



MALIGNANT HYPERTHERMIA A CASE HISTORY APPROACH

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CASE HISTORY¹

A 69 year old man presented for Coronary Artery Bypass Grafting (CABG) with a history of:

- non-insulin dependant diabetes
- severe coronary artery disease
- no previous anaesthetic exposures
- no family history

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CASE HISTORY¹

- Induction with Fentanyl, Lignocaine & Propofol, Vecuronium
- Maintenance with Isoflurane & Fentanyl infusion
- Heart was arrested with cold antegrade & retrograde blood cardioplegia
- Patient temperature was maintained at 34°C

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CASE HISTORY¹

- 4 vessel CABG was performed
- Routine arterial blood gases were taken
- Isoflurane was distilled into the bypass circuit
- Total Isoflurane time was 4.5 hours

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CASE HISTORY¹

- On arrival to Intensive Care Unit the patient developed a tachycardia & became hyperthermic
- A chest x-ray was normal
- Haemodynamics were controlled by Nicardipine infusion (anti hypertensive) & fentanyl
- Arterial Blood gases revealed severe respiratory acidosis – minute volume was adjusted

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CASE HISTORY¹

- Follow-up gases showed increasing CO₂ levels
- Hyperkalemia
- Temperature was increasing
- Musculoskeletal stiffness was noted
- Masseter rigidity
- Malignant Hyperthermia was finally suspected

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MALIGNANT HYPERTHERMIA



Malignant Hyperthermia (MH) is an acute pharmacogenetic (autosomal dominant) disorder, which develops during or immediately after the application of general anaesthesia involving volatile agents and/or depolarising muscle relaxants²

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MALIGNANT HYPERTHERMIA

- This occurs in genetically predisposed humans
- The disorder is as a result of a defect in calcium channel regulation in the skeletal muscle cells²

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MALIGNANT HYPERTHERMIA

Definition: A catastrophic, often fatal syndrome triggered by;

Anaesthetic Triggers

- Inhalational agents
- Depolarizing muscle relaxants
- Incidence in Australia is not estimated
- 1:3,000 to 1:50,000 anaesthetics³

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MALIGNANT HYPERTHERMIA

Non Anaesthetic Triggers



- Certain myopathies (i.e. King Denborough) ²
- Exertional heat illness (EHI) ²
- Massive trauma

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PATHOPHYSIOLOGY

Intracellular skeletal muscle defect

- Excessive amounts of calcium are released from the sarcoplasmic reticulum in skeletal muscle
- Calcium → contraction → heat → O₂ consumption → CO₂ → calcium → contraction → acid → heat

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PATHOPHYSIOLOGY



- Ryanodine is a large protein molecule
- It covers the opening on the sarcoplasmic reticulum
- Ryanodine regulates calcium release
- The majority of Malignant Hyperthermia susceptibility individuals have a defect in the ryanodine receptor type 1 (RYR1) gene³

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MALIGNANT HYPERTHERMIA

- Although its pathogenesis is relatively well understood, there is wide variability in:
 - time of onset
 - presentation of clinical signs & symptoms
- In some circumstances the delayed onset may hinder timely recognition and treatment⁴

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GENETICS

- More than 80 genetic defects have been linked to Malignant Hyperthermia (MH)
- Susceptibility is an autosomal dominant inherited disorder of skeletal muscle²

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RESEARCH TELLS US....

- Researchers looked at 24 cases of MH in cardio-thoracic patients
 - In 14 cases MH occurred during or shortly after bypass
 - Dantrolene was used in all but 1 case where the patient died
 - All other patients who received Dantrolene survived⁵

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RESEARCH TELLS US....

- Research by Larach et al. (2010)⁶
 - 286 cases studied
 - Young males 74.8%
 - 6.5 % had a family history
- '77 of 152 patients reported 2 previous unremarkable anaesthetics'⁶
- In 1995, it was reported that 50% of cases had had previous anaesthesia⁷
- 12 Anaesthetics and triggered fatally on the 13th⁷

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RESEARCH TELLS US....

- In 10 cases skin liquid crystal temperature probes did not trend ↑ temp
- Accurate temperature monitoring during general anaesthesia and early Dantrolene administration may decrease MH mortality by 35%
- 21 experienced haematological / neurological complications with a temp less than 41.6 (human critical thermal maximum)⁶

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TRIGGERING

- MH is most likely to occur in the operating theatre¹⁰
- It can also present in the PACU and possibly up to 12 hours post-operatively¹⁰

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PAEDIATRIC RESEARCH¹¹

- Retrospective study with 3 age groups;
- 0 – 24 months (n=35),
 - 25 months – 12 years (n=163)
 - 13 – 18 years (n= 66)
 - There were 351 subjects aged 18 years and younger who had episodes from 1960 – 2011

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PAEDIATRIC RESEARCH¹¹

- The middle age cohort was more likely to develop masseter spasm
- The youngest age cohort was more likely to develop skin mottling
- Sinus tachycardia, hypercarbia, and rapid ↑ temp were the most commonly observed physical examination findings
- Masseter spasm was significantly more common in children who received suxamethonium

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PAEDIATRIC RESEARCH¹¹

- Dantrolene was administered in 73% of episodes
- The average initial doses = 2.4 mg/kg
- The average total dose = 5.9 mg/kg
- Doses were similar across groups

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PAEDIATRIC RESEARCH¹¹

- Overall, 21.6% of patients reported side effects after Dantrolene administration
- Common was muscle weakness, which was more commonly reported in the oldest age cohort (the youngest group would not have been able to report such an effect)
- There were 10 MH-associated deaths in the entire cohort
- Six of these deaths occurred in the middle age group (3.7%), 4 occurred in the oldest age group (6.1%)

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PAEDIATRIC RESEARCH¹¹

- Five of these patient deaths (50%) received Dantrolene during the course of their treatment
- Reactivation of symptoms after initial treatment occurred in 14.4% of cases, with no difference across age cohorts
- Two of these cases were fatal despite treatment with Dantrolene: one in the middle age group (4-year-old, 6 hours after the initial event), and 1 in the oldest age group (14-year-old, 24 hours after the initial event)

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PAEDIATRIC RESEARCH¹¹

“In summary, our main hypothesis, that there are age-related differences in clinical characteristics of acute MH among different age cohorts during childhood, was confirmed”

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PAEDIATRIC RESEARCH¹¹

“In general, older subjects with presumed greater muscle mass demonstrated a greater likelihood of higher body temperatures and higher potassium levels, while the youngest subjects had greater levels of metabolic acidosis”

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PEADIATRIC RESEARCH¹¹

“Our secondary hypothesis, that we would be able to identify specific groups of children at risk for development of acute MH, was unproven, because nearly all children in all age groups were phenotypically normal before developing MH”

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TRIGGER AGENTS

Volatile Inhalational agent

- Isoflurane
- Sevoflurane
- Desflurane
- Halothane
- Enflurane
- Ether, Cyclopropane



Depolarizing muscle relaxants

- Suxamethonium Chloride

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SAFE AGENTS



- Intravenous agents
 - Propofol
 - Barbiturates
 - Benzodiazepines
 - Opiates
- Muscle relaxants
 - Non-depolarizing
- Inhalation agents
 - Nitrous oxide
- Local anaesthesia - Amides / esters

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SIGNS OF MALIGNANT HYPERTHERMIA

Early (S & S may be seen in any order)

- Tachycardia
- Tachypnoea
- Sweating
- Sudden rise in end – tidal CO₂
- Temperature
- Ventricular extra systole
- Unstable B/P
- Rigidity (immediately after suxamethonium)
- Masseter muscle rigidity



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SIGNS OF MALIGNANT HYPERTHERMIA

Research showed frequent early signs were:

- Hypercarbia
- Sinus tachycardia
- Masseter spasm
- In 63.5% temp was the 1st to 3rd sign⁶

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SIGNS OF MALIGNANT HYPERTHERMIA

Late

- Cyanosis
- Skin mottling
- Hyperkalemia
- Myoglobinuria
- Elevated Creatine Kinase



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TREATMENT

- Stop trigger agents immediately
- Change anaesthetic machine/circuit
- Stop or expedite surgery
- Administer 100% oxygen – hyperventilate
- Call for help – press emergency bell
- Obtain malignant hyperthermia kit
- Administer Dantrolene 2.5mg/kg with no upper limit (updated Dantrolene)

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TREATMENT

- Notify nursing supervisor & pharmacy department
- Send orderly for buckets of ice
- Cool patients and monitor temperature
- Ice to axilla and groin
- Cool I.V. fluids
- Cooling blanket (Polar Bear)
- Assist in line insertion
- Central line
- Arterial line



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ASSIST IN TREATMENT OF:

- Arrhythmia's
- Electrolyte imbalance
- Maintenance of cardiac function
- Urinary catheterisation
 - Careful observation of output and colour of urine

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DANTROLENE SODIUM (DANTRIUM)

- Dantrolene is a skeletal muscle relaxant
- Decreases the amount of calcium released by the sarcoplasmic reticulum
- Reverses the pathophysiology of Malignant Hyperthermia
- Case fatality rate has fallen from 70% in the 1970's to less than 10 % in 2006
- Preparation: 20mg vials – powder to be mixed with 60mls **sterile water**
- Sterile water or room temperature

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DANTROLENE SODIUM (DANTRIUM)

- It is extremely important that sterile water used for reconstituting dantrolene is not mistakenly infused into the patient. Suggestions to reduce the risk of this life-threatening error include:
 - Use of 100 ml water for injections plastic bottles
 - Additional labelling of sterile water bags (if 100 ml bottles are not available) in the MH box as "NOT for intravenous infusion"¹²
- Sodium Hydroxide and 3g Mannitol

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**DANTROLENE SODIUM (DANTRIUM)
OLD CALCULATIONS...**

- Initial dose $2.5\text{mg} \times 70\text{kg} = 175\text{mg} = 9$ vials
- $10\text{mg} \times 70\text{kg}$ (old upper dose limit) = $700\text{mg} = 35$ vials
- The median dose of Dantrolene was $5.9\text{mg}/\text{kg}^6$
- The average total dose (paeds) = $5.9\text{mg}/\text{kg}^{11}$

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DANTROLENE SODIUM (DANTRIUM)

- Subsequent doses may be required over the coming hours or days - $1\text{mg}/\text{kg}$ 6 hourly for the first 24-48 hours¹²
- pH 9.5 – care must be taken to: prevent extravasation, be watchful for thrombophlebitis
- Solution must be protected from light and used within 6 hours²

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DANTROLENE

- Pfizer has releasing a new formulation of Dantrolene (Dantrium IVTM) in Australasia
- After more than 20 years of concern about the difficulties of emergency preparation of this drug, improvements in the lyophilisation (freeze-drying)

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UPDATED DANTROLENE

- There were no changes to:
 - dose per vial (20mg)
 - diluent (60 mL sterile water for injection)
 - dose (2.5mg/ kg increments regardless of age, with no upper dose limit)

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UPDATED DANTROLENE

If in doubt about the diagnosis, consider that:

- Dantrolene is a safe drug with the provision of appropriate ventilatory support²
- Extreme hyperthermia can result in cell death and an unsalvageable situation²
- Not all symptoms of MH need to be present to make the diagnosis²

Complications

- Massive CO₂ production, skeletal muscle rigidity, tachyarrhythmias, unstable haemodynamics, respiratory acidosis, cyanosis, hyperkalaemia, lactic acidosis, fever, and eventually (if untreated) death.²
- MH can present some or all of these features²

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TESTING

- All current Australian and New Zealand laboratories follow the guidelines of the European Malignant Hyperthermia Group for In Vitro Contracture Testing and Molecular genetic testing for MH²

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MHANZ²

Dantrolene stocks:•

- MHANZ recommends that a minimum of 24 (20 mg) vials of DANTRIUM® or 2 (250 mg) vials of RYANODEX ® are held in any anaesthetising location where triggering anaesthesia is performed
- Larger or remote hospitals should carry at least 36 vials as access to further stocks in an MH crisis may be very limited

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MHANZ guidelines

MHANZ guidelines

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NEW MHANZ GUIDELINES 2025 - WEBSITE

- Malignant Hyperthermia Australia and New Zealand, a group of anaesthetists responsible for Malignant Hyperthermia (MH) investigation, has released an updated website which can be accessed at www.malignanthyperthermia.org.au including revised MH resource kit. The comprehensive kit includes the following components:
- MH Poster
- MH Crisis Initial Management
- MH Crisis Coordinators Overview
- MH Crisis Task Cards (Resuscitation, Dantrolene or ryanodex, Anaesthetic assistant, Lines and investigations, Cooling, Surgical Team and Logistics)

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PACU

Patients susceptible to MH may be managed in the normal post anaesthetic care unit and do not need to be isolated from other postoperative patients²

Volatile anaesthetic levels in parts per million safe for occupational exposure are also safe for susceptible patients. • Standard post-operative monitoring as per ANZCA guidelines including standard PACU discharge criteria is appropriate²

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QUESTIONS



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