Malignant hyperthermia: clinical features and management

DENBOROUGH and Lovell (1960) gave the first description of an extreme reaction being caused by anaesthetic agents. The reaction, called malignant hyperthermia (MH), had a mortality rate of 80 per cent. It was some 20 years before a drug (dantrolene) was developed that would reduce this rate to less than 2–3 per cent.

MH is estimated to occur in about one in every 15,000 children who receive an anaesthetic and one in every 50,000 adults. Reactions occur most commonly in young adolescents (19–20 years) and during ear, nose and throat operations and dental surgery, when the triggering agents are frequently used. MH is a potentially fatal condition, and it is important that all health care staff are fully aware of its signs, symptoms and treatments. It affects all races. Patients with this condition have no signs or symptoms except when they are exposed to an anaesthetic. It is characterised by increasing body temperature and metabolic rate, tachycardia, hypotension, cyanosis and muscle rigidity.

MH is an inherited disorder, but DNA studies have shown that the inheritance is more complicated than simple autosomal dominance because MH has been found to be more common in men than in women (Frederich et al, 1990).

Diagnosis of MH is difficult, which is due, in part, to the varied symptoms that characterise it and to the fact that patients can develop the syndrome not only in the operating theatre or the recovery room but also in the ward for up to 48 hours after surgery (Hopkins, 2000). This article is concerned only with MH that is induced by an anaesthetic agent, although cases have occurred as a result of Ecstasy ingestion. Delays in making the correct diagnosis can prove fatal. Practitioners should be aware of the agents that are known to trigger an MH reaction and the clinical manifestations of the condition. Treatment includes discontinuing the triggering agent, administering dantrolene and cooling the body.

**BOX 1. AGENTS TRIGGERING MH**

**GASES**
- Desflurane
- Enflurane
- Halothane
- Isoflurane
- Sevoflurane

**MUSCLE RELAXANT**
- Suxamethonium

**BOX 2. AGENTS SAFE TO USE WITH PATIENTS LIKELY TO DEVELOP MH**

**TYPES OF AGENT**
- Barbiturates
- Benzodiazepines
- Local anaesthetics
- Nitrous oxide
- Opioids

**INDIVIDUAL DRUGS**
- Atracurium
- Atropine
- Cisatracurium

**BOX 3. COMMON CLINICAL SIGNS OF MILD AND FULMINANT MH**

- Acidoses
- Cardiac dysrhythmia
- Hypercapnia (the most sensitive indicator)
- Hypertension
- Hypoxaemia
- Myoglobinuria
- Skeletal muscle rigidity (the earliest sign may be restricted to the jaw)
- Tachycardia
- Tachypnoea
- Temperature elevation (usually a late sign)

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**ABSTRACT**


Malignant hyperthermia is a syndrome that has no symptoms until the individual is given an anaesthetic, although cases have occurred as a result of Ecstasy ingestion. Delays in making the correct diagnosis can prove fatal. Practitioners should be aware of the agents that are known to trigger an MH reaction and the clinical manifestations of the condition. Treatment includes discontinuing the triggering agent, administering dantrolene and cooling the body.

Most Ecstasy-related deaths are caused by fulminant hyperthermia (Wake, 1995).

**Triggering agents**

MH manifests itself only after the susceptible individual has been exposed to a triggering agent. Most patients who have a condition known to be associated with MH have had a previous uneventful general anaesthetic (Faulds et al, 2000). However, a number of agents have been found that trigger an MH reaction (Box 1), and today there are several agents that are safe to use with patients who are likely to develop MH (Box 2).

**Clinical features**

Once the patient has been exposed to the triggering agent, calcium is released from the sarcoplasmic reticulum of muscle cells. High levels of intracellular calcium increase the body’s metabolic rate and make the muscles contract and become rigid, a process that results in heat production. Other reactions include tachycardia, tachypnoea, sweating and cyanosis. Blood pressure initially rises and then falls sharply.

The rapid increase in body temperature (>4°C/hr) can result in its reaching as high as 42.7°C (109°F). At the same time, the body chemistry becomes further deranged as potassium, magnesium and phosphates enter the extracellular fluid, and sodium moves into the cells. The increase in potassium levels affects the heart, and the continuing changes in body chemistry result in hypoxia, hypercapnia and acidosis. The continuous muscle contraction causes breakdown of the muscle fibres (rhabdomyolysis), resulting in myoglobin and potassium leak-
ing into the blood. The myoglobin can cause damage to the renal tubes and acute renal failure. In addition, tissue damage can result in disseminated intravascular coagulation.

MH has many common clinical signs (Box 3), which makes a quick diagnosis difficult. The clinical picture can vary tremendously from a mild to a fulminant case. (It is important to note that the symptoms in the list in Box 3 are alphabetical, to indicate that they are in no order of importance.)

Diagnosis
The clinical diagnosis of MH is complicated by the fact that the signs can be confused with those of several other conditions (Box 4). The diagnosis is often determined on the sequence and combination of events that take place.

Early researchers into MH thought that the condition could be linked to other diseases and that, by identifying these, it would be possible to obtain a picture of those who might be affected. Various investigations were carried out for signs of common aetiology (Curran et al, 1999; Strazis and Fox, 1993; Brownell, 1988). As a result of these and many other studies, a checklist has been compiled that can be used to help health care professionals make early decisions on how to manage patients who need an anaesthetic but who seem to be susceptible to developing MH (Box 5).

Managing malignant hyperthermia episodes
The key to successful management of MH is its early diagnosis. The urgency of the situation cannot be over-emphasised. Treatment consists of discontinuing the triggering agent (if this happens during surgery), and supportive therapy. Before dantrolene was available, treatment consisted of actively cooling the patient and treating specific symptoms; as a result, the mortality rate was nearly 80 per cent.

Dantrolene is thought to reduce muscle tone and metabolic rate by preventing the ongoing release of calcium from the muscle cells. It does not interfere with the reversal of muscle relaxants, but it may cause significant muscle weakness in patients who have pre-existing muscle disease, so caution is needed. Because dantrolene takes more than 20 minutes to mix with water, at least two medical staff will be required to manage a crisis. The drug is given intravenously (1mg/kg) and a response can occur in minutes. If the patient does not respond, the dose can be repeated every five minutes up to a total dose of 10mg/kg.

Dantrolene is very alkaline, and therefore irritating to the skin, so care must be taken to prevent its infiltration into the surrounding tissue. Sodium bicarbonate (8.4 per cent) is given to treat metabolic acidosis; again, care must be taken to prevent infiltration into the surrounding tissue. To correct any hyperkalaemia, 50 per cent dextrose (50ml) and insulin (10 units) are given over 30 minutes. The patient is also hyperventilated with 100 per cent oxygen until he or she has stabilised.

Simultaneously, active cooling should begin with refrigerated 0.9 per cent saline (1–2L given intravenously) or bags soaked in ice. Surface cooling can also be achieved by giving sponge baths, applying ice packs to the armpits and groin, and using fans. However, care must be taken to avoid peripheral vasoconstriction, as this will prevent further heat loss. The aim is to reduce the body temperature to within 1–3 degrees of normal. If the patient is still in theatre, peritoneal lavage with refrigerated 0.9 per cent saline may be carried out. Urine output needs to be maintained by the use of intravenous fluids and drugs such as frusemide. Guidelines developed at the Malignant Hyperthermia Unit in Leeds for managing patients who develop malignant hyperthermia while under anaesthetic are shown in Box 6.

Post-crisis management
Following initial stabilisation, the patient should be transferred to an intensive care or high dependency unit for at least 24 hours, or until vital signs have returned to a normal level. The patient is monitored closely for complications of MH, the most common of which is cardiac arrest.

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normal. Dantrolene should be continued during this period (its half-life is only five hours) at 1mg/kg every six hours for 24–72 hours, depending on the patient’s response to treatment.

Once the patient has been stabilised, the dantrolene is administered orally for several days. Post-crisis, potassium and creatine phosphokinase levels should be monitored, and renal function checked in case of the onset of myoglobinuria. Clotting status should also be checked, and the patient’s temperature monitored.

Halothane-Caffeine-Contracture test
Once the patient is over the acute episode, he or she should be tested for MH. Currently, the most specific diagnostic test is the Halothane-Caffeine Contracture test. This is carried out three months after the MH episode and involves taking 2g of the quadriceps muscle for biopsy. The muscle is exposed to either halothane or caffeine and the response is measured. If the muscle contracts in the presence of halothane or low concentrations of caffeine, the patient is considered to be susceptible to MH. The only test centre in the UK is at St James’ University Hospital, Leeds.

Conclusion
MH is a potentially fatal syndrome that can catch out the unsuspecting health care professional. It can present as a dramatic fulminate form or as an insidious, relatively mild abortive form. With the increasing number of surgical procedures being carried out today, the chances of a practitioner encountering a patient who develops MH are also increasing. A full medical history should be obtained before surgery and previous reactions to anaesthetics investigated. If the operation is urgent and cannot wait until investigations have been carried out, it should be assumed that the patient is MH-sensitive. This means using only those drugs known to be safe; monitoring body temperature as well as carbon dioxide levels, heart rate and blood pressure; carrying out pulse oximetry during the operation, and having dantrolene ready.

The UK malignant hyperthermia referral centre and national MH register is based in Leeds: The MH investigation Unit Academic Department of Anaesthesia Clinical Sciences Building St James’ University Hospital Leeds LS9 7TF Tel: 0113 206 5274.

REFERENCES

**DIAGNOSIS**
Consider MH if:
- Masseter muscle spasm occurs after suxamethonium
- Unexplained, unexpected tachycardia occurs, together with an unexplained, unexpected increase in end-tidal CO₂

**EARLY MANAGEMENT**
- Withdraw all trigger agents, that is, all anaesthetic vapours
- Install a clean anaesthetic breathing system and hyperventilate
- Abandon surgery if feasible
- Give dantrolene (initially 1mg/kg intravenously and repeat as required up to 10mg/kg)
- Measure arterial blood gases, K⁺ and creatine phosphokinase
- Measure core temperature
- Initiate surface cooling avoiding vasoconstriction

**INTERMEDIATE MANAGEMENT**
- Control serious arrhythmias, for example with beta-blockers
- Control hyperkalaemia and metabolic acidosis

**LATER MANAGEMENT**
- Carry out clotting screening to detect disseminated intravascular coagulation
- Take first voided urine sample for myoglobin estimation
- Observe urine output for developing renal failure
- Promote diuresis with fluids/mannitol (20mg dantrolene contains 3mg mannitol)
- Repeat creatine phosphokinase test at 24hr

**LATE MANAGEMENT**
- Consider other diagnoses and carry out appropriate investigations, for example vanillyl mandelic acid test, thyroid function tests, white cell count, chest X-ray
- Consider the possibility of:
  - Myopathy – carry out electromyography and consult a specialist
  - Recreational drug ingestion, for example, Ecstasy
  - Neuroleptic malignant syndrome
- Counsel the patient and/or his/her family regarding the implications of MH
- Refer the patient to the MH Unit

These guidelines from the Leeds Malignant Hyperthermia Unit are supported by the Association of Anaesthetists of Great Britain and Ireland and the British MH Association.