Pharmacopoeias. In *US*.
USP 31 (Chlorzoxazone). A white or practically white, practically odourless, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in methyl alcohol; soluble in solutions of alkali hydroxides and ammonia. Store in airtight containers.

Adverse Effects and Treatment

The most common adverse effects of chlorzoxazone are drowsiness and dizziness. There may occasionally also be gastrointestinal irritation and gastrointestinal bleeding has been reported rarely. Other effects that have occurred are headache, overstimulation, and rarely sensitivity reactions including skin rashes, petechiae, ecchymoses, urticaria and pruritus; very rarely, angioedema or anaphylactoid reactions may occur. Some patients taking chlorzoxazone have developed jaundice and liver damage suspected to be caused by the drug.

After overdosage there may be gastrointestinal disturbances, drowsiness, dizziness, headache, malaise, and sluggishness followed by marked loss of muscle tone, hypotension, and respiratory depression. Emptying the stomach by lavage should be considered, followed by activated charcoal and supportive therapy.

Effects on the liver. Hepatotoxicity, sometimes fatal, has been associated with chlorzoxazone treatment.[1]

1. Powers BJ, *et al.* Chlorzoxazone hepatotoxic reactions: an analysis of 21 identified or presumed cases. *Arch Intern Med* 1986; **146:** 1183–6.

Overdosage. Overdosage and coma occurred on 2 occasions in a patient taking chlorzoxazone; on the second occasion, the patient responded to intravenous flumazenil.[1]

1. Roberge RJ, *et al.* Two chlorzoxazone (Parafon forte) overdoses and coma in one patient: reversal with flumazenil. *Am J Emerg Med* 1998; **16:** 393–5.

Torticollis. There has been a report of a patient with a spasmodic torticollis-like syndrome, consisting of tonic deviation of the head to the right, clenching of the teeth, and dysarthria, which developed repeatedly within 2 hours of ingesting chlorzoxazone for low back pain.[1] Intravenous injection of benzatropine mesilate 1 mg gave rapid relief of symptoms.

1. Rosin MA. Chlorzoxazone-induced spasmodic torticollis. *JAMA* 1981; **246:** 2575.

Precautions

Chlorzoxazone should not be given to patients with impaired liver function and should be stopped if signs of liver toxicity appear. Patients should be advised to report to their doctor any signs or symptoms of possible liver toxicity such as fever, rash, jaundice, dark urine, anorexia, nausea, vomiting, or right upper quadrant pain. Chlorzoxazone may cause drowsiness; patients affected should not drive or operate machinery.

The urine of patients taking chlorzoxazone may be coloured orange or reddish-purple by a phenolic metabolite.

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

Interactions

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

Disulfiram. A study[1] of the efficacy of disulfiram as an inhibitor of the cytochrome P450 isoenzyme CYP2E1 (an enzyme involved in the metabolism of chlorzoxazone) found that a single 500-mg dose of disulfiram reduced plasma clearance of chlorzoxazone by 85%, resulting in a doubling of the latter's peak plasma concentrations and prolongation of its elimination half-life from a mean of 0.92 to 5.1 hours.

1. Kharasch ED, *et al.* Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther* 1993; **53:** 643–50.

Isoniazid. Isoniazid inhibited the clearance of chlorzoxazone by 56% when given to 10 slow acetylator subjects resulting in an increase in sedation, headache, and nausea.[1] Two days after stopping isoniazid there had been a rebound increase in the clearance of chlorzoxazone by 56% over the pre-isoniazid clearance value. Similar but less pronounced effects have also been reported[2] in rapid acetylators with chlorzoxazone's pharmacokinetic parameters returning to baseline values in 2 days.

1. Zand R, *et al.* Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. *Clin Pharmacol Ther* 1993; **54:** 142–9.
2. O'Shea D, *et al.* Modulation of CYP2E1 activity by isoniazid in rapid and slow N-acetylators. *Br J Clin Pharmacol* 1997; **43:** 99–103.

Pharmacokinetics

Chlorzoxazone is reported to be completely absorbed after oral doses and peak plasma concentrations are achieved after 1 to 2 hours. It is rapidly metabolised in the liver via the cytochrome P450 isoenzyme CYP2E1, mainly to 6-hydroxychlorzoxazone, and excreted in the urine primarily as the glucuronide metabolite. The elimination half-life of chlorzoxazone is about 1 hour.

Uses and Administration

Chlorzoxazone is a centrally acting skeletal muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain. Its effects begin within an hour of an oral dose and last for 3 to 4 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual initial oral dose is 500 mg three or four times daily; the dose can often be reduced subsequently to 250 mg three or four times daily, although doses of up to 750 mg three or four times daily may be given if necessary. Chlorzoxazone is also given with analgesics in compound preparations.

Preparations

USP 31: Chlorzoxazone Tablets.

Proprietary Preparations (details are given in Part 3)
Chile: Fenarol-S†; ***Denm.:*** Paraflex; ***Hong Kong:*** Solaxin; ***Hung.:*** Myoflexin; ***India:*** Parafon DSC; ***Indon.:*** Solaxin; ***S.Afr.:*** Paraflex; ***Swed.:*** Paraflex; ***Thai.:*** Chlorzox†; ***Turk.:*** Paraflex; ***USA:*** Paraflex; Parafon Forte DSC; Remular-S.

Multi-ingredient: ***Arg.:*** Ibupirac Flex; Paraflex AN; Paraflex Plus; Rucaten Forte; ***Austria:*** Parafon; ***Braz.:*** Paralon; ***Canad.:*** Acetazone Forte; Acetazone Forte C8; Back-Aid; Parafon Forte; Tylenol Aches & Strains; ***Chile:*** Beserol-S; Brevex; Desdol; Flectadol; Tonoflex; Winasorb Flex; ***Fin.:*** Paraflex comp†; ***Hong Kong:*** Relaxin-P†; ***India:*** Cip-Zox; Dolocide MR; Duodil; Fenaplus-MR; Flamar-MX; Flexon-MR; Myospaz; Myospaz Forte; New Panazox; Nicip MR; Osteoflam-MR; Pacizox; Parafon; Systaflam; ***Malaysia:*** Paras; ***Mex.:*** Parafon Forte; Reumophan; Tafirol Flex; ***Philipp.:*** Parafon; ***S.Afr.:*** Parafon; ***Swed.:*** Paraflex comp†; ***Thai.:*** Cezox; Myora; Myoserv†; Parafon; ***Turk.:*** Mepadol; Muskazon; Parafon; ***USA:*** Flexaphen.

Cyclobenzaprine Hydrochloride *(USAN, rINNM)*

Cyclobenzaprine, Chlorhydrate de; Cyclobenzaprini Hydrochloridum; Hidrocloruro de ciclobenzaprina; MK-130 (cyclobenzaprine); Proheptatriene Hydrochloride; Ro-4-1557 (cyclobenzaprine); RP-9715 (cyclobenzaprine). 3-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-*NN*-dimethylpropylamine hydrochloride.

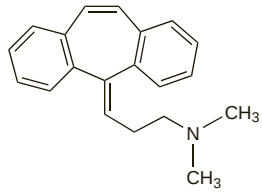
Циклобензаприна Гидрохлорид

$C_{20}H_{21}N,HCl = 311.8$.

CAS — 303-53-7 (cyclobenzaprine); 6202-23-9 (cyclobenzaprine hydrochloride).

ATC — M03BX08.

ATC Vet — QM03BX08.



(cyclobenzaprine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cyclobenzaprine hydrochloride:
Cyclo; Cyclone.

Pharmacopoeias. In *US*.
USP 31 (Cyclobenzaprine Hydrochloride). A white to off-white, odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and in dichloromethane; insoluble in hydrocarbons.

Adverse Effects, Treatment, and Precautions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and shares their adverse effects and precautions (see Amitriptyline, p.376). Cyclobenzaprine should be used with caution in the elderly and patients with hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

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

The elderly. Symptoms of toxicity[1] (hallucinations, insomnia, and restlessness) were seen in a 76-year-old patient taking cyclobenzaprine at therapeutic doses. US licensed product information states that the elderly may be more likely to experience adverse effects such as hallucinations and confusion..

In another study[2] the mean elimination half-life of cyclobenzaprine in the elderly was longer than in younger subjects and clearance was reduced. It was suggested that it should be used in a reduced dose or frequency in the elderly.

1. Douglass MA, Levine DP. Hallucinations in an elderly patient taking recommended doses of cyclobenzaprine. *Arch Intern Med* 2000; **160:** 1373.
2. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Neuroleptic malignant syndrome. Report of a neuroleptic malignant-like syndrome associated with cyclobenzaprine in a 36-year-old man.[1] It was not clear whether the syndrome was due to an idiosyncratic reaction or to an overdose.

1. Theoharides TC, *et al.* Neuroleptic malignant-like syndrome due to cyclobenzaprine. *J Clin Psychopharmacol* 1995; **15:** 79–81.

Overdosage. Treatment of cyclobenzaprine overdose is mainly symptomatic and supportive. A large retrospective study[1] found that cyclobenzaprine hydrochloride overdoses of up to 1 g rarely present with the serious cardiovascular and neurological effects seen with tricyclic antidepressant overdoses. There were no reports of seizures, life-threatening arrhythmias, or fatalities. However, 150 patients required treatment in the intensive care unit, 13 patients needed assisted ventilation, and 8 were unresponsive to stimuli. It was noted that observation may be sufficient for overdoses of under 50 mg in children.

1. Spiller HA, *et al.* Five-year multicentre retrospective review of cyclobenzaprine toxicity. *J Emerg Med* 1995; **13:** 781–5.

Interactions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and may be subject to similar interactions (see Amitriptyline, p.379). The CNS effects of cyclobenzaprine may be enhanced by alcohol or other CNS depressants.

Antidepressants. A patient who already had QT prolongation associated with use of cyclobenzaprine and *fluoxetine*. developed torsade de pointes, progressing into ventricular fibrillation, when given *droperidol* as premedication prior to surgery.[1] QT abnormalities resolved on stopping cyclobenzaprine.

1. Michalets EL, *et al.* Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* 1998; **32:** 761–5.

Antipsychotics. For a report of an interaction between cyclobenzaprine and *droperidol*, see Antidepressants above.

Pharmacokinetics

Cyclobenzaprine hydrochloride is readily and almost completely absorbed from the gastrointestinal tract, although plasma concentrations vary considerably among individuals given the same dose. About 93% is bound to plasma proteins and has a reported effective half-life of 8 to 37 hours. It is extensively metabolised, principally to glucuronide conjugates, and excreted in the urine. Cytochrome P450 isoenzymes CYP3A4, CYP1A2, and to a lesser extent CYP2D6 mediate its demethylation. Some unchanged drug appears in the bile and is excreted in the faeces.

◊ References.

1. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Uses and Administration

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle relaxant, related to the tricyclic antidepressants. It acts mainly at the brain stem to decrease tonic somatic motor activity influencing both alpha and gamma motor systems. Additional activity at spinal cord sites may be involved. Effects begin within 1 hour of a dose by mouth; the effects of a single dose have been reported to last as long as 12 to 24 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual dose is 5 mg three times daily given by mouth, increased if necessary to 10 mg three times daily. Treatment for more than 2 or 3 weeks is not recommended. A starting dose of 5 mg with less frequent dosing is recommended for elderly patients. For doses in patients with hepatic impairment, see below. A modified-release preparation of cyclobenzaprine hydrochloride is also available for once-daily dosing.

Administration in hepatic impairment. A starting dose of 5 mg of cyclobenzaprine hydrochloride by mouth, and perhaps less frequent dosing than usual (see above), is recommended for those with mild hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

Back pain. A meta-analysis[1] of 14 studies concluded that cyclobenzaprine hydrochloride, in the short term, improves low back pain (p.7). Doses given to patients were titrated and ranged from 10 to 60 mg daily with a median dose of 30 mg daily. Patients improved moderately in the first 4 days of treatment, with the effects of cyclobenzaprine hydrochloride gradually declining with time although there was some evidence of continued improvement at 2 weeks. Further studies are needed to determine the optimal length of use in the management of acute back pain. Adverse effects were common, occurring in at least 53% of patients.

1. Browning R, *et al.* Cyclobenzaprine and back pain: a meta-analysis. *Arch Intern Med* 2001; **161:** 1613–20.

Fibromyalgia. Studies of the efficacy of cyclobenzaprine in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p.13), have produced conflicting results but a meta-analysis[1] of 5 such studies suggested that cyclobenzaprine had some modest benefit in the condition. Patients were more likely to report overall improvement and moderate reductions in individual symptoms, particularly sleep, while taking the drug.

1. Tofferi JK, *et al.* Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum* 2004; **51:** 9–13.

Preparations

USP 31: Cyclobenzaprine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Miosan; Mirtax; Musculare; ***Canad.:*** Flexeril†; Flexitec†; Novo-Cycloprine; ***Chile:*** Ciclamil; Masterelax†; Medarex; Nostaden; Reflexan; Relexil; Tensamon; Tensiomax; Tensodox; Tonalgen; Ziclob; ***Ital.:*** Flexiban; ***Port.:*** Flexiban; ***Spain:*** Yurelax; ***USA:*** Amrix; Fexmid; Flexeril.

Multi-ingredient: ***Arg.:*** Dorixina Relax; ***Braz.:*** Dolamin Flex; ***Mex.:*** Yuredol; ***Venez.:*** Dorixina Flex.

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.

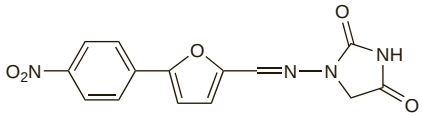
Натрий Дантролен

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