically insoluble in chloroform and in ether. A 0.2% solution in water has a pH of 3.7 to 4.7. Store at a temperature of 2° to 8°. Protect from light.

USP 31 (Methysergide Maleate). A white to yellowish-white or reddish-white, crystalline powder. Is odourless or has not more than a slight odour. Soluble 1 in 200 of water and 1 in 165 of alcohol; soluble 1 in 3400 of chloroform; practically insoluble in ether, pH of a 1 in 500 solution is between 3.7 and 4.7. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Adverse Effects

Gastrointestinal effects such as nausea, vomiting, heartburn, and abdominal pain are common on initial treatment with methysergide maleate, as are dizziness and drowsiness. Other CNS effects reported include ataxia, insomnia, weakness, restlessness, lightheadedness, euphoria, and hallucinations. Peripheral or localised oedema, leg cramps, and weight gain have occurred and there have been occasional reports of skin rashes, loss of hair, joint and muscle pain, neutropenia, and eosinophilia. Orthostatic hypotension and tachycardia have been observed. There have been isolated reports of myocardial infarction particularly in patients with ischaemic heart disease or when given with other vasoconstrictive drugs, both of which are contra-indications for methysergide therapy.

Arterial spasm has occurred in some patients, and may present as paraesthesia of the extremities or anginal pain, as with ergotamine (p.620); if such symptoms occur methysergide should be withdrawn, although rebound headaches may be experienced if it is withdrawn suddenly. Vascular insufficiency of the lower limbs may represent arterial spasm or fibrotic changes. Treatment should be stopped at the first signs of impaired peripheral circulation. Retroperitoneal fibrosis, with obstruction of abdominal blood vessels and ureters, pleuropulmonary fibrosis, and fibrotic changes in heart valves have occurred in patients on longterm treatment. Methysergide must be withdrawn immediately if fibrosis occurs. Retroperitoneal fibrosis is usually reversible, but other fibrotic changes are less readily reversed.

Fibrosis. Fibrosis has been associated with the long-term use of methysergide maleate. In one early report1 in 27 patients retroperitoneal fibrosis was attributed to use of methysergide for periods of 9 to 54 months in doses ranging from 2 to 28 mg daily. There was partial or complete regression of fibrosis in 13 of the patients whose treatment was withdrawn. Improvement usually began within a few days, in some cases with the aid of prednisone. The other 14 patients were treated by surgery; those few who continued taking methysergide had difficult postoperative courses. Cardiac murmurs occurred in 7 patients, and regressed wholly or partially in 3 after therapy was stopped. Fibrotic changes affecting the aorta, heart valves, and pulmonary tissues occurred in a few of the patients. Others have reported the development of endocardial fibrosis indicated by cardiac murmurs in 48 patients receiving methysergide.² The murmurs gradually regressed in 27 when methysergide was stopped. Retroperitoneal fibrosis was present in 9 patients and pleuropulmonary fibrosis in 2. A patient with fibrosis of the iliac vein has been described.3

A few cases of retroperitoneal fibrosis associated with ergotamine tartrate or dihydroergotamine have also been noted.1 These 2 drugs have also been implicated in a few other cases of retroperitoneal fibrosis or other fibrotic disorders in patients taking high doses for long periods.4-7

- 1. Graham JR, et al. Fibrotic disorders associated with methysergide therapy for headache. N Engl J Med 1966; 274: 359-68.
- 2. Bana DS, et al. Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. Am Heart J 1974; 88: 640-55.
- 3. Bucci JA, Manoharan A. Methysergide-induced retroperitoneal fibrosis: successful outcome and two new laboratory features *Mayo Clin Proc* 1997; **72:** 1148–50.
- 4. Lepage-Savary D, Vallières A. Ergotamine as a possible cause of retroperitoneal fibrosis. Clin Pharm 1982; 1: 179-80.
- Robert M, et al. Fibrotic processes associated with long-term ergotamine therapy. N Engl J Med 1984; 311: 601 and 602.
- Damstrup L, Jensen TT. Retroperitoneal fibrosis after long-term daily use of ergotamine. *Int Urol Nephrol* 1986; 18: 299–301.
- 7. Malaquin F, et al. Pleural and retroperitoneal fibrosis from dihy-

Treatment of Adverse Effects

droergotamine. N Engl J Med 1989; 321: 1760.

Methysergide maleate should be withdrawn immediately if fibrosis develops. Corticosteroids have been used to treat fibrosis, although surgery may be required.

Precautions

As for Ergotamine Tartrate, p.620.

In addition, methysergide maleate is contra-indicated in valvular heart disease, pulmonary and collagen diseases, diseases of the urinary tract, phlebitis and cellulitis of the lower extremities, and debilitated states. It should be used with caution in patients with peptic ulcer disease because it may increase gastric acidity. Patients should be closely supervised. Methysergide should not be given continuously for more than 6 months and should normally be withdrawn gradually (see Uses and Administration, below). However, it should be withdrawn immediately if symptoms of fibrosis or arterial spasm develop.

Porphyria. Methysergide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals or in-vitro systems.

Interactions involving those ergot alkaloids used primarily in the management of migraine are discussed under ergotamine (p.621). References specific to methysergide may be found there under the headings Antimigraine Drugs and Beta Blockers.

Pharmacokinetics

Methysergide maleate is rapidly absorbed from the gastrointestinal tract with maximum plasma concentrations being obtained within about one hour of ingestion. It is 66% bound to plasma proteins. Methysergide undergoes extensive first-pass hepatic metabolism to methylergometrine (p.2011). About 50% of an oral dose is excreted in the urine as unchanged drug and metabolites. The elimination of methysergide is biphasic; half-lives of about 2.7 hours and 10 hours have been reported for the 2 phases respectively.

1. Bredberg U, et al. Pharmacokinetics of methysergide and its metabolite methylergometrine in man. Eur J Clin Pharmacol 1986;

Uses and Administration

Methysergide maleate is a semisynthetic ergot alkaloid. It is a potent serotonin antagonist and, compared with ergotamine, has only weak vasoconstrictor and oxytocic effects. It may be used to prevent severe recurrent migraine (p.616) and headache attacks during cluster periods (p.616), although its use has declined because of adverse effects. It is ineffective in the treatment of

Methysergide is given orally as the maleate but doses are often expressed in terms of the base; 1.33 mg of methysergide maleate is equivalent to about 1 mg of methysergide. A usual dosage is 2 to 6 mg daily given in divided doses with meals. It is suggested that treatment should be started with 1 mg at bedtime and doses increased gradually over about 2 weeks; the minimum effective dose should be used. In some other countries doses are expressed in terms of the maleate, a usual dose of which is 4 to 8 mg daily. Careful and regular observation of the patient is essential because of the high incidence of adverse effects and it is recommended that treatment should only be carried out under hospital supervision. If treatment still proves to be ineffective after 3 weeks, further use is unlikely to be of benefit. Treatment should not be continued for more than 6 months, after which it should be gradually withdrawn over 2 or 3 weeks and then stopped for at least a month for reassessment. Some have considered that treatment courses should not exceed 3 months without a break.

Methysergide maleate has also been used to control diarrhoea associated with carcinoid syndrome (p.643) in high doses equivalent to 12 to 20 mg of methysergide daily.

As a serotonin antagonist, methysergide might be expected to help reverse the serotonin syndrome (p.416).

Preparations

BP 2008: Methysergide Tablets; USP 31: Methysergide Maleate Tablets.

Proprietary Preparations (details are given in Part 3) Austral.: Deseril; Belg.: Deseril; Braz.: Deserila; Canad.: Sansert; Fr.: Deseril; Ger.: Deseril†; Neth.: Deseril†; S.Afr.: Deseril†; Switz.: Deseril†; UK: Deseril.

Naratriptan Hydrochloride

(BANM, USAN, rINNM)

GR-85548A; GR-85548X (naratriptan); Hidrocloruro de naratriptán; Naratriptan, Chlorhydrate de; Naratriptani Hydrochloridum. N-Methyl-3-(I-methyl-4-piperidyl)indole-5-ethanesulfonamide hydrochloride.

Наратриптана Гидрохлорид

 $C_{17}H_{25}N_3O_2S$, HCI = 371.9

CAS — 121679-13-8 (naratriptan); 121679-19-4 (naratriptan hydrochloride); 143388-64-1 (naratriptan hydrochloride).

ATC — N02CC02.

ATC Vet - QN02CC02.

$$H_3C$$
 N
 N
 CH_3
 $(naratriptan)$

Pharmacopoeias. In US.

USP 31 (Naratriptan Hydrochloride). A white to pale yellow solid. Soluble in water. Store in airtight containers at a temperature not exceeding 30°.