Malignant hyperthermia: Turn
AN INHERITED DISORDER, malignant hyperthermia (MH) is a life-threatening reaction to certain common inhalational anesthetic agents or the depolarizing skeletal muscle relaxant succinylcholine in susceptible people. Characterized by a hypermetabolic state, it causes tachycardia, sustained generalized muscle contractions, and high body temperature that may exceed 110º F (43.3º C).\textsuperscript{1,2} MH usually occurs during surgery or within an hour after exposure to the triggering agent, but it can develop up to 36 hours later.\textsuperscript{1-3}

When MH was first identified, mortality from the disorder was 80%. With greater awareness of the risk and the discovery of dantrolene sodium, the only drug that effectively treats MH, mortality has dropped to about 5%.\textsuperscript{3} Death from MH is usually secondary to cardiovascular collapse.\textsuperscript{2}

Nurses who care for patients during or after surgery must be knowledgeable about signs, symptoms, and treatments so they can identify MH immediately and respond appropriately. In addition, nurses assessing patients preoperatively must be able to identify patients at risk so the anesthesia provider can administer drugs that don’t trigger MH. Finally, because susceptibility to MH is inherited, nurses must educate patients and their families about the risk. This article discusses how to identify patients at risk, respond to a crisis, and educate patients and their families.

**Genetic basis**

Over 80 genetic defects have been linked to MH. Because MH susceptibility is an autosomal dominant inherited disorder, a child or sibling of a susceptible patient has a 50% chance of inheriting a defective gene.\textsuperscript{2} Two dramatic experiences from my career illustrate the risks faced by families susceptible to MH.

As a nursing instructor in a rural hospital, I met RB, a 15-year-old male scheduled for an orthopedic procedure. Admitted via the outpatient surgical center, RB was taken to the OR where he underwent induction of general anesthesia with sevoflurane and succinylcholine.

Thirty minutes into the procedure, RB developed tachycardia: HR 102/minute from a baseline of 72/minute. His end-tidal carbon dioxide (ETCO\textsubscript{2}) level was slightly elevated and his temperature increased to 101.5º F (38.6º C) from a baseline of 99.3º F (37.4º C). Arterial blood gas (ABG) values showed respiratory acidosis with pH of 7.3 (normal, 7.35 to 7.45) and a PaCO\textsubscript{2} of 48 mm Hg (normal, 35 to 45 mm Hg). The surgeon suspected that RB was experiencing MH and aborted the procedure.
RB was hyperventilated with 100% oxygen and the surgical team initiated the MH protocol developed by the Malignant Hyperthermia Association of the United States (MHAUS), which includes I.V. administration of dantrolene. RB was transferred to the ICU for observation. Fortunately, he responded quickly to treatment and was transferred out of the ICU in 24 hours.

Several months later, I assisted with the care of RB’s uncle, who was admitted to the ICU with an acute MH crisis. TJ, 43, had been scheduled for abdominal surgery in an outpatient surgical center. He too was given sevoflurane and succinylcholine. Shortly after induction, TJ developed a rapid rise in ETCO₂, sinus tachycardia with frequent premature ventricular contractions, and generalized muscular rigidity. ABG values indicated severe respiratory acidosis. TJ was cyanotic and his core body temperature was 103.6°F (39.8°C). The MH protocol was initiated immediately and TJ was transferred to an acute care hospital for a higher level of care. But despite prompt and appropriate treatment, TJ died.

Who’s at risk?
In susceptible patients, MH is triggered by certain specific drugs: the depolarizing muscle relaxant succinylcholine and the inhalational anesthetic agents isoflurane, desflurane, sevoflurane, enflurane, halothane, ether, and methoxyflurane.2 (See Safe or unsafe?) Patients may develop an acute MH crisis at initial exposure to a triggering drug, or after several apparently uneventful exposures. Some evidence indicates that strenuous exercise or heat exposure can also trigger MH in susceptible people.4

Patients at risk for MH can safely undergo surgery as long as they’re induced with nontriggering agents, such as propofol. Local anesthetics are also safe.2 Not all patients susceptible to MH are diagnosed because they may never be exposed to triggering agents—or, if their exposure time is brief, their signs and symptoms may escape notice because they’re nonspecific and mild. Uncomplicated cases can be difficult to diagnose.1

For these reasons, the exact incidence of MH is unknown. The incidence of MH episodes may range from 1 in 5,000 to 1 in 65,000 administrations of general anesthesia with triggering agents.2 MH occurs most commonly in children and young adults. It’s more common in men than in women, and found equally among various ethnicities.3 MH occurs worldwide but is more common in areas that have MH-susceptible families. In the United States, the incidence of MH is especially high in Wisconsin, West Virginia, Nebraska, and Michigan due to concentrations of MH-susceptible families.1,2 Patients with certain pre-existing muscle disorders associated with genetic abnormalities, such as central core myopathy, are also at risk.3 However, most muscular and neuromuscular disorders aren’t associated with MH.2

What goes wrong?
MH is a hypermetabolic crisis set in motion by excess calcium release from muscle. After a susceptible person is exposed to a triggering agent, genetic muscle receptor abnormalities lead the sarcoplasmic reticulum in skeletal muscle to release excessive calcium. (See Making a muscle.) This leads to sustained muscle contraction and rigidity, increasing metabolism and generating heat.2,3 Eventually the overworked cells are depleted of oxygen and adenosine triphosphate (ATP), their energy source. These changes produce carbon dioxide and cellular acidosis. An eventual switch to anaerobic metabolism accelerates acidosis.2,5

As stores of ATP in muscle cells are depleted, cells die and release potassium into the bloodstream. The resulting hyperkalemia can trigger fatal cardiac dysrhythmias. Dying cells also release the pigment myoglobin, causing myoglobinemia. Myoglobin forms precipitate in the renal tubules, resulting in acute kidney injury.1

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Safe or unsafe?1,2

These drugs are MH triggers

Inhalation anesthetic agents:
• desflurane
• enfurane
• halothane
• isoflurane
• methoxyflurane
• sevoflurane
• ether

Depolarizing muscle relaxant:
• succinylcholine

These drugs are safe to use as anesthetic agents in MH-susceptible patients:
• barbiturates/I.V. anesthetics such as ketamine and propofol
• the inhaled nonvolatile general anesthetic nitrous oxide
• local anesthetics such as lidocaine and mepivacaine
• opioids such as fentanyl and morphine
• muscle relaxants such as doxacurium and vecuronium
• antianxiety agents such as midazolam and diazepam.

Note: Visit the Malignant Hyperthermia Association of the United States website for a more complete list of safe drugs: www.mhaus.org.
If the acute MH crisis continues, the patient will experience multiple potentially fatal complications, such as acute kidney injury, left ventricular dysfunction secondary to hypertension, pulmonary edema, and disseminated intravascular coagulation (DIC).1

An MH crisis must be differentiated from disorders causing similar signs and symptoms, such as traumatic brain injury; hypoxic encephalopathy; neuroleptic malignant syndrome; heat stroke; thyroid storm; pheochromocytoma; sepsis; cocaine, amphetamine, and salicylate toxicity; or alcohol withdrawal.3,6

Recognizing the danger

Signs and symptoms of MH include the following. Note that hyperthermia is a later sign of MH and is usually not present early in the crisis.3

- **Hypercapnia.** A progressive, unexpected increase in ETCO2 is the earliest and most sensitive sign that a patient might be experiencing MH.3,5 Normal ETCO2 is 35 to 45 mm Hg.7 In MH, the ETCO2 value may double or even triple on capnography. Be suspicious if you find an unexplained increase in ETCO2 that doesn’t respond to increased ventilation or additional administration of anesthetic.8

- **Tachycardia.** Although an early sign of MH, tachycardia is nonspecific.

- **Generalized muscle rigidity,** especially of the jaw, trunk, and extremities. According to Noble (2007), muscle rigidity, especially masseter muscle rigidity, is seen in 75% of patients experiencing an MH episode.9 When masseter muscle rigidity is present, the patient’s mouth can’t be opened after exposure to the triggering drug. However, transient masseter muscle rigidity is normally associated with the administration of succinylcholine and doesn’t necessarily indicate MH unless it persists after potential triggering agents are discontinued.3

- **ECG changes.** Hyperkalemia may cause premature ventricular contractions, which may progress to life-threatening ventricular tachycardia or ventricular fibrillation.3

- **Rhabdomyolysis.** Destruction of skeletal muscle releases large amounts of the enzyme creatine kinase (CK) and myoglobin, which accumulates in the kidneys. Red or tea-colored urine is a sign of myoglobinuria. Levels of serum CK and urine myoglobin, which peak about 14 hours after the acute MH episode, vary depending on the patient’s muscle mass and the severity of the patient’s condition.3

- **Hyperthermia.** An increase in body temperature, usually a later sign, confirms the suspicion of MH. The patient’s temperature may rise 1°C every 5 minutes and might even exceed 105º F (40.6º C). Severe hyperthermia is associated with DIC.3

- **Electrolyte imbalances.** Besides hyperkalemia, monitor for hyperphosphatemia and hypocalcemia.

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**Making a muscle**

(A) Connective tissue components of a skeletal muscle. (B) Striations of the myofibril showing the overlap of contractile proteins and the A and I bands, the H zone, and the Z and M lines. (C) The relaxed and contracted states of the myofibril showing the position of actin filaments (blue) between the myosin filaments (pink) in the relaxed muscle (top) and pulling of the Z membranes toward each other (bottom) as the muscle contracts. (D) The sarcoplasmic reticulum with T tubules.

• Other signs and symptoms. Progression of an MH crisis results in mottling and cyanosis of the skin, and a mixed respiratory and metabolic acidosis. The patient is at increased risk for sudden cardiac death. The clinical signs indicate that the body can’t keep up with the increased metabolic demand, resulting in multisystem organ failure.

Respond quickly
If you suspect your patient is experiencing an MH crisis, take action immediately. DeJohn (2008) believes there is a strong correlation between the timing of interventions and positive patient outcomes.

During surgery, the first priority is to discontinue the use of any inhalational anesthetics and succinylcholine, optimize oxygenation and ventilation, and administer dantrolene immediately. Postoperatively, priorities for treating an MH crisis are identified by MHAUS as follows. (The MH treatment protocol and treatment sheet are available on the MHAUS website; see Resources for healthcare providers and patients.)

• Team initiation. Collaboration among all members of the health team is crucial. The team leader assigns roles as would be done to manage any crisis. Notify the anesthesia provider, the surgeon, and the critical care intensivist immediately. Prepare for insertion of an arterial line and central venous access if not already in place. Assign a nurse to the MH cart, which should be standard equipment in any facility where surgical procedures are performed, and have the MH protocol and treatment sheet available. Staff roles, such as team leader, medication nurse, recorder, lab liaison, I.V. access nurse, lavage nurse, and ice liaison, should be defined ahead of time.

• Administer dantrolene. Consider the gold standard, dantrolene sodium is the only known effective treatment for MH. Dantrolene is classified as a direct-acting skeletal muscle relaxant. It may stop skeletal muscle contraction by interfering with calcium release from the sarcoplasmic reticulum, reversing skeletal muscle hypermetabolism.

Dantrolene is supplied in vials and must be reconstituted before administration. MHAUS recommends having 36 vials of dantrolene available at all times. Each 65-mL vial contains 20 mg of dantrolene sodium and 3 g mannitol, plus sodium hydroxide to maintain a pH of 9 to 10.

At least two qualified team members should be available to reconstitute and administer the drug. The powder can be reconstituted only with 60 mL of sterile preservative-free water for injection. It’s incompatible with 5% dextrose, 0.9% sodium chloride, bacteriostatic water for injection, and other acidic solutions, and precipitates if added to a glass container for infusion. Shake the vial for about 20 seconds until the solution is clear. The reconstituted solution should be used within 6 hours and protected from direct light.

Administer dantrolene as prescribed by rapid I.V. bolus until signs subside or the maximum cumulative dose (10 mg/kg) is reached. Because MH signs and symptoms recur in up to 25% of patients after initial treatment, maintenance doses of dantrolene should continue for 48 hours after the last observed sign of acute MH. If signs continue despite ongoing treatment, additional dantrolene doses or a dantrolene infusion may be required.

Monitor the venous access site closely for signs of dantrolene extravasation, including pain, erythema, and edema, which can lead to tissue necrosis due to its high pH. Administer fluid resuscitation as prescribed to prevent dantrolene-related crystalluria.

• Provide adequate oxygenation. Administer oxygen at 100% to meet the patient’s high metabolic demands. The patient will most likely be endotracheally intubated if arriving from the OR. If not, prepare to assist with intubation as indicated. Hyperventilate the patient as prescribed, increasing the rate and tidal volume to compensate for increased PaCO2.

Collaborate with the respiratory therapist to monitor ETCO2 by continuous capnography. Assess the patient for signs and symptoms of fluid volume overload, such as pulmonary crackles, because the patient will be receiving large amounts of I.V. fluids. Closely monitor continuous pulse oximetry and ABG values.

• Maintain hemodynamic stability. Place the patient on a continuous cardiac monitor and frequently assess BP, heart rate, core body temperature, and central venous pressure. An arterial line is beneficial not only for continuous BP monitoring but also for frequent arterial blood sampling.

Ventricular dysrhythmias can occur approximately 20 minutes after the patient becomes hyperthermic.

Resources for healthcare providers and patients
Malignant Hyperthermia Association of the United States (MHAUS)
607-674-7901
http://www.mhaus.org

MH hotline for emergencies only:
800-644-9737 (in US and Canada)
001-1-315-464-7079 (from outside the United States)
Dysrhythmias may resolve once acidosis and hyperkalemia are corrected. MHAUS recommends treating persistent life-threatening dysrhythmias with standard drug therapy, but warns against using calcium channel blockers with dantrolene. This combination can cause hyperkalemia or cardiac arrest.  

- **Correct metabolic abnormalities.** The hypermetabolism of MH causes both respiratory and metabolic acidosis. This is treated by hyperventilation to two to three times the predicted minute volume with 100% oxygen. MHAUS recommends treating hyperkalemia with hyperventilation, I.V. calcium, I.V. sodium bicarbonate, and I.V. insulin-glucose. Check blood glucose levels hourly if the patient is receiving I.V. insulin.

- **Initiate cooling measures.** Monitor core body temperature continuously via esophageal, rectal, or bladder probes. Several team members are needed to cool the patient externally with cooling blankets and ice bags, and internally by administering cool I.V. fluids and lavaging the nasogastric tube and urinary catheter with cool fluids. Cooling by convection with wet towels and a fan can be very effective as well. Once the patient’s temperature reaches 38°C, cooling efforts are minimized; however, continue to closely monitor the patient’s temperature.  

- **Provide fluid resuscitation.** Ideally, central venous pressure should be monitored to assess fluid volume status. Insert an indwelling urinary catheter for accurate hourly output measurements. A three-way urinary catheter can also be used to promote active cooling through continuous bladder irrigation. A urine output of 1 to 2 mL/kg/hour is necessary to prevent acute kidney injury. Adequate fluid resuscitation helps treat cellular hypoxia and prevent worsening of acidosis if ongoing volume loss and diuresis is a concern. MHAUS recommends that for treating acute rhabdomyolysis and myoglobinuria, urine output should be maintained above 2 mL/kg/hour. This can be achieved by hydration and diuretics. A sodium bicarbonate infusion is also recommended for alkalization of urine, with close lab monitoring of urine and serum pH values.

**Staff education**

All staff members caring for patients recovering from general anesthesia should receive education about MH, with periodic reviews and updates. In addition:

- an MH cart stocked with dantrolene and other emergency supplies needed during an MH crisis should be readily available. The MH cart should be checked frequently to ensure that expired supplies are removed and replaced.

- Staff should have access to an ice machine, cooled I.V. fluids, and a cooling blanket.

- An MH treatment protocol should be developed or adapted and made readily available to all staff. Posters and wallet cards with the recommended MH protocol are available from MHAUS.

- Post the MHAUS 24-hour emergency hotline—800-644-9737—in a prominent place on the unit.

- Fill out an adverse medical reaction to anesthesia (AMRA) form when a patient is diagnosed with MH and send it to MHAUS.

**Testing confirms the diagnosis**

The gold standard for identifying patients susceptible to MH is the caffeine-halothane contracture test (CHCT), which involves an excisional muscle biopsy. According to MHAUS, it’s performed only in specialized centers; there are 30 centers worldwide and only 6 in North America. Because the CHCT test must be performed on a fresh muscle specimen, the patient must travel to one of these centers for testing. Contractile responses to caffeine and halothane are measured relative to baseline muscle tension.

Genetic testing can also be done to look for genetic mutations commonly associated with MH. Genetic testing is less costly but has a significant false-negative rate for MH susceptibility.

**Prevention and teaching**

A thorough preoperative assessment can help minimize the risk of MH. When obtaining a patient’s health history, establish if the patient has experienced any adverse reactions to anesthesia. Also ask if the patient knows of any blood relatives who experienced an adverse reaction.
(such as muscle rigidity) or unexplained death during anesthesia.

After recovering from an acute MH crisis, patients should be informed about the disorder and genetic counseling should be offered. Family members should also be tested. Only one parent needs to carry a defective gene for the child to inherit the disease.

Tell patients who are or may be susceptible to MH that while they must avoid surgery involving triggering drugs, the anesthesia provider can administer alternative drugs that won’t trigger a crisis. Encourage them to spread the word among family members, who could also be at risk. Warn patients to avoid excessive heat, stress, vigorous exercise, alcohol, and cocaine in addition to MH-triggering anesthetics.

Empower patients and their families to learn more about reducing risks and complications by seeking information from MHAUS, which offers resources for both healthcare professionals and patients and families affected by MH. Recommend that anyone susceptible to MH wear a medical alert bracelet or tag.

Awareness of risk factors, detection of early signs, and prompt appropriate treatment are the keys to prevent complications and death from this anesthetic emergency.

REFERENCES

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