MANAGEMENT OF
MALIGNANT HYPERTHERMIA

YOU'VE ONLY GOT A FEW MINUTES...

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 SaO_2 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% O_2 (Do not waste time changing the circuit or the anaesthetic machine)
- Commence non triggering anaesthesia (TIVA)

Dantrium® Intravenous
(dantrolene sodium for injection)

This protocol has been approved by the Australian and New Zealand College of Anaesthetists.

December 05: Product information is supplied on the back of this chart.

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
  - $CaCl_2$ 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, CK, 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
- Monitor the patient for at least 24hrs post reaction
  - Recurrence may occur… LARGE amounts of Dantrolene may be needed in the first 24 hrs

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

PRODUCT INFORMATION

Dantrium® IV 20 mg

Dantrolene sodium powder for injection

NAME OF DRUG

Dantrolene sodium

DESCRIPTION

DANTRIUM powder for injection is a sterile lyophilised formulation of dantrolene sodium, and in this form provides a preparation for intravenous use. Each 70 mL vial contains 20 mg dantrolene sodium, 3 g mannitol and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL of sterile water for injections (without a bacteriostatic agent). Dantrolene sodium is classified as a direct-acting skeletal muscle relaxant. Chemically, the drug is hydrated 1-[[[5-(4- nitrophenyl)-2-furanyl]methylene]-amino]-2,4-imidazolidinedione sodium salt. The structural formula for the hydrated salt is: The hydrated salt contains approximately 15% water ($3^1/_2$ moles) and has a molecular weight of 399. 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 neuromuscular 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 isolated muscle preparations, dantrolene sodium uncouples the excitation and contraction of skeletal muscle, probably by interfering with the release of calcium from the sarcoplasmic reticulum.

In the 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 preventing 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 is found in measurable amounts in blood and urine. In addition, its major metabolites in body fluids are the 5-hydroxy analogue and the acetamido analogue. Another metabolite with an unknown structure appears related to acetylamino-dantrolene. Dantrolene sodium may also undergo 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 phenobarbitone nor diazepam appears to affect dantrolene sodium metabolism.

The mean biologic half-life of dantrolene sodium after intravenous administration is about 5 hours. Based on assays of whole blood and plasma, slightly greater amounts of dantrolene are 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, diphenylhydantoin, or phenylbutazone. Binding to plasma proteins is reduced by warfarin and clofibrate and increased by tolbutamide.

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 requiring 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 questionable biologic significance.

INDICATIONS

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

CONTRAINDICATIONS

None.

WARNINGS

The use of DANTRIUM 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 increased oxygen requirements, 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 DANTRIUM, care must be taken to prevent extravasation 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 vial of DANTRIUM 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 seen with dantrolene sodium capsules: Dantrolene sodium has a potential for hepatotoxicity, and should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and not-fatal) 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. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to dantrolene sodium for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age, and in patients taking other medication(s) in addition to dantrolene sodium.

Dantrolene sodium should be used only in conjunction with appropriate monitoring of hepatic function including frequent determination of SGOT or SGPT.

Fatal and non-fatal liver disorders of an idiosyncratic or hypersensitivity type may occur with dantrolene sodium therapy.

Pregnancy: (Category B2) The safety of DANTRIUM for injection in women who are or who may become pregnant has not been established; it should be given only when the potential benefits have been weighed against the possible risk to mother and child. Dantrolene crosses the placenta.

Use in Lactation: No data are available concerning the use of dantrolene in nursing mothers. Dantrolene has been detected in human breast milk.

Drug Interactions: The combination of therapeutic doses of intravenous dantrolene sodium and verapamil in halothane/alpha-chloralose anaesthetised swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalaemia. It is recommended that the combination of intravenous dantrolene sodium and calcium channel blockers, such as verapamil, not be used during reversal of a malignant hyperthermia crisis until the relevance of these findings to humans is established.

Administration of dantrolene sodium may potentiate vecuronium-induced neuromuscular block.

Caution should be exercised in the concomitant administration of tranquillising agents. Dantrolene causes dizziness, drowsiness, and weakness; alcohol and other CNS depressants may intensify this effect.

ADVERSE REACTIONS

There have been occasional reports of death following malignant hyperthermia crisis even 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 diluent volume and mannitol needed to deliver intravenous dantrolene sodium possibly contributed.

There have been reports of thrombophlebitis 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 DANTRIUM use have been hepatitis, seizures, and pleural effusion with associated eosinophilia, pericarditis. None of the reactions reported in patients taking oral DANTRIUM have been reported in patients treated with shortterm DANTRIUM 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, aplastic anaemia, anaphylaxis, backache, chills, constipation rarely progressing to signs to intestinal obstruction, crystalluria, diarrhoea, difficult erection, difficult urination and/or urinary retention, diplopia, eczematoid eruption, erratic blood pressure, exacerbation of cardiac insufficiency, excessive tearing, fatigue, feeling of suffocation, fever, gastric irritation, general malaise, myalgia, GI bleeding, haematuria, headache, heart failure, increased nervousness, increased urinary frequency, insomnia, leucopenia, light-headedness, liver function test disturbances, lymphocytic lymphoma, mental confusion, mental depression, nausea, phlebitis, pruritus, speech disturbance, swallowing difficulty, sweating, tachycardia, transient lowering of G.F.R. and renal plasma flow after 8 weeks' therapy has been reported, urinary incontinence and/or nocturia, urticaria, visual disturbance, and vomiting.

DOSAGE AND ADMINISTRATION

As soon as the malignant hyperthermia reaction is recognised, all anaesthetic agents should be discontinued. DANTRIUM for injection should be administered by continuous rapid intravenous push beginning at a minimum dose of 1 mg/kg, and continuing until symptoms subside 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 DANTRIUM for injection should be continuous until symptoms subside. 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 treatment.

Children's dose

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

Preparation

Each vial of DANTRIUM for injection should be reconstituted by adding 60 mL of sterile water for injections (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.

Store reconstituted solutions at controlled room temperature (15°C - 25°C). Store unreconstituted product below 25°C and avoid prolonged exposure to light.

OVERDOSAGE

Symptoms which may occur in case of overdose include, but are not limited to, muscular weakness and alterations in the state of consciousness (e.g. lethargy, coma), vomiting, diarrhoea and crystalluria.

PRESENTATION

DANTRIUM 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 reverse MH. In a 70 kg man this dose would require about 36 vials. Such a volume has been administered in approximately 90 minutes.

SPONSOR

Pfizer Australia Pty Ltd
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38-42 Wharf Road
West Ryde NSW 2114
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 regimens recommended differ from those registered for Dantrium by Pfizer in New Zealand. Pfizer can only recommend the Medsafe approved dosing regimens which are printed above.