Malignant hyperthermia

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Malignant hyperthermia (MH) is an uncommon, life-threatening, acute pharmacogenetic disorder of the skeletal muscle cell. It manifests in susceptible individuals as a hypermetabolic response on exposure to halogenated volatile anaesthetics and depolarizing muscle relaxants. There may also be a relationship between susceptibility to MH, heat stroke and exercise-induced rhabdomyolysis. The pathophysiology of the crisis involves an uncontrolled release of cytoplasmic free calcium from the sarcoplasmic reticulum leading to activation of energy-producing biochemical pathways. Organ system failure and rhabdomyolysis may occur as a result of high fever, hyperkalaemia and acidosis. The ryanodine receptor, the calcium-release channel of the sarcoplasmic reticulum, is the primary locus for malignant hypothermia susceptibility. Multiple mutations in the gene for the ryanodine receptor protein are causative. Other genes may also be involved.

A classical fulminant crisis presents with a rising end-tidal carbon dioxide, skeletal muscle rigidity, tachycardia, hyperthermia and acidosis. Mortality may be as high as 70% if the syndrome is not recognized and treated. Immediate discontinuation of triggering agents, oxygenation, and correction of acidosis and electrolyte abnormalities, cooling and dantrolene are essential for treatment of the syndrome. Thanks to clinical and research investigations, widespread education and the introduction of dantrolene sodium, the mortality from MH is less than 5%. This chapter provides an overview and an update of MH.

Key words: malignant hyperthermia; life-threatening condition; ryanodine receptor; halothane; caffeine; calcium ion; dantrolene; rhabdomyolysis; in vitro contracture test; myopathy.
Malignant hyperthermia (MH) is an uncommon, potentially fatal pharmacogenetic disorder. The pathophysiological change is an uncontrolled release of cytoplasmic free calcium from the sarcoplasmic reticulum of the skeletal muscle leading to increased metabolism. The syndrome is generally induced on exposure to potent inhalation anaesthetic drugs and/or succinylcholine.1–4 The MH syndrome occurs in humans, in various breeds of swine and in other animals.

The first publication suggesting a link between anaesthesia, hyperthermia and an inherited syndrome appeared in 1960. Denborough5 described deaths during anaesthesia in more than 10 family members and postulated a previously undescribed inborn error of metabolism inherited as a dominant trait responsible for deaths.6 Denborough and colleagues documented elevated creatine kinase (CK) in many members of the family. At a later time, this syndrome was named malignant hyperpyrexia or malignant hyperthermia. Isaacs and Barlow independently observed that some relatives of MH patients had high serum CK activities.7 Meanwhile, Kalow and Britt studied the contractile behaviour of isolated skeletal muscle in vitro and found that the dog muscle contracted on exposure to chloroform. Later, they observed that muscle from MH-susceptible persons had an augmented contracture response to caffeine in vitro.8 The following year, Ellis et al demonstrated a similar phenomenon with halothane.9 An important breakthrough occurred when it was demonstrated that dantrolene sodium prevents and modifies the clinical syndrome in susceptible swine.10,11 Subsequently the efficacy in humans was demonstrated.12

The primary defect in MH-susceptible patients is the skeletal muscle calcium-release channel, commonly termed the ryanodine receptor (RYR1). The agents that trigger MH increase RYR1 activity and disturb the calcium ion regulation, leading to sustained muscle contraction and hypermetabolism.

In North America and Europe, the incidence of MH is currently estimated to be 1:15 000 anaesthetics for children and adolescents and 1:50 000–1:150 000 anaesthetics for adults.13–15 The prevalence for this syndrome in the general population is unknown although it may be as common as one in 2000.16 Malignant hyperthermia is more common in men.17 Neither family history nor previous exposure to anaesthesia reliably predicts its occurrence18 and about half of the cases follow a past uneventful exposure.19 The syndrome has been reported in young infants and in pregnant women without adverse fetal effects.20–23 MH may occur whenever the ‘triggering’ agents (Table 1) are used in susceptible patients regardless of the setting. There is evidence that some patients who are susceptible to MH may also develop heat stroke, exercise-induced rhabdomyolysis and hyperthermia and acidosis with the use of certain drugs such as 3,4-methyleneoxy methamphetamine (MDMA) also known as ecstasy. Cardiac arrest may occur in these clinical situations due to hyperkalaemia, acidosis and/or hyperthermia.

When MH was first recognized as a complication of anaesthesia, the case-fatality rate was 70%. Today, with prompt use of the drug dantrolene, widespread education as to the causes and manifestations of the syndrome and the introduction of diagnostic testing, the mortality rate is below 5% in countries with sophisticated medical delivery systems.24

**PATHOPHYSIOLOGY**

Susceptibility to MH is an inherited disorder; in humans it has an autosomal dominant pattern, while in susceptible pigs there is autosomal recessive mode of inheritance.
Administration of triggering agents—such as all halogenated anaesthetic agents and/or succinylcholine—leads to an uncontrolled release of free calcium from the sarcoplasmic reticulum. The gene responsible for elaboration of RYR1 is located on chromosome 19.24,25 To date, more than 40 point mutations in the gene encoding RYR1 are believed to be causal for MH susceptibility in humans. Mutations in the same gene are contributory to central core disease, which is also known to predispose to MH. Genetic heterogeneity has been reported in MH-susceptible individuals and alternative loci have been proposed on chromosomes 17, 7 and 3. No candidate genes associated with the disease are known in these regions.16

In MH-susceptible patients, the RYR1 is in a more open resting state than normal, leading to a 50% reduction in the calcium ion loading capacity and loading rate.2 In MH-susceptible humans, a sudden rise in myoplasmic calcium ion (Ca^{2+}) is the critical initial event26, with the peak intracellular Ca^{2+} release rate being three times greater than in

<table>
<thead>
<tr>
<th>Table 1. Trigger agents and safe agents for malignant hyperthermia.</th>
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<td><strong>Trigger agents</strong></td>
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<tr>
<td>1. Depolarizing muscle relaxants, e.g.</td>
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<tr>
<td>i. Succinylcholine</td>
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<td>2. Volatile anaesthetic drugs</td>
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<tr>
<td>i. Halothane</td>
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<tr>
<td>ii. Isoflurane</td>
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<tr>
<td>iii. Enflurane</td>
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<tr>
<td>iv. Sevoflurane</td>
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<tr>
<td>v. Methoxyflurane</td>
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<td>vi. Desflurane</td>
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<td><strong>Safe agents</strong></td>
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<tr>
<td>1. All non-depolarizing muscle relaxants, e.g.</td>
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<tr>
<td>i. Vecuronium</td>
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<tr>
<td>ii. Rocuronium</td>
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<tr>
<td>iii. d-Tubocurarine, etc.</td>
</tr>
<tr>
<td>2. Nitrous oxide</td>
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<tr>
<td>3. Intravenous anaesthetics, e.g.</td>
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<tr>
<td>i. Ketamine</td>
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<td>ii. Propofol</td>
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<tr>
<td>iii. Etomidate</td>
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<tr>
<td>iv. Thiopental</td>
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<td>4. Vasopressors, e.g.</td>
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<tr>
<td>i. Noradrenalin (norepinephrine)</td>
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<tr>
<td>ii. Adrenalin (epinephrine)</td>
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<tr>
<td>iii. Dopamine</td>
</tr>
<tr>
<td>iv. Dobutamine</td>
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<tr>
<td>5. Miscellaneous</td>
</tr>
<tr>
<td>i. Local anaesthetics</td>
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<tr>
<td>ii. Opiates</td>
</tr>
<tr>
<td>iii. Benzodiazepines</td>
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<tr>
<td>iv. Barbiturates</td>
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healthy individuals. Also, the threshold for the cytoplasmic Ca\(^{2+}\) release is much lower in MH-susceptible pigs than in healthy pigs. These mechanisms result in a continued interaction between actin and myosin, with sustained muscle contractures. In addition, biochemical pathways are activated in an attempt to resequester the released calcium, but to no avail. This leads to breakdown of adenosine triphosphate (ATP), lactic acidosis, hypercarbia and hyperthermia.

Other theories have been proposed for the increase in intracellular calcium levels. Inositol-1,4,5-triphosphate (IP\(_3\)), being an intracellular second messenger, opens dihydropyridine receptors and mediates release of Ca\(^{2+}\) from the sarcoplasmic reticulum. In vitro studies showed that the IP\(_3\)-mediated release of Ca\(^{2+}\) is much more effective in MH-susceptible specimens than in the non-susceptible ones, and that dantrolene blocks these effects. Additionally, the basal levels of IP\(_3\) are higher in MH-susceptible individuals.

The plasma concentrations of serotonin (5-HT) during stress and during onset of halothane-induced MH in pigs is increased. It has been suggested that activation of skeletal muscles by direct stimulation of 5-HT receptors with specific ligands could evoke MH. The in vitro studies in skeletal muscle preparations from MH patients with 5-HT receptor agonists and antagonists suggest the role of the 5-HT system in the development of MH. Overall, the exact mechanism by which triggering substances initiate an MH crisis has not been fully elucidated yet.

In classical MH, skeletal muscle appears to be the principal site of hypermetabolism resulting from sustained muscle contraction. This increases the body’s use of ATP, and metabolic stimulation leads to increased carbon dioxide production along with lactic as well as respiratory acidosis. The development of generalized skeletal muscle rigidity indicates that the muscle can no longer produce ATP, a function crucial to the reversal of the malignant hyperthermia process even if calcium release can be halted. Skeletal muscle hypermetabolism is not always accompanied by contracture as the threshold for Ca\(^{2+}\)-induced hypermetabolism (0.6–0.7 mmol/l) is lower than the threshold for inducing contracture (0.75–1.0 mmol/l). The depletion of ATP stores results in disruption of the skeletal muscle cellular membranes, allowing potassium, calcium, creatine kinase and myoglobin to leak into the extracellular fluid space. Potassium loss from the muscle cells results in metabolic acidosis and cardiac arrhythmias. Mitochondrial sequestration of calcium may also be defective in some MH patients. The breakdown of skeletal muscle cells with microscopic areas of muscle necrosis allows released myoglobin to cause myoglobinuria, disseminated intravascular coagulation and possible renal failure.

The primary compensatory mechanisms include (i) heat loss through sweating and cutaneous vasodilatation—although increased circulating catecholamines may increase heart rate, produce cutaneous vasoconstriction and increase systemic vascular resistance, thereby restricting heat loss; (ii) increased cardiac output, which may not meet metabolic demand but which may result in decreased mixed venous oxygen content, decreased arterial oxygen content and lactic acidosis; and (iii) increased respiratory rate, which may not be adequate to maintain normocarbia and which results in increased end tidal carbon dioxide (EtCO\(_2\)). The temperature rise is related to the surrounding temperature, the initial temperature of the patient and the degree of vasoconstriction versus vasodilation. The secondary systemic manifestations are the cardiac arrhythmias, disseminated intravascular coagulation and renal failure. Death can result from cardiac arrest, brain damage, internal haemorrhaging or failure of other body systems.
CLINICAL FEATURES AND DIAGNOSIS

MH is potentially fatal if undetected by the anaesthetist. It is important to remember that the clinical signs are not uniform and their onset is variable. For instance, the occurrence of MH after several hours of uneventful anaesthesia has been reported. The most frequent and earliest sign of MH crisis is an unexplained, unexpected tachycardia together with an unexplained, unexpected rise (over minutes to hours) in EtCO₂, the most sensitive indicator of potential MH (Table 2). The other common signs include masseter muscle spasm, tachypnoea. A specific sign of MH is body rigidity, and if MH is suspected, peripheral muscle rigidity should be checked. Respiratory and metabolic acidosis usually occurs in fulminant MH. Temperature elevation is often a late sign and is best detected by core measurements such as in tympanic, oesophageal, pulmonary artery, etc. The other late signs are the complex arrhythmias, cyanosis, hypotension, electrolyte abnormalities and rhabdomyolysis.

Tachycardia is seen in almost all patients as one of the early signs of malignant hyperthermia and may occur within 30 minutes of the induction of anaesthesia. Tachycardia probably results from an increase in catecholamine release and has been blunted experimentally with propranolol. Signs of intraoperative MH, such as sinus

### Table 2. Management of MH crisis.

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<tr>
<th>Diagnosis</th>
<th>Treatment</th>
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<tr>
<td>1. Unexplained, unexpected increase in end-tidal carbon dioxide (most sensitive indicator of potential MH)</td>
<td>1. Stop potent inhalation agents, succinylcholine</td>
</tr>
<tr>
<td>2. Unexplained, unexpected tachycardia and masseter muscle spasm usually follow the carbon dioxide increase</td>
<td>2. Increase minute ventilation to lower end tidal CO₂</td>
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<tr>
<td>4. Skeletal muscle rigidity</td>
<td>4. Prepare and administer dantrolene: 2.5 mg/kg initial dose, titrate dantrolene to tachycardia, hypercarbia. The suggested upper limit is 10 mg/kg, but more may be given as needed</td>
</tr>
<tr>
<td>5. Temperature elevation (often a late sign)</td>
<td>5. Begin cooling measures, if hyperthermic: iced solutions, ice packs to groin, axilla and neck. Nasogastric lavage with iced solution. More aggressive measures as needed. Stop cooling measures at 38.5 °C</td>
</tr>
<tr>
<td>6. Laboratory abnormalities: blood—coagulation profile, electrolytes, arterial blood gas, creatine kinase; urine—myoglobin</td>
<td>6. Treat arrhythmias as needed. Do not use calcium channel blockers</td>
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7. Secure blood gases, electrolytes, CK, coagulation profile, blood and urine for myoglobin; check values every 6–12 hours. Treat hyperkalaemia with hyperventilation, glucose and insulin as needed

8. Continue dantrolene at 1 mg/kg every 4–8 hours for 24–48 hours

9. Ensure urine output of 2 ml/kg/hour with mannitol, furosemide, fluids as needed

10. Evaluate need for invasive monitoring and continued mechanical ventilation

11. Observe patient in ICU for at least 36 hours

12. Refer patient to the European MH group [www.emhg.org] or the MH Association of United States [www.mhaus.org]
tachycardia, hypertension and tachypnoea, may be misinterpreted as inadequate anaesthetic depth and ‘treated’ by administering a higher concentration of inhaled anaesthetic. The skin takes on a mottled appearance with cyanotic areas and patches of bright red flushing.\textsuperscript{44} Generalized rigor mortis-like skeletal muscle rigidity occurs in approximately a third of patients and is usually associated with a more fulminant course. Swollen and tender muscles are common after crises. Succinylcholine may induce muscle rigidity in patients with myotonia, hypokalaemic periodic paralysis and perhaps with other myopathies, regardless of their relationship to MH.\textsuperscript{45}

Otherwise unexplained hypercarbia is the first distinct physiological evidence and the most sensitive indicator of potential MH in the operating theatre; it is easily detected by the rising EtCO\textsubscript{2} when minute ventilation is kept constant. Thus, a mixed metabolic and respiratory acidosis is the most notable finding, which stimulates sympathetic outflow leading to tachycardia. The change in arterial pressure is not usually marked in the early phases of malignant hyperthermia. This may reflect opposing effects of increased sympathetic drive and locally mediated peripheral vasodilatation secondary to tissue acidosis.

Masseter muscle spasm, jaw rigidity or trismus may occur in up to 1\% of children induced with inhalation agents and then given succinylcholine.\textsuperscript{45} This incidence is nearly three times as great in children having strabismus surgery, consistent with the correlation between malignant hyperthermia and mild myopathy.\textsuperscript{46} Hence, succinylcholine-induced masseter rigidity is often a predictive sign of MH. On contracture testing, up to 50\% of patients will be MH-susceptible and its likelihood is increased if the post-operative CK is above 20 000 U/l. On the other hand, not all those who develop trismus are MH susceptible.\textsuperscript{47} Nevertheless, succinylcholine-induced masseter rigidity should be regarded as a warning sign of MH. The clinical episode may take 20–30 minutes to be manifest. Patients displaying trismus under these conditions should have elective surgery postponed. Urgent surgery may be continued using non-trigger agents for MH. All patients exhibiting this sign will display myoglobinuria and therefore should be admitted to a unit for observation for 24 hours and myoglobin and CK levels determined.

Increasing body temperature is a relatively late indicator of the hypermetabolic response and is sometimes absent.\textsuperscript{48} The temperature increases because continuous muscle contracture generates more heat than the body can dissipate to the environment. Central thermoregulation presumably remains intact during malignant hyperthermia. At a rate of increase of 1 °C every 5 minutes, the body temperature can rise above 46 °C. In a crisis, the patient progresses in as few as 20 minutes to severe acidosis, shock, and ventricular fibrillation.\textsuperscript{49} Vital organs such as liver may contribute significantly to the heat generation.\textsuperscript{50,51} Heat production in malignant hyperthermia can be profound, with fivefold increases in oxygen consumption and carbon dioxide production.\textsuperscript{52} Oxygen stores in the body are used up very rapidly, at two to three times the normal rate, which results in profound hypoxia and severe stress on the heart. The mixed venous tension of oxygen decreases and that of carbon dioxide increases, reflecting a significant increase in oxygen extraction by skeletal muscle.

Early in the course, serum potassium values rise to between 6 and 14 mEq/l.\textsuperscript{53} After several hours, hypokalaemia may develop as a result of potassium re-distribution and diuretic administration. Glucose and potassium are released, presumably from the breakdown of glycogen.\textsuperscript{45} Cardiac output and cardiac oxygen extraction increase substantially, apparently as a result of increased levels of circulating catecholamine.\textsuperscript{54}

Increasing evidence indicates that some MH patients may develop problems without exposure to anaesthetic agents. Some patients who exhibit exercise-induced
rhabdomyolysis have been found to be susceptible to MH on biopsy testing and on genotyping. Some patients who suffer from heat stroke or heat prostration may also be susceptible to MH. Only rarely has a diagnosis of true awake MH been confirmed by genetic testing.

**Mimics of MH**

Several disorders have features that resemble MH and may be confused with the syndrome. The neuroleptic malignant syndrome is a disorder marked by hyperthermia, acidosis, hyperkalaemia and myoglobinuria following use of a wide variety of neuroleptics, especially haloperidol. Patients taking mono-amino-oxidase inhibitors who receive meperidine will manifest with hyperthermia, acidosis and an increase in creatine kinase concentration. This reaction may be fatal. Other conditions that may resemble the MH situation include-but are not limited to-iatrogenic overheating, thyroid storm in thyrotoxicosis, heat illness, pheochromocytoma, sepsis, and intrathecal injection of high osmolar contrast agents. Disorders that may resemble MH are listed below:

- Thyroid storm
- Neuroleptic malignant syndrome
- Iatrogenic overheating
- Heat illness
- Pheochromocytoma
- Sepsis
- Cocaine, ecstasy overdose
- Hypoxic encephalopathy
- Faulty equipment for measuring temperature, carbon dioxide
- Intrathecal injection of inappropriate radiological contrast agent
- Sudden cardiac arrest in a patient with occult myopathy

Patients with Duchenne muscular dystrophy, Becker’s dystrophy, other dystrophies and various forms of myotonia may develop life-threatening hyperkalaemia on exposure to MH triggering agents, especially succinylcholine. This should be treated with standard measures to reduce potassium levels. The reaction does not appear to be related to susceptibility to malignant hyperthermia.

**TREATMENT**

Upon establishing the diagnosis, immediately discontinue the triggering agents and administer 100% oxygen. Call for additional experienced help. Hyperventilate at two to three times the predicted minute ventilation. Maintain anaesthesia with opioids, sedatives, and non-depolarizing muscle relaxants as needed. Immediately mix and administer dantrolene sodium 2.5 mg/kg intravenously as a bolus, and administer subsequent doses used as necessary, until no signs of the MH crisis are evident. Dantrolene is then infused at 10 mg/kg over an additional 24 hours. If more than 20 mg/kg body weight is not successful, the diagnosis of MH should be reconsidered. Treat life-threatening acidosis with bicarbonate. If arrhythmias occur do not use calcium channel blockers. Such arrhythmias usually respond to treatment of acidosis.
and hyperkalaemia. Lidocaine is acceptable in the treatment of ventricular arrhythmias. Cool the patient as needed, employing a variety of techniques. Forced air and circulating water are non-invasive methods; if they prove insufficient peritoneal lavage or ice-water immersion should be considered. Cooling should be suspended when the temperature reaches 38°C because of the possibility of continued downward drift. Cold intravenous fluids may be administered. Bicarbonate is used for metabolic acidosis if the acute episode is not promptly reversed by dantrolene. Most arrhythmias respond to the correction of hyperkalaemia and acidosis. Of note, calcium channel blockers have no specific role in arrhythmias during MH crisis and are contraindicated. These drugs interact with high-dose dantrolene and can cause severe hyperkalaemia and cardiac arrest. Hyperkalaemia may be life-threatening, and immediate treatment with glucose, insulin, bicarbonate, hyperventilation and calcium should be used. Rhabdomyolysis is treated with adequate hydration and, if necessary, diuretics.

After stabilization, dantrolene administration is continued for at least 36 hours and the patient is admitted to the intensive care unit for at least 48 hours. Recrudescence of MH has been reported in up to 25% of treated cases within 48 hours of an episode.

Laboratory testing should be performed immediately and at periodic intervals. Assess arterial and venous blood gases, electrolytes, coagulation parameters, more frequently during the crises. Myoglobin levels should be determined and myoglobinuria assessed. A quick check for myoglobinuria consists of using a rapid test for haeme and observing urine for red blood cells. If the haeme test is positive and no red cells seen, myoglobinuria may be inferred. CK should be determined every 12–24 hours because peak CK occurs after 14 hours of the episode.

Dantrolene sodium

Initially synthesized as a possible antibiotic, dantrolene was found to cause muscle weakness in animals. It was determined that the basis for the weakness is inhibition of intracellular calcium release from the sarcoplasmic reticulum. Dantrolene is a specific treatment for acute malignant hyperthermia crisis. However, it has also been used with some success for emergency treatment of life-threatening hyperthermia of other aetiologies such as neuroleptic malignant syndrome and hyperthermia associated with overdoses of various drug classes as well as fever.

Oral dantrolene (a drug related to diphenylhydantoin) was developed in 1967 for the treatment of muscle spasms in cerebral palsy and similar diseases. It was first reported effective in porcine malignant hyperthermia in 1975. However, attempts to dissolve oral capsules were hindered by the drug’s poor solubility, which limited the use of dantrolene to oral prophylaxis for susceptible patients. A lyophilized preparation for intravenous use was released in 1979. Administered intravenously, 3.5 mg/kg of dantrolene depresses muscle twitch in swine by 95%. In humans, the twitch depression is greater than 70% inhibited by 2.5 mg/kg of the drug. This dose was shown to be effective in the treatment of MH first in a multicentre trial followed by many individual reports.

The elimination half-life of dantrolene is approximately 9 hours and is not significantly influenced by pregnancy or pre-operative medication with diazepam or Phenobarbital. The drug is metabolized in the liver primarily to 5-hydroxydantrolene, which is excreted in the urine. Pharmacologically, 5-hydroxydantrolene has roughly
half the activity of the parent compound and has a half-life of approximately 15 hours. The pharmacokinetics are similar in paediatric patients. The drug cannot be removed to any appreciable extent by dialysis. 60 Although dantrolene inhibits excitation–contraction coupling 64,65 recent studies indicate that RYR1 is its direct molecular target.3,19 It slows calcium release by the sarcoplasmic reticulum and decreases the total amount released.66 Although this decreases twitch tension, dantrolene alone cannot abolish it. Its effects on twitch tension height are similar in normal and susceptible muscle. 62 Dantrolene has no direct effect on actin/myosin binding 67 and no effect on the neuromuscular junction.65

Dantrolene increases the contraction activation threshold voltage at the sarcoplasmic reticulum and blocks Ca2+ release, probably by limiting the interaction between Ca2+ and calmodulin.1 It cannot completely prevent the MH response, but does prevent Ca2+ from reaching the threshold at which increased muscle tone is evident.68

EVALUATION OF SUSCEPTIBILITY TO MH

Since the mid-1970s the standard diagnostic test for MH has been the in vitro measurement of muscle contracture response to graded concentrations of caffeine and the anaesthetic halothane. The test is referred to as either the caffeine/halothane contracture test (CHCT) or the in vitro contracture test (IVCT). This is the standard test for diagnosing susceptibility to MH.

The test must be performed on a biopsy of approximately 2 g of muscle from the vastus lateralis or medialis within 5 hours of harvesting. The patient is anaesthetized with general anaesthesia or with a femoral nerve block or one of its variants. In all cases the anaesthetic drugs used must be safe for MH-susceptible patients. Direct muscle infiltration with local anaesthetic is contraindicated because it could affect tissue viability. Usually biopsy is not recommended for children below 5 years of age because of the large amount of muscle required. Supramaximal stimuli cause muscle bundles of approximately 100–150 mg in size to contract. The force of contraction is measured. The two versions of the testing protocol are the European and the North American versions.41,69 The essential differences are that the European protocol utilizes incremental exposure to halothane while that of North America utilizes exposure to 3% halothane; and the European version requires testing of two muscle bundles for each drug whereas that of North America requires testing of three muscle bundles for each drug.

Currently, the sensitivity of these standardized test protocols is 97–99% and the specificity is 85–90%. 41 Other pharmacological agents such as chlorocresol (4-chloro-m-cresol)69 and ryanodine (a specific and potent ligand of RYR1)70 are sometimes used to assess susceptibility, but the specificity remains less than 100%.

A variety of new approaches to the diagnosis of MH are under development.71 This is the result of rapid advances in molecular genetics, biochemistry and cellular physiology. Some of these approaches involve harvesting a small number of muscle cells and growing them in cell culture. Using specific dyes, it is then possible to view the changes in cellular calcium ion concentration upon exposure to halothane, caffeine or other drugs that lead to cellular calcium release in real time. Cells from MH-susceptible patients will show an enhanced release of cellular calcium as well as a drop in pH upon exposure to caffeine or chlorocresol that is dramatic. B lymphocytes have been found to contain ryanodine receptor sites (the calcium-release channel), much as muscle cells.
The B lymphocytes from MH patients also display exaggerated changes in cellular calcium levels upon exposure to caffeine and other calcium-release agents compared to normals. Another approach has been the use of nuclear magnetic resonance spectroscopy to measure ATP, pH, creatine phosphate and other high-energy phosphates non-invasively. With exercise, MH susceptibles demonstrate a greater depletion of high-energy phosphates and fall in pH, compared to normals.

Yet other investigators have shown that in vivo microinjection of caffeine in muscle elicits an accentuated rise in CO₂ output and hydrogen ion in MH-susceptible individuals. It is generally felt, however, that molecular genetic diagnostics holds the greatest promise for a minimally invasive, specific diagnostic test. Molecular genetic testing has the advantage of being highly reproducible, very specific and requiring only small amounts of biological material, and it may, with time, become relatively inexpensive. DNA may be harvested and stored for many years without very sophisticated storage techniques.

Investigations beginning in the early 1990s have demonstrated that mutations in the gene encoding the calcium-release channel in skeletal muscle are mostly responsible for MH susceptibility. Over 40 mutations in this gene have been described as being causal for MH and a few other genes have also been linked to MH susceptibility, but in only a few patients. This has led to the development of guidelines for clinical molecular genetic testing by the European MH group.

Given the initial successes in the use of molecular genetic analysis in European centres, in terms of reducing the need for invasive biopsy—especially in families with a known history of MH, it is felt that molecular genetic testing will help better define the many different clinical presentations of MH both in and out of operating theatres.

**PATIENT COUNSELLING**

In humans, susceptibility to malignant hyperthermia has an autosomal dominant inheritance. Neither family history nor previous exposure to anaesthesia reliably predicts the occurrence of MH, because penetrance is variable. The first-degree relatives of susceptible patients have a 50% chance of being susceptible to malignant hyperthermia. Potentially susceptible patients and their relatives should be informed of preventive methods. It should be explained that safe agents are used in administering general anaesthesia (Table 2) and that dantrolene will certainly be available. In case of a suspected malignant hyperthermia reaction, the patient is referred for an appropriate consultation with a detailed report from the anaesthetist responsible. Patients must be clearly instructed to inform their anaesthesia provider about their risk for MH. Potentially susceptible patients could wear or carry identification as to their susceptibility.

Counselling patients with clinically equivocal or aborted crises is difficult because the only generally accepted diagnostic test is both expensive and invasive. Therefore, if there is any question, the patient should be treated as MH-susceptible and counselled as to the advisability of contracture testing.

For example, if a patient develops masseter muscle rigidity after succinylcholine, the following should be considered. Other signs of MH may not have occurred because: (a) 50% of masseter spasm occurs in patients who are not susceptible; (b) anaesthesia was discontinued (with or without dantrolene treatment), allowing little opportunity for other symptoms to develop; or, (c) the patient is susceptible but malignant hyperthermia was not triggered (susceptible patients typically have been exposed to
triggering anaesthetics without complication several times prior to diagnosis. The patient should be advised that their risk of susceptibility is approximately 50% and that a muscle biopsy is necessary to determine the diagnosis. As in other equivocal cases, the decision to perform a biopsy should be made by both the anaesthesiologist and the patient. Fortunately, various resources are available to assist the patient and the anaesthetist in dealing with malignant hyperthermia:

European MH Group
Secretary of the EMHG, St James’ University Trust Hospital, University Department of Anaesthesia, Clinical Science Building, Beckett Street, GB-Leeds LS9 7TF, UK.
Tel: +44 113 206 52 74
Fax: +44 113 283 69 72
E-mail: msjpjh@leeds.ac.uk
Internet address: http://www.emhg.org

Malignant Hyperthermia Association of the United States
11 East State Street, PO Box 1069, Sherburne, NY 13460 USA.
Telephone: +1 607 674 7901
Fax: +1 607 674 7910
E-mail: info@mhaus.org
Internet Address: http://www.mhaus.org
MH Hotline (for acute cases): North America: +1 800 644 9737 (800 MH HYPER)
International: +1 315 464-7079

North American MH Registry
[Part of MHAUS; records the detailed events surrounding MH events as well as clinical correlation between clinical history and biopsy results]
Children’s Hospital of Pittsburgh, 3705 Fifth Avenue, Room 7449, Pittsburgh, PA 15213 USA.
Telephone: +1 888 274 7899
E-mail: bwb + @pitt.edu
Internet address: http://naregistry.mhaus.org

SUMMARY

Malignant hyperthermia is an uncommon, life-threatening, acute pharmacogenetic disorder of the skeletal muscle cell. It manifests in susceptible individuals as a hypermetabolic response on exposure to halogenated volatile anaesthetics and depolarizing muscle relaxants, with uncontrolled release of cytoplasmic free calcium and consecutive systemic organ failure. Molecular genetics established that the skeletal muscle ryanodine receptor on chromosome 19 is the primary malignant hyperthermia-susceptible locus. A classic fulminant MH crisis presents with a rising end-tidal carbon dioxide, skeletal muscle rigidity, tachycardia, hyperthermia and acidosis, leading to death if not treated. Immediate discontinuation of triggering agents, supplemental oxygenation, and correction of acidosis and electrolyte abnormalities, treatment of arrhythmias, cooling and administration of dantrolene are the mainstays of therapy. RYR1 is the direct molecular target of dantrolene. Presently the case-fatality rate is only 5% due mainly to pre-operative screening of at-risk patients as well as prompt intraoperative detection of MH signs and timely treatment with dantrolene sodium.
To reduce further the morbidity and mortality, anaesthesia providers should be well read about MH crisis and should strengthen their clinical vigilance.

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