Dantrolene Sodium *(BANM, USAN, rINNM)*

Dantrolène Sodique; Dantroleno sódico; F-440; F-368 (dantrolene); Natrii Dantrolenum; Sodyum Dantrolen. The hemiheptahydrate of the sodium salt of 1-[5-(4-nitrophenyl)furfurylideneamino]imidazolidine-2,4-dione.

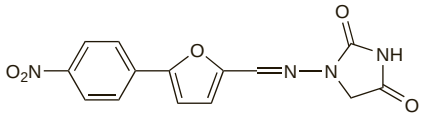
Натрий Дантролен

$C_{14}H_9N_4NaO_5,3H_2O$ = 399.3.

CAS — 7261-97-4 (dantrolene); 14663-23-1 (anhydrous dantrolene sodium); 24868-20-0 (dantrolene sodium, hemiheptahydrate).

ATC — M03CA01.

ATC Vet — QM03CA01.



(dantrolene)

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2008 (Dantrolene Sodium). A yellowish-orange to orange crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in acetone; sparingly soluble in methyl alcohol.

USP 31 (Dantrolene Sodium). A fine orange to orange-brown powder. Sparingly soluble in acetone, in dimethyformamide, and in glycerol. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects associated with dantrolene sodium tend to occur at the start of treatment, but are often short lived and can be controlled by adjusting the dose. The most common adverse effects are drowsiness, dizziness, fatigue, weakness, and general malaise. Diarrhoea may be severe enough to require withdrawal. If diarrhoea recurs on restarting dantrolene, then treatment should probably be stopped permanently. Other adverse effects reported include nausea and vomiting, anorexia, constipation, abdominal cramps, gastrointestinal bleeding, tachycardia, unstable blood pressure, dyspnoea, rashes (often acneform), pruritus, chills and fever, headache, myalgia, nervousness, insomnia, confusion, visual disturbances, mental depression, dysphagia and speech disturbances, and seizures. Haematuria, crystalluria, urinary frequency and retention, and incontinence may occur. Rare but serious adverse effects include hepatotoxicity which may be fatal (see below) and pleural effusion with pericarditis.

Serious adverse effects do not appear to be a problem with the short-term use of intravenous dantrolene sodium in the treatment of malignant hyperthermia.

Effects on the liver. Dantrolene has caused hepatotoxicity with raised liver enzyme values, jaundice, and hepatitis;[1-3] fatalities have been reported.[1,3] Not all patients experienced symptoms such as anorexia, nausea, or abdominal discomfort before the onset of disease and the severity of hepatic injury was unrelated to clinical presentation. In the first report[1] the 14 fatalities occurred with doses in excess of 200 mg daily; a later review[3] found the mean dose associated with 27 fatalities to be 582 mg daily, while reports of non-fatal liver toxicity (95 cases) were associated with a mean dose of 263 mg daily. The onset of hepatic injury was usually between 1 and 6 months after starting treatment and fatalities were not reported in the first 2 months. Only rarely did injury develop before 45 days of treatment. Females appeared to be at greater risk of serious liver injury and the severity of reaction appeared to be age-related with most fatalities occurring in patients over 30 years of age. The liver injury was usually hepatocellular and might include ascending cholangitis; there was little evidence of hypersensitivity.

1. Utili R, *et al.* Dantrolene-associated hepatic injury: incidence and character. *Gastroenterology* 1977; **72:** 610–16.
2. Wilkinson SP, *et al.* Hepatitis from dantrolene sodium. *Gut* 1979; **20:** 33–6.
3. Chan CH. Dantrolene sodium and hepatic injury. *Neurology* 1990; **40:** 1427–32.

Effects on the lungs. Pulmonary oedema associated with heart failure,[1] and pleural effusions with eosinophilia[2-4] have been reported rarely in patients receiving dantrolene. These reactions generally resolve on withdrawal of the drug but resolution may take several months; corticosteroid therapy may be of benefit in dantrolene-related eosinophilic pleural effusion.[3]

1. Robillart A, *et al.* Insuffisance cardiaque par surdosage en dantrolène. *Ann Fr Anesth Reanim* 1986; **5:** 617–19.
2. Mahoney JM, Bachtel MD. Pleural effusion associated with chronic dantrolene administration. *Ann Pharmacother* 1994; **28:** 587–9.
3. Felz MW, Haviland-Foley DJ. Eosinophilic pleural effusion due to dantrolene: resolution with steroid therapy. *South Med J* 2001; **94:** 502–4.
4. Le-Quang B, *et al.* Dantrolene and pleural effusion: case report and review of literature. *Spinal Cord* 2004; **42:** 317–20.

Lymphomas. A case of fatal lymphocytic lymphoma was associated with prolonged dantrolene therapy (600 mg daily) for progressive spastic paraplegia.[1]

1. Wan HH, Tucker JS. Dantrolene and lymphocytic lymphoma. *Postgrad Med J* 1980; **56:** 261–2.

Precautions

It is recommended that dantrolene sodium should not be given to patients with active liver disease. Liver-function tests should be performed in all patients before and during treatment; if abnormal values are found, treatment should generally be stopped. The risk of liver injury may be increased in patients over 30 years of age, in females (especially those taking oestrogens), in those with a history of liver disease, and with doses above 400 mg daily (see under Effects on the Liver, above). Dantrolene sodium should be used with caution in patients with cardiac or pulmonary disorders. It should not be given to patients who use their spasticity to maintain posture or function or to patients with acute muscle spasm.

Dantrolene sodium may cause drowsiness; patients affected should not drive or operate machinery.

Interactions

The CNS effects of dantrolene sodium may be enhanced by alcohol or other CNS depressants. Use with other potentially hepatotoxic drugs such as oestrogens may possibly increase the risk of liver damage and should be avoided.

Calcium-channel blockers. Severe hyperkalaemia and myocardial depression occurred with intravenous dantrolene for prophylaxis of malignant hyperthermia in a patient also taking *verapamil* for angina.[1] The peak serum-potassium concentration was 7.1 mmol/litre 2.5 hours after the dantrolene infusion. *Nifedipine* was substituted for verapamil in a subsequent operation and only a small increase in serum potassium occurred after dantrolene. Ventricular fibrillation and cardiovascular collapse associated with hyperkalaemia have been seen with this combination in *animal* studies, and the manufacturers recommend that calcium-channel blockers and intravenous dantrolene should not be used together.

1. Rubin AS, Zablocki AD. Hyperkalaemia, verapamil, and dantrolene. *Anesthesiology* 1987; **66:** 246–9.

Pharmacokinetics

Dantrolene sodium is slowly and almost completely absorbed from the gastrointestinal tract after oral doses. It is metabolised in the liver mainly to the hydroxylated metabolite, which is nearly as potent as dantrolene sodium, and the acetamide metabolite which has weak muscle relaxant activity. It is excreted in the urine, mainly as metabolites with a small amount of unchanged dantrolene; some is excreted in the bile. Dantrolene is bound extensively to plasma proteins. The elimination half-life of oral dantrolene is about 9 hours, although half-lives of up to 12 hours have been reported after intravenous use.

Uses and Administration

Dantrolene sodium is a muscle relaxant with a direct action on skeletal muscle. It uncouples muscular contraction from excitation, probably by interfering with the release of calcium from the sarcoplasmic reticulum.

It has an important role when given orally, for the symptomatic relief of chronic, severe spasticity (p.1887). It is also given, usually by intravenous injection, for the treatment of malignant hyperthermia.

For **spasticity**, the initial oral dose is 25 mg daily increased gradually as necessary, at 7-day intervals, over about 7 weeks to a maximum dose of 100 mg four times daily. If no response is achieved within 45 days treatment should be stopped. In children, US licensed product information suggests a dose of 500 micrograms/kg once daily, increased gradually if necessary to 2 mg/kg three times daily; dosage four times daily may be necessary for some children but a dose of 100 mg four times daily should not be exceeded.

In the treatment of **malignant hyperthermia**, dantrolene sodium is given, with supportive measures, in an initial dose of 1 mg/kg by rapid intravenous injection, repeated, if necessary, to a total dose of 10 mg/kg. An average dose of 2.5 mg/kg is usually effective. If a relapse or recurrence occurs, dantrolene should be given again at the last effective dose. In the USA, doses of 1 to 2 mg/kg orally four times daily have been recommended for up to 3 days after the crisis to prevent recurrence, and similar doses have been given for 1 to 2 days before surgery in individuals thought to be at risk of developing the syndrome. Prophylactic doses may also be given intravenously; 2.5 mg/kg has been recommended, infused over about 60 minutes, starting about 75 minutes before anticipated anaesthesia, with further doses during anaesthesia and surgery if signs of malignant hyperthermia develop.

Hyperthermia. Dantrolene is used in the treatment of hyperthermia associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, which occurs in the neuroleptic malignant syndrome (see below and p.972) and in malignant hyperthermia (see below). There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents such as carbon monoxide,[1] MAOIs,[2] and ethyltenamfetamine.[3] However, after suggestions that it might also be of use in cocaine intoxication, the manufacturers[4] warned physicians that they should not regard dantrolene as an effective treatment for all types of hyperthermia and rigidity accompanying poisoning.

Dantrolene has been tried as part of treatment for heat stroke (see under Fever and Hyperthermia, p.10) but does not appear to affect outcome.[5]

1. Ten Holter JBM, Schellens RLLAM. Dantrolene sodium for treatment of carbon monoxide poisoning. *BMJ* 1988; **296:** 1772–3.
2. Kaplan RF, *et al.* Phenelzine overdose treatment with dantrolene sodium. *JAMA* 1986; **255:** 642–4.
3. Tehan B. Ecstasy and dantrolene. *BMJ* 1993; **306:** 146.
4. Fox AW. More on rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1989; **321:** 1271.
5. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002; **346:** 1978–88.

MALIGNANT HYPERTHERMIA. Malignant hyperthermia (malignant hyperpyrexia) is a rare but potentially fatal syndrome associated with general anaesthesia, in which a sudden increase in the concentration of calcium in muscle cytoplasm initiates a series of metabolic disturbances. The disorder appears to be genetically determined and is more common in males. In susceptible individuals a reaction may be induced by inhalation anaesthetics (mainly halogenated hydrocarbons), suxamethonium, prolonged anaesthesia, pre-operative exercise, muscle trauma, fever, or anxiety. However, many reactions occur in individuals who have had uneventful general anaesthesia previously. Early signs and symptoms of the syndrome include tachycardia, unstable blood pressure, hypercapnia, rising temperature, and hyperventilation followed by metabolic acidosis and hyperkalaemia. Muscle rigidity develops in many patients and later there may be evidence of muscle damage including raised serum concentrations of creatine phosphokinase and other enzymes, myoglobinaemia, and myoglobinuria. Hyperthermia develops relatively late. Other late complications may include renal failure, intravascular coagulopathy, and pulmonary oedema.

Treatment should be started as soon as possible after symptoms appear with dantrolene being given by rapid intravenous injection until symptoms disappear.[1-3] Supportive treatment must also be given including immediate withdrawal of anaesthesia, giving oxygen, correction of acidosis with sodium bicarbonate, control of hyperkalaemia with insulin, and cooling procedures (see p.10).

The incidence of reactions in susceptible individuals can be reduced by avoiding triggering agents. Dantrolene has also been given prophylactically, but a high incidence of adverse effects has been reported,[4] and such use is not generally recommended.[3] Susceptibility to malignant hyperthermia can be detected by histological examination of muscle fibres obtained by biopsy and study of their response to caffeine and/or halothane *in vitro*. Although such testing remains the gold standard for determining susceptibility, genetic testing is also being developed as an alternative.[5]

Dantrolene has been suggested[6] for use as a secondary drug in the treatment of a related and potentially fatal syndrome that has developed in some children after induction of anaesthesia with halothane and suxamethonium (see also Children, under Precautions of Suxamethonium, p.1911).

1. Britt BA. Dantrolene. *Can Anaesth Soc J* 1984; **31:** 61–75.
2. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.

3. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
4. Wedel DJ, *et al.* Clinical effects of intravenously administered dantrolene. *Mayo Clin Proc* 1995; **70:** 241–6.
5. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA* 2005; **293:** 2918–24.
6. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; **77:** 1054.

Neuroleptic malignant syndrome. Dantrolene has been used, usually alone or with bromocriptine, in the treatment of neuroleptic malignant syndrome (p.972), although some workers have not found it to be of use,[1] and evidence from controlled trials is lacking.[2] Doses reported for dantrolene have varied greatly.[3,4] For those patients unable to swallow and when rapid control of symptoms is required, doses of 1 mg/kg or more have been given initially by intravenous injection. Up to 600 mg has been given daily by mouth in divided doses.

1. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.
2. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
3. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.
4. Harpe C, Stoudemire A. Aetiology and treatment of neuroleptic malignant syndrome. *Med Toxicol* 1987; **2:** 166–76.

Tetanus. Dantrolene has effectively controlled muscle spasms in the treatment of tetanus (see p.1901). It has also been used as an adjunct[1] to neuromuscular blockade; there are conflicting reports[2,3] of its value in avoiding mechanical ventilation.

1. Tidyman M, *et al.* Adjunctive use of dantrolene in severe tetanus. *Anesth Analg* 1985; **64:** 538–40.
2. Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. *Anaesthesia* 1993; **48:** 969–71.
3. Possamai C, *et al.* Dantrolene infusion in severe tetanus. *Anaesthesia* 1997; **52:** 610.

Preparations

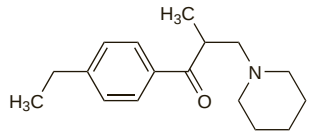
BP 2008: Dantrolene Oral Suspension;
USP 31: Dantrolene Sodium Capsules; Dantrolene Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Dantrium; ***Belg.:*** Dantrium; ***Braz.:*** Dantrolen; ***Canad.:*** Dantrium; ***Chile:*** Dantrium; ***Denm.:*** Dantrium; ***Fr.:*** Dantrium; ***Ger.:*** Dantamacrin; ***Gr.:*** Dantrium; Dantrolen; ***Hong Kong:*** Dantrium†; ***Irl.:*** Dantrium; ***Israel:*** Dantrium; ***Ital.:*** Dantrium; ***Neth.:*** Dantrium; ***NZ:*** Dantrium; ***Port.:*** Dantrium†; ***S.Afr.:*** Dantrium; ***Switz.:*** Dantamacrin; ***UK:*** Dantrium; ***USA:*** Dantrium.

Eperisone Hydrochloride *(rINNM)*

Épérisone, Chlorhydrate d'; Eperisoni Hydrochloridum; Hidrocloruro de eperisona. 4′-Ethyl-2-methyl-3-piperidinopropiophenone hydrochloride.

Эперизона Гидрохлорид
$C_{17}H_{25}NO,HCl$ = 295.8.
CAS — 64840-90-0 (eperisone); 56839-43-1 (eperisone hydrochloride).



(eperisone)

Pharmacopoeias. In *Jpn.*

Profile
Eperisone is a centrally acting skeletal muscle relaxant that has been used in the symptomatic treatment of muscle spasm (p.1887) and spasticity (p.1887). It may also have a vasodilator action. Eperisone hydrochloride has been given by mouth in usual doses of 50 mg three times daily after food.

Effects on the skin. A non-pigmenting fixed drug eruption developed in a 42-year-old woman after taking oral diclofenac sodium and eperisone hydrochloride.[1] There was no residual hyperpigmentation and the rash and accompanying itching and burning sensation resolved within 7 days after stopping both drugs. On rechallenge with eperisone, an erythematous plaque developed at the same site within a couple of hours. The lesion disappeared within 5 days with no sequelae.

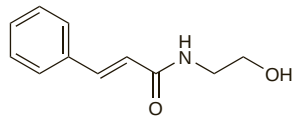
1. Choonhakarn C. Non-pigmenting fixed drug eruption: a new case due to eperisone hydrochloride. *Br J Dermatol* 2001; **144:** 1288–9.

Preparations
Proprietary Preparations (details are given in Part 3)
Indon.: Eprinoc; Epsonal; Forelax; Forres; Myonal; Myonep; Myori; Permyo; Rizonax; Zonal; ***Jpn:*** Myonal; ***Malaysia:*** Myonal; ***Philipp.:*** Myonal; ***Singapore:*** Myonal; ***Thai.:*** Myonal.

Idrocilamide *(rINN)*

Idrocilamida; Idrocilamidum; LCB-29. *N*-(2-Hydroxyethyl)cinnamamide.

Идроциламид
$C_{11}H_{13}NO_2$ = 191.2.
CAS — 6961-46-2.



Adverse Effects
When given by mouth idrocilamide was reported to produce abdominal pain, nausea, and drowsiness. Excitement, euphoria and hallucinations, and depression may occur.

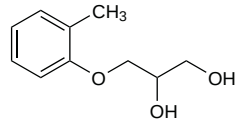
Uses and Administration
Idrocilamide is a centrally acting muscle relaxant. It is reported to have local muscle relaxant and anti-inflammatory effects and is now mainly used topically.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Srilane; ***Fr.:*** Srilane; ***Hong Kong:*** Srilane†; ***Switz.:*** Talval.

Mephenesin *(BAN, rINN)*

Cresoxydiol; Glykresin; Mefenesiini; Mefenesin; Mefenesina; Méphénésine; Mephenesinum. 3-(*o*-Tolyloxy)propane-1,2-diol.

Мефенезин
$C_{10}H_{14}O_3$ = 182.2.
CAS — 59-47-2.
ATC — M03BX06.
ATC Vet — QM03BX06.



NOTE. The name tolynol has been applied to both mephenesin and *p*,α-dimethylbenzyl alcohol (p.2294).

Pharmacopoeias. In *It.*

Profile
Mephenesin is a centrally acting skeletal muscle relaxant used for the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. Its clinical usefulness is considered to be limited by its brief duration of action. It is given orally in doses of 1.5 to 3 g daily in divided doses. It is also applied topically, usually with rubefacients.

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

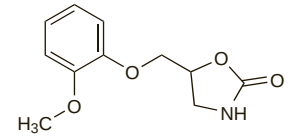
Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Decontractyl; ***Ger.:*** DoloVisano M.

Multi-ingredient: ***Belg.:*** Algipan; ***Fr.:*** Algipan; Decontractyl; Traumalgyl; ***India:*** Acks; Flamar; Inflazone; Medicreme; Relaxyl; ***Ital.:*** Relaxar; ***S.Afr.:*** Spasmend.

Mephenoxalone *(rINN)*

AHR-233; Mefenoksalon; Mefenoxalona; Méphénoxalone; Mephenoxalonum; Methoxadone; OM-518. 5-(2-Methoxyphenoxymethyl)oxazolidin-2-one.

Мефеноксалон
$C_{11}H_{13}NO_4$ = 223.2.
CAS — 70-07-5.
ATC — N05BX01.
ATC Vet — QN05BX01.



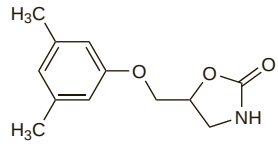
Profile
Mephenoxalone has actions similar to those of meprobamate (p.1006). It has been given orally in a dose of 200 to 400 mg three times daily as a muscle relaxant in the treatment of muscle spasm (p.1887). It has also been given for the treatment of anxiety.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Dimexol; Dorsiflex; ***Neth.:*** Dorsiflex; ***Turk.:*** Dorsiflex.
Multi-ingredient: ***Turk.:*** Dorsilon.

Metaxalone *(BAN, USAN, rINN)*

AHR-438; Metaxalona; Métaxalone; Metaxalonum. 5-(3,5-Xylyloxymethyl)oxazolidin-2-one.

Метаксалон
$C_{12}H_{15}NO_3$ = 221.3.
CAS — 1665-48-1.



Adverse Effects, Treatment, and Precautions
As for Chlorzoxazone, p.1895.

Metaxalone may cause drowsiness; patients affected should not drive or operate machinery.

Patients taking metaxalone excrete in the urine a metabolite which gives a false positive reaction to copper sulfate-based tests for glycosuria.

Interactions
The CNS effects of metaxalone may be enhanced by alcohol and other CNS depressants.

Pharmacokinetics
Metaxalone is absorbed from the gastrointestinal tract, metabolised in the liver, and excreted in urine as metabolites. The plasma elimination half-life is about 2 to 3 hours.

Uses and Administration
Metaxalone is a centrally acting skeletal muscle relaxant. Its mode of action may be related to its sedative properties.

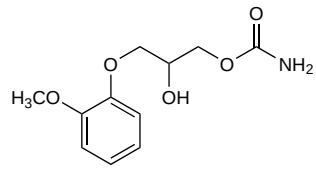
It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual oral dose is 800 mg three or four times daily.

Preparations
Proprietary Preparations (details are given in Part 3)
USA: Skelaxin.

Methocarbamol *(BAN, rINN)*

Guaiphenesin Carbamate; Méthocarbamol; Methocarbamolum; Metocarbamol; Metokarbamol; Metokarbamoli. 2-Hydroxy-3-(2-methoxyphenoxy)propyl carbamate.

Метокарбамол
$C_{11}H_{15}NO_5$ = 241.2.
CAS — 532-03-6.
ATC — M03BA03.
ATC Vet — QM03BA03.



Pharmacopoeias. In *US.*

USP 31 (Methocarbamol). A white powder, odourless or having a slight characteristic odour. M.p. about 94° or, if previously ground to a fine powder, about 90°. Soluble 1 in 40 of water at 20°; sparingly soluble in chloroform; soluble in alcohol only with heating; insoluble in *n*-hexane and in benzene. Store in airtight containers.

Adverse Effects
Adverse effects reported with methocarbamol include nausea, vomiting, anorexia, lightheadedness, dizziness, lassitude, drowsiness, restlessness, anxiety, confusion, tremor, vertigo, blurred vision, fever, headache, convulsions, and hypersensitivity reactions including rashes, pruritus, urticaria, angioedema, and conjunctivitis with nasal congestion.

After injection patients may experience flushing and a metallic taste; incoordination, diplopia, nystagmus, vertigo, syncope, hypotension, bradycardia, and anaphylaxis have been reported. There may be sloughing and thrombophlebitis at the site of injection.

Precautions
Methocarbamol is contra-indicated in coma or pre-coma states, brain damage, myasthenia gravis, or in patients with a history of epilepsy. Caution is advisable in renal or hepatic impairment.