Dantrolene sodium and management of malignant hyperthermia

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This article will identify the clinical signs of malignant hyperthermia (MH) and the institution of a corrective treatment. Thorough guidelines are offered for the identification and management of MH through the pre-, intra-, and post-operative period. The role of dantrolene sodium in the treatment of MH will also be explored.

Malignant hyperthermia (MH) is an inherited muscle disorder suffered by patients who undergo a stressful situation or acute trauma or who have been given certain anesthetic agents. MH has been called the most common cause of anesthesia-related death in North America, contributing a large percentage of the 15,000 to 20,000 of such deaths recorded annually. The 53% mortality rate of today compares favorably with the 90% rate in 1960, but it is still high.

Though not confined to one specific age group, MH is most prevalent in young healthy patients who have a large muscle mass. Many orthopedists have found that patients who demonstrate weakness, cramping of extremities, twitching, and intolerance of exercise during hot weather are susceptible to developing MH. Many of the patients studied were found to have underlying musculoskeletal problems, such as kyphosis, scoliosis, or recurrent dislocation of joints. Mental or physical stress can also be a contributory cause of MH outside the operating theater.

Anesthetic agents have been implicated in the cause of MH since the disorder was first diagnosed. It is now speculated that the anesthetic agent acts as a "triggering mechanism" for this complication. Unfortunately for the anesthetist, these "triggering" agents are commonly employed in anesthetic management plans. Halothane, a heavily halogenated inhalation agent, and succinylcholine, a skeletal muscle relaxant, are the agents most frequently accused of triggering MH. It must be remembered that although these agents may serve as "triggering mechanisms," for MH to occur a dominant gene must be present that predisposes the patient to the complication.

Pathophysiology

Although the exact cause of the acute catabolic crisis of MH is not yet clear, the most commonly agreed upon cause is the release of calcium from the calcium-storing membrane (sarcoplasmic reticulum) of the muscle cell. Abnormal transport of calcium could result, causing the recurrent contractions of the sarcomere and consequent muscle rigidity. When this occurs, the metabolic rate speeds up, resulting in an increased heart rate and increased CO₂ production.

As the metabolic rate increases, the rate of oxygen consumption also increases, resulting in hypoxia of the peripheral tissues. The end result
is lactic acidosis. The lactic acidosis causes further loss of integrity of the cell wall with ensuing electrolyte imbalances. These imbalances lead to an elevated serum potassium, serum calcium, and occasionally serum phosphorus. Early in the sequence serum calcium will rise but later will drop, contributing to the further loss of calcium into the muscle cell.

The patient will develop deep, rapid respirations in an attempt to clear the excess CO₂ in the hypermetabolic tissue. Consumption coagulopathy can occur as a result of loss of platelets, fibrinogen, and Factor VIII. A deposition of myoglobin in the renal tubules will cause a decrease in urine output. Myoglobin buildup is caused by muscle tissue damage. If lab studies show an increase in blood urea nitrogen, acute tubular necrosis can be expected to occur.

Acute pulmonary edema, secondary to left ventricular failure, is a possible occurrence that can compound the problem of edema. If the patient dies within one or two hours after the initial onset of MH death can usually be related to ventricular fibrillation. If death should occur later, it is probably secondary to electrolyte imbalances, coagulopathy, pulmonary edema or acid-base abnormalities. If the patient is in a coma and dies several days thereafter, death is probably due to brain damage or renal failure.

Clinical signs

The signs of MH must be readily recognized in order that a successful plan of care may be devised for these afflicted patients. (See Table I.) Many of the early signs of impending MH include tachycardia, tachypnea, unstable blood pressure, arrhythmias, cyanosis, mottling of the skin, fever, rigidity, and profuse sweating. (Fever is sometimes a late sign, and rigidity is not always present.)

The first signs that occur are an increase in heart rate (up to 200 beats/minute), tachypnea, and dysrhythmias. Tachycardia and the dysrhythmias that occur are probably secondary to the high fever, anoxia, acidosis and shift in electrolyte balance, rather than a direct action on the myocardium. Tachypnea is a result of the patient's effort to rid himself of the excess CO₂ that has built up in the hypermetabolic muscle tissue.

Rigidity has always been considered a classic sign of MH, especially when it occurs after the administration of succinylcholine. It is believed to be caused by recurrent contractions of the sarcomere that result from abnormal calcium transport.

The dysrhythmias that may occur usually begin as sinus tachycardia, which may progress to ventricular tachycardia and eventually to ventricular fibrillation and death. Hyperventilation will usually occur, but may not be observed because of the effect of muscle relaxants or even of the anesthetic agents themselves. Fever elevation of as much as two degrees every five minutes has been seen, and fever may rise as high as 47.5°C preceding the patient's death. However, this symptom may not present itself until late in the complication. The carbon dioxide absorber granules may change color relatively fast and become hot to the touch, demonstrating the profound hyperventilation of the patient.

As the course progresses, an increase in venous PCO₂ occurs, with a rapid fall in pH. There is also a shift in electrolytes. Serum calcium will initially rise, but as the complication develops, it will drop. Serum potassium, and occasionally serum phosphorus, will rise. The electrolyte shift is believed to be caused by loss of integrity of the sarcolemma and by the increasing ion stream from the muscle cells. The end result of the shift in pH

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is severe acidosis and eventual necrosis of the muscle tissues. Recognition and management

Early recognition of the signs indicative of MH and prompt implementation of a management plan are essential for there to be any hope of the patient's survival. The diagnosis is determined by observation of the clinical signs and verified by arterial blood gas (ABG) studies. The ABG studies are used to determine the extent of the respiratory and metabolic acidosis. They will show a marked increase in CO₂ with subsequent fall in pH, venous desaturation, and metabolic acidosis, which is reflected by decreasing PaO₂ and a fall in pH. Once the diagnosis has been made, the anesthetist must make the surgeon aware of the complication so the procedure can be terminated as quickly as possible. The anesthetist must at the same time stop the anesthetic course, including administration of all anesthetic agents and muscle relaxants. All the rubber connecting tubing and the anesthesia machine must be changed. A few institutions have what is called a “virgin” anesthetic gas machine, which is used exclusively when a case of MH is suspected. A “virgin” machine is a fresh machine in which no halogenated agents have been used. If no “virgin” anesthetic gas machine is available, a non-rebreathing portable Ambu bag that will deliver 100% oxygen should be used.

Hyperventilation with 100% oxygen is the next step. (See Table II for a complete list of treatments.) This will help correct the respiratory acidosis and supply sufficient oxygen for the tissues, which are deprived of oxygen in the hyperthermic state. After the arterial blood gas has been drawn, correction of the metabolic acidosis with sodium bicarbonate is necessary. Giving sodium bicarbonate 100 mEq immediately, and up to 600 mEq as indicated by arterial pH, will help correct the acidic state. Further evaluation of the acidotic state should be guided by PaCO₂ and base excess.

Hyperkalemia should be treated with the administration of 10 ml of 50% dextrose with the addition of 10 u of regular insulin. This will help drive the potassium back into the injured cells.

Actively cooling the patient is essential. Any conceivable method may be used. The patient may be immersed into an ice water bath if the surgical area is closed. Lavaging the peritoneal cavity with iced saline will prove beneficial in lowering the patient's temperature. Cooling should be continued until the patient's temperature returns to 38°C and should be resumed if needed later. Though not done frequently, extracorporeal circulation can be utilized. Surface cooling blankets can be employed, although they will not supply enough temperature gradient to be used as a sole means of cooling, except in the pediatric patient, where there is a greater surface area compared to body mass.

Maintenance of adequate urinary output is essential. Mannitol (1 gm/kg of body weight) and furosemide (1 mg/kg of body weight) will help maintain an adequate urine flow and rid the tubules of excessive sodium and myoglobin buildup. A retention urinary catheter is needed to monitor the urine output.

Dantrolene sodium (Dantrium®) 1 mg/kg IV should be administered. Dantrolene sodium as an IV preparation has been on the market several

### Table II

**Treatment of malignant hyperthermia**

1. Stop anesthesia and surgery immediately
2. Hyperventilate patient with 100% oxygen
3. Administer dantrolene sodium (1 mg/kg) as soon as possible
4. Administer procainamide if required for arrhythmias
5. Initiate cooling
6. Correct acidosis
7. Treat hyperkalemia
8. Secure monitoring lines: ECG, temperature, Foley catheter, arterial pressure, central venous pressure
9. Maintain patient until danger of subsequent episodes is past
10. Maintain urine output
11. Administer dantrium orally if desired in the post-crisis period
years, but it only recently (August, 1979) became available for the treatment of MH in the United States. Prophylactic treatment with oral preparations is also available for patients in whom this affliction is suspected. Monitoring the patient is necessary to the successful treatment of MH. Electrocardiography, central venous pressure, temperature, and blood pressure readings are essential until the patient is stable. Frequent ABG studies will help the anesthetist to determine if the combined acidotic states are being corrected. Serum electrolytes, glucose, BUN, SGOT, CPK and calcium will assess the patient's response to treatment.

The following signs will indicate positive response to corrective treatment: a lightening of the comatose condition; a return to normothermia; a reduction in heart rate; and stability of blood pressure. If these signs are observed, the patient may be transferred to the intensive care unit where close observation can be continued until symptoms have ceased.

The necessity of a careful preanesthetic evaluation cannot be overemphasized. If there has been a suspected case of MH in the family, the "trigger" agents must be avoided and prophylactic dantrolene sodium must be given in the preoperative period and continued intraoperatively and postoperatively. Extensive monitoring of all parameters should be instituted before induction of anesthesia.

The role of dantrolene sodium in treatment

Dantrolene sodium is a direct muscle relaxant that acts on skeletal muscle specifically. It does not affect neuromuscular transmission or excitability of the surface membrane, but recent studies have shown that it interferes with the release of calcium from the sarcoplasmic reticulum. In the anesthetic-induced MH patient, it is postulated that the "trigger agent" causes the release of calcium from the sarcoplasmic reticulum, causing a breakdown of the muscle tissue. Dantrolene sodium will help reduce the severity of MH by reversing or attenuating the effects of calcium release.

To date, the use of dantrolene sodium has caused no untoward effects except a slight increase in blood pressure and heart rate. As soon as MH is diagnosed, an initial dose of dantrolene sodium (1 mg/kg of body weight) should be given. If symptoms persist, the dosage should be repeated up to a cumulative dose of 10 mg/kg of body weight. The usual dosage, based on clinical studies, of 2.5 mg/kg of body weight has achieved favorable results.

It is also wise to continue administration of dantrolene sodium at a dosage of 1-2 mg/kg of body weight for at least one to three days postoperatively to lessen the chances of reoccurrence of MH. Dantrolene sodium can also be used prophylactically in the preoperative period for the patient who is known or suspected to be susceptible to MH. Dosage should be 1-2 mg/kg of body weight, given at 12 hours and 4 hours prior to the induction of anesthesia.

It must be remembered that dantrolene sodium is not a substitute for treatment of MH. The previous supportive measures must also be instituted to better the chances of a satisfactory outcome for the patient.

Summary

As stated earlier, the prognosis for a patient afflicted with MH is very discouraging. An appropriate plan of care is the patient's only chance to survive MH. Thus, the anesthetist must act promptly and accurately when a suspected case of MH arises in the surgery suite. Before initiating any anesthetic, the anesthetist must have a treatment plan in mind for management of MH if it should occur. Since the advent of dantrolene sodium, the prognosis for patients who suffer an MH crisis has greatly improved. To date, this drug has provided the patient with the greatest protection against MH, and consequently is the preferred drug in the treatment of MH.

REFERENCES

AUTHORS

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AANA Journal Course

Test Yourself Answers

(Questions appeared on page 402)

1. (a) The surgical microanastomosis may be facilitated.
   (b) Impedance to blood flow is reduced.
   (c) Microcirculation to the surgical site is assured.

2. The use of an inhalational agent is preferred because of the vasodilation it promotes. The agent that meets the requirements of the least biotransformation is isoflurane.

3. Continuous axillary block provides the vasodilation necessary for the preoperative, intraoperative, and postoperative periods, which is necessary for surgical success.