Contents

Chapter 1
Introduction to Malignant Hyperthermia

Chapter 2
Symptoms of a Malignant Hyperthermia Crisis

Chapter 3
How to Treat with Dantrolene Sodium IV formulation

Chapter 4
Summary
Chapter 1: Introduction to Malignant Hyperthermia

After reading this chapter you will be able to:

- Understand the causes and pathology of malignant hyperthermia
- Appreciate the key points of malignant hyperthermia diagnosis
- Identify possible risk factors for malignant hyperthermia
What is Malignant Hyperthermia?

- Malignant hyperthermia (MH) is a hypermetabolic response to certain general anaesthetics and/or succinylcholine.
- It is characterised by otherwise unexplained increases in a patient’s CO₂ production (see opposite) and body temperature, as well as tachycardia and hyperkalaemia.
- Episodes of MH are rare; estimates of total prevalence range from 1 in 10,000 to 1 in 220,000 anaesthetic procedures.
- The highest incidence appears to be in children and young people (mean age 18.3 years) with 52.1% of all cases occurring in children under the age of 15 years. Incidence of MH crises is 1:15,000 in children and 1:50,000 in adults.
- The estimated genetic prevalence is 1 in 2,000, with males being 2.5–4.5 times more likely to develop MH than females. The prevalence of MH susceptibility is thought to be up to 50% in individuals with an MH-susceptible first-degree family member.
- The mortality rate is high: 70–80% if untreated. This equates to 0.0082 deaths per 100,000 inpatient surgeries.
Causes of Malignant Hyperthermia

- Malignant hyperthermia is usually triggered by exposure to volatile halogenated inhalational anaesthetic drugs, such as halothane, enflurane, isoflurane, desflurane and sevoflurane\textsuperscript{4,10}

- The likelihood of survival in an MH crisis decreases in patients who receive a volatile anaesthetic and the depolarising agent succinylcholine in combination, compared with volatile anaesthetics alone\textsuperscript{4}

- Several cases of MH triggered by succinylcholine alone have also been reported\textsuperscript{3,11}

- It has been suggested that phosphodiesterase type III inhibitors and serotonergic drugs are potential triggers of MH, but a consensus on this has not yet been reached\textsuperscript{4,12}

Agents with the potential to induce a malignant hyperthermia crisis\textsuperscript{4}

**Volatile anaesthetics**
- Halothane
- Enflurane
- Isoflurane
- Desflurane
- Methoxyflurane
- Sevoflurane

**Depolarising agent**
- Succinylcholine
Pathological Response

- An MH crisis is caused by hypersensitivity of the associated ryanodine receptor, RYR1, to volatile halogens\textsuperscript{4,5}
- During healthy physiological excitation-contraction coupling in skeletal muscle cells, depolarisation of the neuromuscular junction causes the voltage-dependent calcium channel, the dihydropyridine (DHP) receptor, to open
- Subsequently RYR1 stimulates release of calcium from the sarcoplasmic reticulum
- Influx of calcium into the cytosol stimulates contraction of skeletal muscle filaments
- Contraction is terminated when calcium is actively pumped back into intracellular stores, causing the muscle filaments to relax\textsuperscript{4,5}

Healthy physiological excitation-contraction coupling in skeletal muscle cells\textsuperscript{13}
During an MH crisis, the triggering agent induces sustained opening of RYR1. Mutated isoforms of this receptor often have a lower voltage threshold for channel opening, which increases the probability the channel will exist in its open state\textsuperscript{14,15}. Additionally, the mutated RYR1 is hypersensitive to volatile halogens\textsuperscript{16}. Sustained opening of RYR1 results in uncontrolled release of calcium from the sarcoplasmic reticulum\textsuperscript{4,5}. The subsequent prolonged muscle contraction induces hypermetabolism and direct effects on skeletal muscle such as rigidity and rhabdomyolysis\textsuperscript{1,2,4,5}. 

Effect of MH triggering agent on RYR1\textsuperscript{4}
Genetic Susceptibility

- Malignant hyperthermia susceptibility is an autosomal dominant condition. The estimated genetic prevalence is 1 in 2,000\(^1\). Genetic mutations in RYR1 are thought to contribute to up to 70% of all cases of MH\(^5\). The most frequent RYR1 mutations are R614C, G2434R and G341R, which together, are thought to account for over 10% of all cases of MH\(^6\).

- Despite the association of more than 180 mutations in RYR1 with MH, only 33 are functionally consistent with MH pathogenicity\(^17\).

- The locus CACNL1A3 encodes one of the five subunits of the dihydropyridine receptor and mutations within it have been shown to be associated with MH susceptibility\(^18\).

Causes of malignant hyperthermia\(^5,6\)

- Mutations in RYR1
  - R614C, G2434R and G341R
  - Other RYR1 mutations
- Other causes
## Conditions Associated with Malignant Hyperthermia

Malignant hyperthermia susceptibility is associated with several conditions\(^1,7,25\):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Volatile anaesthetics</th>
<th>Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central core myopathy</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Multicore myopathy</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>King-Denborough syndrome</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Native American myopathy</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Hypokalaemic periodic paralysis</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Exertional rhabdomyolysis</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Dystrophinopathies</td>
<td>Use limited amounts (if essential)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Myoadenylate deaminase deficiency</td>
<td>Try to avoid</td>
<td>Try to avoid</td>
</tr>
<tr>
<td>McArdle disease</td>
<td>Try to avoid</td>
<td>Try to avoid</td>
</tr>
<tr>
<td>Carnitine palmitoyl transferase type 2 deficiency</td>
<td>Try to avoid</td>
<td>Try to avoid</td>
</tr>
<tr>
<td>Myotonia</td>
<td>Not contraindicated</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Diagnosis During Anaesthesia

- Malignant hyperthermia is frequently difficult to diagnose; clinical presentations and first signs of MH are highly variable, with some patients exhibiting only a subset of symptoms
- The principle diagnostic feature of MH is an unexplained increase in end-tidal (ET)CO$_2$ concentration or hyperventilation. Accompanying symptoms are shown in the adjacent table
- The onset of treatment, however, impacts which symptoms manifest. Partial pressure of CO$_2$ $>60$ mmHg (8 kPa) is indicative of the most serious form of MH, fulminant MH, the severity of which is characterised by rapid progression to multiorgan failure and circulatory collapse if untreated, and ultimately death

Accompanying symptoms of a malignant hyperthermia crisis

- Increase in ETCO$_2$
- Increased O$_2$ requirement
- Tachycardia
- Hyperkalaemia
- Hyperthermia
- Arrhythmia
- Muscular rigidity
- Rhabdomyolysis
- Disseminated intravascular coagulation
- Metabolic and respiratory acidosis
Differential Diagnosis

- Capnography and blood gas analysis enable detection of pathophysiological symptoms of MH\(^1\)
- Differential diagnoses are possible as several symptoms of MH are also characteristic of other conditions\(^1,4\)

Possible differential diagnoses\(^1,4\):

- Sepsis
- Thyroid storm
- Phaeochromocytoma
- Iatrogenic overheating
- Inadequate anaesthesia*
- Anaphylactic reaction
- Drug intoxication
- Serotonin syndrome
- Malignant neuroleptic syndrome

*Especially if masseter spasm is the only symptom
Laboratory Diagnosis of Susceptibility

- Laboratory diagnosis of MH susceptibility is most commonly employed after a suspected MH crisis or in individuals with a family history of MH\textsuperscript{4,6,17}

- The most widely used and accepted laboratory method of diagnosing MH susceptibility is the \textit{in vitro} contracture test where a patient undergoes a muscle biopsy to isolate muscle fibre segments, which are then exposed to halothane or caffeine \textit{in vitro}\textsuperscript{6,17}. A positive result to one or both compounds, depending on the protocol used, indicates MH susceptibility\textsuperscript{1,4}

- The diagnostic threshold for the European Malignant Hyperthermia Group (EMHG) protocol is contracture of ≥0.2 g to ≤2% halothane and ≥0.2 g to ≤2.0 mmol/L caffeine administered individually\textsuperscript{5,6,17}

- The \textit{in vitro} contracture test is an expensive and invasive procedure, however, and can yield false results. DNA analysis offers an alternative assessment of susceptibility; it can prove inconclusive due to the wide range of susceptibility loci associated with MH, although its accuracy is improving\textsuperscript{1,6,17}
Non-Anaesthesia Induced Manifestations

- Cases of MH can occur independent of trigger compounds (anaesthetics and/or succinylcholine) in individuals who are awake and active\textsuperscript{4,19–21}

- A fatal case of MH was reported in a 12-year old boy following excessive exercise. It was revealed post-mortem that he had a mutation in the gene encoding RYR1\textsuperscript{19}

- Furthermore, many other patients presenting with an exercise-induced MH-like episode have tested positive for MH susceptibility using the \textit{in vitro} contracture test\textsuperscript{4}

- Episodes of MH have also been suspected in patients following recreational drug and alcohol abuse, although the MH susceptibility status in these specific patients is unknown\textsuperscript{20,21}
Anaesthesia in Patients with Malignant Hyperthermia Susceptibility

- It is vital that anaesthetists are aware of a patient’s MH susceptibility status if this information is available. This can involve discussions with patients in which any personal or family history of MH is discussed.
- For any patients with confirmed or suspected MH susceptibility, anaesthetists should revise treatment so that any contact with MH-triggering substances is avoided.
- No other specific treatment or monitoring should be required by the patient, especially if medical staff are vigilant about the presence of MH symptoms.
- Crucially, sufficient quantities of Dantrolene Sodium IV must be easily and rapidly accessible in all units where MH-triggering substances are used, in anticipation of any suspected cases of MH.

Examples of safe medications for MH-susceptible patients:

**Intravenous Anaesthetics:**
- Diazepam, etomidate, hexobarbital, ketamine, methohexital, midazolam, pentobarbital, propofol, thiopental

**Inhaled Non-Volatile General Anaesthetic:**
- Nitrous oxide

**Local Anaesthetics:**
- Amethocaine, articaine, bupivacaine, dibuclidean, etidocaine, eucaine, lidocaine, levobupivacaine, mepivacaine, procaine, prilocaine, ropivacaine, stovaine, proracaine hydrochloride

**Narcotics (Opioids):**
- Alfentanil, anileridine, codeine, diamorphine, fentanyl, hydromorphone, meperidine, methadone, morphine, naloxone, oxycodone, phenoperidine, remifentanil, sufentanil

**Muscle Relaxants:**
- Arduan, curare, gallamine, methocarbamol, metocurine, mivacron, neuromax, nimbex, norcuron, pavulon, tracrium, zemuron
Malignant Hyperthermia Organisations

- The European Malignant Hyperthermia Group (EMHG) was formed to promote understanding, awareness and optimum care of MH.

- The EMHG encourages research into the pathophysiology and treatment of MH, supporting patients should they agree to participate in research. They also provide a forum for physician and/or patient discussions, which is hoped to improve patient care. The EMHG also publishes guidelines for the treatment of MH.

- The Malignant Hyperthermia Association of the United States (MHAUS) is a non profit organisation founded in 1981, whose mission is to promote optimum care and scientific understanding of MH and related disorders.

- Their website provides support to healthcare professionals, as well as MH patients and their families with information on MH, forums, blog, FAQs and 24-hour MH emergency hotline.
Chapter 1: Questions

1. Who is most at risk of MH?
   a) Young males
   b) Women aged >45 years
   c) Anyone undergoing surgery for the first time

2. Which of the following agents can be responsible for triggering MH?
   a) Local anaesthetics such as lidocaine
   b) Volatile halogenated anaesthetics (e.g. halothane)
   c) Opioids such as fentanyl

3. What is the pathological process of MH?
   a) Depression of central nervous system activity at the hypothalamus that regulates internal body temperature
   b) Excessive release of acetylcholine at the neuromuscular junction stimulating uncontrolled post-synaptic depolarisation
   c) An uncontrolled increase in calcium in the skeletal muscle cell causing sustained contraction
Chapter 1: Questions

4. Genetic mutations in which of the following proteins are responsible for the majority of cases of MH?
   a) The ryanodine receptor, RYR1
   b) The dihidropyridine receptor
   c) The nicotinic acetylcholine receptor

5. What is the principle diagnostic feature of MH?
   a) Bradycardia
   b) Hypocalcaemia
   c) Increased ETCO₂

6. Why can diagnosis of MH often be difficult?
   a) All general anaesthetics induce a rise in ETCO₂
   b) Symptoms of MH will often not improve following administration of 20 mg/kg Dantrolene Sodium IV
   c) Several symptoms of MH are also characteristic of other rare conditions so differential diagnoses should be considered
7. How is MH susceptibility confirmed?

a) A history of MH  
b) Hyperkalaemia >6.0 mEq/L  
c) DNA screening and/or *in vitro* contracture testing

8. How should patients with confirmed MH susceptibility be treated during surgery?

a) All procedures involving general anaesthesia should be avoided if possible  
b) Volatile halogen anaesthetics and/or succinylcholine should be avoided, and mechanisms to actively cool the patient’s core body temperature should be employed from the start of surgery  
c) Volatile halogen anaesthetics and/or succinylcholine should be avoided, but no further specific treatment is required

9. Which of the following is the best resource for more information on MH?

a) The label of Dantrolene Sodium IV vials  
b) The EMHG website  
c) The circulating nurse present during surgery
Chapter 2: Symptoms of a Malignant Hyperthermia Crisis

After reading this chapter you will be able to:

- Identify the signs and symptoms of MH
- Use a clinical grading scale to diagnose an MH crisis
- Understand the risks of recrudescence of MH
Diagnosis of Malignant Hyperthermia

- Early diagnosis and treatment of MH is crucial. However, several symptoms associated with MH are not MH-specific and can be associated with other conditions making diagnosis of MH difficult\(^1,4\)
- Diagnosis of MH is based on both clinical and laboratory findings. Clinical symptoms are usually sufficient to establish a diagnosis at the time of presentation
- The crucial factor when assessing MH manifestation should be the presence of symptoms following exposure to a triggering agent in the absence of any other apparent cause\(^2\)\(^6\)
- The timescale for the onset of MH can vary: manifestation can occur immediately after exposure to the triggering agent or hours after its discontinuation\(^1\)\(^2\)\(^6\)
- The onset of MH is generally later after exposure to trigger agents desflurane and/or isoflurane compared with halothane and/or sevoflurane\(^2\)\(^7\)
- The contracture test will indicate whether an individual is MH susceptible, which, when coupled with a historical incidence of MH symptoms, is sufficient to confirm diagnosis\(^1\)\(^7\)
### Early Clinical Signs

- Early recognition of an MH crisis is imperative for a positive prognosis and treatment should start immediately that an MH crisis is suspected\(^2\)
- The most frequent first signs of MH are hypercapnia, sinus tachycardia and masseter muscle rigidity, according to an analysis of MH cases in North America\(^5\)

#### Early clinical signs according to EMHG guidelines\(^1,2\)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased CO(_2) production</td>
<td>Hypermetabolism</td>
</tr>
<tr>
<td>Increased O(_2) consumption</td>
<td></td>
</tr>
<tr>
<td>Metabolic and respiratory acidosis</td>
<td></td>
</tr>
<tr>
<td>Sweating and mottling of the skin</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Cardiovascular effects</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Unstable arterial pressure</td>
<td></td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Direct consequences of prolonged muscle contraction</td>
</tr>
<tr>
<td>Masseter spasms (lockjaw)</td>
<td></td>
</tr>
</tbody>
</table>
Late Clinical Signs

- According to the EMHG guidelines, later clinical signs of an MH crisis include:
  - Hyperkalaemia, which can lead to severe cardiac arrhythmias and cardiac arrest
  - Elevated blood myoglobin levels leading to myoglobinuria
  - Elevated blood creatine phosphokinase levels

- A rapid increase in core body temperature may also be observed, although a diagnosis of MH should not depend on this as it can be a relatively late, or even absent, symptom.

- A high core body temperature and occurrence of disseminated intravascular coagulation are usually indicators of MH complications such as cardiac arrest and even death.
Clinical Grading Scale

- A clinical grading scale of MH symptoms was developed by Larach and colleagues in order to assist diagnosis.
- As shown on the next slide, the scale lists the clinical findings and their manifestations, along with a scoring system. For every specific symptom that is present, the number of points applicable is added to the patient's score, which is summed to give the likelihood that an MH crisis is occurring.
- The scale is more accurate when diagnosing MH in patients who achieve a high score.
- However, it is not so accurate for patients in whom some symptoms may not be present or data may not be available. If few symptoms present, or if those that do are rare, a patient’s total score may be low.
- This could mean a diagnosis of MH is dismissed and so the grading scale should not be used in isolation in these cases.
### Clinical Grading Scale

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Indicator</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis</td>
<td>ETCO$_2$ &gt;55 mmHg (7.3 kPa) or PaCO$_2$ &gt;60 mmHg (8.0 kPa)</td>
<td>15</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>Unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Base deficit &gt;8 mEq/L or pH &lt;7.25</td>
<td>10</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Generalised rigidity or severe masseter muscle rigidity</td>
<td>15</td>
</tr>
<tr>
<td>Muscle breakdown</td>
<td>Serum creatine kinase &gt;20,000 IU</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Cola coloured urine</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Excess myoglobin in urine or serum</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Plasma K$^+$ &gt;6 mEq/L</td>
<td>3</td>
</tr>
<tr>
<td>Temperature increase</td>
<td>Rapidly increasing temperature &gt;38.8ºC</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>Rapid reversal of signs with Dantrolene Sodium IV</td>
<td>5</td>
</tr>
<tr>
<td>Family history</td>
<td>Consistent with autosomal dominant inheritance</td>
<td>15</td>
</tr>
</tbody>
</table>

ETCO$_2$=end tidal CO$_2$; PaCO$_2$=partial pressure of CO$_2$

A patient’s “total score” is calculated by adding the scores listed for their symptoms in the table on the left. The table below is then used to determine the likelihood that the patient is experiencing an MH crisis.

<table>
<thead>
<tr>
<th>Score Range</th>
<th>Rank</th>
<th>Description of Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>Almost never</td>
</tr>
<tr>
<td>3–9</td>
<td>2</td>
<td>Unlikely</td>
</tr>
<tr>
<td>10–19</td>
<td>3</td>
<td>Somewhat less than likely</td>
</tr>
<tr>
<td>20–34</td>
<td>4</td>
<td>Somewhat greater than likely</td>
</tr>
<tr>
<td>35–49</td>
<td>5</td>
<td>Very likely</td>
</tr>
<tr>
<td>&gt;50</td>
<td>6</td>
<td>Almost certain</td>
</tr>
</tbody>
</table>

Adapted from Reference 28
A system of classification of MH crises according to clinical presentation and severity has been suggested, although it is not currently recommended for use in the EMHG treatment guidelines

The most serious cases are described as fulminant; these are potentially fatal and occur with multiple metabolic and muscular manifestations

Abortive MH crises are moderate in severity and present with metabolic and muscular manifestations but are not as severe as those that are fulminant

Mild MH crises involve mild metabolic changes without muscle involvement, but can often be accompanied by masseter spasms. This can involve masseter muscle rigidity with evidence of muscle injury, masseter muscle rigidity associated with metabolic changes or masseter muscle rigidity alone

Atypical MH crises can manifest as sudden death or unexplained cardiac arrest during anaesthesia and can be associated with post-operative fever, rhabdomyolysis, renal failure and/or suspected family history

## MH Crisis Severity

- **Fulminant**
  - (Multiple metabolic and muscle manifestations, potentially fatal)

- **Abortive**
  - (Metabolic and muscle manifestations, but not as severe as in fulminant)

- **Mild**
  - (Mild metabolic changes, no muscle involvement)
Chapter 2: Questions

1. What is the timescale for the onset of MH?
   a) Symptoms manifest within 20 minutes of exposure to the triggering agent
   b) The timescale can vary; symptoms can manifest immediately after exposure to the triggering agent or hours after its discontinuation
   c) Symptoms usually manifest after removal of the triggering agent, following accumulation of sufficient levels in the patient’s body

2. What is the principle early clinical sign of MH?
   a) Hyperkalaemia
   b) Hyperthermia
   c) Hypercapnia

3. Which of the following are considered late clinical signs of MH?
   a) Hyperkalaemia, elevated blood myoglobin and elevated blood creatine phosphokinase
   b) Hypercalcaemia, myoglobinuria and muscular dystrophy
   c) Hypernatraemia, bradycardia and masseter hypertrophy
Chapter 2: Questions

4. How is the Larach Clinical Grading Scale useful?

a) It allows a diagnosis of MH to be dismissed in patients who do not present with the full spectrum of MH symptoms
b) It allows the likelihood that an MH crisis is occurring to be assessed based on the presence of symptoms
c) It assesses MH susceptibility based on the presence of symptoms

5. What does a rank of 6 on the Larach Clinical Grading Scale suggest?

a) Malignant hyperthermia is almost certain
b) The patient has no family history of MH
c) Malignant hyperthermia is occurring but is not life threatening

6. Which of the following is the most severe MH crisis?

a) Malignant hyperthermia with multiple metabolic and muscular manifestations
b) Malignant hyperthermia that presents with metabolic and muscular manifestations
c) Malignant hyperthermia that presents with metabolic changes and masseter spasms, without additional muscle involvement
After reading this chapter you will be able to:

- Understand the mechanism of action of Dantrolene Sodium IV
- Understand how to use Dantrolene Sodium IV to treat a MH crisis
- Calculate the correct dose of Dantrolene Sodium IV
- Minimise the risk of complications associated with Dantrolene Sodium IV
Available Treatment Options

- Dantrolene Sodium IV is the first specific drug treatment licensed for MH in Europe since 2014 and has been assessed to have a favourable risk/benefit profile.

- Recently, the US Food and Drug Administration (FDA) approved a nanocrystalline Dantrolene Sodium suspension (DSS) for the treatment of MH\textsuperscript{38,39}.

- This treatment is 150-times more concentrated and has an increased solubility\textsuperscript{39}. Therefore, 250 mg of nanocrystalline Dantrolene Sodium suspension (DSS) can be reconstituted in 5 mL water.
What is Dantrolene Sodium IV?

- A lyophilised formulation of Dantrolene Sodium IV is used for the treatment of MH. Dantrolene Sodium IV should be reconstituted and administered intravenously as soon as the symptoms of an MH crisis are suspected\(^2,29\).

- Dantrolene Sodium IV is a skeletal muscle relaxant; it diminishes sustained muscle contraction and attenuates the hypermetabolic response characteristic of MH\(^29\).

- Since the introduction of Dantrolene Sodium IV in 1975, mortality rates of MH have decreased from 70–80% to approximately 5% and administration of treatment within 20 minutes of symptom manifestation dramatically reduces the risk of MH complications\(^4,11\).

- A minimum starting dose of 2 mg/kg is recommended by the EMHG guidelines, which should be gradually titrated up to 10 mg/kg as required if the patient is unresponsive at lower doses\(^2\). Dantrolene Sodium IV is supplied in 20 mg vials, to be reconstituted with 60 mL sterile water for injection and then filtered using the blunt fill needle with filter provided\(^30\). Local or National guidelines should be consulted for the recommended starting dose.
Pharmacology and Properties

- Dantrolene Sodium IV depresses excitation-contraction coupling in the skeletal muscle. Dantrolene Sodium IV is an antagonist of the RYR1 receptor, which is located within the membrane of the sarcoplasmic reticulum of skeletal muscle cells.

- Dantrolene Sodium IV binds to, and blocks, the RYR1, inhibiting the release of calcium from intracellular stores. This prevents any further rise in intracellular calcium, allowing the concentration to be restored to physiological levels.

- It also reduces the percentage of free intracellular calcium and so less is available to initiate muscle contraction.

- When administered intravenously to healthy volunteers, Dantrolene Sodium IV is associated with loss of grip strength and weakness in the legs, demonstrating its ability to dampen muscle contraction.

- Prophylactic use of oral Dantrolene Sodium has been proposed for MH-susceptible patients. However, being at risk of MH does not guarantee occurrence of an episode and oral therapy does not ensure the required plasma concentration will be achieved, with patients experiencing adverse effects; an example being severe muscle weakness associated with pulmonary depression observed after oral dantrolene prophylaxis.
### Managing a Malignant Hyperthermia Crisis

#### Recognition
- Unexplained increase in ETCo2 AND
- Unexplained tachycardia AND
- Unexplained increase in oxygen requirement
  (Previous uneventful anaesthesia does not rule out MH)
- Temperature changes are a late sign

#### Immediate Management
- **STOP** all trigger agents
- **CALL FOR HELP**: Allocate specific tasks (action plan in MH kit)*
- Install clean breathing system and HYPERVENTILATE with 100% O2 high flow
- Maintain anaesthesia with intravenous agent
- ABANDON/FINISH surgery as soon as possible
- Muscle relaxation with non-depolarising neuromuscular blocking drug

#### Monitoring & Treatment
- Give dantrolene
- Initiate active cooling avoiding vasoconstriction
- **TREAT**:  
  - **Hyperkalaemia**: calcium chloride, glucose/insulin, NaHCO3
  - **Arrhythmias**: magnesium/neomycine/midazolam/phenformin
  - **AVOID** calcium channel blockers - interaction with dantrolene
  - **Metabolic acidosis**: hyperventilating, NaHCO3
  - **Myoglobinuria**: forced alkaline diuresis (reanmitol / furosemide & NaHCO3); may require renal replacement therapy later
  - **DIC / FFP, cryoprecipitate, platelets**
  - Check plasma CK as soon as able

**DANTROLENE**
- 2.5mg/kg immediate iv bolus.
- Repeat 1mg/kg boluses as required to max 10mg/kg

**For a 70kg adult**
- **Initial bolus**: 9 vials dantrolene 20mg (each vial mixed with 50ml sterile water)
- Further boluses of 4 vials dantrolene 20mg repeated up to 7 times.

**Continuous monitoring**
- Core & peripheral temperature ETCo2
- SpO2
- ECG
- Invasive blood pressure CVP
- Repeated bloods
  - ABG
  - U&Es (potassium)
  - FBC (haematocrit / platelets)
  - Coagulation

#### Follow-up
- Continue monitoring on ICU, repeat dantrolene as necessary
- Monitor for acute kidney injury and compartment syndrome
- Repeat CK
- Consider alternative diagnosis: myopathies, hypermetabolism, hypothalamic
- Counsel patient & family members
- Refer to MH unit (see contact details below)

*(Adapted from AAGBI Guidelines)*

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*For MH kit details please refer to the AAGBI website*
When and How Should Dantrolene Sodium IV be Administered?

- Dantrolene Sodium IV should be administered within 20 minutes of the first adverse sign of MH to reduce the risk of further complications such as renal and/or cardiac dysfunction

- Each 20 mg vial of Dantrolene Sodium IV requires reconstitution in 60 mL sterile water. The recommended starting dose of Dantrolene Sodium IV is 2 mg/kg in the EMHG guidelines

- For example, an average 73 kg patient would require a starting dose of 146 mg according to the EMHG guidelines. With 20 mg of Dantrolene Sodium IV in each vial, this patient would require 7.3 vials at this dose. The EMHG guidelines state that infusion of Dantrolene Sodium IV should be repeated until cardiac and respiratory systems stabilise

- The prescribing information advises that rapid intravenous administration should continue until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached

- However, the EMHG guidelines state that the maximum dose of 10 mg/kg may be exceeded if deemed necessary

---

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Dose (mg/kg)</th>
<th>Number of vials needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>2</td>
<td>7.3 vials</td>
</tr>
</tbody>
</table>

The formula used to calculate the number of Dantrolene Sodium IV formulation vials is:

\[
\text{Number of vials} = \left(\frac{\text{Patient Weight (kg)} \times \text{Dose (mg/kg)}}{20 \text{ mg}}\right)
\]
The proportion of adults who are overweight has risen by approximately 10% worldwide since 1980\(^3\). As a result, hospitals are treating overweight patients more frequently. It is important to recognise that this increases the requirement for Dantrolene Sodium IV, since the required dose to treat an MH crisis can not be predicted and it may exceed the maximum of 10mg/kg.

The EMHG guidelines recommend that Dantrolene Sodium IV is titrated up to 10 mg/kg or over if symptoms do not cease\(^2\). Therefore, a patient who weighs 98 kg could require 980 mg Dantrolene Sodium IV if they are unresponsive at lower doses and this would require 49 vials of Dantrolene Sodium IV.

Graph showing that sites with only 24 vials\(^3\) will not be able to readily provide the maximum dose to patients weighing over 48 kg.
Patient Factors (2)

- A recent audit of 16 UK hospitals revealed that a median of only 24 Dantrolene Sodium IV vials were immediately available\(^ {34}\)

- All surgical sites should consider the amount of Dantrolene Sodium IV stocked to ensure sufficient amount is available for obese patients who are unresponsive to lower doses

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Number of Vials to Achieve Dantrolene Dose of: (^ {22})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>45</td>
<td>2.3</td>
</tr>
<tr>
<td>58</td>
<td>2.9</td>
</tr>
<tr>
<td>73</td>
<td>3.7</td>
</tr>
<tr>
<td>88</td>
<td>4.4</td>
</tr>
<tr>
<td>103</td>
<td>5.2</td>
</tr>
<tr>
<td>118</td>
<td>5.9</td>
</tr>
<tr>
<td>133</td>
<td>6.7</td>
</tr>
<tr>
<td>148</td>
<td>7.4</td>
</tr>
</tbody>
</table>

The variability and unpredictability of the amount of vials to treat an MH crisis is emphasised in the table, based on the patient’s weight and required dose of Dantrolene Sodium IV. The part of the table highlighted in red shows the amount of vials required exceeding the median of 24 vials stocked in UK hospitals\(^ {34}\)
Logistics of Administration

- Dantrolene Sodium IV is provided in vials containing 20 mg Dantrolene Sodium IV, each one to be reconstituted in 60 mL sterile water. The reconstituted product is filtered with the blunt fill needle with filter (provided) when drawing up the solution into the syringe. Dantrolene Sodium IV should be administered as soon as MH is suspected according to the EMHG guidelines and within 20 minutes of the first adverse sign to reduce the risk of complications\(^2,11,30\).

- To minimise any delay in administration, Dantrolene Sodium IV stocks should be stored in a location that is easily and rapidly accessible\(^35\).

- More than one person should reconstitute the Dantrolene Sodium IV and one of the first responses upon recognition of an MH crisis should be a call for extra assistance to aid in this and other tasks\(^35\).
In addition to administration of Dantrolene Sodium IV, symptomatic treatment should be undertaken as shown in the table below:\textsuperscript{2}

Further details of symptomatic treatment can be found in the EMHG guidelines and the MHAUS website\textsuperscript{2,35}

### Symptomatic treatment of patients experiencing an MH crisis\textsuperscript{2}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>Active cooling with ice packs and intravenous delivery of up to 3000 mL chilled (4\textdegree C) 0.9% saline and other cooling devices should also be employed to facilitate this. Vasoconstriction should be avoided and all cooling methods should be withdrawn once body temperature is below 38.5\textdegree C</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Dextrose-insulin infusion, calcium chloride and dialysis</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Hyperventilation and sodium bicarbonate</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Amiodarone and/or β-blockers</td>
</tr>
</tbody>
</table>
Complications Associated with Dantrolene Sodium IV administration

- There are no contraindications associated with the use of Dantrolene Sodium IV\(^2^9\).

- The following adverse reactions are listed in the product information as associated with the use of intravenous Dantrolene Sodium IV\(^3^0\):
  - Pulmonary oedema
  - Thrombophlebitis
  - Urticaria
  - Erythema
  - Injection site reactions

- None of the adverse reactions occasionally reported with long-term oral Dantrolene Sodium use for the treatment of muscle spasticity, such as hepatitis, seizures and pleural effusions, is associated with short-term intravenous Dantrolene Sodium IV therapy\(^2^9-3^1\).

- An analysis of patients who received Dantrolene Sodium IV for the treatment of MH revealed that the most frequent complication was muscle weakness, the likelihood of which increased dose-dependently\(^2^9,3^6\).

- Other frequent adverse reactions included phlebitis, which is likely to be due to Dantrolene Sodium IV high pH (pH 9) and its relative insolubility, and gastrointestinal upset\(^2^9,3^6\).
Complications Associated with Delayed Dantrolene Sodium IV administration

- As well as the adverse reactions associated with Dantrolene Sodium IV itself, delay in administration leads to increased MH complications such as renal and/or cardiac dysfunction\(^\text{11}\).
- When \(\geq 20\) minutes elapsed between the onset of MH and treatment initiation, complication rates increased to \(\geq 30\%\); for patients whose treatment was delayed beyond 50 minutes, complication rates increased to 100\%\(^\text{11}\).

The effect of the time taken to treat MH on the rate of complications\(^\text{10}\).
Recrudescence

Following identification and treatment of MH, some patients experience recrudescence, i.e., the reappearance of symptoms after a period of quiescence. However, there is little evidence to support which patients are at risk and why.

One study analysed recrudescence in patients with a prior MH crisis grading score ≥20; recrudescence occurred in 20% of the patients analysed. Features associated with a higher risk of recrudescence were muscular body type, MH score ≥35, increased core body temperature and >150 minutes from induction to manifestation of MH symptoms.

Anaesthetists should be aware that patients presenting with some or all of these features may be at higher risk of recrudescence of MH. Given the possibility of recrudescence, patients should be monitored for at least 24 hours in an intensive care unit following initial treatment.

Recrudescence should be treated with Dantrolene Sodium IV as required. Administration of Dantrolene Sodium IV for at least 24 hours is expected to decrease the frequency of recrudescence.

Risk of recrudescence in patients who have experienced an MH crisis

- Recrudescence: 20%
- No recrudescence: 80%

Recrudescence risk factors:
- Muscular body type
- MH score ≥35
- Increased core body temperature
- >150 minutes from induction to symptoms
Future Treatment Options

- As clinical trials are lacking and most are conducted on healthy volunteers, it is currently difficult to compare the safety of the nanocrystalline Dantrolene Sodium suspension with that of the currently used product, the Dantrolene Sodium IV\textsuperscript{39}.

- Research into alternative approaches to treat MH is focusing on new ways to modulate RYR1 activity and calcium homeostasis, although alternative treatments are yet to be developed\textsuperscript{40}.
Chapter 3: Questions

1. How does Dantrolene Sodium IV act as a skeletal muscle relaxant?

a) Dantrolene Sodium IV stimulates active transfer of calcium from the cytosol into the sarcoplasmic reticulum
b) Dantrolene Sodium IV binds to myosin heads, inhibiting formation of cross bridges between myosin and actin
c) Dantrolene Sodium IV blocks RYR1, preventing further release of calcium from the sarcoplasmic reticulum into the cytosol

2. What should be done upon recognition of an MH crisis?

a) Administration of all trigger agents must be stopped immediately, anaesthesia switched to a non-trigger agent and the patient should be hyperventilated. An emergency should be declared, assistance from more staff requested, and all surgery terminated as soon as possible
b) Administration of all trigger agents must be stopped immediately, anaesthesia switched to a non-trigger agent and assistance from more staff requested so that surgery can continue
c) Surgery can continue without interruption if hyperthermia is simultaneously treated using ice packs to initiate active cooling and chilled saline delivered intravenously
Chapter 3: Questions

3. When should Dantrolene Sodium IV be administered?

a) Dantrolene Sodium IV should be administered prophylactically whenever volatile halogen anaesthetics and/or succinylcholine are used
b) Dantrolene Sodium IV should be administered as soon as MH is suspected and within 20 minutes of the first adverse sign to reduce the risk of complications
c) Dantrolene Sodium IV should be administered following withdrawal of volatile halogen anaesthetics and/or succinylcholine after every surgical procedure

4. What starting dose of Dantrolene Sodium IV is recommended by the EMHG guidelines?

a) 2 mg/kg
b) 2.5 mg/kg
c) 10 mg/kg

5. Why should surgical sites consider re-evaluating the amount of Dantrolene Sodium IV that they keep?

a) Malignant hyperthermia is common and sites frequently use up all their stocks
b) More Dantrolene Sodium IV is required to treat an increasingly heavy patient population, as dose is based on patient’s response to the treatment and his/her body weight
c) Because reconstitution takes a long time, more Dantrolene Sodium IV may be needed to effectively treat a patient
6. How many vials of Dantrolene Sodium IV could an average 73 kg patient require when administered 5 mg/kg?

a) 18.25  
b) 20  
c) 36

7. How many vials of Dantrolene Sodium IV would an obese patient weighing 93 kg require when administered 10 mg/kg?

a) 36.5  
b) 46.5  
c) 56.5

8. Where should Dantrolene Sodium IV be stored?

a) In a location that is easily and rapidly accessible for staff members involved in surgery 
b) In an isolated and secure unit at a surgery site to avoid contamination of other medicines 
c) Surgeons and anaesthetists should always carry Dantrolene Sodium IV with them in case of suspected MH
Chapter 3: Questions

9. How should symptomatic hyperthermia be treated?
   a) Positioning ice packs around the patient’s body and intravenous delivery of chilled saline
   b) Administering vasoconstrictors such as phenylephrine
   c) No additional treatment is required if Dantrolene Sodium IV is administered immediately

10. Which of the following complications are associated with intravenous Dantrolene Sodium IV administration?
    a) Phlebitis and muscle weakness
    b) Masseter muscle spasm and rhabdomyolysis
    c) Hepatitis and seizures

11. What is expected to decrease the frequency of recrudescence of MH?
    a) Efficient and rapid treatment of hypercapnia
    b) Titrating Dantrolene Sodium IV up to the highest recommended dose of 10 mg/kg
    c) Administering Dantrolene Sodium IV for at least 24 hours
Chapter 4: Summary

This chapter will summarise:

- Introduction to MH
- The symptoms of a MH crisis
- How to treat with Dantrolene Sodium IV
Malignant Hyperthermia

- Malignant hyperthermia (MH) is a hypermetabolic response of the skeletal muscle to certain volatile halogenated inhalational anaesthetic drugs and/or succinylcholine.
- The triggering agent stimulates prolonged opening of the ryanodine receptor, RYR1, leading to uncontrolled release of calcium into the cytosol, sustained muscle contraction and hypermetabolism.
- Patient susceptibility can be confirmed by DNA screening to detect the presence of one of the known mutations associated with MH.
- Susceptibility can also be investigated in the laboratory using the in vitro contracture test, in which the response of skeletal muscle tissue to triggering agents is measured.
- More information about MH, including treatments and research, can be found on the websites for the European Malignant Hyperthermia Group (EMHG), the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the Malignant Hyperthermia Association of the United States (MHAUS).
Recognition of Malignant Hyperthermia

- Prolonged skeletal muscle contraction induces hypermetabolism, which is characterised by increases in end-tidal (ET)\(\text{CO}_2\), \(\text{O}_2\) consumption and body temperature
- Accompanying symptoms include tachycardia, hyperkalaemia, disseminated intravascular coagulation (DIC); and direct effects on the skeletal muscle such as rigidity and rhabdomyolysis
- Differential diagnosis should be considered as several symptoms are not MH-specific and can be associated with other conditions
- The Larach clinical grading scale lists symptoms and a scoring system. For every symptom that is present, the number of points applicable is added to the patient's score, which is summed to give the likelihood that an MH crisis is occurring
Treatment with Dantrolene Sodium IV

- Dantrolene Sodium IV, is a skeletal muscle relaxant indicated for the treatment of MH.
- Treatment with Dantrolene Sodium IV should be initiated immediately, once MH is suspected. All trigger agents must be stopped, a clean breathing system installed hyperventilating with 100% O$_2$ at high flow and all surgery stopped.
- Each 20 mg vial of Dantrolene Sodium IV requires reconstitution in 60 mL sterile water and then filtration using blunt fill needle with filter (provided) before administration.
- The recommended starting dose of Dantrolene Sodium IV is 2 mg/kg in the EMHG guidelines, which should be repeated and titrated up if necessary, until symptoms subside.
- The amount of Dantrolene Sodium IV required is calculated according to patient weight and the dose the patient responds to, thus, surgical sites should consider their stock levels of Dantrolene Sodium IV as the proportion of adults who are overweight in the population is increasing.
Achieving Rapid Administration of Dantrolene Sodium IV

- An MH response protocol should be in place to optimise the speed and quality of response to an MH crisis.
- All surgical staff should be aware of the location of Dantrolene Sodium IV.
- Dantrolene Sodium IV should be administered as soon as MH is suspected, according to the EMHG guidelines.
- Delays in administration beyond 20 minutes of the first adverse sign lead to an increase in the incidence of MH complications such as renal and/or cardiac dysfunction.
Monitoring the Patient After an MH Crisis

- Once the patient is stabilised, maintain continuous monitoring of body temperature, ETCO\textsubscript{2}, O\textsubscript{2} consumption and heart rate
- Some patients experience recrudescence following treatment of MH
- Features associated with a higher risk of recrudescence are muscular body type, high score on the Larach scale, increased core body temperature and >150 minutes from induction to symptom manifestation
- Patients must be monitored for >24 hours in an intensive care unit, with Dantrolene Sodium IV treatment repeated if necessary
- Dantrolene Sodium IV stocks should also be sufficient to treat recrudescence as well as ongoing surgery of new patients
- Following recovery, patients should be referred for laboratory testing to assess susceptibility
Further Considerations

- A nominated person in each surgical site should be responsible for checking the stocks of Dantrolene Sodium IV.

- Regular checks of Dantrolene Sodium IV stock on site should be taken in order to avoid availability issues.
References

References


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