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Malignant hyperthermia

By the perioperativeCPD team

Introduction

First described in 1960, malignant hyperthermia (MH) is a genetic disorder of skeletal muscle and is a rare but potentially fatal anaesthetic emergency. It is triggered when a MH-susceptible individual is exposed to a volatile anaesthetic (eg, halothane, isoflurane, sevoflurane, desflurane) or suxamethonium. The only drug known to treat MH is Dantrolene.

This module is largely based on the 'Malignant hyperthermia 2020 Guidelines' from the Association of Anaesthetists.

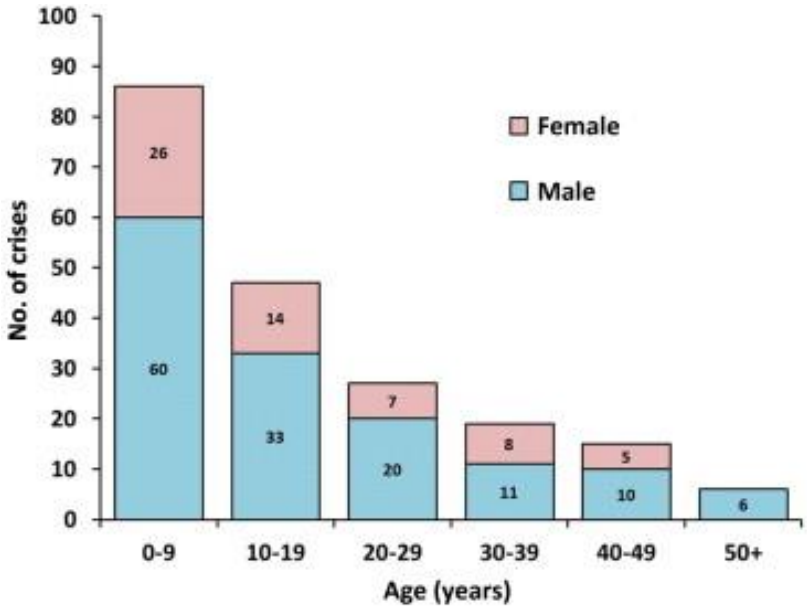
The full guidelines can be found at:
https://anaesthetists.org/Home/Resources-publications/Guidelines/Malignant-hyperthermia-2020

Incidence

Malignant hyperthermia has been estimated to occur anywhere between 1:10,000 and 1:150,000 general anaesthetics but these estimates are subject to a very large margin of error.

The number of cases each year has fallen slightly, and this fall mirrors the reduction in the use of suxamethonium. The number of cases occurring during inhalational anaesthesia without suxamethonium has probably remained reasonably constant over the past 40 years.

The highest reported incidence of MH occurs in paediatric populations and there is also a consistently higher incidence of MH reactions in men compared with women. The reasons for the age and sex distribution of MH reactions are unknown.



Incidence of MH in 200 cases in Europe

Mortality

When malignant hyperthermia was first described mortality was estimated to be 70–80%. Mortality, at least in the UK, began to decline throughout the 1970s. This was before the introduction of i.v. dantrolene and has been attributed to increased awareness of the condition and the understanding of the need to discontinue triggering anaesthetics as soon as the diagnosis is made. Despite the availability of dantrolene, deaths from MH still occur with a mortality rate of approximately 4% in the UK. This shows that dantrolene may be unsuccessful in preventing death from MH unless treatment is implemented early in the course of a reaction.

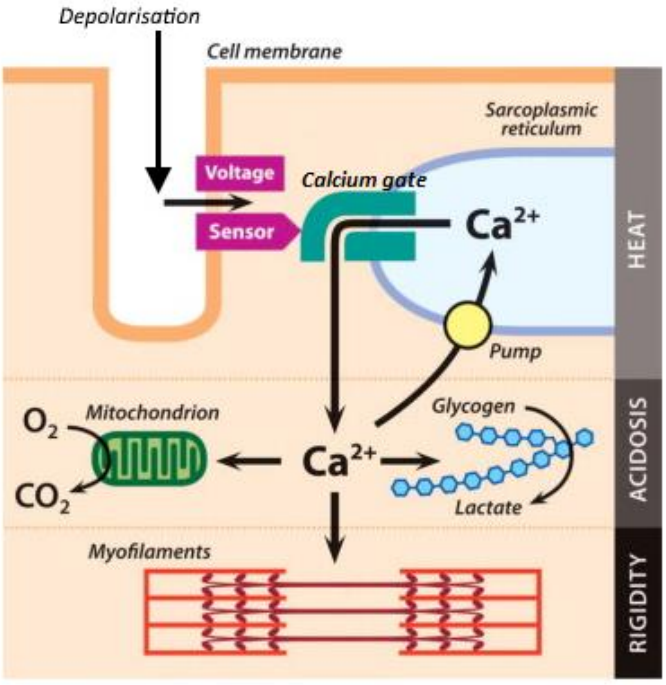
One reason that diagnosis may be delayed is if the anaesthetist incorrectly assumes that a history of uneventful anaesthesia precludes the possibility that the patient is at risk of developing MH. This is not the case and there are reports of patients who have received multiple apparently uneventful anaesthetics before they have a reaction. There is one case in America where a man triggered for MH on his 31st anaesthetic, every anaesthetic before that was uneventful. The reasons why susceptible individuals may not trigger when exposed to triggering agents are not fully understood.

Pathophysiology

Skeletal muscles are made of long bundles of thin cells. During strenuous exercise, the rate of energy use in skeletal muscles can increase by more than 100-fold, almost instantly. To meet this energy demand cells contain mitochondria to convert nutrients into ATP, which stores energy. ATP (adenosine triphosphate) is an energy-carrying molecule used in cells as it can release energy very quickly.

A normal muscle contraction is triggered when an action potential travels along a nerve to the muscles. The process within the muscle cell or fibre begins when acetylcholine crosses the neuromuscular junction and binds to receptors on the muscle cell membrane. The intracellular process associated with muscle contraction then begins with calcium release from within the sarcoplasmic reticulum, causing the muscle cell to trigger a muscle contraction. The sarcoplasmic reticulum is the main intracellular calcium store in skeletal muscle cells and after a normal contraction the muscle relaxes as the calcium is pumped back into the sarcoplasmic reticulum.

In a case of malignant hyperthermia, the calcium gate in the sarcoplasmic reticulum becomes stuck open, resulting in the non-stop release of calcium within the muscle cell. This causes a prolonged muscle contraction and the muscle cell works continuously to try to pump the excess calcium back into the sarcoplasmic reticulum. Both of these use very large amounts of energy (ATP) within the cell, which requires increasingly larger amounts of both oxygen and glucose to produce. The by-product of this hypermetabolic activity is large amounts of CO_2 and heat.



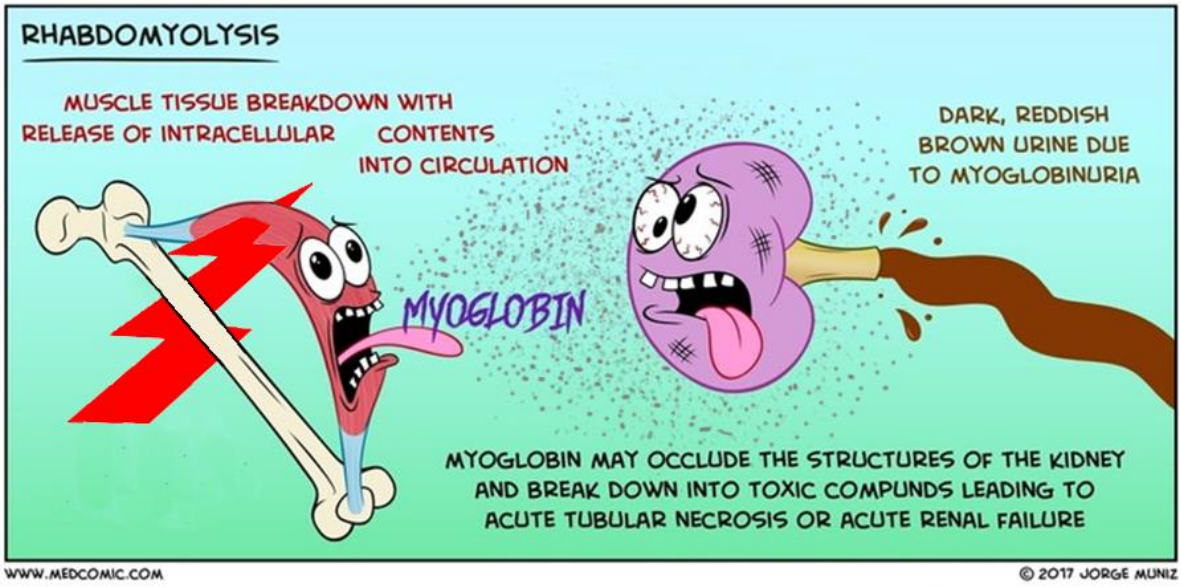
A very simplified muscle cell

Over time, sustained contraction generates more heat than the body is able to dissipate. Marked hyperthermia occurs minutes to hours following the initial onset of symptoms. In some cases, core body temperature may rise 1°C every 5-10 minutes.

This MH reaction is potentially life threatening because skeletal muscle constitutes 40% of body mass. Oxygen delivery is often incapable of meeting the metabolic demands of the hyper-stimulated muscle and there may well be arterial oxygen desaturation.

When the muscle cells run out of oxygen, metabolism becomes anaerobic with the resulting production of lactate. The increase in lactic acid and CO_2 production soon lead to metabolic acidosis. Eventually the muscle cells run out of energy, break down and release their contents into the central circulation (rhabdomyolysis) causing kidney damage.

Rhabdomyolysis is the breakdown of damaged skeletal muscle. Muscle breakdown causes the release of myoglobin into the bloodstream. Myoglobin is the protein that stores oxygen in your muscles. If you have too much myoglobin in your blood, it can cause kidney damage.



Dantrolene is the only known drug used to treat MH. The mechanism of action of dantrolene is by blocking calcium release from the sarcoplasmic reticulum within skeletal muscle.

Clinical presentations

The clinical signs of MH present perioperatively in several possible patterns:

1. Immediately following anaesthetic induction, manifested by masseter muscle rigidity (MMR) in the presence of suxamethonium (succinylcholine) and/or volatile agents.

The earliest indication the anaesthetist may have that a patient is susceptible to MH is the observation of excessive muscle rigidity (often restricted to the masseter muscles, the strongest muscles in the jaw) following the administration of suxamethonium. It is known that, prior to the onset of paralysis, suxamethonium often induces masseter muscle spasm (MMS) although this is more marked after inhalation induction with a volatile anaesthetic than following intravenous anaesthetic induction.

In patients susceptible to MH, this response is more likely to be extreme. Extreme MMS can be defined in terms of the intensity and duration of jaw rigidity. The inability to open the patient's mouth 2 min after the administration of suxamethonium, or easily demonstrable resistance to mouth opening 4 min after administration, should be a cause for concern.

2. Intraoperatively during any phase of the anaesthetic, manifested by gradually worsening hypercarbia, tachycardia, metabolic acidosis, and sometimes generalised rigidity.

The most consistent manifestation of MH is an increasing heart rate. Unexplained tachycardia occurs in over 95% of MH cases.

The timing of MH reactions is highly variable. A reaction may become apparent within 10 min of exposure to triggering agents or the onset may be delayed for several hours, especially with the use of desflurane.

3. After the cessation of the anaesthetic agent, but usually within minutes.
The diagnosis of an MH reaction can be made after the discontinuation of inhalational anaesthesia. Some of these reactions could, in retrospect, be seen to have started during the anaesthetic but in others the first signs have clearly been after the discontinuation of the inhalational agent. Aside from cardiac surgery, which may delay onset, the longest reported interval between discontinuation of the inhalational agent and the development of a likely MH episode is 40 minutes.

● Following successful treatment, reoccurrence occurs in up to 25 percent of patients and is more likely in patients with increased muscle mass.

Important: There is a widespread misconception that acute MH begins with hyperthermia as the first presenting sign. Hyperthermia is generally a later sign of MH and is typically absent when the diagnosis is initially suspected.

Diagnosis

The key to making the diagnosis of MH in a timely manner is to be aware of its possibility whenever triggering agents are used and to have an appropriately tuned index of suspicion. Although MH has no specific characteristics, the cardinal clinical features result from excessive carbon dioxide production.

An unexplained, unexpected increase in carbon dioxide production should alert the anaesthetist to the possibility of an MH reaction. It is not possible to easily control $ETCO_2$ by increasing minute ventilation during an MH reaction.

If the patient is spontaneously breathing there will be an increase in respiratory rate and subsequently increased $ETCO_2$.

The increased carbon dioxide production will be accompanied by an otherwise unexplained and unexpected increase in heart rate – it is the upward trend in heart rate that is more useful than attainment of a specific value.

Box 1 Diagnostic features of malignant hyperthermia

- Unexplained, unexpected increase in $ETCO_2$
- Unexplained, unexpected increase in heart rate
- Unexplained, unexpected increase in temperature

If the patient's temperature has been monitored during the onset of an MH reaction it will usually have started to increase by the time the diagnosis is made, but often it will not have reached beyond the upper limit of normal by the time treatment is instituted.

Onset of generalised muscle rigidity during the course of an MH reaction (as opposed to an immediate response to suxamethonium), which may occur even in the presence of non-depolarising muscle relaxant, is a worrying development as it is likely to herald the late stage of an MH reaction that will be irreversible.

Management of a malignant hyperthermia reaction

The key to successful management of MH is its early diagnosis. On recognition of a reaction, several modes of treatment must be instigated simultaneously. The urgency of the situation cannot be over emphasised. Delay in commencing treatment of MH is associated with increased mortality and the severity and number of complications. The principles of treatment are firstly to reverse the reaction and secondly to treat the consequences of the reaction.

There are three approaches to reversing the MH process and these should be applied together.

Box 2 Reversing the malignant hyperthermia process **First call for help**

1. Eliminate the agent
    - Turn off and remove vaporiser (start propofol infusion or other iv anaesthetic)
    - Give 100% oxygen at maximum flow
    - Increase minute ventilation 2–3 x normal
    - Insert activated charcoal filters on inspiratory and expiratory limbs of circuit
2. Administer dantrolene sodium
3. Commence active body cooling

This will require assistance so if MH is suspected get help immediately. As well as needing numbers to help to mix dantrolene, which is difficult, the patient will be requiring invasive monitoring (arterial and central lines) urinary catheter and active cooling.

1. Eliminate the trigger agent

The vaporiser should be turned off and removed from the anaesthetic machine, 100% oxygen should be delivered at maximum flow and the patient's minute ventilation should be increased to 2–3 times normal.

A recent innovation is the availability of activated charcoal filters, which can be placed on inspiratory and expiratory limbs of the anaesthetic machine in order to adsorb inhalational anaesthetics. Activated charcoal filters should be available in every UK hospital where general anaesthesia is administered. The charcoals filters absorb the trace amounts of anaesthetic vapour (isoflurane, sevoflurane and desflurane) so that anaesthetic vapours do not reach the patient. Placement of the charcoal filters on the anaesthetic machine allows the machine to be immediately vapour-free (less than 5 parts per million of vapour).

Activated charcoal filters

This removes the need to change the anaesthetic machine for a vapour-free machine which is dangerous, wastes time and removes essential personal from the essential tasks of mixing and administering dantrolene. Changing a working anaesthetic machine for one that is probably rarely used or checked, in a busy operating theatre, during an MH crisis when large volumes of 100% oxygen are needed diverts resources away from the patient when they need it the most.

The soda lime and circuits may be changed but only when appropriate and safe.

If using proactively with a MH susceptible patient, on a preflushed anaesthetic machine, they will last a minimum of 12 hours if fresh gas flows are kept above 3 litres/minute. If inserted during a case for a MH crisis where inhalational anaesthetic have been used, the filters must be changed every 30 minutes with fresh gas flows maintained over 10 litres/minute.

Note: remember to remove the charcoal filters at the end of the MH crisis, before the next case as they could cause awareness if they are left on. They are coloured orange to help identify them and prevent their being left on.

Many operating theatres will have dedicated MH trolleys with everything that is immediately needed including dantrolene, water for injection, charcoal filters and up to date guidelines.

2. Give dantrolene

Secondly, dantrolene sodium is an antidote to MH in that it inhibits the excessive release of calcium into the muscle cell. Dantrolene is a powder that is poorly soluble in water. It is presented in 20 mg vials and each vial is reconstituted with 60 ml of sterile water, which may require 5 min of vigorous shaking.

In an acute MH reaction, the dose of dantrolene should be titrated against its effect. Many MH reactions will respond to discontinuation and elimination of the triggering agents such that the reaction has been reversed before an initial dose of dantrolene can be prepared. If this is not the case, the initial dose of dantrolene is 2– 3 $mg.kg^{1}$.

The dose is provided as a range so that a rapid dose calculation can be made in the emergency situation (Box 3). Indeed, from a practical point of view, due to the difficulty reconstituting dantrolene, in adults it is recommend that each syringe of dantrolene is administered as soon as it is made up rather than waiting for the complete initial dose to be ready. Dantrolene can be infused in this way until the initial goals of treatment are realised.

Dantrolene

Remember a 70kg patient requiring $10mg.kg^{1}$ will need 35 vials of Dantrolene. A patient who weighs 98 kg could require 980 mg dantrolene if they are unresponsive at lower doses and this would require 49 vials of dantrolene, each taking up to 5 minutes to mix.

The recommended treatment goals are reduction of $etCO_2$ to less than 6 kPa (45mmHg) with normal minute ventilation and core temp < 38.5°C. Administration of dantrolene should continue despite the product data sheet stipulating a maximum dose of 10 mg.kg. In this situation, as well as continuing dantrolene, full attention should be made to aggressive body cooling.

Reoccurrence of MH can occur, and it has been reported up to 14 h after control of the initial reaction. However, it is not recommended to administer prophylactic dantrolene after control of the initial reaction as it is not required in the majority of cases and is associated with muscle weakness and nausea. If reoccurrence does occur, further bolus doses of dantrolene should be administered. Continuous infusion of dantrolene is associated with a high incidence of thrombophlebitis due to the high osmolarity of the solution.

Box 3: Administration of dantrolene

- Titrate dose to effect
- Initial dose 2–3 $mg.kg^{-1}$
- Takes time to reconstitute so administer each syringe as it is prepared.
- Keep giving additional doses of 1 $mg.kg^{-1}$ every 5 minutes till treatment goals achieved
- Treatment goals
  - $ETCO_2$ < 6 kPa with normal minute ventilation
  - and core temp < 38.5°C

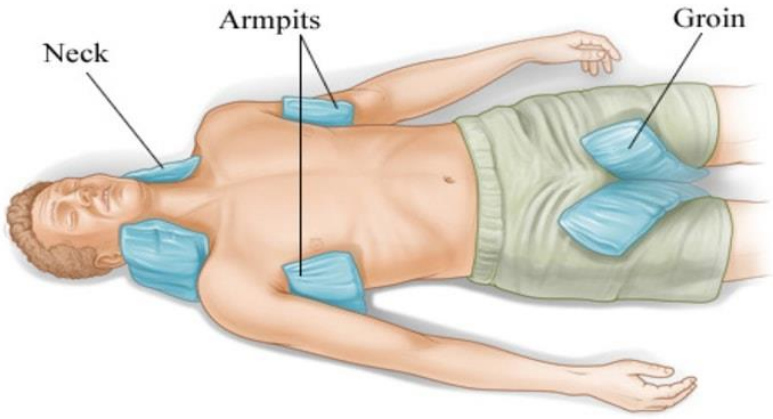
Pause dantrolene when goals achieved but may have to give more if CO_2 or temperature rises

3. Active body cooling

The third approach to reversing the MH process is active body cooling: a raised body temperature enhances muscle cell calcium release and sensitises the myofilaments to the effects of calcium causing generalised muscle rigidity, compromising perfusion and thereby delivery of dantrolene.

Cooling can involve the use of wet sheets, refrigerated saline (up to 3000 mL,4ºC), cold naso-gastric lavage, ice packs to the groin/axillae. Care must be taken to avoid peripheral vasoconstriction that results from overzealous application of ice to the skin as that prevents heat loss through radiation.

In extreme cases, and where appropriate technology is available, cooling can be rapidly affected by heat exchange, either through dialysis or by the heat exchanger of a cardiopulmonary bypass machine. All cooling methods should be withdrawn once body temperature is below 38.5ºC.



Active body cooling sites

Management of the consequences of malignant hyperthermia

In order to facilitate further management, basic routine monitoring should be supplemented by core temperature monitoring, central line and direct arterial blood pressure monitoring which also enables regular blood sampling (Box 4). A urinary catheter should be inserted to monitor urine output, urine pH and for myoglobinuria. Blood samples should be sent for arterial blood gas analysis, biochemistry, clotting indices, haematocrit and platelet count.

Box 4 Managing the consequences of malignant hyperthermia

Monitor for and treat:

- Acidosis
- Hyperkalaemia
- Arrythmias
- Myoglobinurua
- Disseminated intravascular coagulation
- Compartment syndrome

Acidosis

The primary management of acidosis is through hyperventilation, but it is suggested there is a low threshold for the administration of sodium bicarbonate, as low pH values are associated with a poor outcome in MH. Sodium bicarbonate will aid the reuptake of potassium ions into the cells and also alkalinise the urine.

Hyperkalaemia

Treatment of hyperkalaemia (high potassium) should be with sodium bicarbonate and/or glucose with insulin. If potassium levels get to high they can cause fatal arrhythmias. Haemofiltration should be considered if hyperkalaemia is not otherwise controlled and if the appropriate equipment and expertise is available.

Arrhythmias

The most frequent form of arrhythmia associated with MH is tachycardia. It is recommend using a relevant anti-arrhythmic agent with which the anaesthetist is most familiar such as amiodarone, a short-acting beta-blocker or magnesium.

Myoglobinuria

Myoglobinuria describes the presence of myoglobin, a muscle protein, in the urine (cola-cola coloured urine). Myoglobin is released by to muscle cell death due to MH. Myoglobinuria should be anticipated and the aim should be a urine output high at > 2 ml.kg^{1}.h^{1}.

Disseminated intravascular coagulopathy

Disseminated intravascular coagulation (DIC) is a rare but serious condition that causes abnormal blood clotting throughout the body's blood vessels. The occurrence of disseminated intravascular coagulopathy during an MH reaction is associated with poor outcome. It is recommended to startl treatment using platelets, fresh frozen plasma and cryoprecipitate. Tranexamic acid is not indicated in this situation.

Compartment syndrome

Any patient who develops myoglobinuria should be monitored postoperatively for the development of compartment syndrome. The principal means of monitoring for compartment syndrome due to MH is clinical. The awake patient is likely to complain of pain should compartment syndrome develop. In the sedated patient, regular assessment of the limbs for swelling, muscle softness and peripheral pulses or peripheral oxygen saturation should be made. If there is any suspicion that compartment syndrome has developed, the compartmental pressures should be measured. The treatment for compartment syndrome is fasciotomies.

Post-malignant hyperthermia management

If the MH reaction is successfully treated in the operating theatre, and ongoing management of its consequences is not required, then there is no contra-indication to the continuation and completion of the surgical procedure under i.v. anaesthesia.

Reoccurrence of MH is well described: the likelihood and severity is related to the severity of the initial MH episode. If the reaction was treated in its early stages, as defined by response to discontinuation of the triggering agents without the need for dantrolene, it is reasonable to wake the patient after surgery, monitor them for at least 1 h in the post-anaesthesia care unit before returning then to the postoperative ward.

It would be unwise to discharge the patient from hospital within 24 h of the end of surgery in which a suspected MH reaction has occurred. If dantrolene was required to reverse the initial MH reaction, the patient should be monitored and nursed in a high dependency unit or ICU for at least 24 h after the event.

Before discharge from hospital the patient and their family should be informed about the suspected diagnosis of MH. They should be provided with written information about the suspected diagnosis and its implications for future anaesthetic management in their family. They should be specifically advised to warn all blood relatives of the patient that can be contacted about the risk of MH and the need to mention this should any member of the family require admission to hospital. Each member of the family should be advised that this information applies to them until it is proved otherwise using definitive diagnostic tests. The patient and family should be provided with details of the UK MH Registry (www.ukmhr.ac.uk), where information for patients and relatives about all aspects of MH can be found.

Patient referral and follow-up

There are two alternatives for investigation of MH susceptibility. The first is DNA screening and this is relatively cheap, minimally invasive and convenient for the patient, but DNA screening has only an approximate 50% sensitivity for detecting MH susceptibility.

Definitive diagnosis of MH susceptibility relies on specialised tests carried out on freshly excised muscle strips taken at open biopsy (the in-vitro contracture test). Because fresh muscle specimens are required, the patient needs to travel to a MH Unit for the tests. For patients who have experienced a suspected MH reaction, DNA testing is often used in the first instance. If a genetic change associated with MH is not found, the patient will then undergo the muscle biopsy tests if they are old enough (aged> 10 y).

Anaesthesia for patients with an increased risk of developing malignant hyperthermia

Patients at increased risk of developing MH must not be exposed to potent inhalational anaesthetics or suxamethonium. The easiest way to avoid these agents is to avoid general anaesthesia by substituting a regional anaesthetic technique if appropriate. In situations where general anaesthesia is required, strategies to avoid the triggering agents are essential. Nowadays, suxamethonium is invariably reserved for either a rapid sequence induction or in the rescue of a patient developing acute upper airway obstruction in the peri-operative period.

The anaesthetist should have a plan to use alternative agents or techniques to replace suxamethonium or avoid the circumstances in which it would otherwise be used. Potent inhalational agents can be substituted in the patient at risk of MH who requires general anaesthesia by the use of a total intravenous anaesthetic (TIVA) technique.

As there is the possibility that residual quantities of inhalational agents in an anaesthetic machine might trigger an MH reaction, the anaesthetic machine should be appropriately prepared so as to avoid this possibility. Most studies of the elimination of potent inhalational anaesthetics from anaesthetic machines and workstations have used a target of 5 ppm as the maximum safe concentration of inhalation agent. This probably provides for a large safety margin.

Elimination of trace quantities of inhalational agent may be done by flushing the machine for 20-30 minutes with 100% oxygen and keeping the fresh gas flows high during the case. The time required to achieve the target reduction in anaesthetic concentration depends on the individual anaesthetic machine. The recent introduction of activated charcoal filters provides an alternative means for avoiding administration of trace quantities of inhalational agents to patients at increased risk of MH.

Conclusion

Malignant hyperthermia is triggered when a MH-susceptible individual is exposed to a volatile anaesthetic (eg, halothane, isoflurane, sevoflurane, desflurane) or suxamethonium and is caused by the excessive release of calcium within the skeletal muscle cell.

Time is of importance if malignant hyperthermia is suspected. It should be suspected if there is:

- Unexplained, unexpected increase in $ETCO_2$
- Unexplained, unexpected increase in heart rate
- Unexplained, unexpected increase in temperature

Once the diagnosis made the management involves reversing the process by:

- Eliminating the agent
- Administering dantrolene
- Active body cooling

To do this help is needed and an up to date and stocked MH trolley are essential.

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