tient may involve trial and error. Triptans should not be used in patients with major risk factors for, or suffering from, cardiovascular disease. The main concern with all triptans is their potential for coronary vasoconstriction and no triptan appears to be safer than the others.

If **ergotamine** is used it should be given at the first warning of an attack; the earlier it is given, the more effective the treatment. Since its oral bioavailability is poor and may be 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, or in severe cases the phenothiazines chlorpromazine or prochlorperazine, may be given. Dihydroergotamine may be of use if parenteral treatment is required; it can also be given intranasally but there is less experience with this route.

Patients who rapidly develop severe migraine may be given **parenteral** dihydroergotamine or sumatriptan. Some consider parenteral metoclopramide to be suitable first-line treatment. If there is no response to these drugs, dopamine antagonists such as chlorpromazine or prochlorperazine given parenterally may be effective in relieving the pain of acute migraine attacks. Prolonged attacks (status migrainosus) may require intravenous administration of dihydroergotamine with metoclopramide.

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 opioid agonist-antagonist butorphanol, given by nasal spray, has been advocated, but its place in therapy, if any, remains to be established. Other drugs under investigation include botulinum A toxin and CGRP antagonists; intravenous 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 should be considered in those aged 12 years and over.

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 or twice 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. Drugs suggested for prophylaxis have a range of actions which reflects uncertainty over the pathogenesis of migraine. It is important to give prophylactic drugs for an adequate period before assessing their efficacy. Once an optimum effect has been achieved the need for continuing prophylaxis should be reviewed at intervals of about 3 to 6 months.

The main prophylactic drugs are **beta blockers**, tricyclic **antidepressants**, and the **antiepileptics**, topiramate and valproate. Propranolol is considered by many to be the prophylactic drug of choice. Lethargy appears to be the most common adverse effect. Other beta blockers reported to be effective are those that, like propranolol, possess no intrinsic sympathomimetic activity, which include atenolol, metoprolol, nadolol, and timolol. The potential for beta blockers to interact with some serotonin ($5\text{-}HT_1$) agonists and ergotamine should be borne in mind. Tricyclic antidepressants, particularly amitriptyline, given in gradually increasing doses at night are useful for preventing migraine, especially in patients who also have depression or tension-type headache, although antimuscarinic adverse effects may occur. Valproate is also used for preventing migraine. Nausea appears to be the most common adverse effect. Topiramate is the main alternative to valproate. Weight loss and paraesthesia are commonly reported adverse effects. Topiramate and valproate are particularly useful in patients who also have epilepsy or bipolar disorder.

Other drugs have been used for the prophylaxis of migraine: pizotifen, an antihistamine and serotonin antagonist, has been widely used but evidence for its efficacy is limited; it may be tried in children. Of the drugs with calcium-channel blocking activity, flunarizine appears to be effective, and has been suggested for use in children, and verapamil may be useful, but evidence for the efficacy of other calcium-channel blockers such as diltiazem, nifedipine, or nimodipine is less convincing; NSAIDs may be worth trying. The use of methysergide, a potent serotonin antagonist, has declined because of serious adverse effects, in particular retroperitoneal fibrosis. MAOIs such as phenelzine have been used occasionally but are best reserved for severe cases refractory to other forms of prophylactic treatment. Cyproheptadine, an antihistamine and serotonin antagonist, has been used for migraine prophylaxis, particularly in children. Other drugs used for the prophylaxis of migraine have included butterbur, clonidine, cyclandelate, indoramin, feverfew, and the ergot derivative metergoline. Positive results have been seen with magnesium and riboflavin. Other drugs still under investigation, which have shown potential for prevention of migraine attacks are: baclofen, botulinum A toxin, candesartan, gabapentin, lisinopril, and venlafaxine.

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Post-dural puncture headache

For the management of headache associated with lumbar puncture or spinal anaesthesia, see Post-dural Puncture Headache under Local Anaesthetics, p.1851.

Tension-type headache

Tension-type headaches, also referred to as muscle-contraction headaches, are probably the commonest form of headache. They are characterised by bilateral pain, which unlike migraine is continuous and non-pulsatile. The pain is often described by the patient as feeling like a tight band pressed 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 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 isolated acute attacks of tension-type headache (episodic tension-type headache), but others may develop chronic tension-type headache which is difficult to treat.

Treatment is aimed at removing the underlying causes where these can be identified. Simple massage may help if muscle contraction is a prominent component of the pain. Non-opioid analgesics, such as aspirin or other NSAIDs and paracetamol, may be tried for individual acute attacks of headache, but analgesic overuse must be avoided as this can lead to chronic headache resistant to other measures (see Medication-overuse Headache, above). Opioids alone or in combination preparations with other analgesics should also be avoided. Hypnotics or sedatives have sometimes been used in combination preparations with analgesics in the management of tension-type headache that disrupts sleep but, because of the potential for abuse, they should be avoided in chronic headaches. Muscle relaxants appear to have little place in the management of tension-type headache; although some patients may respond, results are generally disappointing. Other drugs that have been tried include valproate and botulinum A toxin. **Prophylaxis** is preferable to regular short-term use of analgesics in controlling chronic tension-type headache. Tricyclic antidepressants, particularly amitriptyline, are generally considered as first choice, although benefit is rarely complete. The mode of action is unclear and appears to be independent of any antidepressant action. In most cases, improvement is seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression. Addition of a beta blocker such as propranolol may sometimes be of benefit for patients with some migraine features.

References.

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2. Kumar KL, Cooney TG. Headaches. *Med Clin North Am* 1995; **79:** 261–86.
3. Anonymous. Management of tension-type headache. *Drug Ther Bull* 1999; **37:** 41–4.
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Almotriptan Malate *(BANM, USAN, rINNM)*

Almotriptan, Malate d'; Almotriptani Malas; LAS-31416 (almotriptan); Malato de almotriptán; PNU-180638E (almotriptan malate). 1-[({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl)sulfonyl]pyrrolidine malate (1:1).

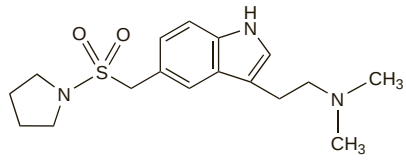
Альмотриптана Малат

$C_{17}H_{25}N_3O_2S,C_4H_6O_5$ = 469.6.

CAS — 154323-57-6 (almotriptan); 181183-52-8 (almotriptan malate).

ATC — N02CC05.

ATC Vet — QN02CC05.



(almotriptan)

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Almotriptan should not be used in patients with severe hepatic impairment since clearance is likely to be markedly impaired, and should be given with caution, and in reduced doses, to patients with mild to moderate hepatic impairment. The dose of almotriptan should also be reduced in patients with severe renal impairment.

Patients with hypersensitivity to sulfonamides may theoretically exhibit a similar reaction to almotriptan.

Incidence of adverse effects. Results from studies involving more than 2500 patients with migraine suggested that adverse effects of almotriptan were infrequent.[1] The commonest adverse effects reported were dizziness, nausea and vomiting, headache, paraesthesia, fatigue, and drowsiness, all of which occurred in less than 3% of patients. The incidence of chest symptoms was 0.2% in 2 large phase III studies.

1. Dodick DW. Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 2001; **41:** 449–55.

Interactions

As for Sumatriptan, p.626.

Pharmacokinetics

After oral doses, peak plasma-almotriptan concentrations are obtained in about 1 to 3 hours, with a bioavailability of about 70%. Protein binding is about 35%. Almotriptan is metabolised, mainly by monoamine oxidase type A to the inactive indole acetic acid derivative and to a lesser extent by cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to the inactive gamma-aminobutyric acid derivative. More than 75% of an oral dose is excreted in the urine and the remainder in faeces. About 40 to 50% of the dose in the urine and 5% in the faeces is excreted as unchanged drug. The plasma elimination half-life is about 3.5 hours in healthy subjects, increasing to about 7 hours in severe renal impairment.

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

◊ References.

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2. McEnroe JD, Fleishaker JC. Clinical pharmacokinetics of almotriptan, a serotonin 5-HT receptor agonist for the treatment of migraine. *Clin Pharmacokinet* 2005; **44:** 237–46.

Uses and Administration

Almotriptan malate is a selective serotonin ($5\text{-}HT_1$) 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. Almotriptan is given orally as the malate, and doses are expressed in terms of the base; almotriptan malate 8.75 mg is equivalent to about 6.25 mg of almotriptan.

The usual dose of almotriptan is 12.5 mg in the UK and 6.25 or 12.5 mg in the USA. 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. No more than 2 doses should be taken in a 24-hour period. For doses in hepatic and renal impairment see below.

◊ References.

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Administration in hepatic or renal impairment. In patients with hepatic or severe renal impairment, no more than 12.5 mg of almotriptan should be taken in 24 hours; a starting dose of 6.25 mg may be used. Almotriptan is contra-indicated in patients with severe hepatic disease.

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

Further references.

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Preparations

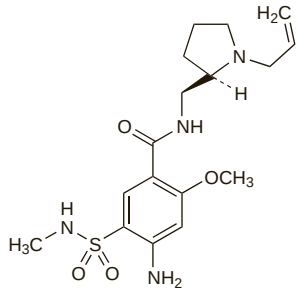
Proprietary Preparations (details are given in Part 3)
Belg.: Almogran; ***Canad.:*** Axert; ***Denm.:*** Almogran; ***Fin.:*** Almogran; ***Fr.:*** Almogran; ***Ger.:*** Almogran; ***Irl.:*** Almogran; ***Ital.:*** Almogran; Almotrex; ***Neth.:*** Almogran; ***Norw.:*** Almogran; ***Port.:*** Almogran; Amignul; ***Spain:*** Almogran; Amignul; ***Swed.:*** Almogran; ***UK:*** Almogran; ***USA:*** Axert.

Alpiropride *(rINN)*

Alpiroprida; Alpiropridum. (±)-*N*-[(1-Allyl-2-pyrrolidinyl)methyl]-4-amino-5-(methylsulfamoyl)-*o*-anisamide.

Альпироприд

$C_{17}H_{26}N_4O_4S$ = 382.5.
CAS — 81982-32-3.



Profile

Alpiropride is a dopamine antagonist that has been given orally for the treatment and prophylaxis of migraine.

Preparations

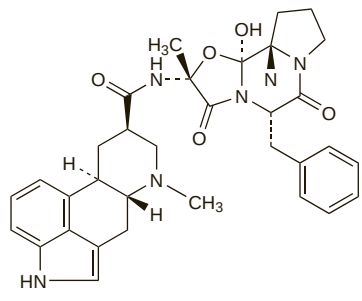
Proprietary Preparations (details are given in Part 3)
Port.: Rivistel†.

Dihydroergotamine *(BAN, rINN)*

Dihidroergotamina; Dihydroergotamiini; Dihydroergotamin; Dihydroergotaminum. (5′*S*,8*R*)-5′-Benzyl-9,10-dihydro-12′-hydroxy-2′-methyl-3′,6′,18-trioxoergotaman.

Дигидроэрготамин

$C_{33}H_{37}N_5O_5$ = 583.7.
CAS — 511-12-6.
ATC — N02CA01.
ATC Vet — QN02CA01.



Dihydroergotamine Mesilate *(BANM, rINNM)*

Dihidroergotamin-mezilát; Dihidroergotamino mesilatas; Dihydroergotamiinimesilaatti; Dihydroergotamine, mésilate de; Dihydroergotamine Mesylate *(USAN)*; Dihydroergotamine Methanesulphonate; Dihydroergotamini mesilas; Dihydroergotamin-mesilat; Dihydroergotamin-mesylát; Dihydroergotaminy mezylan; Mesilato de dihidroergotamina.

Дигидроэрготамина Мезилат

$C_{33}H_{37}N_5O_5,CH_4O_3S$ = 679.8.
CAS — 6190-39-2.
ATC — N02CA01.
ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Dihydroergotamine Mesilate). Colourless crystals or a white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 4.4 to 5.4. Protect from light.
USP 31 (Dihydroergotamine Mesylate). A white to slightly yellowish powder, or off-white to faintly red powder, having a faint odour. Soluble 1 in 125 of water, 1 in 90 of alcohol, 1 in 175 of chloroform, and 1 in 2600 of ether. pH of a 0.1% solution in water is between 4.4 and 5.4. Protect from light.

Dihydroergotamine Tartrate *(BANM, rINNM)*

Dihidroergotamino tartratas; Dihidroergotamin-tartarát; Dihydroergotamiinitartraatti; Dihydroergotamine, tartrate de; Dihydroergotamini tartras; Dihydroergotamin-tartarát; Dihydroergotamintartrat; Tartrato de dihidroergotamina.

Дигидроэрготамина Тартрат

$(C_{33}H_{37}N_5O_5)_2,C_4H_6O_6$ = 1317.4.
CAS — 5989-77-5.
ATC — N02CA01.
ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dihydroergotamine Tartrate). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. A 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p.620, although vasoconstriction may be less pronounced and the frequency of nausea and vomiting lower with dihydroergotamine mesilate than with ergotamine tartrate. Dihydroergotamine does not appear to produce physical dependence.

Effects on the cardiovascular system. There are conflicting reports on the risk of vasospasm in patients given dihydroergotamine with heparin for thromboembolism prophylaxis. Vasospastic or necrotic reactions have been reported on several occasions during such therapy.[1-4] In an Austrian study of 147 290 patients given drug prophylaxis for thromboembolism, complications attributable to ergotism were seen in 142 of 61 092 (0.23%) who received dihydroergotamine and heparin.[5] Others,[6] however, observed only 1 case of vasospasm in 5100 trauma patients (0.02%) given the combination. In 1989 the Swedish Adverse Drug Reactions Advisory Committee reported[7] that up to the end of September 1987 the manufacturer had received 201 reports of vasospastic reactions associated with the use of *Orstanorm* (dihydroergotamine + lidocaine) with heparin. Permanent damage occurred in 59% of these patients. Vasospastic reactions had occurred more frequently in patients who had undergone surgery for trauma and the prognosis for such patients was generally poorer than for others. Since the risk of permanent damage appeared to be related to treatment length the Committee recommended that this preparation should not be given for more than 7 days. The possibility of such reactions and the contra-indications of dihydroergotamine should be borne in mind when using this form of prophylaxis (see Venous Thromboembolism, under Uses, below).

1. van den Berg E, *et al.* Ergotism leading to threatened limb amputation or to death in two patients given heparin-dihydroergotamine prophylaxis. *Lancet* 1982; **i:** 955–6.
2. van den Berg E, *et al.* Vascular spasm during thromboembolism prophylaxis with heparin-dihydroergotamine. *Lancet* 1982; **ii:** 268–9.
3. Monreal M, *et al.* Skin and muscle necrosis during heparin-dihydroergotamine prophylaxis. *Lancet* 1984; **ii:** 820.
4. Kilroy RA, *et al.* Vascular spasm during heparin-dihydroergotamine prophylaxis. *Clin Pharm* 1987; **6:** 575–7.
5. Gatterer R. Ergotism as complication of thromboembolic prophylaxis with heparin and dihydroergotamine. *Lancet* 1986; **ii:** 638–9.
6. Schlag G, *et al.* Risk/benefit of heparin-dihydroergotamine thromboembolic prophylaxis. *Lancet* 1986; **ii:** 1465.
7. Swedish Adverse Drug Reaction Advisory Committee. Dihydroergotamine + lidocaine – vasospasm. *Bull Swed Adverse Drug React Advisory Committee* 1989; (54): 1.

Fibrosis. For reference to fibrosis associated with the administration of dihydroergotamine, see Methysergide Maleate, p.623.

Precautions

As for Ergotamine Tartrate, p.620.

Cardiovascular disorders. For specific contra-indications and precautions in cardiovascular disorders, see under Ergotamine, p.621.

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

Interactions

As for Ergotamine (p.621).

Use with other vasoconstrictive drugs, including supplementary antimigraine treatment with ergotamine or sumatriptan, should be avoided.