Know who is susceptible:
Malignant Hyperthermia may occur in any patient, including patients who have previously had uneventful general anaesthesia.

MH is more likely with:
- Diagnosed malignant hyperthermia susceptibility after halothane/caffeine contracture test on biopsied muscle
- Malignant Hyperthermia susceptible relatives
- Significantly & consistently raised resting serum CK
- Several very rare muscle disorders

Know the signs & symptoms:
NOT ALL NEED TO BE PRESENT TO INITIATE TREATMENT.

Early:
- Prolonged masseter muscle spasm after suxamethonium
- Inappropriately raised end tidal carbon dioxide or tachypnoea during spontaneous respiration
- Inappropriate tachycardia
- Cardiac arrhythmias particularly ventricular ectopic beats

Developing:
- Rapid rise in temperature (0.5°C per 15 minutes)
- Progressive metabolic and respiratory acidosis (ABG)
- Hyperkalaemia
- Profuse sweating
- Cardiovascular instability
- Decreased SaO₂ or mottling of skin
- Generalised muscular rigidity

Late:
- ‘Cola’ coloured urine - due to myoglobinuria
- Generalised muscle ache
- Grossly raised serum CK
- Coagulopathy
- Cardiac arrest

Differential diagnoses:
- Inadequate anaesthesia or machine malfunction
- Sepsis or infection
- “Thyroid storm”
- Ecstasy or other recreational drugs
- Phaeochromocytoma
- Neuroleptic Malignant Syndrome
- Intracerebral infection or haemorrhage

Management:
IMMEDIATE MANAGEMENT WITH DANTROLENE IS ESSENTIAL

Stop the TRIGGER:
- Declare an emergency and where possible stop the surgery
- Turn off volatile agent and HYPERVENTILATE with very high flows (15L/min) of 100% O₂ (Do not waste time changing the circuit or the anaesthetic machine)
- Commence non triggering anaesthesia (TIVA)

Give DANTROLENE AS A PRIORITY:
- 2.5mg/kg IV initial push and repeat as necessary
- Dosing is the same for paediatric patients
- Mobilise other sources of dantrolene (you may need at least 36 ampoules)
- Mix each ampoule with 60mls sterile water

SIMULTANEOUSLY TREAT THE LIFE THREATENING EFFECTS:
- Treat the hyperkalaemia
  - Hyperventilate and treat the acidosis
  - CaCl₂ 10%(0.15ml/kg = 10mls = 7mmol in adults)
  - Insulin 0.15u/kg + dextrose 50% 0.5ml/kg (10u + 50ml in adults)
- Cool the patient if T > 38.5°C
  - IV normal saline at 4°C; surface cooling with ice
  - Consider peritoneal lavage with normal saline at 4°C
- Treat the acidosis
  - Hyperventilate to at least normocapnia
  - Consider sodium bicarbonate 0.5 mmol/kg IV as necessary to maintain pH >7.2
- Treat arrhythmias (if resistant consider hyperkalaemia as cause)
  - Lignocaine 1–2mg/kg
  - Amiodarone 2–3mg/kg over 15 minutes
  - Procainamide 15mg/kg over 15 minutes

IN ADDITION TO ROUTINE ANAESTHETIC MONITORING:
- Monitor core temperature
- Insert an arterial line
- Send urgent bloods
  - ABG, U+E, FBC, COAG & myoglobin
  - Repeat frequently to monitor success of therapy
- Insert urinary catheter
  - Maintain urine output above 2ml/kg/hr
- Insert central venous line
  - DO NOT delay Dantrolene therapy with attempted CVL placement

When the patient is stabilised:
ALL PATIENTS WITH KNOWN OR SUSPECTED MH REACTIONS MUST BE ADMITTED TO ICU

Give early consideration to:
- Mobilising additional sources of dantrolene
- Transferring patients with fulminant reactions to major centres

Notify your local MH Investigation Unit of ANY clinically suspicious reactions so that patients & family members can be investigated in the future.

NEW ZEALAND:
Department of Anaesthesia. Palmerston North Hospital. 64 6 356 9169

NEW SOUTH WALES:
Department of Anaesthesia. Westmead Children’s Hospital. 61 2 9845 0000

VICTORIA:
Department of Anaesthesia. Royal Melbourne Hospital. 61 3 9342 7000

WESTERN AUSTRALIA:
Department of Anaesthesia. Royal Perth Hospital. 61 8 9224 1038
No data are available concerning the use of Dantrolene sodium. The combination of therapeutic doses of dantrolene sodium, 3 g mannitol and sufficient sodium hydroxide to yield a pH of approximately 9.5, when reconstituted with 20 mL of sterile water for injection (without a bacteriostatic agent), is classified as a direct-acting skeletal muscle relaxant. The drug is hydrated 1.0 (19-4-nitrophenyl-2-fluranylmethylene)-amino-2-3-methyldaidalone sodium salt. The structural formula for the hydrated salt is: The hydrated salt contains approximately 15% water (37 moles) and has a molecular weight of 336. The anhydrous salt has a molecular weight of 336.

**PHARMACOLOGY**

Dantrolene sodium is a muscle relaxant acting specifically on skeletal muscle. It does not affect neural transmission nor does it have measurable effects on the electrically excitable surface membrane. Studies have shown that in the presence of dantrolene sodium, the responses of the muscle to caffeine are decreased or delayed. In in vitro muscle preparations, dantrolene sodium uncouples the excitation and contraction of skeletal muscle, possibly by interfering with the release of calcium from the sarcoplasmic reticulum.

In an anaesthetic-induced malignant hyperthermia syndrome, evidence points to an intrinsic abnormality of muscle tissue. In affected humans and swine, it has been postulated that "triggering agents" induce a sudden rise in myoplasmic calcium either by interfering with the sarcoplasmic reticulum from accumulating calcium adequately, or by accelerating its release. This rise in myoplasmic calcium activates acute catabolic processes common to the malignant hyperthermia crisis. Dantrolene sodium may prevent the increase in myoplasmic calcium and the acute catabolism within the muscle cell by interfering with the release of calcium from the sarcoplasmic reticulum to the myoplasm. Thus, the physiologic, metabolic, and biochemical changes associated with the crisis may be reversed or attenuated.

Specific metabolic pathways in the degradation and elimination of dantrolene sodium in humans have been established. Dantrolene sodium is metabolized in the liver and urine. Its major metabolites in body fluids are the 5-hydroxy and the acetylamido analogue. Another metabolite with an unknown structure appears related to acetylamino-Dantrolene. Dantrolene sodium is also subject to hydrolysis and subsequent oxidation forming nitrophenylfuroic acid.

Since dantrolene sodium is metabolised by the liver, enhancement of its metabolism by other drugs is possible. However, neither phenobarbital nor diazepam appears to affect dantrolene sodium metabolism.

The major biologic half-life of dantrolene sodium after intravenous administration is about 5 hours. Based on assays of whole blood plasma levels, the amounts of dantrolene sodium associated with red blood cells than with the plasma fraction of blood. Significant amounts of dantrolene are bound to plasma proteins, mostly albumin, and this binding is readily reversible. Binding to plasma protein is not significantly altered by diazepam, diphenhydantoin, or phenylbutazone. Binding to plasma proteins is reduced by warfarin and clofibrate and increased by thiazides.

In animals dantrolene sodium given intravenously has no appreciable effect on the cardiovascular system or on respiratory function. A transient inconsistent effect on smooth muscles has been observed at high doses.

Because of the low drug concentration required for the administration of large volumes of fluid, acute toxicity of a dantrolene sodium intravenous formulation could not be assessed. In 14-day (subacute) studies, the intravenous formulation of dantrolene sodium was relatively non-toxic to rats at doses of 10 mg/kg/day and 20 mg/kg/day. While 10 mg/kg/day in dogs for 14 days evoked little toxicity, 20 mg/kg/day for 14 days caused hepatic changes of irreversible biologic significance.

**INDICATIONS**

Dantrolene sodium is indicated, along with appropriate supportive measures, for the management of the fulminating hypermetabolism of skeletal muscle characteristic of malignant hyperthermia or malignant hyperthermia crisis. It should be administered by intravenous injection as soon as the malignant hyperthermia reaction is recognized (i.e. tachycardia, tachypnea, central venous desaturation, hypercarbia, metabolic acidosis, skeletal muscle rigidity, increased utilization of anesthetic circuit carbon dioxide absorber, cyanosis and mottling of the skin, and, in many, fever).

**CONTRAINDICATIONS**

None.

**WARNINGS**

The use of DANTIRUM for injection in the management of malignant hyperthermia crisis is not a substitute for previously known supportive measures. These measures must be individualised, but it will usually be necessary to discontinue the suspect triggering agents, attend to the patient's cardiac and respiratory function, manage the metabolic acidosis, institute cooling when necessary, attend to urinary output, monitor for electrolyte imbalance.

**PRECAUTIONS**

Because of the high pH of the intravenous formulation of DANTIRUM, care should be taken to prevent the introduction of the intravenous solution into the surrounding tissues. When mannitol is used for prevention or treatment of late renal complications of malignant hyperthermia, the 3 g of mannitol needed to dissolve each 20 mg of DANTIRUM for injection should be taken into consideration.

Adverse effects such as weakness, dizziness and drowsiness may persist for up to 48 hours after treatment and patients must not operate machinery or engage in other hazardous activity during this time. Caution is also indicated at meals on the day of administration because difficulty swallowing and choking have been reported.

**Hepatotoxicity**

Intravenous administration of 20 mg/kg/day for 14 days caused hepatic necrosis in dogs. Administration of 20 mg/kg/day for 14 days caused hepatotoxicity, and should not be used in patients other than those referred to above. Symptomatic hepatitis (fatty and non-fatty) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg/day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury (fulminating hepatic failure) although this did not result in overt hepatic failure in any case. Caution is therefore indicated at meals on the day of administration because difficulty swallowing and choking have been reported.

**ADVERSE REACTIONS**

There have been occasional reports of death following malignant hyperthermia crisis when treated with intravenous dantrolene sodium. Most of these deaths can be accounted for by late recognition, delayed treatment, inadequate dosage, lack of supportive therapy, intercurrent disease and/or the development of delayed complications such as renal failure or disseminated intravascular coagulopathy. In some cases there are insufficient data to completely exclude therapeutic failure of dantrolene sodium. There are rare reports of fatality in MH crisis, despite initial satisfactory response to intravenous dantrolene sodium, which involve patients who could not be weaned from dantrolene sodium after initial treatment. There are rare reports of pulmonary oedema developing during the treatment of MH crisis in which the dilluent volume and mannitol needed to deliver intravenous dantrolene sodium possibly contributed to the occurrence of this complication. There have been reports of thromboembolism following administration of dantrolene sodium; the incidence of this complication is unknown.

There have been rare reports of urticaria and erythema possibly associated with administration of intravenous dantrolene sodium and at least one case of anaphylaxis.

The administration of intravenous dantrolene sodium to human volunteers is associated with loss of grip strength and weakness in the legs, as well as drowsiness and dizziness.

The serious reactions reported with chronic oral DANTIRUM use have been hepatitis, seizures, and pleural effusion with associated eosinophilia, pericarditis. None of the reactions reported in patients taking oral DANTIRUM have been reported in patients treated with short-term DANTIRUM for injection therapy for malignant hyperthermia.

The following additional events have been reported in patients receiving oral dantrolene: abdominal cramps, abnormal hair growth, acne-like rash, anorexia, alteration of taste, aperistic anaemia, anaphylaxis, backache, chills, constipation rare to unusual signs to intestinal obstruction, crystalluria, diarrhea, difficult urination, dizziness, drowsiness, difficulty in swallowing, fever, gastric irritation, general malaise, myalgia, GI bleeding, haematoma, headache, heart failure, increased nervousness, increased urinary frequency, insomnia, leukopenia, light-headedness, liver function test disturbances, mental confusion, mental depression, nausea, phlebitis, pruritus, speech disturbance, swollen leg, sweating, tachycardia, transient lowering of GFR and renal plasma flow after 8 weeks' therapy has been reported, urinary incontinence and/or nocturia, urticaria, visual disturbance, and vomiting.

**DOSEAGE AND ADMINISTRATION**

As soon as the malignant hyperthermia reaction is recognised, all anaesthetic agents should be discontinued. DANTIRUM for injection should be administered by continuous rapid intravenous push beginning at a minimum dose of 1 mg/kg, and continuing until symptoms subsides or the maximum cumulative dose of 10 mg/kg has been reached. If the physiologic and metabolic abnormalities reappear, the regimen may be repeated.

It is important to note that administration of DANTIRUM for injection should be continued until symptoms subsides. The effective dose to reverse the crisis is directly dependent upon the individual's degree of susceptibility to malignant hyperthermia, the amount and time of exposure to the triggering agent, and the time elapsed between onset of the crisis and initiation of therapy.

**Children's dose**

Experience to date indicates that the dose for children is the same as for adults.

**Preparation**

Each vial of DANTIRUM for injection should be reconstituted by adding 20 mL of sterile water for injection (without a bacteriostatic agent), and the vial shaken until the solution is clear. The contents of the vial must be protected from direct light and used within 6 hours after reconstitution.


**OVERDOSAGE**

Symptoms which may occur in cases of overdose include, but are not limited to, muscular weakness and atrophy in the state of consciousness (e.g. sleep, coma), cardiac disturbance, and crystalluria.

**PRESENTATION**

DANTIRUM Powder for injection 20 mg 6's

Please Note: In some subjects as much as 10 mg/kg of dantrolene sodium has been needed to attain a therapeutic effect in 70 kg man that dose would require about 36 vials. Such a volume has been administered in approximately 90 minutes.

**SPONSOR**

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TGA approval date: 3 June 2004
Date of last amendment: 3 December 2004
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This protocol has been approved by the Australian and New Zealand College of Anaesthetists, but the dosing recommendations recommended differ from those registered for Dantrium by Pfizer in New Zealand. Pfizer can only recommend the Medsafe approved dosing regimes which are printed above.