

Antimigraine drugs

Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be initiated for migraine. Untreated, migraine attacks last for several hours and sometimes for as long as 3 days.

Migraine headache is frequently accompanied by episodes of gastrointestinal disturbance including nausea and vomiting. The headache may be preceded or accompanied by aura (classical migraine) which is characterised by visual disturbances such as flickering lines and fragmented vision or sensory disturbances such as tingling or numbness; rarely, hemiparesis or impaired consciousness may occur. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients who experience migraine.

Emotional or physical stress, lack of or excess sleep, missed meals, menstruation, alcohol and specific foods including cheese and chocolate are often identified as precipitating factors; oral contraceptives may increase the frequency of attacks. Avoidance of such precipitating factors can be of great benefit in preventing or reducing the frequency of attacks and should be addressed in detail. Women taking combined oral contraceptives who experience an onset or increase in frequency of headaches should be advised of other contraceptive measures.

The two principal strategies of migraine management are treatment of acute attacks and prophylactic treatment.

Acute migraine attack

Treatment of acute attacks may be non-specific using simple analgesics, or specific using an ergot alkaloid such as ergotamine. If nausea and vomiting are features of the attack, an antiemetic drug may be given. Treatment is generally by mouth; some drugs are available as suppositories which may be administered if the oral route is not effective (poor oral bioavailability, or absorption from the gut impaired by vomiting) or not practicable (patient unable to take drugs orally).

Simple analgesics including NSAIDs (nonsteroidal anti-inflammatory drugs) can be effective in mild to moderate forms of migraine if taken early in the attack; most migraine headaches respond to **paracetamol**, **acetylsalicylic acid** or an NSAID such as **ibuprofen**. Peristalsis is often reduced during migraine attacks and, if available, a dispersible or effervescent preparation of the drug is preferred because of enhanced absorption compared with a conventional tablet. The risk of Reye syndrome due to acetylsalicylic acid in children can be avoided by giving paracetamol instead. Frequent and prolonged use of analgesics by migraine sufferers may lead to analgesic-induced headache.

Ergotamine should be considered only when attacks are unresponsive to non-opioid analgesics. It is poorly absorbed when taken orally or sublingually. Rectal suppositories may offer an advantage when other routes of administration are unsatisfactory. To be fully effective ergotamine must be taken in adequate amounts as early as possible during each attack. Adverse effects limit how much ergotamine can be used in a single attack and consequently the recommended dosage should never be exceeded, and at least four days should elapse between successive treatments. Even

normal dosage can lead to dependence, tolerance to adverse effects and to a withdrawal syndrome on discontinuing the drug. To avoid dependence the frequency of administration should be limited to no more than twice a month. Adverse effects include nausea, vomiting, diarrhoea and vertigo; chronic ergotism is characterized by severe peripheral vasoconstriction which can lead to gangrene in the extremities. The severity of adverse effects prevents the use of ergotamine for migraine prophylaxis.

An antiemetic such as **metoclopramide**, given as a single dose orally or by intramuscular injection at the onset of a migraine attack, preferably 10–15 minutes before the analgesic or ergotamine, is useful not only in relieving nausea but also in restoring gastric motility, thus improving absorption of the antimigraine drug.

Products which contain barbiturates or codeine are undesirable, particularly in combination with ergotamine, since they may cause physical dependence and withdrawal headaches.

Analgesics

Acetylsalicylic acid

Tablets, acetylsalicylic acid 300 mg, 500 mg

Dispersible tablets, acetylsalicylic acid 300 mg [not included on WHO Model List]

Suppositories, acetylsalicylic acid 300 mg [not included on WHO Model List]

Uses:

acute migraine attacks; tension headache; pyrexia, mild to moderate pain and inflammation (section 2.1.1); antiplatelet (section 12.5)

Contraindications:

hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (Reye syndrome); gastrointestinal ulceration; haemophilia; not for treatment of gout

Precautions:

asthma, allergic disease; impaired renal or hepatic function (Appendices 4 and 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; G6PD-deficiency; dehydration; **interactions:** Appendix 1

Dosage:

Treatment of acute migraine attack, *by mouth* preferably with or after food, **ADULT** 300–900 mg at first sign of attack, may be repeated every 4–6 hours if necessary; maximum 4 g daily; **CHILD** under 16 years not recommended

Treatment of acute migraine attack, *by rectum* , **ADULT** 600–900 mg inserted at first sign of attack, may be repeated every 4 hours if necessary; maximum 3.6 g daily; **CHILD** under 16 years not recommended

Adverse effects:

generally mild and infrequent but high incidence of gastrointestinal irritation with slight asymptomatic blood loss, increased bleeding time; bronchospasm and skin reactions in hypersensitive patients; see also section 2.1.1

Paracetamol

Tablets , paracetamol 300 mg, 500 mg

Dispersible tablets , paracetamol 500 mg [not included on WHO Model List]

Suppositories , paracetamol 250 mg, 500 mg [not included on WHO Model List]

Uses:

acute migraine attacks, tension headache; mild to moderate pain, pyrexia (section 2.1.2)

Precautions:

hepatic impairment (Appendix 5); renal impairment; alcohol dependence; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **overdosage:** section 4.2.1;

interactions: Appendix 1

Dosage:

Treatment of acute migraine attack, *by mouth*, **ADULT** 0.5–1 g at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 g daily; **CHILD** 6–12 years 250–500 mg at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours

Treatment of acute migraine attack, *by rectum* , **ADULT** and **CHILD** over 12 years 0.5–1 g at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours; **CHILD** 6–12 years 250–500 mg at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours

Adverse effects:

rare, but rashes, blood disorders; **important:** liver damage (and less frequently renal damage) following overdosage

Ibuprofen

Tablets , ibuprofen 200 mg, 400 mg

Uses:

acute migraine attacks, tension headache; mild to moderate pain and inflammation, pyrexia (section 2.1.3)

Contraindications:

hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration

Precautions:

hepatic or renal impairment (Appendices 4 and 5); preferably avoid if history of peptic ulceration; cardiac disease; elderly; pregnancy and breastfeeding (Appendices 2 and 3); coagulation defects; allergic disorders; **interactions:** Appendix 1

Dosage:

Treatment of acute migraine attack, *by mouth* preferably with or after food, **ADULT** 400–600 mg at first sign of attack, may be repeated every 6–8 hours if necessary, maximum 2.4 g daily; **CHILD** 8–12 years 200 mg at first sign of attack, may be repeated every 6–8 hours if necessary

Adverse effects:

gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastrointestinal haemorrhage; hypersensitivity reactions including rash, angioedema, bronchospasm; headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, renal failure; rarely hepatic damage; very rarely exfoliative dermatitis, purpura; prolonged administration, see section 2.1.3

Ergot alkaloid**Ergotamine tartrate**

Drug subject to international control under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988)

Tablets , ergotamine tartrate 1 mg

Suppositories , ergotamine tartrate 2 mg [not included on WHO Model List]

Uses:

treatment of acute migraine attacks unresponsive to analgesics

Contraindications:

pregnancy (Appendix 2) and breastfeeding (Appendix 3); children; peripheral vascular disorders, coronary artery disease, obliterative vascular disease and Raynaud syndrome, severe hypertension, sepsis; severe renal or hepatic dysfunction (Appendices 4 and 5); hyperthyroidism; porphyria

Precautions:

elderly; daily rebound headaches indicative of ergotamine dependence; discontinuation after regular normal dosage may result in withdrawal headache; risk of peripheral vasospasm (advise patient to stop medication immediately if numbness or tingling in extremities or anginal pain develops and to contact doctor);

interactions: Appendix 1

Dosage:

Treatment of acute migraine attack, *by mouth or by rectum* , **ADULT** 1–2 mg at first sign of attack, maximum 4 mg in 24 hours; do not repeat at intervals of less than 4 days, maximum 8 mg in any one week; not to be used more than twice in any 1 month; **CHILD** not recommended

Adverse effects:

nausea, vomiting, vertigo, abdominal pain, diarrhoea, muscle cramps, increased headache; precordial pain, myocardial ischaemia; rarely myocardial infarction; repeated high dosage may cause ergotism with gangrene and confusion; pleural and peritoneal fibrosis may occur with excessive use

Antiemetic**Metoclopramide hydrochloride**

Tablets , metoclopramide hydrochloride 10 mg

Injection (Solution for injection), metoclopramide hydrochloride 5 mg/ml, 2-ml ampoule

Uses:

nausea and vomiting associated with migraine; nausea and vomiting in gastrointestinal disorders and cytotoxic therapy (section 17.2)

Contraindications:

gastrointestinal obstruction, haemorrhage or perforation; 3–4 days after gastrointestinal surgery; phaeochromocytoma

Precautions:

hepatic or renal impairment (Appendices 4 and 5); elderly; children and young adults; pregnancy (Appendix 2) and breastfeeding (Appendix 3); epilepsy; porphyria;
interactions: Appendix 1

Dosage:

Nausea and vomiting of migraine, *by mouth or by intramuscular injection* , **ADULT** single dose of 10–20 mg at first sign of attack preferably 10–15 minutes before antimigraine drug; **ADOLESCENT** single dose of 5–10 mg (5 mg if body weight less than 60 kg)

Adverse effects:

extrapyramidal effects (especially in children and young adults); drowsiness, restlessness, diarrhoea; prolonged administration, see section 17.2

Migraine prophylaxis

Prophylactic treatment should be considered for patients in whom treatment of acute migraine attacks with analgesics or ergotamine is ineffective, or in whom attacks occur more than once a month, or for those with less frequent but severe or prolonged attacks. Prophylaxis can reduce the severity and frequency of attacks but does not eliminate them completely; additional symptomatic treatment is still needed. However, long-term prophylaxis is undesirable and treatment should be reviewed at 6-monthly intervals. Of the many drugs that have been advocated beta-adrenoceptor antagonists (beta-blockers) are most frequently used. **Propranolol**, a non-selective beta-blocker and other related compounds with similar profile such as **atenolol** are generally preferred. The potential for beta-blockers to interact with ergotamine should be borne in mind. Tricyclic antidepressants, such as **amitriptyline** (section 24.2.1) or calcium-channel blocking drugs such as **verapamil** (section 12.1) may be of value.

Propranolol hydrochloride

Propranolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives

Tablets , propranolol hydrochloride 20 mg, 40 mg, 80 mg, 160 mg [80 mg and 160 mg not included on WHO Model List]

Uses:

prophylaxis of migraine

Contraindications:

asthma or history of obstructive airways disease, uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma

Precautions:

first-degree atrioventricular block; renal impairment (Appendix 4); liver disease (Appendix 5); pregnancy and breastfeeding (Appendices 2 and 3); portal hypertension; diabetes mellitus; myasthenia gravis; history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline));

interactions: Appendix 1

Dosage:

Prophylaxis of migraine, *by mouth* **ADULT** initially 40 mg 2–3 times daily, increased by same amount at weekly intervals if necessary; usual range 80–160 mg daily; **CHILD** under 12 years, 20 mg 2–3 times daily

Adverse effects:

bradycardia, heart failure, hypotension, conduction disorders, bronchospasm, peripheral vasoconstriction, exacerbation of intermittent claudication and Raynaud phenomenon, gastrointestinal disturbances, fatigue, sleep disturbances including nightmares; rarely, rash, dry eyes (reversible), exacerbation of psoriasis