Antimigraine Drugs

Cluster headache
Cluster headache (migrainous neuralgia, hemicrania cephalic, Horton’s headache) is of unknown aetiology but may be neurovascular in origin.1–5 Patients have one or more short-lived attacks of intense unilateral head pain, usually at the same time of day (often at night). These are associated with autonomic symptoms such as conjunctival injection or lacrimation, miosis or miosis, nasal congestion or rhinorrhea, forehead or facial sweating, and eyelid edema. Restlessness during the attacks is characteristic. The period during which attacks occur is called a cluster period; it may last several weeks or months. In the typical episodic form of cluster headache, cluster periods are followed by periods of remission lasting for months or years but in the more rare chronic form, patients may have cluster periods lasting for more than a year, or with short periods of remission in between. Substances such as alcohol, histamine, or glycerol trinitrate can precipitate headache attacks during cluster periods, but not during periods of remission. There is no effective prophylaxis to prevent cluster headaches, which are relieved by withdrawal of the offending drug, but the mechanisms that lead to these clusters are unknown.1–5 It may also trigger cluster headaches.

Tension-type headache
This term is applied to patients with a history of headache or migraine who do not meet the criteria for chronic tension-type headache.6 7 It is a common condition, affecting around 20% of the population.8 It is characterised by a range of symptoms, including headache, generalized muscle tenderness, and sensitivity to light and noise. The symptoms typically occur in episodes lasting from hours to days and are relieved by rest, analgesic medication, or both.

Cluster headache is managed with a combination of acute and prophylactic therapy. The choice of therapy is based on the severity and frequency of attacks, as well as the patient’s response to previous treatments. Acute treatment options include the use of triptans, intranasal sumatriptan, or intranasal oxymetazoline. Prophylactic therapy options include the use of antidepressants, anticonvulsants, and other medications such as dihydroergotamine and indometacin.


References

Migraine
Migraine is characterised by recurrent attacks of headache that typically last 4 to 72 hours. Attacks persisting for longer than 72 hours are referred to as status migrainosus. 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 there may be 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 occurring in about 75% of patients with migraine. Premonitory symptoms may occur before a migraine attack (with or without aura). Familial hemiplegic migraine is a rare syndrome in which migraine with aura may be preceded or accompanied by dysarthria, ataxia and hemiparesis. In addition, aura migraine is another rare form of migraine with aura in which there may be disturbances of the brain stem or cortex accompanied by symptoms of decreased level of consciousness, vertigo, ataxia, dysarthria, and diplopia.

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

There are several factors that may precipitate migraine attacks. These include anxiety, physical and emotional stress, a change in sleep pattern, bright lights, fasting, some foods, and menstruation. Menstrual migraine is characterised by attacks without aura which are most likely to occur within 2 days of the start of menstruation. Migraine may be precipitated by drugs including, some oral contraceptives and oestroproges, and glycerol trinitrate. The frequency of migraine attacks can be reduced if such precipitating factors can be identified and avoided. Quiet, darkness and sleep can ease an attack, with sleep heralding recovery.

The drug treatment of migraine may be tailored to the severity of individual disease from the outset (stratified care) or may begin with simple analgesics and be subsequently adjusted according to response (step strategy). In the UK, stepped care seems to be increasingly preferred. Acute treatment of menstral migraine is the same as for migraine; however, as menstrual migraine may be of longer duration, treatment may need to be repeated over several consecutive days.

Simple analgesics (paraetanol or NSAIDs including aspirin) are effective if taken at the earliest signs of an attack (promptly) and are sometimes included in oral compound analgesic preparations. However, the frequent use of analgesics is best avoided as it can increase the risk of developing chronic migraine.

Drugs used with analgesics in antimigraine preparations include caffeine and the opioid analgesics ondansetron and prochlorperazine. Sumatriptan is included in compound antimigraine preparations. Prochlorperazine also

All cross-references refer to entries in Volume A periods. Other drugs under investigation include gabapentin, mezezomal, and topiramate.8,9,10

Paroxysmal hemiancia is a rare variant of cluster headache associated with an increase in migraine attack frequency.1 Overuse of medication may lead to a faster rate and at lower dosage which 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.

Migraine is characterised by attacks without aura which are most likely to occur within 2 days of the start of menstruation. Migraine may be precipitated by drugs including, some oral contraceptives and oestroproges, and glycerol trinitrate. The frequency of migraine attacks can be reduced if such precipitating factors can be identified and avoided. Quiet, darkness and sleep can ease an attack, with sleep heralding recovery.

The drug treatment of migraine may be tailored to respond to the maximum possible dose of a drug within a week. Verapamil is usually considered the preferred therapy of choice.2,3,4,5 Particular in patients with chronic long-lasting or intractable headache, lithium may also be useful for the episodic or chronic form of the disorder.6,7,8,9,10 Despite a lack of studies, oral corticosteroids are occasionally considered by some to be effective in the prophylaxis of cluster headache.4,11,12 including those with short-lasting cluster periods (less than 2 months). Methysergide, pizotifen and valproate may also be tried.3,4,5,6,11 Ergotamine may be used rectally in the short-term management of episodic cluster headache, if attacks are predictable.6,10 It should not be used for prolonged

have the advantage of gastric emptying and normal peristalsis. If nausea and vomiting are prominent, re- 
mucosal blood flow. In the majority of cases, prophylactic treatment is 
attacks not responding to simple analgesics such as 
NSAIDs may be treated with specific antimigraine drugs 
such as the selective serotonin (5-HT1) antagonist, sumatriptan 
(HT1) agonists are preferred.

Serotonin (5-HT1) agonists are highly effective in relieving 
attacks of migraine and nausea of a migraine attack. There 
are a number of triptans available; patient characteristics 
and previous experience of triptans can sometimes be 
unpredictable. Some patients experience recurrence of the 
headache within 24 to 48 hours and often respond to a 
second dose; the best way to treat the individual 
patient may involve trial and error; a change in formulation 
should also be considered. Triptans should not be used in 
patients with a high risk factor, or suffering from 
cardiopulmonary disease. The main concern with all 
triptans is their potential for coronary vasospasm and 
triptans and do not appear to be safer than others. Medication-overuse 
headaches have also been noted with triptan use.

Ergot derivatives are rarely needed now in the treatment 
of migraine. If ergotamine is used it should be given at 
the first warning of an attack; the earlier it is given, the 
more likely it is to be effective. The oral bioavailability is good 
and most of the drug is reduced further during a 
migraine attack. Ergotamine has sometimes been given in sublingual or 
rectal preparations. Ergotamine can also exacerbate nausea 
and vomiting, metoclopramide or domperidone 
severe cases the phenothiazines chlorpromazine or pro- 
cyclizine may be used but may be less effective. Ergotamine 
may be of use if parenteral treatment is required; it can also be given 
intranasally but there is less experience with this route. 
Parenteral ergot derivatives may find combination treatment, such as a simple analgesic with 
a triptan, helpful particularly in prolonged attacks.

Other drugs that may be given alone or in combination 
include corticosteroids or pethidine. Lidocaine has been 
given intravenously for the emergency treatment of 
migraine; intranasal lidocaine has also been tried. The 
optic agonists, including phenoxybenzamine, given by nasal 
spray, has been advocated, but its place in therapy, if any, 
remains to be established. Other drugs that have been 
investigated include: intravenous antiepileptic agents, 
valproic acid has also shown promise in aborting acute 
attacks.

Guidelines have been issued for the treatment of 
migraine in children and adolescents. For acute 
treatment, ibuprofen and paracetamol were found to be 
effective in children aged 6 years and over. Sumatriptan, 
nasal spray, is used to abort aborting acute attacks.

Prophylactic treatment should be considered for patients 
in whom abortive measures are ineffective or 
migraine attacks occur frequently, or for those with 
less frequent but severe or prolonged attacks. Some recommend prophylaxis if attacks occur more often than once a 
month. Prophylaxis can reduce the severity and/or 
frequency of attacks but does not eliminate them 
completely and patients still need additional abortive or 
symptomatic treatment. Sumatriptan, given by nasal 
spray, has been advocated, but its place in therapy, if any, 
remains to be established. Other drugs that have been 
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Tension-type headache

Tension-type headaches, also referred to as muscle- 
contraction headaches, are probably the commonest form of 
chronic head pain. Although tension-type headaches are 
unlike migraine is continuous and non-pulsatile. The pain is 
often described by the patient as feeling like a tight band 
persisting around the head. Headaches of this type may 
be precipitated by many factors including psychosocial stress 
or muscular stress. Many patients also have associated 
symptoms of anxiety, mood disturbance, or depression. 
Tension-type headaches and migraine often co-exist and may then be referred to as 
combination or mixed headaches. Some patients only 
experience tension-type headaches, while they may 
also suffer from migraine. Others may develop chronic tension-type headache which is difficult to treat.

Tension-type headaches are relatively common. The 
headache guidelines for their management, however, are the 
migraine treatment guidelines. In a patient with 
untreated migraine is continuous and non-pulsatile. The pain is 
often described by the patient as feeling like a tight band 
persisting around the head. Headaches of this type may 
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Almotriptan Malate (BAN, INN, JAN) Almotriptan, Malate d; Almotriptan; malate de; Almotriptan Malas; LAS-31416 (almotriptan); Malate de almotriptan; PNL-180038; Анмоктиртатна Малар

Almotriptan malate is a selective serotonin (5-HT1) agonist with actions and uses similar to those of sumatriptan. It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Almotriptan is given orally as the malate, and does not cause hypotension or vasodilation. Almotriptan malate is 8.7% soluble in water and 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Almotriptan malate is a selective serotonin (5-HT1) agonist with actions and uses similar to those of sumatriptan. It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Almotriptan is given orally as the malate, and does not cause hypotension or vasodilation. Almotriptan malate is 8.75% soluble in water; 8.25% 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2. Almotriptan should be given with caution to patients with hepatic impairment or severe renal impairment. Patients with hypersensitivity to sumatriptan may theoretically show a similar reaction to almotriptan. Oral almotriptan may be used for the acute treatment of migraine, and to terminate an acute attack of cluster headache. Oral almotriptan is usually given orally, usually as a single dose of 2 mg, for the treatment of acute attacks of migraine while lower oral doses are recommended for migraine prophylaxis.

Dihydroergotamine Malate (BAN, INN, JAN) Dihydroergotamine, Mesilate (Intranasal), Dihydroergotamine; Dihydroergotamine, Mesilate (Intranasal); Dihydroergotamine, Mesilate (Intravenous); Dihydroergotamine, Mesilate (Topical); Dihydroergotamine, Mesilate (Intranasal) (Inhale); Dihydroergotamine, Mesilate (Topical) (Spray)

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

For the treatment of migraine and to terminate an acute attack of cluster headache, dihydroergotamine mesilate is usually given by subcutaneous or intramuscular injection in doses of 1 mg repeated, if necessary, after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg, to terminate an acute attack of cluster headache. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 2 mg. Oral administration of 0.5 mg to 1 mg may be necessary after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg, to terminate an acute attack of cluster headache. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 2 mg. Oral administration of 0.5 mg to 1 mg may be necessary after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg, to terminate an acute attack of cluster headache. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 2 mg. Oral administration of 0.5 mg to 1 mg may be necessary after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg, to terminate an acute attack of cluster headache.
Dihydroergotamine has been suggested for use in the prevention of hypertensive episodes associated with epidural or spinal anesthesia, and for the management of which is discussed in Treatment of Acute Porphyria, p. 619.3. It has also been tried in the management of hypertensive episodes associated with haemodialysis.1 3.

Venous thromboembolism. Standard prophylaxis for sur-
Ergotamine Tartrate

Ergotamine is an alkaloid derived from ergot (p. 2137.1). It is used in migraine and cluster headache. It has also been used to treat acute attacks of migraine (p. 670.3) unresponsive to non-opioid analgesics, one of the main drugs used to treat acute attacks of migraine is sumatriptan (p. 672.3). Ergotamine may be of use in patients with refractory orthostatic hypotension (p. 1634.3). Ergotamine is believed to be less selective than dihydroergotamine (p. 672.3) in its actions and affects both venous capacitance and peripheral resistance. However, the oral bioavailability of ergotamine is greater than that of dihydroergotamine and there have also been some reports of successful treatment with inhalable1–3 or rectal4 ergotamine. Adverse effects

Usages and Administration

Ergotamine is a polyhydric colloid water-soluble white or yellow-white crystalline powder. It may contain 2 molecules of methanol of crystallisation. Slightly soluble in alcohol. Aqueous solutions slowly become turbid, owing to the formation of a partial solid solution, which may be prevented by the addition of tartaric acid. A 0.25% suspension in water is of pH 4.0 to 5.5. Store in air-tight glass containers at a temperature of 2 to 8 degrees and protect from light.

Stability in solution. Reference.


References.


Oral hypotension. Ergotamine and dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p. 1634.3). Ergotamine is believed to be less selective than dihydroergotamine and there have also been some reports of successful treatment with inhalable1–3 or rectal4 ergotamine. Adverse effects

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 emetic 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 occur myocardial ischemia and inching in hyperventilatory patients. Treatment should be stopped if symptoms of vasoconstriction develop. Susceptible patients, especially those with a history of ischemia or 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, diarrhea, extreme thirst, coldness, tingling, weakness, and cyanosis. Intravenously given ergotamine is not emetic or hypotensive, shock, confusion, convulsions, and unconsciousness; fatalities have been reported. Further symptoms of peripheral 12 and central ischemia such as distal ischemia and gangrene, cerebral and ocular hemorrhages, and cerebrovascular disturbances, as seen in chronic ergot poisoning, may also occur but may be delayed. In chronic toxic ingestion, resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, the 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, sometimes beginning at the fingers. Anginal pain, tachycardia or bradycardia, and hypotension or hyperventilation have been reported. Myocardial infarction occurred infrequently. Removal of occlusive peripheral fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Chronic, intractable contractures (reboutcher headache) made the condition also a major withdrawal symptom following the development of ergotamine dependence (see under Precautions, p. 675.1). Other adverse effects include psychic effects, psychoses, and convulsions. On rare occasions symptoms of vasoconstriction of blood vessels in the skin, the eye, intestines, and kidneys occur. Anorectal ulceration, sometimes leading to rectal necrosis and stenosis or rectovaginal fistula, has been described. In rare cases of excessive use of suppositories containing ergotamine.


References.

Precautions
Ergotamine tartrate is contraindicated in patients with severe or uncontrolled hypertension, shock, severe or persistent sepsis, peripheral vascular disease, ischaemic heart disease, cardiac arrhythmias, temporal arteritis, hyperthyroidism, or hepatic or renal impairment. It is also contraindicated in those with biliary or hemiplegic migraine. Ergotamine tartrate should not be used with care in patients with prostatic hypertrophy. It is contraindicated in pregnancy because of its oxytocic effect. Acidental dosage of ergotamine in the newborn may result in suprapubic hyperemia and possible pulmonary congestion. In those with a family history of ischaemic heart disease, caution should be exercised.

Antivirals.
There have been reports of ergotism in patients given ergotamine concomitantly with 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 indinavir in one, and nelfinavir in another. One of the patients given ritonavir, who had taken 1 mg of ergotamine tartrate over the 4 days before presentation, also developed signs of cerebral vascular involvement and eventually went into an irreversible coma.

The metabolism of ergot alkaloids may be inhibited by dalfopristin or eravacycline.

Beta blockers.
Peripheral vasodilation was reported in a patient with migraine after addition of propranolol to regular use of Cafergot (ergotamine dihydrogen tartrate) suppositories twice daily. 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. However, antiviral vasodilation has been reported after use of methysergide with propranolol to treat ergotism. Such combinations should therefore be used with caution.

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

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 reduced by a high first-pass hepatic metabolism. Ergotamine has been given recrally 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. Calcineurin is sometimes included in oral and rectal preparations of ergotamine to improve its absorption. The latter is absorbed more reliably whether it does not seem to be clear. Drugs such as metolazone 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 isoform CYP3A4; the majority of metabolites are excreted in the bile. About 4% of a dose is excreted in the urine. 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 and its metabolites have been detected in breast milk.

References.

The symbol † denotes a preparation no longer actively marketed.

Pregnancy.
Ergotamine is contra-indicated in pregnancy because of its oxytocic effect. Acidental dosage of ergotamine in the newborn may result in suprapubic hyperemia and possible pulmonary congestion. In those with a family history of ischaemic heart disease, caution should be exercised.

Antidepressants. There have been isolated case reports of ergotism in patients given dihydroergotamine with amitriptyline, imipramine, paroxetine, or sertraline.

Antimigraine drugs. Oral occlusion has been reported in 2 patients given metyrapone with a high parental dosage of ergotamine tartrate; the combination should be avoided. Use of ergotamine as supplement-

38e Martindale, copyright Pharmaceutical Press
Migraine. Feverfew is a traditional herbal remedy used in the prophylaxis of migraine. Its effects have been attributed to the plant's content of sesquiterpene lactones, which have been standardised to provide a minimum of 0.2% parthenolide, is available in some powder, which has been standardised to provide a minimum of 0.2% parthenolide. 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 animal studies, clinical trials have not shown that feverfew alleviates haemostatic parameters. Feverfew should be withdrawn. Contact dermatitis has also been reported. Gastrointestinal effects such as nausea, vomiting, diarrhoea and constipation occur rarely. Feverfew should be taken with a meal to reduce nausea. Feverfew should be withdrawn if symptoms of anaphylaxis occur. Feverfew should be withdrawn if symptoms of anaphylaxis occur. Feverfew should be withdrawn if symptoms of anaphylaxis occur. Feverfew should be withdrawn if symptoms of anaphylaxis occur.

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